Panic Disorder: An Integrative Assessment of Brain, Body and Cognitive Function

A Thesis Presented for the Degree of Doctor of Philosophy

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Abstract

Panic disorder is a highly generalised anxiety disorder in the sense that, even in the absence of panic, it is associated with wide–ranging abnormalities across multiple levels of function (e.g., central and peripheral physiology, behaviour, cognition, affect) (Friedman, 2007). Although the extant research literature has typically examined responses to explicitly threat–related stimuli in PD, it is increasingly recognised that panic disordered individuals differ from unaffected controls in their response to normatively non–threatening events, including 'resting state' paradigms (Grillon, 2008). In comparison to less integrative research designs, multivariate, multi–level research may more comprehensively characterise function during the disorder's tonic, between–panic manifestation. The present research therefore examined PD in the between–panic state with an integrative psychophysiological and neuropsychological assessment comprising a range of normatively non–threatening paradigms.

Clinical participants with current PD (n = 53) and demographically–matched healthy control participants (n = 106) completed an extensive laboratory–based assessment of brain, body and cognitive function, the results of which are reported as three studies. In Study 1, quantitative electroencephalography and autonomic (cardiovascular and electrodermal) measures were concomitantly recorded during two resting state conditions. The findings of this study demonstrate multiple abnormalities of brain and body function at rest in PD. Findings of note include diminished synchronised electrocortical activity within the alpha–1 frequency range, increased heart rate and decreased beat–to–beat heart rate modulation (*i.e.* heart rate variability) in PD compared to controls. In Study 2, event–related potential (ERP), autonomic and behavioural

measures were obtained during performance of an auditory oddball task, to examine sensory information processing and the allocation of attention to goal–relevant, non–threatening stimuli in PD. Patients and controls differed on numerous ERP and behavioural indices. ERP findings of note include reduced P3 amplitude to infrequent auditory tones in PD compared to controls, and increased N1 amplitude to frequent, irrelevant tones. Study 3 examined cognitive function in PD with an extensive neuropsychological test battery comprising tests selected to assess the core cognitive domains of attention, memory, executive functions, language and sensory–motor function. The results support a selective deficit in the cognitive domain of sustained attention, but normative function in the other assessed cognitive domains.

Considered together, many of the research findings indicate either impaired attentional processing or diminished capacity for attentional processing in PD. The findings also fit a theoretical model of diminished physiological flexibility, which proposes that in generalised anxiety disorders such as PD there is less physiological differentiation of baseline activity and stress–related reactivity to minor everyday and laboratory stressors (Thayer & Lane, 2000; Friedman, 2007; Hoehn–Saric, 2007). The integrative assessment identified numerous differences between patients and controls (*i.e.* disorder markers) spanning multiple levels of function. As different types of disorder markers (e.g., risk factors versus maintenance factors) may differentially benefit clinical practice and research (Zvolensky *et al.* 2006c), future research is needed to classify the identified markers so that their potential utility may be realised.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Vikki Wise and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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I acknowledge the support of the Brain Resource International Database (under the auspices of Brain Resource Ltd. www.brainresource.com) for use of the normative and clinical data. Access to the database for scientific purposes is overseen by a scientific network (BRAINnet; www.brainnet.net.org.au), which is coordinated independently of the commercial operations of Brain Resource Ltd.

Finally, to my mum, my partner, and to those friends who made a difference – THANK YOU.

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List of Abbreviations

APF	alpha peak frequency
ANS	autonomic nervous system
APA	American Psychiatric Association
BLA	basolateral nucleus of the amygdala
BMI	body mass index
BNST	bed nucleus of the stria terminalis
BRID	Brain Resource International Database
BSQ	Body Sensations Questionnaire
CA	central nucleus of the amygdala
CAN	Central Autonomic Network
CBT	cognitive–behavioural therapy
CNS	central nervous system
COWA	Controlled Oral Word Association test
CPT	Continuous Performance Test
CR	conditioned response
CRT	Choice Reaction Time
CS	conditioned stimulus
CVD	cardiovascular disease
CVLT	California Verbal Learning Test
DASS	Depression Anxiety Stress Scales
DPF	diminished physiological flexibility
DSM	Diagnostic and Statistical Manual of Mental Diseases
DV	dependant variable
ECG	electrocardiogram

EDA	electrodermal activity
EEG	electroencephalogram
EMG	electromyography
EOG	electrooculogram
ERP	event–related potential
FAA	frontal alpha asymmetry
fMRI	functional magnetic resonance imaging
GABA	gamma–aminobutyric acid
GAD	generalised anxiety disorder
G–G	Greenhouse–Geisser correction
H–F	Huynh–Feldt correction
HF	high frequency
HR	heart rate
HRV	heart rate variability
ICD	International Classification of Diseases
LF	low frequency
LSA	limited symptom (panic) attack
LTM	long term memory
MDD	major depressive disorder
mPFC	medial prefrontal cortex
MTL	medial temporal lobe
NS.SCR	non–specific skin conductance response
OCD	obsessive–compulsive disorder

OR	orienting reflex
PD	panic disorder
PDA	panic disorder with agoraphobia
PDSS	Panic Disorder Severity Scale
PFC	prefrontal cortex
PNS	parasympathetic nervous system
PTSD	post–traumatic stress disorder
QEEG	quantitative electroencephalography
REC	Resting Eyes Closed
REO	Resting Eyes Open
RT	reaction time
SAD	social anxiety disorder
SCL	skin conductance level
SCR	skin conductance response
SDS	Sheehan Disability Scale
SEM	standard error of mean
SGI	Sensory Gating Inventory
SNS	sympathetic nervous system
SNRI	serotonin and noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAI	State–Trait Anxiety Inventory
TMT	Trail Making Test
UCS	unconditioned stimulus

Overview of Thesis

This thesis presents an integrative assessment of brain, body and cognitive function in Panic Disorder (PD). The thesis content, broadly speaking, comprises two parts. The first part of the thesis (Chapters 1 and 2) presents background information of a general nature. The purpose of these two chapters is to provide a comprehensive overview of PD, and of fear and anxiety – the two emotions which, iteratively, define its course. The second part of the thesis (Chapters 3 – 9) presents the research conducted for this thesis. The content of each thesis chapter is now briefly described.

Chapter 1 presents a comprehensive overview of PD. The focus of Chapter 1 is twofold. The primary focus is on the clinical phenomenology of PD. Thus the chapter includes discussions of the disorder's diagnostic criteria, prevalence, comorbidities, prototypical course, personal and societal costs, and treatment. Panic disorder aetiology is the chapter's secondary focus. Various aetiological models of PD are discussed, as are genetic and environmental risk factors for PD.

Chapter 2 discusses fear and anxiety. This discussion places these two, distinct emotions within a broad evolutionary context. Evolution–based disciplines make a fundamental distinction between *ultimate* and *proximate* explanations of a given trait or disorder (Nesse, 1999). Put briefly, proximate explanations concern individual differences in illness vulnerability (Nesse, 1999). Thus the original research presented in Chapters 3 – 9 represents a proximate approach in that it aims to identify patient–control differences. By contrast, ultimate explanations consider why all members of a species share a vulnerability to a particular disorder (Nesse, 1999). Chapter 2 emphasises ultimate

explanations of human fear and anxiety, as these two, complementary levels of explanation are viewed as essential to a comprehensive, integrative account of human vulnerability to a given disease (Gluckman *et al.* 2011; Nesse, 2011). Much of Chapter 2 is devoted to *defensive responses*, which are the phylogenetically ancient foundations of human fear and anxiety. Other topics covered include sensory information appraisal and threat detection mechanisms; adaptive versus maladaptive fear and anxiety, and; the CNS and ANS organisation of fear and anxiety.

Chapter 3 introduces the research conducted for this thesis. Because this research is presented as three separate studies in Chapters 6 – 8, and each of these chapters presents empirical and conceptual background information of specific pertinence to that study, Chapter 3 discusses the present research in necessarily broad terms. The first major chapter section characterises the extant PD literatures of relevance to the present research. The other major chapter section explicates the rationale for the present research, with reference to five key research features. These are: 1) between–subjects design; 2) focus on tonic as opposed to phasic PD; 3) comparison of PD and healthy controls in a 'weak' situation; 4) subject selection and subject numbers, and 5); data integration.

Chapter 4 presents the overarching methodology of the research conducted for this thesis. As the three experimental chapters incorporate a Method section describing aspects of the research methodology of specific relevance to that study (e.g., data collection procedures, stimulus materials, statistical analyses), Chapter 4's description of the methodology is necessarily restricted to those elements that are common to all three studies. Thus the chapter presents the respective study criteria for clinical and control participants and discusses the methods of participant recruitment. Chapter 4 also

describes the overall data collection procedure and stimulus materials in common to each study. Notably, clinical measures are described. Finally, the chapter describes the data cleaning, data reduction and statistical analysis methodologies in common to each study.

Chapter 5 presents demographic and clinical data for the respective research samples. The chapter presents three types of data, relating to: between–group demographic comparisons; clinical severity measures, and; clinical heterogeneity within the panic disordered sample.

Chapter 6 presents Study 1: Brain & Body Function 'at Rest'. Before presenting the study methodology and results, the chapter describes the psychophysiological techniques used to derive indices of brain and body resting state function for Study 1, and reviews quantitative electroencephalography and autonomic findings for PD. This is followed by a discussion of the 'resting state', specifically, those elements of the psychophysiology laboratory environment which may exert a differential effect on panic disordered and healthy control subjects. The results of Study 1 have previously been published in substantially similar form (Wise *et al.* 2010, see Appendix L).

Chapter 7 presents Study 2: Sensory Information Processing. Before presenting the study methodology and results, the chapter presents background information relating to adaptive sensory information processing, sensory gating, the auditory oddball task and event–related potentials. This is followed by a discussion of empirical findings of relevance for Study 2. The results of Study 2 have previously been published in substantially similar form (Wise *et al.* 2009, see Appendix M).

Chapter 8 presents Study 3: Cognitive Function. The chapter begins by defining the major cognitive domains encompassed by the neuropsychological assessment, and reviewing empirical findings of relevance to the study. Following this background information, the Study 3 research methodology and results are presented.

Chapter 9 presents the overall thesis conclusions. The chapter brings together findings from Studies 1 – 3 and discusses the possible implications of the overall pattern of results. Given the theoretical and clinical importance of distinguishing different types of disorder markers (e.g., risk *vs.* maintenance factors, state *vs.* trait markers) (Kraemer *et al.* 2001; Zvolensky *et al.* 2006c), evidence for a possible role of the observed patient–control differences in PD aetiology and maintenance, where available, is discussed. Finally, the chapter concludes with a discussion of several research strategies for future PD research which may yield useful information for PD theory and clinical practice.

Chapter 1

Panic Disorder

1.1 Overview of Chapter

The focus of this chapter is twofold. The primary focus of the chapter concerns panic disorder (PD), its clinical phenomenology and treatment. Despite being categorically defined, PD is a highly heterogeneous clinical phenotype. The secondary focus of the chapter concerns aetiological mechanisms in PD. Panic disorder – as per other anxiety disorder phenotypes (Domschke & Dannlowski, 2010) – is considered aetiologically complex, in that liability is determined by the interaction of multiple susceptibility genes and environmental stressors (Maron *et al.* 2010; Klauke *et al.* 2010).

The chapter begins with a description of panic attacks, the presence of which is a necessary, but not sufficient, condition for a PD diagnosis. This is followed by a description of the disorder's diagnostic criteria, which include persistent between–panic anxiety, and a discussion of the distinction between PD with and without agoraphobia.[1] Discussions of the disorder's prevalence, comorbidities, prototypical course, personal and societal costs, and treatment follow.

Next, the discussion turns to PD aetiology. Aetiological models of PD are discussed. To date, biological and psychosocial accounts predominate, but are largely unintegrated (Clark & Beck, 2010; Pilecki *et al.* 2010). Then, the relative contribution

of genetic and environmental risk factors for PD is discussed. In psychiatric phenotypes, aetiological mechanisms operate at multiple organisational levels within a dynamic hierarchy that, ultimately, link genotype to phenotype (Hamer, 2002; Kendler, 2008). Identified risk factors for PD span the biological/genetic, psychological, social, and cultural/economic levels of function (Craske & Zucker, 2002; Zvolensky *et al.* 2006c; Feldner *et al.* 2008). Finally, the chapter concludes with a description of the steps which are required to develop an integrative, multi–level model of PD aetiology.

Overall, the present chapter in conjunction with Chapter 2, provide foundational information for later chapters (Chapters 3 – 9), which present the original research conducted for this thesis.

1.2 Panic Disorder Clinical Phenomenology

Naturalistic studies show that PD is an anxiety disorder that generally has a chronic course, albeit of waxing and waning severity (Keller *et al.* 1994; Faravelli *et al*. 1995; Roy–Byrne & Cowley, 1995; Liebowitz, 1997; Pollack & Otto, 1997; Katschnig & Amering, 1998; Shear *et al.* 1998; Pollack & Marzol, 2000; Rubio & López–Ibor Jr., 2007; Batelaan *et al.* 2010b). Although established treatments benefit many panic disordered individuals (Mitte, 2005; Bandelow *et al.* 2007), treatment refractoriness, in the sense of inadequate treatment response, treatment non–response, or relapse, remains high (Bandelow & Rüfer, 2004; Busch & Milrod 2004; Landon & Barlow, 2004; Diemer *et al.* 2010). The presence of recurrent panic attacks is, appropriately, central to the clinical phenomenology of PD.

1.2.1 Panic Attacks

A panic attack, according to the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM–IV),[2] is a brief, discrete episode of intense fear or discomfort, of sudden onset, and with rapid resolution (American Psychiatric Association: APA, 1994). Panic attacks are, thus, defined by their suddenness, perceived intensity, and brevity. To meet criteria for a full panic attack, at least four from a list of 13 physical and cognitive criterion symptoms must be present during the episode. These symptoms include: heart pounding, or accelerated heart rate; sweating; trembling; dyspnoea; chest pain or discomfort; dizziness or faintness; derealisation (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; numbness or tingling, and; chills or hot flushes (APA, 1994). Attacks meeting all other criteria, but in which fewer than four symptoms are present, are called limited–symptom attacks (LSA) (APA, 1994). In recent revisions of DSM (e.g., DSM–III to DSM–IV–TR) panic attack criteria have not changed substantially, although DSM–IV–TR explicitly states that the attack must occur "in the absence of real danger" (APA, 2000, p. 430). For a full list of DSM–IV panic attack criterion symptoms, see Table 1.

As the 13 DSM–IV criterion symptoms for panic are highly varied (Barlow *et al.* 1994), and the number of criterion symptoms present may vary substantially (Craske *et al.* 2010), panic attacks are highly variable in their expression (Barlow *et al.* 1994; Whittal *et al.* 1996; Ietsuga *et al.* 2007; Brandão *et al.* 2008). Moreover, the varied symptoms implicate a variety of different somatic, brain and cognitive processes in panic attacks. A substantial cluster of panic symptoms (e.g., cardiovascular symptoms, sweating, trembling, chest pain, chills, flushes, nausea) implicate autonomic nervous

*Table 1: DSM–IV criteria for panic attack.**

NOTE:
This table is included on page 4 of the print copy of the thesis held in the University of Adelaide Library.

*Adapted from DSM–IV (APA, 1994). DSM–IV–TR criteria specify that the attack must occur "in the absence of real danger" (APA, 2000), but are otherwise unchanged.

system (ANS) activation (Jeejeebhoy *et al.* 2000; Barlow, 2002; Roth, 2005; Davies *et al.* 2008). For example, cardiovascular panic symptoms implicate sympathetic ANS predominance, secondary to diminished parasympathetically–mediated inhibition (Porges, 1992; Friedman & Thayer, 1998b; Thayer & Lane, 2000; Friedman, 2007), whereas arousal–related sweating is sympathetically mediated (Dawson *et al.* 2000). Other symptoms, such as dyspnoea, dizziness, numbness or tingling may reflect hyperventilation and hyperventilation–induced hypocapnea (Roth, 2005; Meuret *et al.* 2006; Meuret *et al.* 2009). Cognitive panic symptoms (e.g., fears of dying, losing

control, or going crazy), which are catastrophic cognitions relating to the feared consequences of the panic attack, have been proposed variously to represent either a cause (Goldstein & Chambless, 1978; Clark, 1986; Beck & Clark, 1997) or a consequence (Klein, 1993) of other panic symptoms. Alternatively, such conscious cognitions may be an inexorable component of panic in that direct electrophysiological stimulation of brain regions implicated in fear responses elicits feelings of terror and of impending death in neurosurgical patients (Nashold *et al.* 1969; Jenck *et al.* 1995). Finally, in contradistinction to the other DSM panic symptoms, depersonalization (being detached from oneself) and derealisation (feelings of unreality) (APA, 1994), which may occur either transiently or tonically in PD (Cox & Swinson, 2002; Mendoza *et al.* 2010), may implicate disturbances of central nervous system (CNS) processing of sensory information (Sierra & Berrios, 1998; Simeon *et al.* 2000; Marx *et al.* 2008).

Adding to the heterogeneity of panic, a number of non–criterion panic symptoms, which may even be more prevalent than criterion symptoms (Cox *et al.* 1994), may be present. Commonly reported such symptoms include: an overwhelming urge to flee the situation; feeling helpless, confused or disoriented; difficulty swallowing; fidgetiness; sense of time distortion; blurred vision; weakness in legs or the sensation of walking on an unstable surface, and; hypersensitivity to light and sound (Nesse, 1987; Aronson & Logue, 1988; Craske & Barlow, 1988; Cassano *et al.* 1989; Starcevic *et al.* 1993; Cox *et al.* 1994; Toni *et al.* 1996; Bovasso & Eaton, 1999; Cassano *et al.* 1999; Kenardy & Taylor, 1999).

DSM–IV distinguishes three types of panic attacks, according to the presence/absence of an apparent situational trigger. The first type, which are alternatively referred to as *unexpected*, *uncued*, or *spontaneous* panic attacks, occur in the absence of an apparent situational trigger (*i.e.* "out of the blue") (APA, 1994). The other two types, collectively referred to as *cued panic attacks*, occur when the onset of panic is either almost invariably, or is more likely, to occur upon exposure to a situational trigger. These are called *situationally bound* and *situationally predisposed* panic attacks, respectively (APA, 1994). In cued panic attacks, the attack is perceived by the individual to be clearly associated with a situational trigger (APA, 2000). Such panic attack cues may be external (e.g., agoraphobic situation such as a supermarket) or internal to the individual (e.g., panic–related physical sensations, thoughts, and imagery) (Street *et al.* 1989; Craske, 1991; Kenardy & Taylor, 1999; Barlow, 2002), although it wasn't until DSM–IV–TR (APA, 2000) that internal situational cues were incorporated in panic attack criteria. Thus, the difference between cued and uncued panic attacks is not the veridical presence versus absence of a situational trigger – the distinguishing feature is whether a situational cue is *perceived* by the individual (Barlow *et al.* 1994; APA, 2000).

The occurrence of panic attacks does not necessarily indicate the presence of PD: Panic attacks may occur in the context of many other psychiatric disorders and, in particular, other anxiety disorders (Reed & Wittchen, 1998; Kessler *et al.* 2006; Craske *et al.* 2010). For example, individuals with specific phobia, social phobia, and post–traumatic stress disorder (PTSD) may panic when confronted with the specific object or situation of their fear (e.g., spider or snake, public speaking, reminder of a traumatic event) (APA, 2000). Moreover, epidemiologic studies frequently report a

lifetime prevalence for occasional panic attacks of ~20%, a figure which includes many individuals not meeting criteria for any psychiatric diagnosis (Edelman, 1992; Kessler *et al.* 2006; Wittchen *et al.* 2010). When these attacks do not progress to PD they are referred to as non–clinical panic attacks (Bouton *et al.* 2001). However, despite this benign label, the occurrence of panic attacks is a strong risk marker for the subsequent development of a range of psychopathologic conditions including but not limited to PD (review Craske *et al.* 2010: Barlow, 2002; Goodwin *et al.* 2004; Baillie & Rapee, 2005; Wittchen *et al.* 2008; Kinley *et al.* 2011), for greater illness severity, suicidality, and for poorer treatment response (Goodwin & Hamilton, 2001; Wittchen *et al.* 2003; Bittner *et al.* 2004; Goodwin & Roy–Byrne, 2006; Bolton *et al.* 2008).

Given that panic attacks are not exclusive to PD, the occurrence of panic attacks is a necessary, albeit insufficient, condition for a diagnosis of PD: Both the context in which the attacks occur and the psychological and behavioural sequelae of the attacks are important to the differential diagnosis of the disorder.

1.2.2 Panic Disorder

Panic disorder was first classified as a distinct nosological entity in the third edition of DSM (APA, 1980). However, accounts of a clinically similar syndrome have long appeared in the literature, albeit subsumed under different names (review Hinton *et al.* 2002: McLure–Tone & Pine, 2009). With subsequent editions of DSM (*i.e.* DSM–III–TR, DSM–IV, DSM–IV–TR) (APA, 1987; 1994; 2000) there have been relatively minor changes to the criteria for PD, and the disorder's essential features have remained consistent (Roy–Byrne *et al.* 2006; McLure–Tone & Pine, 2009). Therefore, although clinical participants in the present research met DSM–IV criteria for PD, the

DSM version used for determination of diagnosis in other empirical findings reported herein will not be indicated. Notably, however, since DSM–IV the presence of chronic anxiety between successive attacks has been required to diagnose PD (Craske *et al.* 2010). This revision, given the relative ubiquity of panic attacks (Kessler *et al.* 2006; Wittchen *et al.* 2010), emphasises the phobic response to panic attacks in PD, and aids its differential diagnosis (Craske *et al.* 2009; Pollack *et al.* 2010).

The central feature of panic disorder is the presence of recurrent, unexpected (*i.e.* spontaneous) panic attacks (APA, 1994; 2000). Cued panic attacks, although not essential for a diagnosis of PD, are common (APA, 1994; 2000). The second main diagnostic criterion for PD stipulates that at least one of the panic attacks is followed one month or more of persistent concern about having further attacks, and/or worry about the implications of the attack, and/or a significant change in behaviour related to the attacks (APA, 1994; 2000). This sustained between–panic anxiety concerning the repeated occurrence of panic attacks is called *anticipatory anxiety* (Shear *et al.* 1998; Bouton *et al.* 2001). Agoraphobia is the third diagnostic feature of PD. In DSM, PD is diagnosed categorically according to the presence or absence of agoraphobia (*i.e.* Panic Disorder with Agoraphobia; Panic Disorder without Agoraphobia) (APA, 1994; 2000). For complete DSM–IV criteria for PD see Table 2.

The criteria for PD, therefore, delineate two, temporally distinct manifestations of the disorder. Firstly, the disorder's *phasic* manifestation is marked by recurrent, brief episodes of intense fear (*i.e.* panic attacks). And secondly, sustained between–panic anxiety and agoraphobia characterise the disorder's alternate, *tonic* manifestation. For a discussion of the distinction between fear and anxiety, see Chapter 2.

Table 2: DSM–IV criteria for panic disorder with or without agoraphobia.*

NOTE:
This table is included on page 9 of the print copy of the thesis held in the University of Adelaide Library.

*Adapted from DSM–IV (APA, 1994).

1.2.2.1 Panic Attacks in Panic Disorder

Although the presence of spontaneous panic attacks is necessary for a diagnosis of PD (APA, 1994; 2000), and are common at the disorder's inception (Faravelli *et al.* 1992; Bouton *et al.* 2001), a preponderance of cued relative to uncued panic attacks typically develops as the disorder evolves (APA, 2000). This may be, in part, because the distinction between cued and uncued panic attacks rests upon the individual's skill at identifying functionally related panic antecedents (Craske, 1991; Bouton *et al.* 2001), a skill which may change over time (Whittal *et al.* 1996; White & Barlow, 2002). Another factor in the shift to predominantly cued attacks is the conditioning of interoceptive and contextual cues which are present at the time of the initial spontaneous panic attacks (Goldstein & Chambless, 1978; Bouton *et al.* 2001; Mineka & Zinbarg, 2006). In the absence of any immediate precipitant for the attack – at least from the perspective of the panicker – stimuli within the internal and external environments at the time of such an attack may become linked to panic (an unconditioned stimulus; UCS) as conditioned stimuli (CSs) via the associative learning process of classical conditioning (Goldstein & Chambless, 1978; Barlow, 2000; Bouton *et al.* 2001; Battaglia & Oligari, 2005).

Following conditioning, CSs may subsequently elicit a conditioned response (CR) of either panic itself, or of anticipatory anxiety (Bouton *et al.* 2001). For example, individuals with PD often panic or feel apprehensive upon re–entering environments in which panic attacks have previously occurred as the context has become a CS (Mineka & Zinbarg, 2006). Common contextual CSs include supermarkets, shopping centres, lecture theatres, cinemas, and crowds (APA, 2000). Similarly, interoceptive and cognitive conditioning occur when, respectively, benign arousal sensations and

catastrophic cognitions preceding the onset of a panic attack become CSs (Barlow, 2000; Bouton *et al.* 2001). Further, via the process of stimulus generalisation, both internal (*i.e.* bodily sensations, thoughts) and external (*i.e.* contextual) stimuli that are similar to CSs may elicit a CR (Bouton *et al.* 2001; Lissek *et al.* 2010). For example, CRs to the autonomic constituents of panic (e.g., random heart rate fluctuation, or the feeling of shortness of breath) may generalise to similar non–arousal sensations (e.g., exercise–induced sensations) (White *et al.* 2006; Lissek *et al.* 2010). Thus, via the proliferation of cues that may trigger anticipatory anxiety and panic, the initial spontaneous panic attacks may evolve into PD (Barlow, 2000; Bouton *et al.* 2001; Lissek *et al.* 2010).

In general, associative learning is a highly adaptive process as it increases the predictability of danger (LeDoux, 1995; Quirk & Gelhert, 2003; Baas *et al.* 2008). In order to increase the predictability of aversive experiences, the stimulus or the situation that best predicts an aversive event becomes the strongest CS (Grillon, 2008). In the absence of an apparent, discrete cue with which to predict the occurrence of an aversive event, contextual and interoceptive stimuli present at the time of the aversive event become the best (albeit poor) predictors of the event, and so contextual– and interoceptive conditioning is increased (Bouton *et al.* 2001; Grillon *et al.* 2006; Alvarez *et al.* 2008; Grillon, 2008; Lang *et al.* 2009). However, associative learning is not an obligatory process. Rather, a range of individual–difference factors mediate conditioning. For instance, in healthy subjects, individual differences in perceptual/attentional behaviours determine whether or not the CS–UCS contingency is learned (Grillon, 2002; Hoffman, 2008); those who learn a CS–UCS contingency during aversive conditioning (and thus learn to predict the occurrence of an aversive

event) demonstrate a short–lasting CR in the presence of the CS, but not in its absence, whereas individuals who fail to learn the contingency demonstrate sustained anxiety (Baas *et al.* 2008). Therefore, it has been proposed that individual differences in conditioning may serve as diatheses for the development of anticipatory anxiety and thus PD following the initial panic attacks (review Mineka & Oehlberg, 2008: Bouton *et al.* 2001). Indeed, there is evidence of associative learning deficits in PD (Grillon, 2002; Grillon *et al.* 2007; Lissek *et al.* 2009), in addition to other abnormalities during acquisition (review Lissek *et al.* 2005: Lissek *et al.* 2010) and extinction (Acheson *et al.* 2007; Michael *et al.* 2007) phases of aversive learning. Collectively, these deficits in the learning of panic–cue relationships may render panic attacks unsignalled and unpredictable in PD (Grillon *et al.* 2007).

Conditioned interoceptive and contextual stimuli do not invariably trigger panic attacks in PD; these stimuli merely increase the likelihood that panic will occur (Bouton *et al.* 2001; Öhman & Mineka, 2001; Mineka & Zinbarg, 2006). In other words, the ensuing cued panic attacks are situationally predisposed, as opposed to situationally bound. As a corollary, the majority of panic attacks in PD are spontaneous panic attacks or situationally predisposed panic attacks, the occurrence of situationally bound panic being rare in the context of PD (APA, 2000). Yet, as previously indicated, panic attacks are relatively common occurrences across the anxiety disorders and in the general population (Kessler *et al.* 2006; Wittchen *et al.* 2010). Even spontaneous panic attacks are not exclusive to PD (Bouton *et al.* 2001; Kessler *et al.* 2006). There is, therefore, no precise mapping of panic attack type (e.g., spontaneous *vs.* situationally bound *vs.* situationally predisposed) and diagnosis (e.g., PD *vs.* another anxiety disorder *vs.* no diagnosis) (APA, 2000). Rather, the key

difference between those who experience occasional spontaneous panic attacks or those occasioned by a circumscribed set of stimuli, on the one hand, and those who go on to develop PD, on the other, is the exaggerated *response* of the latter to the panic attacks. Specifically, chronic anxiety about panic attacks, not the type or frequency of those attacks, distinguishes the panic disordered individual (APA, 2000). Various data suggest that the perception that panic attacks are unpredictable and uncontrollable plays an important role in the development of diagnostically and clinically significant anxiety in PD (Barlow, 2000; Bouton *et al.* 2001; Grillon *et al.* 2008).

1.2.2.2 Perception of Unpredictability and Uncontrollability

In panic disordered compared to non–clinical panickers, panic attacks are perceived as relatively unpredictable and uncontrollable (Barlow *et al.* 1994; Barlow, 2000; Grillon *et al.* 2007; Grillon *et al.* 2008). This is pertinent as robust and varied experimental data from pre–clinical studies, and from non–clinical and clinically anxious samples indicate that the absence of perceived predictability and controllability of aversive events is central to the development and maintenance of sustained anxiety (reviews Chorpita & Barlow, 1998; Barlow, 2000; Lang *et al.* 2000; Bouton *et al.* 2001; Grillon, 2002; Walker *et al.* 2003; Grillon, 2008; Pêgo *et al.* 2008; Craske *et al.* 2009; Walker *et al.* 2009; Davis *et al.* 2010: Mineka *et a.* 1984; Craske *et al.* 1995; Davis, 1998; Kalin *et al.* 2005; Grillon *et al.* 2006; White *et al.* 2006; Hasler *et al.* 2007; Alvarez *et al.* 2008; Baas *et al.* 2008; Grillon *et al.* 2008; Vansteenwegen *et al.* 2008; Fonteyne *et al.* 2009; Lissek *et al.* 2009). Moreover, preliminary data suggest that people with PD are more susceptible to the anxiogenic effect of event unpredictability and uncontrollability than unaffected individuals (Grillon *et al.* 2008).

The extent to which panic attacks are perceived as predictable and controllable varies, in part, as a function of the eliciting stimulus. For instance, the majority of people who experience isolated panic attacks, but do not meet criteria for PD, are able to attribute the attacks to discrete, controllable events (Norton *et al.* 1986; Rees *et al.* 1998; Battaglia & Ogliari, 2005; Roy–Byrne *et al.* 2006). In contrast, panic attacks in PD typically either occur in the absence of a clear proximal explanation (*i.e.* spontaneous panic attacks) (Roy–Byrne *et al.* 2006) or, in the case of cued attacks, may be cued by multiple cues (e.g., bodily sensations, cognitions, multiple contexts) (Mineka & Oehlberg, 2008; Lissek *et al.* 2010). The ubiquity of panic–eliciting cues contributes to the perception of panic uncontrollability in PD, in that such cues are relatively difficult to avoid (Brown & McNiff, 2009). Cue ubiquity also contributes to panic unpredictability. According to the International Classification of Diseases, 10th revision (ICD–10), panic disorder's essential feature is recurrent panic attacks which are unpredictable in that they are not restricted to any particular situation or set of circumstances (World Health Organisation, 1992). Panic attacks in PD may even occur during states of relaxation, including non–REM sleep (Cohen *et al.* 1985; Adler *et al.* 1987; Craske *et al.* 2001).

Further, to the extent to that panic triggers are perceived at all in PD, they are relatively poor predictors of whether or when a panic attack will occur and so the threat of panic is almost constant (Barlow *et al.* 1994; Barlow, 2000). For instance, bodily sensations by their very nature are in a constant state of flux, and so an individual can never predict whether minor physiologic fluctuations will escalate into panic or not (Acheson *et al.* 2007). With such a learning history, an individual is likely to develop chronic vigilance for signs of physiologic fluctuation, and to react to them

with anxiety and distress, thereby fuelling a vicious cycle of anxiety and panic (Bouton *et al.* 2001). Similarly, many contexts may elicit panic in PD, but contexts are long–lasting cues, and are thus poor predictors of the timing of an attack (Grillon, 2008; Lang *et al.* 2009). Thus, the threat of having a highly aversive experience is ever–present in PD, but the timing of that event is unpredictable (Barlow, 2000).

1.2.2.3 Anticipatory Anxiety

DSM–IV criteria for PD (see Table 2) specify the presence of at least one month of cognitive and/or behavioural changes relating to the occurrence of panic attacks (APA, 1994; 2000). These disorder–specific cognitive and behavioural sequelae of panic in PD are encompassed by the term 'anticipatory anxiety' (Shear *et al.* 1998; Bouton *et al.* 2001). Non–clinical panickers, in contrast, do not meet this criterion (Barlow *et al.* 1994; Craske *et al.* 2010). Anticipatory anxiety, in conjunction with recurrent panic attacks and agoraphobic avoidance, comprise the three core components of PD (Gorman *et al.* 2000; Schmidt & Cromer, 2008).

Cognitive manifestations of anticipatory anxiety (e.g., thoughts, images) have been found to cluster around several common themes. Common themes relate to loss of behavioural control, social evaluation, physical catastrophe, mental catastrophe, and inability to cope (Ottaviani & Beck, 1987; Street *et al.* 1989; Breitholtz *et al.* 1998; Khawaja & Oei, 1998; Cassano *et al.* 1999; Raffa *et al.* 2004; Hicks *et al.* 2005). Common behavioural changes in anticipatory anxiety include avoidance behaviours (e.g. quitting a job, avoidance of travel or social situations), safety behaviours (e.g. being accompanied by a trusted companion), and substance use (e.g., misuse of tranquiliser drugs, alcohol and illicit drugs) (White & Barlow, 2002; Feldner *et al.*

2004; White *et al.* 2006; Craske *et al.* 2010). Overall, these behavioural changes represent adaptations aimed at coping with or reducing distress (White *et al.* 2006).

In general, anxiety states are characterised as sustained aversive states elicited in response to situations of potential, ambiguous or unpredictable threat (Grillon, 2008). Moreover, anxiety responses are multi–componential phenomena that engage multiple response systems across multiple levels of function (e.g., physiology, cognition, behaviour, affect) (Hoehn–Saric *et al.* 2004; Belzung & Philippot, 2007; Blanchard & Blanchard, 2008; Hohoff, 2009). According to DSM–IV–TR, anxiety is an "apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension" (APA, 2000, p. 820). For the person with PD, the ongoing possibility of experiencing a highly aversive panic attack represents an ever–present yet unpredictable threat, which fosters sustained anticipatory anxiety during the inter–panic interval (Bouton *et al.* 2001; Barlow, 2002).

Barlow (2000, p. 1249) describes anxiety thus:

> "At the heart of this structure (anxiety) is a sense of uncontrollability focused largely on possible future threats, danger, or upcoming potentially negative events, in contrast to fear, where the danger is present and imminent."

Specifically, in PD:

> "…anticipation of unpredictable and irregular panic attacks may contribute to the etiology and maintenance of chronic anxiety and subsequent avoidance" (Grillon *et al.* 2008, p. 901).

Thus, conceptualisations of anxiety (whether normal or abnormal) emphasise the presence of potential as opposed to imminent threat, the activation of multiple responses systems, and the sustained nature of the response.

As a corollary of anxiety's multi–componential nature, anticipatory anxiety in PD manifests more broadly than the diagnostically–pertinent realms of conscious cognition and behaviour. For instance, although it should be noted that anxiety is not a homogenous phenomenon (Nitschke *et al.* 1999; Barlow, 2000), anxiety states engage multiple peripheral physiologic response systems such as the cardiovascular, respiratory, electrodermal, musculoskeletal, and neuroendocrine systems (reviews Friedman, 2007; Hoehn–Saric 2007: Brown & McNiff, 2009), and increases activity in a network of forebrain structures (Hasler *et al.* 2007; Engels *et al.* 2007 Mobbs *et al.* 2009). Within the realm of cognition, biases of sensory information processing, that is, of cognitive functions such as appraisal, memory and in particular, attention (Craske *et al.* 2009), are an integral component of anxiety (Barlow, 2000; Belzung & Philippot, 2007; Hohoff, 2009). Anxiety biases information processing to facilitate critical functions such as threat detection, distinguishing threat–relevant from non–threatening stimuli, and remembering where noxious stimuli where previously encountered (Barlow, 2000; Belzung & Philippot, 2007; Hasler *et al.* 2007; Blanchard & Blanchard, 2008; Hohoff, 2009). In the presence of potential, yet unpredictable threat, a state of hypervigilance towards potential sources of threat in the environment (whether internal or external) ensues (Barlow, 2000; Hasler *et al.* 2007).

The normative expression of anxiety is highly adaptive in that it increases the individual's ability to cope effectively with potentially harmful events (Barlow, 2002;

Blanchard & Blanchard, 2008; Hohoff, 2009). In contrast, anxiety is considered pathologic when it is disproportionate to the objective level of threat, persists for longer than is warranted, or causes distress or impairment in functioning (Grillon, 2008). In the context of PD and other anxiety disorders, harmless, disorder–specific stimuli are responded to as if they were in fact threatening, and bias information processing accordingly (meta–analysis Bar–Haim *et al.* 2007: McNally, 1998; Bishop *et al.* 2004; Mobini & Grant, 2007; Craske *et al.* 2009; Friedman & Kreibig, 2010). In PD, the disorder–specific object of threat pertains to bodily sensations and associated contexts, that is, those stimuli that have come to be associated with panic attacks (Craske & Waters, 2005). Anticipatory anxiety in PD is pathologic in that it is excessive (*i.e.* panic attacks are not actually harmful) and causes significant functional impairment (APA, 2000). Chronic anxiety manifests as an inflexible and restrictive response repertoire across multiple levels of function (e.g., physiology, cognition, behaviour, affect) (Thayer & Friedman, 2002). Importantly, the various manifestations of anticipatory anxiety contribute to PD maintenance via a positive feedback loop of anxiety and panic (Barlow, 2000; Öhman *et al.* 2001).

1.2.2.4 Agoraphobia

In DSM, panic disorder is classified according to the presence or absence of agoraphobia. Agoraphobia is a common complication of PD, and is characterized by situational avoidance or anxiety due to the occurrence of repeated panic attacks. According to DSM–IV "the essential feature of Agoraphobia is anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having a Panic Attack" (APA, 1994, p. 396) (see Table 3).

Table 3: DSM–IV criteria for agoraphobia.*

NOTE:
This table is included on page 19 of the print copy of the thesis held in the University of Adelaide Library.

*Adapted from DSM–IV (APA, 1994). *N.B.* agoraphobia is not a discrete diagnosis. The diagnosis is based on the specific disorder in which agoraphobia occurs (e.g., panic disorder with agoraphobia).

Individuals with PD (with or without agoraphobia) are highly sensitive to and avoid a wide range of events (e.g., situations, activities, emotions) that elicit physical

sensations that are viewed as dangerous because they might signal an impending panic attack (Barlow, 2002; Mineka & Oehlberg, 2008; Brown & McNiff, 2009). Common agoraphobic situations – typically places where the individual feels crowded, confined and without an easy exit (Yates, 2009) – include supermarkets, shopping centres, standing in queues, movie theatres, driving and public transport (APA, 1994). These situations are either avoided or are endured with marked distress (APA, 1994). In particular, places and situations which have become associated with panic as CSs may be avoided because the individual fears s/he will panic there in future (Bouton *et al.* 2001; Barlow, 2002). Therefore, agoraphobic avoidance and anxiety concerns the onset of distressing symptoms, not the situation itself (Hallam, 1978; White *et al.* 2006), and situational avoidance represents a behavioural adaptation aimed at reducing or eliminating these symptoms (Craske & Barlow, 1988; Cox *et al.* 1991; Langs *et al.* 2000; Bouton *et al.* 2001; Feldner *et al.* 2004). Over time, however, agoraphobic fear may generalise to other, similar situations and these too may be avoided, leading to marked functional impairment (Mineka & Zinbarg, 2006; Lissek *et al.* 2010). At its most extreme, an individual with agoraphobia may become housebound and dependent upon others (Perugi *et al.* 2007). Agoraphobia has been described as the most severe phobia because of the limitations it imposes on one's life and personal autonomy (Bouton *et al.* 2001).

According to DSM–IV–TR (APA, 2000), approximately one–third to one–half of people in community samples with PD meet criteria for panic disorder with agoraphobia (PDA). However, the National Comorbidity Survey Replication, which is the largest survey of the prevalence and correlates of mental disorders in the USA to date, found that approximately 64% of people with PD met criteria for PDA (Kessler

et al. 2005b). In contrast, the rate of PD complicated by agoraphobia in clinical samples is typically higher (Faravelli & Paionni, 1999); at least two–thirds of panic–disordered patients in treatment–seeking samples meet criteria for PDA (APA, 2000), the higher the proportion presumably reflecting the tendency for individuals with greater impairment to seek treatment (Rapaport *et al.* 1996; Grant *et al.* 2006).

Although DSM defines agoraphobia categorically (*i.e.* either one does, or does not, meet the criteria), agoraphobic avoidance and anxiety vary on a continuum of severity (Faravelli & Paionni, 1999; Bouton *et al.* 2001; White *et al.* 2006), and the majority of people with PD develop some degree of agoraphobia (White & Barlow, 2002; Mineka & Oehlberg, 2008). Panic disorder complicated by agoraphobia, particularly when severe, is generally associated with poorer clinical outcomes (e.g., disorder severity, impairment, help–seeking, illness duration, and prognosis) (Noyes *et al.* 1990; Starcevic *et al.* 1993; Keller *et al.* 1994; Liebowitz, 1997; Katschnig & Amering. 1998; Slaap & den Boer, 2001; Bruce *et al.* 2005; Kessler *et al.* 2005b; Kikuchi *et al.* 2005; Grant *et al.* 2006; Kessler *et al.* 2006; Hackmann, 2007; Rubio & Lopez–Ibor Jr., 2007; Schmidt & Cromer, 2008; Wittchen *et al.* 2008; McLure–Tone & Pine, 2009; Wittchen *et al.* 2010), although there have been null findings (Craske *et al.* 1987; Berle *et al.* 2008).

Avoidant behaviours in PD are pervasive and are not restricted to the typical cluster of common agoraphobic situations (Feldner *et al.* 2004). Because individuals with PD fear bodily sensations that are similar to, or have become associated with panic attacks via interoceptive conditioning (Mineka & Oehlberg, 2008; Brown & McNiff, 2009), they may fear and avoid a broad range of stimuli and activities that elicit such

sensations (Clark, 1986; Barlow, 2002). These include physical activities (e.g., exercise, hot saunas, sexual activity), emotionally arousing situations (e.g., scary movies, arguments), and the use of substances (e.g., caffeine, alcohol, medication, spicy food) (Broocks *et al.* 1997; White & Barlow, 2002; Mineka & Zinbarg, 2006). Other avoidant behaviours may relate more closely to specific feared bodily sensations. Avoidance of restrictive clothing and confined spaces, for example, may be a response to a specific fear to dyspnoea (Cassano *et al.* 1999). Similarly, avoidant behaviours may relate to specific feared consequences of panic. For example, social avoidance in PD represents an attempt to avert humiliation and social scrutiny due to panic symptoms (Busch & Milrod, 2004; Raffa *et al.* 2004).

In the short term, avoidance, as either passive avoidance (e.g., not attending a job interview) or active avoidance (e.g., leaving a supermarket), is associated with a diminution of unpleasant symptoms, and so the behaviour is reinforced (Langs *et al.* 2000; Bouton *et al.* 2001; Feldner *et al.* 2004; Mineka & Zinbarg, 2006). However, in the long term, avoidant behaviour is considered an important mechanism in PD maintenance (Bouton *et al.* 2001; White *et al.* 2006). Importantly, avoidance of feared sensations and contexts prevents the behavioural process of extinction (Barlow, 2002; Myers & Davis, 2002), a form of learning which involves fear reduction through systematic exposure to the CS in the absence of the UCS (Bouton, 2002; Hofmann, 2008). Additionally, avoidance impedes the development of alternative coping strategies and more accurate beliefs about perceived threat stimuli (Shear *et al.* 2007).

In addition to the wide range of situations and stimuli that panic disordered individuals may overtly avoid, more subtle forms of avoidance are also common. Individuals for

whom anticipatory anxiety has generalised to many different contexts and stimuli, and for whom overt avoidance of these situations is not an option, may be more likely to develop relatively subtle forms of avoidance (Barlow, 2000). Each of these covert forms of avoidance (e.g., cognitive avoidance, interoceptive avoidance, experiential avoidance, attentional avoidance) represent efforts to reduce anxiety and avert panic by avoidance of thoughts and sensations relating to panic attacks (Watts, 1989; White & Barlow, 2002; White *et al.* 2006). However, attempts to suppress unwanted thoughts, feelings or sensations are rarely successful; the need to constantly cognitively monitor for the presence of the to–be–avoided stimulus often increases, rather than decreases, the intensity of that stimulus (Wegner, 1997; Levitt *et al.* 2004). Accordingly, the use of avoidance–based coping styles when experiencing unpleasant bodily sensations in PD is associated with a paradoxical increase in the intensity of panic–related thoughts and feelings (Karekla *et al.* 2004; Spira *et al.* 2004; Campbell–Sills *et al.* 2006).

Thus, avoidant behaviours, in addition to restricting the behavioural options of people with PD and, in many cases, creating inter–personal dependency (Cassano *et al.* 1999; Rucci *et al.* 2009), may contribute to the maintenance of the very symptoms and illness that those behaviours aimed to avoid.

1.2.3 Prevalence of Panic Disorder

Epidemiologic studies worldwide consistently indicate that approximately 1.0% to 3.5% of the general population will at some stage in their lifetime develop PD, with or without agoraphobia, with 12–month prevalence rates of between 0.5% and 1.5% (APA, 2000). In their review of recent epidemiological studies of anxiety disorders,

Michael *et al*. (2007) report prevalence rates obtained in 14 studies, each comprising large representative samples from the general adult population of Western countries. Lifetime prevalence rates for PD ranged from 0.5% to 4.7% (median 2.2%), and 12–month prevalence rates ranged from 0.5% to 3.1% (median 2.2%). Panic disorder has been identified in many different cultures worldwide, although its expression may vary from culture to culture (Amering & Katschnig, 1990; Sierra–Siegert & David, 2007; Craske *et al.* 2010). For example, people in some cultures may be more inclined to report physical symptoms, but are reluctant to report cognitive symptoms, such as fear of going crazy (Taylor *et al.* 2007). However, so long as such culture–specific expressions are taken into consideration, cross–cultural rates of PD tend to be fairly consistent (Hinton *et al.* 2002).

In addition to those individuals who meet criteria for PD, epidemiological studies suggest the continuity of PD with relatively more common but less severe 'sub–threshold' conditions, which are characterised by occasional panic attacks or LSA (Kessler *et al.* 2006; Batelaan *et al.* 2007a; McLure–Tone & Pine, 2009). These conditions may represent a prodromal syndrome that predicts the onset of full PD (Fava *et al.* 1988) or residual symptoms from partially remitted PD (Fava & Mangelli, 1999; Corominas *et al.* 2002). In keeping with dimensional views of psychopathology (Goldberg, 1996; Widiger & Samuel, 2005), sub–threshold panic symptomatology appears to occupy an intermediate position between full PD and no panic symptoms in terms of symptom severity and functional impairment (Preisig *et al.* 2001; Kessler *et al.* 2006; Batelaan *et al.* 2007a; b; 2010a; b; Skapinakis *et al.* 2011).

Population estimates consistently indicate that PD occurs more frequently in females

compared to males. For example, in an epidemiologic investigation Weissman *et al.* (1997) found a female preponderance of panic disordered individuals within each of 10 geographically and culturally diverse countries, and female–to–male ratios of ~2:1 have commonly been reported (Kessler *et al.* 1994; Gater *et al.* 1998; Goodwin *et al.* 2005; Wittchen & Jacobi, 2005; Kessler *et al.* 2006). The gender disparity is even greater for PD complicated with agoraphobia (Yonkers *et al.* 1998; Barzega *et al.* 2001; Carlbring *et al.* 2002; Goodwin *et al.* 2005; Bekker & van Mens–Verhulst, 2007; Hackmann, 2007), and some findings suggest that agoraphobia in women may be more severe and chronic when present (Starcevic *et al.* 1998; Turgeon *et al.* 1998; Yonkers *et al.* 1998; Schmidt & Koselka, 2000).

1.2.4 Comorbidity in Panic Disorder

The term 'comorbidity', as originally applied in medicine, denoted cases in which a *distinct* additional clinical entity co–occurred with the index disorder (Maj, 2005). This definition implies distinct aetiology, pathology, and treatment implications for each 'comorbid' condition (Widiger & Samuel, 2005). However, in applying this definition to psychiatric disorders, the delineation of putatively distinct clinical entities has been problematic (Lilienfeld *et al.* 1994). For instance, the substantial phenomenological overlap of anxiety and mood disorders at both the sub– and supra–diagnostic levels (Brown *et al.* 1998; Mineka *et al.* 1998; Preisig *et al.* 2001), in addition to evidence of shared aetiological mechanisms (e.g., Hettema *et al.* 2006) suggests the presence of non–distinct clinical entities (Watson, 2005; Goldberg *et al.* 2009). 'Comorbidity', therefore, has come to imply concomitance or co–occurrence longitudinally of more than one diagnostic entity, irrespective of whether those entities are distinct or not (Mineka *et al.* 1998; Wittchen *et al.* 2001; Maj, 2005). The term,

therefore, as used herein, will denote the co–occurrence within an individual of multiple diagnoses, either concurrently or longitudinally. Furthermore, although comorbidity encompasses both psychiatric and medical diagnoses, and medical comorbidity in PD is substantial (Schmidt & Telch, 1997; Goodwin *et al.* 2005; Muller *et al.* 2005; Simon & Fischmann, 2005; Roy–Byrne *et al.* 2008; Talati *et al.* 2008), the generic term will specifically denote psychiatric comorbidity.

Patients with PD, in addition to a spectrum of anxiety and fear symptoms (Cassano *et al.* 1999), typically have very high rates of clinically significant comorbidity. Although treatment–seeking in psychiatric samples is generally associated with more substantial comorbidity (Rapaport *et al.* 1994; Rodriguez *et al.* 2004), comorbidity in both community and clinical samples of PD, particularly of major depressive disorder (MDD), other anxiety disorders, and substance use disorders is high (APA, 2000). Of substance use disorders, alcohol abuse and dependence are particularly prevalent (Zimmermann *et al.* 2003; Kessler *et al.* 2006).

Comorbidity rates in three large studies encompassing both clinical and community samples in the USA exemplify the extent of comorbidity burden in PD. Firstly, in a large sample of primary care patients who were not seeking treatment for psychiatric problems, 83% of patients meeting criteria for PD also met criteria for at least one other current Axis 1 diagnosis, and 79% met criteria for any other anxiety and/or mood disorder (Rodriguez *et al.* 2004). Lifetime comorbidity in these patients was even higher: 95% met criteria for lifetime comorbidity of at least one other Axis 1 diagnosis, and 90% met criteria for any other anxiety and/or mood disorder. Similarly, 60% of PD patients presenting for treatment at university–affiliated anxiety clinics in

the USA met criteria for at least one other Axis 1 diagnosis, with 59% meeting criteria for another anxiety disorder and/or mood disorder (Brown *et al.* 2001). Percentages of lifetime comorbidity in this sample were 81% (any other Axis 1 diagnosis) and 76% (any other anxiety and/or mood disorder). Finally, in a large community study, comorbidity rates associated with a lifetime diagnosis of PD was higher than for other anxiety disorders: over 92% of people with a lifetime diagnosis of PD met criteria for at least one other psychiatric diagnosis (Kessler *et al.* 1997). And, in a recent replication study, lifetime comorbidity rates were: any other diagnosis (83.1%), any other anxiety disorder (66.0%), MDD (34.7%), and alcohol abuse or dependence (25.0%) (Kessler *et al.* 2006). The corresponding figures for PDA were 100%, 93.6%, 38.5% and 37.3%.

In terms of their relative comorbidity burden, not all studies have distinguished between PD with and without agoraphobia. In those studies which did, PDA was associated with even greater comorbidity than PD without agoraphobia (review Wittchen *et al.* 2010: Kessler *et al.* 2006). The extensive rates of comorbidity reported for PD with or without agoraphobia suggest that PD in the pure form, that is, PD uncomplicated by another concurrent or lifetime disorder, is the exception rather than the rule. Furthermore, comorbidity in PD is of clinical significance, being associated with poor outcomes on a range of indices such as disorder chronicity, treatment response and relapse, treatment–seeking behaviour, suicidality, likelihood of receiving multiple drug treatments, psychosocial functioning, and impairment (Noyes *et al.* 1990; Ball *et al.* 1995; Brown *et al.* 1995; Hollifield *et al.* 1997; Schmidt & Telch, 1997; Baldwin, 1998; Candilis *et al.* 1999; Starcevic *et al.* 1999; Mennin & Heimberg,

2000; Roy–Byrne *et al.* 2000; Slaap & den Boer, 2001; Cramer *et al.* 2005; Eguchi *et al.* 2005; Diaconu & Turecki, 2007; Kroenke *et al*. 2007; Allen *et al.* 2010).

1.2.5 Course of Panic Disorder

Although the course of PD and of its associated comorbidities is highly variable (Keller *et al.* 1994; Liebowitz, 1997; Katschnig & Amering, 1998; Batelaan *et al.* 2010a), a prototypical course of the disorder may be described. Panic disorder typically begins relatively early in life; both epidemiologic (Weissman *et al.* 1997; Katerndahl & Realini, 1998; Kessler *et al.* 2005a) and clinical (Eaton *et al.* 1994; Barzega *et al.* 2001; Brown *et al.* 2001) studies report that the peak age of onset for PD is in the twenties, and in a significant proportion of cases the disorder begins in childhood or adolescence (Battaglia *et al.* 1995; Venturello *et al.* 2002).

The onset of the disorder is typically marked by the occurrence of a sudden attack of overwhelming inner terror that, to the individual, appears to have come 'from out of the blue' (Neese, 1987; Faravelli *et al.* 1992; Barlow, 2002). Although no immediate precipitant for the attack is apparent to the individual (hence the attack is considered spontaneous), this initial panic attack is often preceded by a period of elevated stress (Faravelli, 1985; Roy–Byrne *et al.* 1986; Watanabe *et al.* 2005; Nutt *et al.* 2008). This initial panic attack is most likely to occur in a public place (Lelliot *et al.* 1989; Faravelli *et al.* 1992; Perugi *et al.* 1998). Furthermore, individuals whose first attack occurred in a typical agoraphobic situation (e.g., shopping centre, public transportation) may be at increased risk of subsequently developing extensive avoidance, as compared to those whose initial experience occurred in atypical agoraphobic situation (e.g., at home) (Faravelli *et al.* 1992; Shulman *et al.* 1994).

After this initial unsettling experience, the individual who goes on to develop PD will typically spend considerable time wondering what caused it to happen, and whether it will happen again (Nesse, 1987; Barlow, 2002; Perugi *et al.* 2007). In the absence of any immediate cause for the attack, she/he will become vigilant for somatic signs that might indicate a further attack (Barlow, 2000; Bouton *et al.* 2001), and is likely to avoid at least some situations because of their concern about further possible attacks (White & Barlow, 2002; Mineka & Oehlberg, 2008). The development of anticipatory anxiety, agoraphobic avoidance and the conditioning of interoceptive and contextual cues typically occurs within the first year of the onset of spontaneous panic attacks (Bouton *et al.* 2001; Kikuchi *et al.* 2005; Perugi *et al.* 2007). Furthermore, the disorder is associated with a temporal accumulation of comorbid conditions (Blanchard & Blanchard, 2008). Once established, the natural course of PD is highly variable (Batelaan *et al.* 2010a). Nevertheless, the increased lifetime relative to short–term prevalence of PD in epidemiologic studies (Michael *et al.* 2007), and results of treatment studies (reviews Mitte, 2005; Bandelow *et al.* 2007; Sánchez–Meca *et al.* 2010), suggest at least partial remittance of the disorder in some individuals.

1.2.6 Quality of Life

Panic Disorder imposes a substantial burden on sufferers, their families, and the wider community (Batelaan *et al.* 2007b). Individuals with PD rate their life circumstances more poorly than do healthy subjects in multiple areas. These include: physical ability, mental health, social function, enjoyment of leisure activities, vitality, somatic pain, and general health (meta–analysis Olatunji *et al.* 2007: Ettigi *et al.* 1997; Hollifield *et al.* 1997; Candilis *et al.* 1999; Rubin *et al.* 2000; Cramer *et al.* 2005; Beard *et al.* 2010). Even individuals with recent onset PD report impaired functioning (Carrera *et*

al. 2006). Of particular importance, a diagnosis of PD is often (Weissman *et al.* 1992; Massion *et al.* 1993; Rosenbaum, 1997; Sareen *et al.* 2005a; Goodwin & Roy–Byrne, 2006; Bolton *et al.* 2008), although not always (Diaconu & Turecki, 2007), an independent predictor of increased suicidal thoughts and acts after adjusting for known suicide risk factors.

Epidemiologic and clinical studies have reported that the presence of comorbid anxiety and/or depressive disorders is associated with an additional, significant burden of functional impairment, above that associated with a diagnosis of PD (Weissman *et al.* 1989; Massion *et al.* 1993; Hollifield *et al.* 1997; Candilis *et al.* 1999; Cramer *et al.* 2005; Goodwin *et al.* 2005). Also, PDA is typically associated with greater impairment than PD without agoraphobia (Carrera *et al.* 2006; Hackmann, 2007; Wittchen *et al.* 2010).

Although few studies have directly compared quality of life in different anxiety disorders, there is evidence that, among the anxiety disorders, PD is associated with some of the greatest burden in terms of personal suffering and societal cost (Hansonn, 2002), but that different anxiety disorders may differentially affect specific areas (Mendlowicz & Stein, 2000). For example, PD ranks among the anxiety disorders (Schonfield *et al.* 1997), and indeed all psychiatric disorders (Goodwin *et al.* 2005; Batelaan *et al.* 2007b), associated with the greatest work–related impairment. Thus, socioeconomic consequences of PD include unemployment and underemployment, loss of productivity, restricted employment opportunities, absenteeism, and financial dependence (Ettigi *et al.* 1997; Oakley–Browne, 1999; Alonso *et al.* 2004; Goodwin *et al.* 2005; Wittchen & Jacobi, 2005; Smit *et al.* 2009; Skapinakis *et al.* 2011).

Health care utilization is another area that is particularly affected by PD. Studies show that both psychiatric and non–psychiatric health care utilization may be greater in PD than in other anxiety disorders or depression (Rief *et al.* 2005; Wang *et al.* 2005; Deacon *et al.* 2008). For instance, Rees *et al.* (1998) found that PD patients' mean direct costs of medical utilization was 11 times greater than that of socio–demographically matched controls without an anxiety disorder, and five times that of patients with social phobia. The somatic nature of many panic symptoms (e.g., palpitations, shortness of breath, and dizziness) contributes to increased health care utilization as people with PD often attribute their panic attacks to medical causes and seek medical treatment for them (Simon & Fischmann, 2005; Yates, 2009). This results in pervasive effects on health care utilization including visits to general practitioners, specialist consultations, repeated diagnostic procedures, ambulance use, and emergency room visits (Markowitz *et al.* 1989; Katon, 1996; Katerndahl & Realini, 1998; Roy–Byrne *et al.* 2000; Deacon *et al.* 2008). One community survey found an odds ratio of 200 for PD in individuals who had sought medical help for multiple medically–unexplained symptoms (Simon & Von Korff, 1991).

Yet, panic symptoms may mimic, and PD may be comorbid with, a variety of general medical conditions (e.g., cardiovascular, respiratory, vestibular, neurological and metabolic) (review Roy–Byrne *et al.* 2008: Stewart *et al.* 1994; Faravelli & Paionni, 1999; Fleet *et al.* 2000; Staab & Ruckenstein, 2003; Lydiard, 2005; Muller *et al.* 2005; Sareen *et al.* 2005b; Simon & Fischmann, 2005; Schur *et al.* 2007; Jette *et al.* 2008; Walters *et al.* 2008; Goodwin *et al.* 2009; Jacob *et al.* 2009; Maron *et al.* 2010). Additionally, panic symptoms occur in other situations such as during exercise, and use of and withdrawal from drugs (Faravelli & Paionni, 1999; White *et al.* 2006).

These factors complicate the identification, presentation and treatment of PD (Simon & Fischmann, 2005) which is frequently misdiagnosed and mismanaged (Kessler *et al.* 1999; Harvison *et al.* 2004). Moreover, few patients receive effective, evidence–based treatment (Wang *et al.* 2000; McHugh *et al.* 2009). Appropriate diagnosis and treatment is, however, associated with a substantial reduction in non–psychiatric health care utilization, significant cost savings in relation to diminished productivity and direct disorder–related expenses, and overall improved quality of life (Ormel *et al.* 1991; Salvador–Carulla *et al.* 1995; Telch *et al.* 1995; Mitte, 2005; Roberge *et al.* 2005; Rufer *et al.* 2010).

1.2.7 Treatment of Panic Disorder

There are numerous, highly varied treatment approaches to PD, each based on somewhat different theoretical rationales. This diversity is, in turn, driven by the considerable diversity of aetiological theories (Roth *et al.* 2005; Pilecki *et al.* 2010; Roth, 2010). Cognitive–behavioural therapy (CBT) and pharmacotherapy are the predominant and recommended treatments for PD at present (Busch & Milrod 2004; Schmidt & Keogh, 2010). Of psychotherapeutic interventions, CBT is the most effective (Mitte, 2005; Siev & Chambless, 2007; Sánchez –Meca *et al.* 2010) and is recommended as first–line treatment (Cloos *et al.* 2005). CBT may involve cognitive and behavioural interventions in combination, or in isolation. The cognitive component of CBT for PD aims to redress information processing biases relating to the over–estimation of danger, with regard to panic–related cues (Landon & Barlow, 2004). Such biases may underlie susceptibility to develop PD, contribute to its maintenance, and predict treatment response (Clark, 1986; Khawaja & Oei, 1998; McNally, 2002; Plehn & Peterson, 2002; Hicks *et al.* 2005; Benítez, 2009; Kutz *et al.*

2010). Behavioural components involve exposure to feared bodily sensations and to situations in which these sensations arise (Landon & Barlow, 2004; Otto *et al.* 2004). The rationale for exposure derives from the behavioural process of extinction (Barlow, 2002; Myers & Davis, 2002) and involves the systematic relearning of safety in the presence of feared cues (Bouton, 2002; Sotres–Bayon *et al.* 2006).

A variety of pharmacologic agents have shown some efficacy in the treatment of PD, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic anti–depressants (TCAs), and benzodiazepines (Mitte, 2005; Pull & Damsa, 2008). At present, SSRIs are the first–line recommended treatment with regard to both efficacy and tolerability (Ballenger *et al.* 1998; Baldwin *et al.* 2005; Bandelow *et al.* 2008). Effective SSRI treatment may ameliorate all of the major symptom components of PD: panic attacks, anticipatory anxiety, and agoraphobic avoidance (Seddon & Nutt, 2007). However, SSRIs, as per all pharmacotherapeutic agents, are associated with side effects, notably sexual dysfunction (Nutt *et al.* 1999; Clayton *et. al.* 2002; McHugh *et al.* 2009). These side effects result in a high rate of treatment discontinuation (Cowley *et al.* 1997), and contribute to greater attrition from pharmacotherapy relative to CBT in clinical trials (Butler *et al.* 2006). Additionally, benzodiazepine class drugs that act on the γ–aminobutyric acid (GABA) neurotransmitter system (Nash & Nutt, 2007), are effective anxiolytics (Graeff *et al.* 2003; Siepmann & Joraschky, 2007; Risbrough, 2009) and have established efficacy for the treatment of PD (Tesar *et al.* 1991; Marks *et al.* 1993). Although benzodiazepines are contraindicated for long–term use because of problems of dependence, sedation and cognitive impairment (Pétersson, 1994;

Baldwin *et al.* 2005; Bandelow *et al.* 2008; Garner *et al.* 2009), they are still frequently used (Bruce *et al.* 2003).

Notwithstanding inconsistencies in the operationalisation of treatment success (Shear *et al.* 1998; Landon & Barlow, 2004), meta–analyses show that both CBT and SSRI mono–treatment are relatively efficacious, with large controlled effect sizes commonly reported (Rayburn & Otto, 2003; Mitte, 2005; Butler *et al.* 2006; Bandelow *et al.* 2007; van Appeldoorn *et al.* 2008; Sánchez–Meca *et al.* 2010). Further, CBT interventions incorporating exposure (with or without cognitive therapy) are relatively efficacious compared to cognitive therapy alone, and are associated with less treatment drop–outs (Mattick *et al.* 1990; Mitte, 2005; Butler *et al.* 2006; Sánchez–Meca *et al.* 2010). Although these first–line treatments benefit a large percentage of treated patients, at least 25% of patients are classified as treatment non–responders in that they do not respond sufficiently or at all to treatment, and relapse and persistence of sub–threshold symptoms remain common outcomes (Ballenger, 1998; Slaap & den Boer, 2001; Bandelow & Rüfer, 2004; Busch & Milrod 2004; Landon & Barlow, 2004; Diemer *et al.* 2010). Additionally, treatment gains tend to be poorly maintained following SSRI relative to CBT cessation (Landon & Barlow, 2004; Butler *et al.* 2006), with relapse occurring in over 50% of patients after withdrawal of medication (Taylor *et al.* 2005, in Seddon & Nutt, 2007). Similarly, treatment gains are better maintained following cessation of CBT, compared to combination treatment of pharmacotherapy and CBT (Otto *et al.* 2010). A tendency for patients receiving pharmacotherapy (with or without CBT) to make external attributions for their improvement (Powers *et al.* 2008) may increase susceptibility for relapse upon discontinuation of medication (Biondi & Picardi, 2003).

Many adjunctive or alternative treatments to CBT and/or pharmacotherapy exist (Diemer *et al.* 2010). However, other treatments are relatively poorly characterised, both in terms of how they work and how well they work (Busch & Milrod 2004; Murray *et al.* 2010). Moreover, although a number of treatments are associated with clinically significant positive outcomes, their mode of action may not be as predicted. For example, in a recent review of six therapies for PD, the selected therapies' putative mechanisms of action included: resolution of unconscious conflicts (psychoanalytic psychotherapy), correction of respiration–related metabolic disturbance (hypercapnic breathing training or hypocapnic breathing training), reduced muscle tension (progressive muscle relaxation), and correction of catastrophic beliefs about panic attacks (cognitive intervention) (Roth, 2010). Interestingly, although the therapies were selected for their differing – and in some cases opposing – theoretical rationales, they were all similarly efficacious. As the therapies' theoretical rationales are either inconsistent with empirical data, or at the very least are non–falsifiable (Roth *et al.* 2005), Roth concludes that these dissimilar therapies have a common mechanism of action, namely, reduction of panic expectancy. Similarly, a review of the progressive muscle relaxation literature concluded that non–specific treatment factors accounted for its efficacy (Conrad & Roth, 2006).

From a clinical perspective, it might seem unimportant whether or not the stated treatment rationale is valid, so long as the treatment is effective. However, no treatment is effective for all PD patients, and even among treatment–responders full remission is rare (Landon & Barlow, 2004). Yet, even low levels of persistent symptoms are associated with significant functional impairment and poor prognosis (Batelaan *et al.* 2007a). Clearly, therefore, there is room for improvement, and more

targeted and effective treatments are needed (Diemer *et al.* 2010). One approach that has demonstrated clinical utility in other clinical populations (e.g., MDD: Papakostas & Fava, 2008) involves the identification of subpopulations of patients who are more or less likely to benefit from a given treatment.

1.2.7.1 Prediction of Treatment Response

Despite substantial treatment response heterogeneity for both pharmacologic and psychological treatments in PD (Slaap & den Boer, 2001; Bandelow & Rüfer, 2004; Busch & Milrod 2004; Bandelow *et al.* 2007; Diemer *et al.* 2010), there is at present no reliable method for identifying a priori patients who are most likely to benefit from a given treatment (Landon & Barlow, 2004; Chavira *et al.* 2009; Garner *et al.* 2009). The prescribing of SSRIs, for instance, remains a matter of trial and error and treatment response typically takes several weeks to gauge (Harmer *et al.* 2009; Leuchter *et al.* 2009; Hunter *et al.* 2010). Delayed treatment response is costly, both financially (e.g., direct treatment costs, workplace participation) and in terms of personal suffering. These costs motivate attempts to identify measures which may discern individuals who may benefit from a given treatment (Deldin & Chiu, 2005; Diemer *et al.* 2010).

In psychiatric research, a wide range of factors have demonstrated utility in predicting treatment response. These include clinical features of the disorder itself, biomarkers (e.g., quantitative electroencephalography or neuroimaging indices, genetic polymorphisms), and neuropsychological indices (Johnstone *et al.* 2005; Hunter *et al.* 2007; Kemp *et al.* 2008; Williams *et al.* 2010). However, relatively speaking, research on predictors of treatment response in PD is in its infancy, the predominant research

focus being the retrospective identification of clinical predictors of treatment non–response (Chavira *et al.* 2009). To date, the most robust predictors of non–response to pharmacotherapy and CBT alike have been greater agoraphobic severity, comorbidity (particularly of personality disorders), and longer illness duration (reviews Slaap & den Boer, 2001; Chavira *et al.* 2009). Recently, the utility of cognitive factors as predictors of treatment response in PD was investigated. Catastrophic cognitions and anxiety sensitivity – two cognitive factors putatively involved in PD development and maintenance according to cognitive–behavioural accounts (e.g., Clark, 1986; Reiss, 1991; Barlow, 2000) – predicted treatment response (Hicks *et al.* 2005; Benitez *et al.* 2009). Additionally, biomarker studies have identified two markers of better SSRI–response in PD: a functional polymorphism of the 5–HT1A (serotonin) receptor (Yevtushenko *et al.* 2010) and baseline differences in the β–adrenoceptor lymphocyte (Lee *et al.* 2008). Although promising, these findings require replication. Markers of differential treatment response, in particular biomarkers, are needed in order to guide clinical decisions and optimise treatment outcomes for individual patients with PD (Bandelow & Rüfer, 2004; Diemer *et al.* 2010).

1.2.8 Panic Disorder Diagnostic Issues

The clinical presentation of PD is highly heterogeneous, with affected individuals differing on numerous symptom dimensions (Batelaan *et al.* 2007a; Brandão *et al.* 2008). Despite sharing some commonalities, people with PD show significant inter–individual variance in each aspect of the disorder (e.g., panic attack frequency and severity, predominant panic symptom constellation, severity of anticipatory anxiety and agoraphobic avoidance, disorder course) and associated comorbid symptomatology (Whittal *et al.* 1996; Coplan & Lydiard, 1998; Cassano *et al.* 1999;

Faravelli & Paionni, 1999; Roy–Byrne *et al.* 2000; Coraminas *et al.* 2002; Meuret *et al.* 2006; Rucci *et al.* 2009; Batelaan *et al.* 2010b). Additionally, there is significant intra–individual clinical variance in that panic and related symptoms in PD are relatively changeable across time (Nandi *et al.* 2009; Pfaltz *et al.* 2010). Moreover, in addition to its heterogeneous clinical presentation, studies of the disorder's family history, treatment response, and neurobiological and neuropsychological features, show that PD is not a homogeneous entity (Coplan & Lydiard, 1998; Onur *et al.* 2006; Domschke & Dannlowski, 2010).

However, within–diagnosis heterogeneity and comorbidity are not unique to PD. Indeed, these features are the norm across all DSM diagnoses (Widiger & Samuel, 2005), notably mood and anxiety disorders (Mineka *et al.* 1998; Krueger & Finger, 2001; Wittchen *et al.* 2003; Andrews *et al.* 2008; Craske *et al.* 2009). Yet, DSM reduces clinical heterogeneity within PD to two categorical diagnoses (*i.e.* Panic Disorder with Agoraphobia, Panic Disorder without Agoraphobia) (APA, 1994; 2000) and concurrent symptomatology meeting criteria for additional diagnoses are termed 'comorbidities'. Such reductionism necessarily forfeits much information (Goldberg, 1996; Widiger & Samuel, 2005; Stein, 2008). A categorical perspective of psychiatric disorders (e.g., DSM) – that these disorders are discrete entities with distinct boundaries – may be contrasted with dimensional accounts. According to dimensional accounts of psychopathology (e.g., Brown *et al.* 1998; Mineka *et al.* 1998; Gottesman & Gould, 2003; Maj, 2005; Widiger & Samuel, 2005; Hyman, 2007; Goldberg *et al.* 2009), clinical heterogeneity and diagnostic comorbidity are artefacts of a categorical system that artificially parses psychopathology into discrete categories, and with thresholds which delimit wellness and illness. By contrast, dimensional accounts

contend that apparently discrete disorders are no more than extreme ends of functional continua (Clark & Watson, 1991; Brown *et al.* 1998; Mineka *et al.* 1998; Widiger & Samuel, 2005; Goldberg *et al.* 2009). These continua also encompass clinically significant, yet diagnostically sub–threshold or non–criterion symptoms (for PD: Cassano *et al.* 1999; Rucci *et al.* 2009; Skapinakis *et al.* 2010). Dimensional accounts aim to parsimoniously represent an individual's symptom constellation on a limited set of symptom dimensions that cut across DSM categories (Goldberg, 1996). However, categorical and dimensional approaches are not mutually–exclusive. For instance, the use of DSM–based selection criteria facilitates interpretation and communication of research findings and reflects the clinical need for reliable diagnosis (APA, 1994), and may be supplemented with dimensional measures to better capture symptom complexity (Shear *et al.* 2007; Stein, 2008); This complementary approach was adopted by the present research.

Within–diagnosis heterogeneity and comorbidity are commonly cited as evidence that the current diagnostic and classification system lacks validity, reliability and utility, and is inherently imprecise (e.g., Brown *et al.* 1998; Mineka *et al.* 1998; Widiger & Clark, 2000; Watson, 2003; Maj, 2005; Watson, 2005; Widiger & Samuel, 2005; Hyman, 2007; Linden & Fallgatter, 2009). Further, it has been proposed that these factors compromise research and clinical practice (Smoller & Tsuang, 1998; Charney, 2003; Bearden & Freimer, 2006; Begleiter & Porjesz, 2006; Andrews *et al.* 2008; Brandão *et al.* 2008; Linden & Fallgatter, 2009; Domschke & Dannlowski, 2010). Although there have been calls for refinement of the DSM system since its inception, there is presently, given the impending publication of DSM–V, a growing quorum of proposals for change (e.g., Watson, 2005; Andrews *et al.* 2009; Goldberg *et al.* 2009;

Craske *et al.* 2009; 2010). To wit, DSM is structured according to phenomenological similarity, leading to calls for an empirically–based nosology informed by objective indices pertaining to actual – not apparent – similarity of different clinical entities (Gottesman & Gould, 2003; Watson, 2005; Hyman, 2007; Linden, 2008; Malhi & Lagopolous, 2008; Goldberg *et al.* 2009; Kendler *et al.* 2011). It is posited that such indices, as derived from several strands of empirical research (e.g., patterns of genetic liability, neurophysiology, comorbidity, and treatment response), would serve to refine or even restructure future psychiatric nosologies (Kendler, 2006; Green *et al.* 2008; Linden & Fallgatter, 2009; Domschke & Dannlowski, 2010).

1.2.9 Summary: Panic Disorder Clinical Phenomenology

Panic Disorder is a complex anxiety disorder with a multifaceted clinical presentation (e.g., spontaneous panic attacks, cued panic attacks, anticipatory anxiety, and agoraphobic avoidance) (APA, 2000). The disorder typically begins at a young age and may persist for years or even decades, and has a pervasive, devastating effect on many areas of functioning, notably employment, physical and emotional wellbeing. For individuals with PD, panic attacks and panic–related stimuli are highly aversive events that are responded to as if they were, in fact, dangerous. As discussed, the emergence of clinically significant anticipatory anxiety distinguishes the individual who goes on to develop PD, from the greater number who experience panic attacks but do not develop PD.

1.3 Panic Disorder Aetiology

1.3.1 Theories of PD Aetiology

A range of theories have sought to explain the onset and course of panic attacks, and

the complications of anticipatory anxiety and agoraphobia in PD. In general, theories of PD fall into one of two broad categories, biological (e.g., Klein, 1993; Gorman *et al.* 2000) and psychological theories (e.g., Clark, 1986; Reiss, 1991; Beck & Clark, 1997). However, biological and psychological theories of PD, and empirical data derived from these two broad approaches, have remained largely unintegrated to date (Windmann, 1998; Clark & Beck, 2010; Pilecki *et al.* 2010). Therefore, while numerous individual *risk factors* [3] have been linked to the development and/or maintenance of PD or specific aspects of its clinical phenomenology (e.g., Bouton *et al.* 2001; Bandelow *et al.* 2002; Craske & Zucker, 2002; Coryell *et al.* 2006; Hicks *et al.* 2005; Zvolensky *et al.* 2006a; Feldner *et al.* 2008; Hirschfeld–Becker *et al.* 2008; Bienvenu *et al.* 2009; Kutz *et al.* 2010), an integrated picture of how these factors interact is yet to emerge (Zvolensky *et al.* 2006c; Clark & Beck, 2010).

There have, however, been several attempts to synthesise a more integrative aetiological account of PD. For example, a learning theory conceptualisation of PD (Goldstein & Chambless, 1978; Wolpe & Rowan, 1988; Bouton *et al.* 2001), although not specifically motivated by a desire to integrate biologic and psychological perspectives, represents a noteworthy exception to the rule of uni–dimensional accounts. This is because aversive conditioning, to which learning theory accounts ascribe a central role in PD development and maintenance (Bouton *et al.* 2001; Mineka & Zinbarg, 2006), is well characterised at both the biologic (*i.e.* neural plasticity) (e.g., Davis *et al.* 2010) and psychosocial levels (psychological predispositions, environmental factors) (e.g., Bouton *et al.* 2001; Öhman & Mineka, 2001; Mineka & Zinbarg, 2006). Similarly, Windmann (1998) presents an account of threat processing which integrates brain– and mind–based theory and evidence.

More recently, Fava & Morton (2009) applied causal modelling to link different components derived from biological and psychosocial theories. Whilst this analysis represents an important attempt to synthesise disparate theoretical approaches, there are several flaws in their model, as highlighted by Pilecki *et al.* (2010). Notably, the former model is not weighted toward evidence–based approaches to PD. For example, psychodynamic theories of PD, for which there is minimal empirical support (Busch & Milrod, 2004), are given equal weight in the model as influential cognitive theories, such as the empirically supported (Khawaja & Oei, 1998) model of Clark (1986). On the other hand, '*anxiety sensitivity'*, that is, a specific tendency to respond fearfully to anxiety symptoms (McNally, 2002), is given little weight in the Fava and Morton model, despite abundant evidence consistent with a causal role in the onset of panic attacks and PD (meta–analysis Olatunji & Wolitzky–Taylor, 2009).

Although Pilecki *et al.* addressed these concerns role in the revised model, they have relegated biological factors to a relatively peripheral role. This represents a major limitation for a nominally integrative account of PD given that: the brain is aetiologically upstream of behaviour (Hamer, 2002); autonomically–mediated symptoms are prominent during both panic and inter–panic anxiety (Hoehn–Saric *et al.* 2004; Roth, 2005; Blechert *et al.* 2007; Friedman, 2007; Doberenz *et al.* 2010; Kang *et al.* 2010) and; interoceptive signals are central to all cognitive accounts of PD (Clark, 1986; Beck & Clark, 1997; McNally, 2002). An integrative account of PD aetiology (and maintenance) must therefore assign a prominent role to both the central– and peripheral nervous systems. Further, because the aetiology of anxiety and psychiatric disorders in general (Hamer, 2002; Begleiter & Porjesz, 2006; Caspi & Moffitt, 2006; Eley, 2007; Fox *et al.* 2007; Jaffee & Price, 2007), and PD in particular

(Klauke *et al.* 2010; Maron *et al.* 2010), is understood to involve complex gene–environment interactions, a comprehensive, integrative account of PD aetiology must incorporate genetic and environmental factors and their interactions.

1.3.2 Genetic and Environmental Factors

1.3.2.1 Relative Contribution of Genotype versus Environment

Controlled family studies demonstrate that PD aggregates in families, by showing increased risk of PD in relatives of affected individuals (review Schumacher *et al.* 2011). Additionally, twin studies, which provide estimates at the aggregate level of the relative proportion of disorder risk attributable to genes versus environmental factors, reveal that genetic factors are largely responsible for the familial clustering of PD (Schumacher *et al.* 2011). A meta–analysis combining genetic epidemiologic findings from family and twin studies (adoption studies of PD have not been undertaken to date) obtained a heritability estimate (h^2) of 0.48 (95% confidence interval = 0.41 – 0.54) (Hettema *et al.* 2001). Non–shared environmental factors, that is, individual–specific influences such as life events and relationships (Eley, 2007), accounted for the balance of the liability. In contrast, the studies in the meta–analysis did not find a main effect for common family environment. More recently, several large twins studies obtained h^2s of 0.30 – 0.46 for PD (Kendler *et al.* 2003; Tsuang *et al.* 2004; Middeldorp *et al.* 2005a). Genetic epidemiologic studies, therefore, show that genetic factors increase one's susceptibility to the disorder, but do not act in isolation, as environmental influences are substantial.

Additionally, multivariate studies have been undertaken to identify heritability factors that cut across different psychiatric disorders. These studies are motivated by the

expectation that highly comorbid and phenomenologically similar disorders are likely to overlap in terms of their genetic diatheses (Lang & Shikishima, 2010). Accordingly, several genetic epidemiologic studies have investigated the pattern of shared and specific liability for PD in combination with MDD and/or several other anxiety disorders, or sub–threshold variants thereof (e.g., Scherrer *et al.* 2000; Kendler *et al.* 2003; Hettema *et al.* 2005; Hettema *et al.* 2006; Mosing *et al.* 2009; Tambs *et al.* 2009; Kendler *et al.* 2011). These studies have consistently found that genetic influences transcend DSM diagnostic boundaries, and account for a moderate to large proportion of their comorbidity. Further, in parallel with univariate analyses, these studies found that non–shared environmental factors accounted for the much of the balance of liability, with minimal effect of common family environment. Although, theoretically, several mechanisms may account for comorbidity of different disorders (e.g., overlapping diagnostic criteria, different manifestations of single disorder, common aetiology, one disorder being a risk factor for another) (Maj, 2005; Widiger & Samuel, 2005), their shared genetic liability suggest that common aetiological processes may account, at least in part, for the observed covariation of PD and its common comorbidities (Middeldorp *et al.* 2005b; Mosing *et al.* 2009).

1.3.2.2 Genetic Risk Factors

Beyond basic evidence of the relative influence of genetic and environmental factors in PD, the precise mechanisms of genetic transmission are yet to be determined (Smoller *et al.* 2008a). To date, molecular genetic studies have analysed in excess of 350 candidate genes and 1000 polymorphisms for their association with PD, although few findings have replicated (Maron *et al.* 2010). Attempts to link the phenotype with specific genetic variants are hampered by several factors.

Firstly, evidence suggests that liability for anxiety disorders and other psychiatric phenotypes is determined by the interaction of multiple genetic factors and environmental stressors (Plomin *et al.* 1994; Vieland *et al.* 1996; van West & Claes, 2004; Fanous & Kendler, 2005; Caspi & Moffitt, 2006; Domschke & Dannlowski, 2010; Klauke *et al.* 2010). For instance, segregation analyses point to a complex (*i.e.* non–Mendelian) mode of genetic transmission in PD, in which multiple risk genes, each of relatively small effect, interact with environmental factors (Vieland *et al.* 1996). In such circumstances, main effects analysis of genetic or environmental risk factors in isolation are likely to have limited power and may not replicate across samples (Kraemer *et al.* 2001; Caspi & Moffitt, 2006). To investigate the interplay of genetic and environmental risk factors the application of a gene–environment interaction approach is needed (Klauke *et al.* 2010). However, gene–environment interaction studies – an underutilised approach in psychiatric genetic research (Caspi & Moffitt, 2006; Eley, 2007) – have yet to be conducted for PD (Klauke *et al.* 2010).

Secondly, it is widely regarded that phenotypic complexity and uncertainty present problems in identifying the genetic underpinnings of the disorder (Kendler, 2006; Smoller *et al.* 2008a). It remains to be determined, for instance, whether phenotypic heterogeneity in PD reflects aetiological heterogeneity (Domschke & Dannlowski, 2010), but increasingly it is becoming apparent that the pathways linking genotypes and complex phenotypes are non–linear (Hamer, 2002; Gottesman & Gould, 2003). In a similar vein, the use of categorical phenotypes in molecular genetic analyses has limited power to detect genetic variants associated with quantitative traits (Lesch, 2001) as there will typically be more unaffected than affected individuals with an at–risk polymorphism, given their relatively low risk (Linden & Fallgatter, 2009).

A third problem is that genetic association studies, which are optimal for the study of complex disorders, rely on candidate genes selected on the basis of evidence of pharmacologic, neurophysiologic or other aetiological involvement (van West & Claes, 2004). However, a relative lack of knowledge of etiological and, in particular, pathophysiological mechanisms, hampers such studies and thus efforts to bridge the genotype–phenotype gap in PD (Maron *et al.* 2010).

Finally, as symptom– and behaviour–level expression is greatly distal from genotype (Gottesman & Gould, 2003; Green *et al.* 2008), effect sizes for gene–behaviour relationships are likely to be modest (Hamer, 2002; Domschke & Dannlowski, 2010). By contrast, theoretical considerations and early empirical data suggest that effect sizes for intermediate phenotypes may be larger (Green *et al.* 2008). Intermediate phenotypes (also called endophenotypes) are quantitative traits that are aetiologically downstream of genotype and upstream of phenotype, and are theoretically influenced by a more restricted set of genes than overall clinical phenotypes (Gottesman & Gould, 2003). In particular, as the brain is an obligatory intermediate between genotype and behavioural phenotype, the use of brain functional indices as intermediate phenotypes may produce larger effect sizes (Glahn *et al.* 2007), and may facilitate the identification of risk genes for complex anxiety disorder phenotypes (Domschke *et al.* 2010).

1.3.2.3 Environmental Risk Factors

A number of environmental risk factors across development have been linked with increased incidence of PD. Factors such as parental separation, poverty and parental dimensions (e.g. criticism/rejection, over–control) are believed to be shared, familial

risk factors for PD (Hirschfeld–Becker *et al.* 2008). However, as previously indicated, non–shared environmental factors account for the greater portion of environmental liability for PD (Kendler *et al.* 2003; Tsuang *et al.* 2004; Middeldorp *et al.* 2005a). Non–shared environmental factors that may increase risk for PD include stress, perinatal factors, and life events (e.g., exposure to violence, loss, social isolation) (Hirschfeld–Becker *et al.* 2008). Individuals with PD relative to unaffected controls report a higher incidence of psychosocial stressors such as early life trauma or abuse, and major life stressors and traumatic events in adulthood (Faravelli, 1985; Roy–Byrne *et al.* 1986; Stein *et al.* 1996; Leskin & Sheikh, 2001; Watanabe *et al.* 2005), with findings suggesting a significant cumulative effect of aversive life events in PD aetiology (Klauke *et al.* 2010). However, the effect appears non–specific to PD in that self–reported exposure to such events did not differ between individuals with PD versus other anxiety disorders (Rapee *et al.* 1990; Hofmann *et al.* 2000; Faravelli *et al.* 2007). On the basis of pre–clinical and developmental studies, early experiences with uncontrollable or unpredictable events have also been proposed as non–specific risk factors for PD and other chronic anxiety states (Bouton *et al.* 2001). Such early experiences are proposed to mediate the anxiogenic effect of subsequent novel or frightening events (e.g., spontaneous panic attacks) (Chorpita & Barlow, 1998; Barlow, 2000). By contrast, early learning experiences relating to unexplained bodily sensations may represent a relatively specific PD risk factor (Bouton *et al.* 2001).

Additionally, various forms of substance use, abuse and dependence are associated with increased risk for panic attacks and PD. Exposure to and withdrawal from alcohol, tobacco, and illicit drugs (especially marijuana and hallucinogens) are established risk factors, although these panic–substance relationships are bidirectional

(review Cosci *et al.* 2007: Zimmerman *et al.* 2003; Morissette *et al.* 2006; Sareen *et al.* 2006; Zvolensky *et al.* 2005a; 2006a; b; 2008; Robinson *et al.* 2008). Additionally, excessive caffeine use may increase risk for PD (Barr Taylor, 2006). Panic symptoms may also be elicited by various physiologic stress states (Faravelli & Paionni, 1999; White *et al.* 2006). For instance, panic symptoms may mimic a variety of medical conditions (e.g., cardiac, respiratory, neurological, or metabolic) which, in turn, are associated with increased risk for panic attacks (Maron *et al.* 2010). As panic attacks are risk factors for PD development (Goodwin *et al.* 2004; Zvolensky *et al.* 2006c), such physiologic stressors may indirectly increase PD risk (Maron *et al.* 2010).

For individuals with a pre–existing diathesis a range of biological and experiential stressors may serve as catalysts for the development of the disorder. However, environmental factors are only contributory because exposure to them does not invariably lead to a disorder: human and pre–clinical studies consistently reveal considerable variability in individuals' responses to environmental stressors (Caspi & Moffitt, 2006). Exemplifying the complex nature of gene–environment interactions, such response heterogeneity can be traced back to individual differences in genetically influenced factors such as personality, temperament, cognition and autonomic physiology (Plomin *et al.* 2001; Jaffee & Price, 2007). For instance, whereas recent stress prospectively predicts the onset of panic attacks (Watanabe *et al.* 2005), individuals higher in anxiety sensitivity are at greater risk of panic in stressful situations (Schmidt *et al.* 1997; 1999; Zvolensky *et al.* 2005b; Schmidt *et al.* 2006a; 2008a; b; Kutz *et al.* 2010). In line, individuals' appraisals of adverse events in adulthood may be of greater relevance to PD onset than the number or type of such events (Klauke *et al.* 2010).

As another example of gene–environment interaction, there is evidence that anxiety sensitivity and cigarette smoking interplay as risk factors for PD: individuals high in anxiety sensitivity use smoking to alleviate anxiety (Zvolensky & Bernstein, 2005), but are more reactive to bodily sensations associated with smoking cessation (Zvolensky *et al.* 2004). In a further gene–environment interaction, anxiety sensitivity in young adults varied as a joint function of 5–HT1A polymorphism variant and childhood maltreatment (Stein *et al.* 2008). Finally, genetic variability appears to drive the risk for the number and type of environmental stressors encountered (Klauke *et al.* 2010), an effect called gene–environment correlation (Lang & Shikishima, 2010).

1.3.3 Toward an Integrative Aetiology of Panic Disorder

Panic symptomatology (Klauke *et al.* 2010; Schumacher *et al.* 2011), as per other forms of psychopathology (Hamer, 2002; Begleiter & Porjesz, 2006), is understood to be aetiologically complex, with risk conferred by the interaction of multiple genetic and non–genetic risk factors. The above examples of gene–environment interactions and correlations exemplify the complex nature of risk for PD. Therefore, PD aetiology may be more comprehensively explained by integrative assessment of multiple risk factors and their interactions, as opposed to main effects analysis of single risk factors in isolation (Kraemer *et al.* 2001; Zvolensky *et al.* 2006c). Furthermore, as empirically supported risk factors for PD span multiple levels of function (e.g., biological/genetic, psychological, social, and cultural/economic) (Craske & Zucker, 2002; Zvolensky *et al.* 2006c; Feldner *et al.* 2008), comprehensive aetiological accounts must integrate multi–level findings. According to prominent cognitive theorists David Clark and Aaron Beck, further advances in knowledge of anxiety disorders will require multidimensional models that integrate and synthesise information from across the

multiple levels of function affected by these disorders (Clark & Beck, 2010). Importantly, this will involve integrating hitherto disparate biological and psychological approaches.

Although it might seem like a daunting challenge to integrate findings and theories from disparate biological and psychosocial perspectives, Kendler (2008) presents an elegant framework which delineates the steps required to construct an integrative aetiological model for psychiatric disorders. The first step he proposes is decomposition of the system, that is, the identification of the many different organisational levels at which disorder risk is conferred (Kendler, 2008). Within a dynamic, multi–level aetiological hierarchy, lower level mechanisms which are relatively distal and higher level mechanisms which are proximal to the phenotype may be delineated (see Figure 1). For instance, the genotype represents the lowest level aetiological mechanism in psychiatric illness (Caspi & Moffitt, 2006), and aggregate genetic factors strongly influence risk for PD (Schumacher *et al.* 2011). By contrast, heritable factors including intermediate phenotypes, being aetiologically downstream of the consequences of genes (Gottesman & Gould, 2003) are relatively higher level mechanisms. However, as the term 'intermediate phenotype' encompasses a wide range of quantitative traits (e.g., neurophysiological, biochemical, endocrine, neuroanatomical, cognitive or neuropsychological) (Gould & Gottesman, 2003; Green *et al.* 2008), finer parsing is required in order to identify all the distinct organisational levels of risk. For instance, the brain is aetiologically intermediate between genotype and, respectively, higher level cognitive and behavioural causal mechanisms (Hamer, 2002; Chamberlain & Sahakain, 2005). In addition, individual environmental risk factors (e.g., exposure to substances, life events) need to be identified.

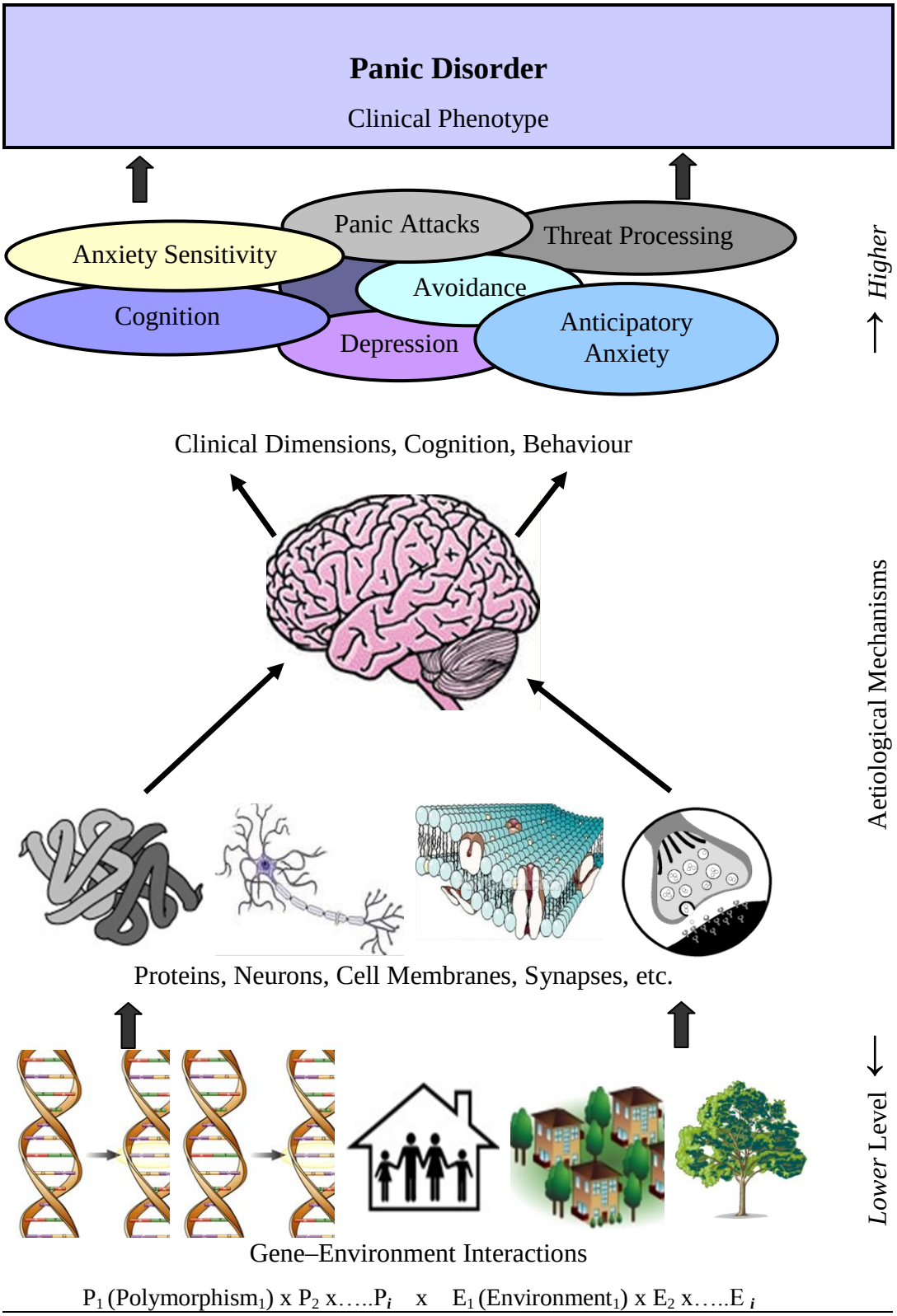

Figure 1: Simplified schematic showing hierarchy of aetiological levels spanning genotype to clinical phenotype.

The second step in the framework proposed by Kendler (2008) is to investigate each part of the system in turn. The final phase Kendler describes is integration, that is, determining how the parts work together to produce the phenotype. This phase includes identifying interactions among the multi–level causal mechanisms. Conceptually, individual risk factors may interact in several distinct ways to alter the outcome of clinical phenotype (Kraemer *et al.* 2001).

On the basis of Kendler's proposed framework, it would appear that there is much work to be done in identifying and clarifying the multi–level causal mechanisms in PD before their eventual reintegration.

1.4 Summary of Chapter

The present chapter presented a general introduction to panic disorder, which comprised two broad areas of focus. Firstly, PD was described at the level of clinical phenotype and associated phenomenology. This discussion encompassed the disorder's diagnostic criteria, comorbidities, prevalence, costs and main forms of treatment. As reviewed, the clinical phenomenology of PD is complex, and comprises cued and uncued panic attacks, anticipatory anxiety and agoraphobic avoidance, in addition to wide–ranging non–criterion panic, anxiety and avoidance symptoms. And, despite being categorically defined, the disorder's clinical phenomenology shows substantial inter–individual heterogeneity.

Panic disorder's early onset and persistence over the lifespan, in conjunction with its cross–cultural penetration, equates to a substantial disorder–imposed burden, in terms of personal suffering, financial costs and resources. Although empirically supported

psychological and pharmacological interventions are available, not everyone responds or responds adequately. Therefore, predictors of treatment response are needed in order to guide clinical decision–making and optimise treatment outcomes for individuals with PD (Bandelow & Rüfer, 2004; Diemer *et al.* 2010). In particular, given the high level of refractoriness following pharmacotherapy cessation (Landon & Barlow, 2004; Butler *et al.* 2006), predictors of a favourable and lasting response to non–pharmacologic interventions are needed.

As discussed, the clinical phenomenology of PD comprises threat responses to neutral or harmless stimuli. This suggests a failure to recognise safety signals, as opposed to exaggerated responses to actual threat (Thayer *et al.* 2012). In PD, panic attacks and panic–associated events (*i.e.* bodily sensations, thoughts and contexts) are the disorder–specific object of threat (Craske & Waters, 2005) and panic attacks in PD are typically elicited in situations that are not inherently dangerous or harmful, and despite posing no real threat, elicit further, debilitating anxiety and avoidance (Nesse, 1987; Maren, 2007). Various data suggest that individuals with PD perceive panic attacks as unpredictable and uncontrollable events, which renders panic attacks especially anxiogenic, and plays an important role in the development of diagnostically and clinically significant anxiety (Barlow, 2000; Bouton *et al.* 2001; Lissek *et al.* 2005; Grillon *et al.* 2008).

The second focus of the present chapter was PD aetiology. Panic disorder aetiology is understood to involve the interaction of multiple susceptibility genes and environmental factors (Maron *et al.* 2010; Klauke *et al.* 2010). Although genetic epidemiological studies show that, in the aggregate, genetic factors strongly influence

risk for PD (Schumacher *et al.* 2011), it is not yet known precisely what is inherited or the mechanisms of its genetic transmission (Smoller *et al.* 2008a). Genetic epidemiological studies also show that the individual's exposure to environmental stressors accounts for a substantial portion of liability for PD (Kendler *et al.* 2003), and numerous environmental factors are putative risk factors for PD (Feldner *et al.* 2008; Kutz *et al.* 2010). These range from relatively non–specific risk factors for anxiety psychopathology (e.g., psychosocial stressors across development; Faravelli *et al.* 2007) to those that appear to be relatively specific for panic psychopathology (e.g., cigarette smoking; Zvolensky *et al.* 2005a).

Empirically supported risk factors for PD span multiple levels of function (e.g., biological/genetic, psychological, social, and cultural/economic) (Craske & Zucker, 2002; Zvolensky *et al.* 2006c; Feldner *et al.* 2008). These levels of risk may be conceived as spanning a hierarchy that links the genotype at the lowest level, ultimately, to the clinical phenotype (Kendler, 2008). Moreover, multi–level risk factors for PD are expected to interact in complex ways (Kraemer *et al.* 2001). They ways in which multi–level risk factors interact for PD are, as yet, barely understood (Zvolensky *et al.* 2006c; Schumacher *et al.* 2011). However, as discussed, the majority of extant aetiological models of PD focus exclusively on either psychological or biological levels of function, and these disparate approaches have yielded empirical data that are largely unintegrated (Windmann, 1998; Clark & Beck, 2010; Pilecki *et al.* 2010). Further advances in the understanding of PD aetiology must account for the many levels of function at which disorder risk is conferred (Clark & Beck, 2010) and, importantly, their interactions (Kraemer *et al.* 2001; Zvolensky *et al.* 2006c; Kendler, 2008).

Although the clinical phenomenology of PD is complex, the disorder's course is essentially marked by prolonged periods of anxiety (*i.e.* anticipatory anxiety) interspersed by brief episodes of fear (*i.e.* panic attacks). The following chapter comprises a discussion of these two emotions. As the symptoms of PD (e.g., panic attacks, anticipatory anxiety, agoraphobic avoidance) are normal fear and anxiety responses, but for their occurrence in excess of situational demands (Nesse, 1987; Blanchard & Blanchard, 2008), the discussion of these emotions is framed within a broad context of their evolved functional significance. Taken together, Chapters 1 and 2 provide foundational information for the present research, which represents an integrative, multi–level assessment of PD during the inter–panic interval.

Notes

1. As panic disorder (PD) is diagnosed according to the presence or absence of agoraphobia (APA, 1994; 2000), throughout this thesis the generic term PD will be used to denote PD with or without agoraphobia, to distinguish it from panic disorder *with* agoraphobia (PDA).

2. As most evidence–based studies on PD use DSM criteria (Barr Taylor, 2006) and, in any case, the ICD–10 description of PD is essentially consistent with recent editions of DSM (Roy–Byrne *et al.* 2006), this thesis will emphasise DSM criteria.

3. A '*risk factor*', according to proposed standardised definitions of risk processes (Kraemer *et al.* 1997), is a variable that is related to, and temporally precedes an outcome (e.g., PD development). By contrast, a '*causal risk marker*' is a variable that, when modified in some way, alters the risk of that outcome (Kraemer *et al.* 1997). As empirical evidence documenting a causal role of risk factors in PD is scanty (Zvolensky *et al.* 2006c), the generic term 'risk factor' will be used herein.

Chapter 2

Fear & Anxiety: An Evolutionary Perspective

2.1 Overview of Chapter

This chapter presents a discussion of fear and anxiety, the two emotions which, iteratively, define the course of panic disorder. Human fear and anxiety are largely products of Darwinian evolution (Tooby & Cosmides, 1990). The present chapter therefore describes these two, distinct emotions within a broad evolutionary perspective. Evolution–based disciplines make a fundamental distinction between *ultimate* [1] and *proximate* explanations of a given trait or disorder (Nesse, 1999). Typically, clinical research focuses on proximate explanations, which concern individual differences in illness vulnerability (Nesse, 1999). The original research presented in Chapters 3 – 9 represents a proximate approach in that it aims to identify patient–control differences, some of which might represent risk factors for PD. By contrast, ultimate explanations consider why all members of a species share a vulnerability to a particular disorder (Nesse, 1999). These two, complementary levels of explanation are viewed as essential to a comprehensive, integrative account of human vulnerability to a given disease (Gluckman *et al.* 2011; Nesse, 2011). Thus, the present chapter emphasises ultimate explanations of human fear and anxiety.

The chapter begins by outlining some basic tenets of evolution–based disciplines. This is followed by a consideration of what an evolutionary perspective of human

fear and anxiety entails, and presents a rationale for considering these emotions – as opposed to panic disorder per se – within such a temporally deep context. An evolutionary account of human fear and anxiety links these emotions with phylogenetically ancient *defensive responses* [2], which have been highly conserved and selected by evolution (Blanchard & Blanchard, 2008), and shaped by recurrent, survival–threatening features of early ancestral environments (Cosmides & Tooby, 2000). Next, the discussion turns to the processes of sensory information appraisal and threat detection, as the detection of threatening or potentially threatening events is required for the activation of fear or anxiety responses (Armony & LeDoux, 1997). The differential properties of specific defensive responses, as delineated by converging lines of human and non–human research, are then discussed. This is followed by discussions of human versus non–human defensive responses and adaptive versus maladaptive fear and anxiety, in humans. The chapter concludes with a discussion of the CNS and ANS organisation of fear and anxiety.

Overall, the present chapter aims to contextualise the present investigation of PD by discussing fear and anxiety within a broad evolutionary context. Given that the expression of these emotions is maladaptive in PD and other anxiety disorders, ultimate–level evolutionary explanations that address questions of phylogeny and adaptive function are needed in order to explain the broad human vulnerability to these conditions (Nesse, 1999).

2.2 An Evolutionary Perspective: Proximate versus Ultimate Explanations

According to evolution theory, those heritable traits that confer greater fitness are propagated via natural selection, whereas those associated with reduced fitness

should be eliminated from the gene pool through negative selection pressure (Darwin, 1996). Although initially limited to physical traits, Darwin later extended this view to behavioural strategies and, importantly, the expression of emotions in humans and non–human animals (Darwin, 1998). Additionally, Darwin, having conducted extensive observational studies of the behavioural expression of emotions across species and across human cultures, proposed that the emotional behaviours of non–human animals might represent analogues of human emotions (Darwin, 1998). Since Darwin, the gene concept has helped formalise the evolutionary principle of individual variations upon which natural selection acts (Gardner & Wilson, 2004), and the genetic contribution to behavioural or other traits may be quantified as heritability estimates (Glahn *et al.* 2007).

Evolution–based disciplines (*i.e.* evolutionary medicine, psychology and psychiatry) address how natural selection has left human bodies and minds vulnerable to disease (Gluckman *et al.* 2011). To address our species' capacity for dysfunction, evolutionary–based disciplines must look beyond the individual to human evolutionary history (Baptista *et al.* 2008). In relation to our species' capacity for mental dysfunction – such as occurs in the anxiety disorders – normal and abnormal human behaviours are considered within a broad, evolutionary perspective (e.g., Gardner & Wilson, 2004; Panksepp, 2006). As human emotions are evolved, adaptive responses (Darwin, 1998), an evolutionary perspective is arguably essential to any complete account of the underpinnings of emotions and emotional psychopathology (Gardner & Wilson, 2004; Shuhama *et al.* 2007).

However, diseases per se are not typically shaped by natural selection and therefore

are not appropriate objects for evolutionary explanation (Nesse, 2011). By contrast, traits that make organisms vulnerable to disease are appropriate targets of evolutionary explanations (Nesse, 2011). For instance, human fear and anxiety, which are defences elicited in response to particular classes of threats (Nesse, 2005b), are largely products of Darwinian evolution (Tooby & Cosmides, 1990). Similarly, the brain structures and mechanisms that underpin threat detection and are integral to the elicitation of these defensive responses have been highly conserved and selected by evolution (LeDoux, 1995; 1996; Öhman *et al.* 2000). Therefore, threat detection and response mechanisms are considered appropriate targets of evolutionary explanations of human vulnerability to the anxiety disorders (Nesse, 2005b; 2011).

According to evolutionary psychologists Leda Cosmides & John Tooby, evolutionary psychology (or psychiatry) does not denote a specific subfield within the discipline; rather, it is conceived as "a *way of thinking* about psychology that can be applied to any topic within it – including the emotions" (Cosmides & Tooby, 2000, p. 91, italics in original). These authors have identified a set of principles that they consider central to an evolutionary perspective of the human mind. These include – to borrow a metaphor from cognitive psychology – the view that the brain is an information processing machine, which generates behaviour appropriate to the environmental circumstances (Cosmides & Tooby, 2000). Additionally, they suggest that our neural circuits, including those mediating emotional responses such as fear and anxiety, were shaped by natural selection pressures, such that those adaptations which solved evolutionarily recurrent problems were selected, with different neural circuits being specialised for solving different adaptive problems.

Within ancestral environments, the recurrent problem of constant potential for harm (Cosmides & Tooby, 2000) favoured the selection and conservation of adaptations that organised either the rapid and effective detection of threat, or alternatively, the rapid and appropriate response to that threat (LeDoux, 1995; 1996; Öhman & Mineka, 2001). Animal defensive responses represent the latter type of adaptation, wherein specific types of threat–related situations reliably and differentially elicit a complex bio–behavioural response (Quinn & Fanselow, 2006; Blanchard & Blanchard, 2008). Finally, given the timescale in which significant evolutionary changes are wrought, they suggest that the modern human brain evolved to suit primitive ancestral environments (Tooby & Cosmides, 1990; Cosmides & Tooby, 2000). So, to apply an evolutionary perspective, human emotions such as fear and anxiety represent biologically–based solutions to recurrent problems encountered within early ancestral environments (Cosmides & Tooby, 2000).

Within evolutionary biology and derived disciplines, a fundamental distinction is made between ultimate and proximate explanations of inherited traits, which represent two, complementary levels of evolutionary causality (Nesse, 1999; Gluckman *et al.* 2011; Scott–Phillips, 2011). This distinction derives directly from the theory of natural selection, which describes both a process (how biological traits associated with greater reproductive success are favoured) and the consequences of that process (traits apparently designed to maximise the organism's fitness) (Gardner, 2009; Scott–Phillips *et al.* 2011). Proximate explanations concern structures and mechanisms at the level of the individual, and may reveal why some individuals, but not others, are vulnerable to a given disease (Nesse, 1999). By contrast, ultimate explanations, which address questions of the adaptive significance and phylogeny of

a given trait (Nesse, 2011), may illuminate why all members of a species are vulnerable to particular disorders, but not others (Nesse, 1999). Therefore, ultimate explanations may illuminate why a propensity for prevalent and heritable psychiatric illnesses such as the anxiety disorders, despite being associated with reduced fitness, is maintained within the human genome (Marks & Nesse, 1994; Nesse, 2005a). Tinbergen (1963) provides a further delineation of the levels of explanation required for evolution–based accounts of heritable traits. He proposed that evolution–based accounts must encompass descriptions of: 1) function (*i.e.* adaptive significance); 2) phylogeny; 3) mechanism, and; 4) development. Wherein the former two represent ultimate explanations, the latter two are proximate explanations (Nesse, 2011). These four components are considered essential to a complete evolution–based account of a given human disease or trait (Gluckman *et al.* 2011).

The following two major chapter sections discuss the processes of threat detection and response, with a particular emphasis on their adaptive significance and phylogeny.

2.3 Sensory Information Appraisal & Detection of Threat

2.3.1 Significance and Attention

Evolutionary accounts emphasise early and reliable detection of threatening stimuli as critical for an animal's survival (Marks & Nesse, 1994; Öhman & Mineka, 2001; Panksepp, 2006). Adaptations which facilitated rapid detection of threat in complex, constantly changing environments have been highly selected by evolution and conserved within genomes (LeDoux, 1995; 1996; Öhman *et al.* 2000). However, the neurocircuitry underpinning threat detection does not simply parse incoming sensory

information into threatening and non–threatening stimuli. Rather, the significance of incoming sensory information is determined according to a spectrum of motivational significance (Sanders *et al.* 2003; Williams, 2006; Gordon *et al.* 2007). Significant stimuli – 'signals' in signal processing terminology (Nesse, 2005b) – engage more attention and prompt greater information gathering, relative to other inputs (Davis & Whalen, 2001; Compton, 2003; Lang & Davis, 2006). Although the construct of attention is complex and variously defined (Riccio *et al.* 2002), the selection of motivationally–relevant input from a complex array is one the key functions of attention (Mogg & Bradley, 1998; Öhman *et al.* 2000).

Because of evolutionary pressures, the organism's driving motivations that determine input relevance relate to survival (*i.e.* maximise pleasure and minimise harm) (Öhman & Mineka, 2001; Gordon *et al.* 2007). Therefore, stimulus attributes and stimuli which have been linked through evolution to danger are particularly salient (Kavaleris & Choleris, 2001; Lang & Davis, 2006). Similarly, stimulus novelty or change within a given temporal or spatial context is an important determinant of significance, as are stimulus intensity or suddenness, because these stimulus attributes may convey threat–related or otherwise behaviourally–relevant information (Williams, 2006). In addition to stimulus–driven (*i.e.* 'bottom–up') attentional biasing, salience and thus attention is also biased in a goal–directed (*i.e.* 'top–down') manner (Sarter *et al.* 2001; Behrmann *et al.* 2004). Further, as potential threat cues include cognitive processes (Barlow, 2002), detectable changes within the interoceptive milieu (McNaughton, 1989; Esquivel *et al.* 2010) and imagined threats (e.g., believing an intruder is in the house) (Bremner, 2004), events need be neither exteroceptive nor objectively threatening to serve as threat cues.

Across species, as a prerequisite for threat detection, incoming sensory information from the external and internal milieu is constantly appraised in terms of its biological relevance for the organism (Armony & LeDoux, 1997; Belzung & Philippot, 2007). As higher perceptual systems have insufficient capacity to permit conscious processing of all sensory input that simultaneously impinges upon the senses in complex environments, only a relatively small subset of environmental information gains access to higher cortical processes and conscious awareness (Escera *et al.* 2000; Posner & Rothbart, 2007). It is therefore crucial to determine input relevance early in the information processing stream so that environmental events of potential functional significance may be selected for further processing, and those of low informational value may be discarded (Compton, 2003; Crottaz–Herbette & Menon, 2006). To facilitate the detection of biologically relevant events within the environment, evolution has shaped our perceptual systems to particular 'bandwidths' of significance (Tooby & Cosmides, 1990; Öhman *et al.* 2000). Yet, even within these bandwidths, we are exposed to a constant stream of environmental events, and without the capacity for efficient selection of inputs, the individual's perceptual processing capacity would quickly be exceeded (Öhman *et al.* 2000). Thus, "attention, emotion, and motivation introduce a value system to sensory processing. These value–based modulations allow the CNS to sculpt sensory experience into a subjective landscape" (Mesulam, 1998, p. 1036). The processing of significant stimuli occurs within emotional systems in the brain which are immediately connected to output functions that regulate and coordinate behaviour across multiple functional domains (Öhman *et al.* 2000). The ANS is a critical part of the fine–tuning of the behavioural response, as stimuli of even remote significance to the individual are likely to elicit ANS responses (Öhman *et al.* 2000; Dindo & Fowles, 2008).

2.3.2 The Neural Circuitry of Threat Detection

The neural circuitry underpinning threat detection and response evolved early in the phylogenetic scale, has been selected though evolution, and has remained essentially unchanged throughout evolution (Armony & LeDoux, 1997; LeDoux, 2000). The amygdala, a small multi–nucleated body that lies within the anterior portion of the medial temporal lobes, is central to this neurocircuitry (Kent & Rauch, 2003; Sanders *et al.* 2003). The anatomical position and functional connectivity of the amygdala support its role as the central node for sensory information appraisal and, additionally, the organising of subsequent fear and anxiety responses (Goddard & Charney, 1997; Davis & Whalen, 2001; Sanders *et al.* 2003; Maren, 2005).

The basolateral nucleus of the amygdala (BLA) serves as the primary sensory interface of the amygdala (Sanders *et al.* 2003). Sensory information from the thalamus, sensory cortices, and the hippocampus converges at the BLA and is rapidly evaluated by the BLA and associated structures (Aggleton, 1993; Armony & LeDoux, 1997; Davis & Whalen, 2001). Sensory inputs to BLA of particular relevance for PD include several pathways conveying interoceptive information (Craig, 2003; Critchley *et al.* 2004) and input from the hippocampus, which transmits multimodal contextual information concerning the time and place of aversive experiences (Fanselow, 2000; Sanders *et al.* 2003; Maren, 2005; Alvarez *et al.* 2008).

Across vertebrate species two afferent pathways convey sensory information to the BLA, a direct subcortical pathway and an indirect cortical pathway (Sanders *et al.* 2003). In the direct pathway, sensory information critical to the rapid triggering of fear is carried by modality–specific tracts running through the anterior thalamus to

the BLA (Turner & Herkenham, 1991 in LeDoux, 1992). This pathway is only capable of representing relatively crude stimulus features (LeDoux, 1992; Sanders *et al.* 2003). Importantly, this 'quick and dirty' thalamic pathway does not require cortical involvement (LeDoux, 1995), and is likely to be involved when fear responses are activated in the absence of explicit awareness that a threat stimulus was present (Whalen *et al.* 1998; Öhman, 2005), and might therefore be involved in the triggering of spontaneous panic attacks (LeDoux, 1995; Rauch *et al.* 2003) which, by definition, occur in the absence of awareness of the triggering stimulus (APA, 2000). The second route, the thalamo–cortico–amygdala pathway is slower, but has the capacity to represent stimulus features in much greater detail than the thalamic pathways (Armony & LeDoux, 1997; LeDoux, 1995).

Threat appraisal may thus be assigned with minimal cortical involvement and processing of the incoming sensory information, on the basis of relatively crude, simple stimulus features (LeDoux, 1996; Öhman, 2005). The system of rapidly appraising incoming sensory information is imperfect and mistakes occur. However, given the relatively benign costs associated with 'false alarms', as compared to the potentially catastrophic cost of failure to adequately prepare for danger (Marks & Nesse, 1994; Barlow, 2000; Pollock *et al*. 2006), threat detection mechanisms erring on the side of caution may have been selected through evolution (Cosmides & Tooby, 2000; Nesse, 2001; 2005b; Eilam *et al.* 2011; Woody & Szechtman, 2011). On the whole, however, the relative automaticity of threat detection is highly adaptive, given the imperative to rapidly identify potential threat (LeDoux, 1995; Öhman, 2005).

2.4 Defensive Responses

Across phyla, defensive responses are complex bio–behavioural responses that are elicited in response to threat–related stimuli or situations (Blanchard *et al.* 2001a; 2008). These highly organised and adaptive responses engage multiple response–systems including physiology (e.g., motoric, autonomic, neuroendocrine, somatic reflexes), behaviour, cognition, perception and affective–subjective experience (Blanchard & Blanchard, 2008), and facilitate harm avoidance or minimisation (Cosmides & Tooby, 2000; McNaughton & Corr, 2004). Within such a scheme, emotions are conceived as superordinate programs that effectively organise these disparate elements into a functionally cohesive whole (Cosmides & Tooby, 2000).

However, different threat contingencies generally require different solutions (Cosmides & Tooby, 2000). Those adaptations that increase the odds of survival when a predator is about to strike may not be optimal when a predator is at a distance, or when there is some uncertainty about whether a threat is present (Blanchard & Blanchard, 1988). Hence, a limited set of qualitatively different defensive responses have evolved to meet different threat contingencies – distinct solutions to distinct problems (Cosmides & Tooby, 2000). As these context–specific patterns of responding provided those individuals that displayed them appropriately with a survival/reproductive advantage, they have been highly selected and conserved by evolution (Cosmides & Tooby, 2000; Shuhama *et al.* 2007; Blanchard & Blanchard, 2008; Hohoff, 2009). Moreover, as different species have repeatedly encountered similar environmental dangers, a common repertory of defensive strategies has arisen across phylogenetically diverse animal species, including humans, to counter those dangers (Quinn & Fanselow, 2006; Shuhama *et al.* 2007).

Many, diverse types of research has contributed to current understanding of mammalian defensive responses and permit the mapping of non–human defences onto the human defensive emotions, fear and anxiety. Several lines of research from these literatures are discussed, below.

2.4.1 Ethological Studies

The work of Caroline and Robert Blanchard (e.g., Blanchard & Blanchard, 1988), who conducted systematic observational and experimental analyses of the behaviours of wild rats in response to cats (an innate threat for the species), has been highly instrumental in the delineation of distinct defensive responses. Their analyses revealed that specific environmental contingencies differentially and reliably alter rodent behaviour (Blanchard & Blanchard, 1988; 2008). They categorised defensive behaviours into three levels, distinguished chiefly on the basis of the presence or absence of an actual danger, and by the predator–prey distance. The first level of defence ('risk assessment') occurs when there is the potential for threat, but a specific threat stimulus is yet to be identified (e.g., when entering a novel environment or an environment in which a cat was previously encountered). Vigilance, which is scanning of the environment in order to identify the source of potential threat, is a critical aspect of risk assessment behaviours (Blanchard & Blanchard, 1988; Blanchard *et al.* 2001a; Blanchard & Blanchard, 2008).

In contrast, the presence of an imminent, clear threat (in this case, a predator) may elicit one of several defensive responses, although the actual response is largely determined by the predator–prey distance and the availability of an escape route (Blanchard & Blanchard, 1988). The second level of defensive behaviour ('distal

threat') occurs when a predator is first detected at a distance. In such situations, the animal's immediate response is to freeze. The freezing response involves the cessation of ongoing activity, profound immobility, orienting to the predator and focused attention (Marx *et al.* 2008). Analyses have shown a dramatic drop in heart rate associated with freezing responses (Campbell *et al.* 1997), and increased sensory acuity (Lang & Davis, 2006). Other changes include potentiated startle reflex and increased electrodermal activity (Marx *et al.* 2008). Freezing is considered adaptive in that it minimises detection (Gallup, 1977; Kalin *et al.* 2005).

Continued approach by the predator sets in motion a sequence of active defensive behaviours. Flight is the typical response if an escape route is available, and with decreasing predator–prey distance, defensive threat, and explosive defensive attack are elicited (Blanchard & Blanchard, 1988). These defensive states are associated with a rapid escalation in heart rate (Marx *et al.* 2008). Collectively, these behaviours represent the third level of defence ('proximal threat'). Overall, these behavioural data indicate that non–human mammals show differential defensive responding to imminent versus potential or uncertain threat, and a further segregation of defensive responding according to the dimension of threat proximity for imminent threat cues. Moreover, comparative studies suggest that other animals including non–mammalian species exhibit homologous defence strategies for comparable threat scenarios (Blanchard *et al.* 2001a). On the basis of their respective phenomenology, rodent risk assessment behaviour in response to poorly defined threat has long been considered a model for human anxiety, whereas defensive responses to imminent threat model human fear, including panic (Blanchard *et al.* 2001a; Blanchard & Blanchard, 2008).

Fanselow and colleagues, another prominent group in this literature, introduced the concept of 'predatory imminence' into the defensive response literature (Fanselow, 1994; Quinn & Fanselow, 2006). Their findings suggested that the prey's *perception* of the current level of risk determines its defensive behaviour. Theoretically, the level of risk spans a continuum from complete safety, on the one end, to consumption by a predator, at the other. In addition to situational factors such as predator–prey distance, they proposed that an animal's perception of threat imminence is influenced by "psychological factors" such as their perception of the predator's behaviour or intention (Quinn & Fanselow, 2006). In their tri–level typology of defensive responding, pre–encounter, post–encounter, and circa–strike defence correspond with risk assessment, distal and proximal threat, respectively.

McNaughton & Corr (2004), in an updating of "Neuropsychology of Anxiety" (Gray & McNaughton, 2000), present a model of defensive responses that is based on two behavioural dimensions: *defensive direction* and *defensive distance*. The model assumes a categorical separation of fear and anxiety on the basis of the Blanchards' etho–experimental analyses. However, they propose that the key factor distinguishing fear and anxiety is not the immediacy versus uncertainty of threat (as posited by the Blanchards) but, rather, what they term defensive direction. Specifically, they conceive fear as operating when leaving a dangerous situation (active avoidance), and anxiety when entering it (e.g., risk assessment approach behaviours) or when withholding entrance (passive avoidance). These functionally distinct behaviours are proposed to be mediated by two parallel neural systems. The second dimension, defensive distance, denotes an internal cognitive construct of intensity of perceived threat, and allows for individual differences in defensive distance for a fixed

objective distance, as per Fanselow and colleagues' predatory imminence construct. Defensive distance, according to the model, applies equally to fear and anxiety, and extremely small defensive distances would elicit the state that is labelled panic, in humans (McNaughton & Corr, 2004). Defensive behaviours, they propose, result from the superimposition of defensive distance on defensive direction.

Ethological analyses reveal one further step in the sequence of defensive responses to increasing threat proximity: tonic immobility (*i.e.* "playing dead" in the early literature) (Bracha *et al.* 2004). Tonic immobility is considered the last–ditch defence against entrapment (Marx *et al.* 2008), and is characterised by profound but reversible immobility and relative unresponsiveness to external stimulation (Gallup, 1977). Animals immobilised in tonic immobility show high autonomic and electrocortical activity despite the near–absence of outward movement (Brandão *et al.* 2008) and, although apparently unresponsive to exteroceptive stimuli, the animal remains highly alert (Marx *et al.* 2008). Evidence suggests that both intense fear and perception of entrapment are necessary for the induction of tonic immobility in non–human animals (Marx *et al.* 2008). Tonic immobility appears to be highly adaptive, as it makes prey less visible and is a potent inhibitor of predatory aggression (Nesse, 1999; Brandão *et al.* 2008).

Overall, ethological findings support the categorical distinction of defensive responses associated with imminent danger versus potential, distal, or temporally uncertain danger. Additionally, several distinct defensive responses may be delineated, which are hierarchically organised according to the dimension of perceived imminence of that threat (see Figure 2).

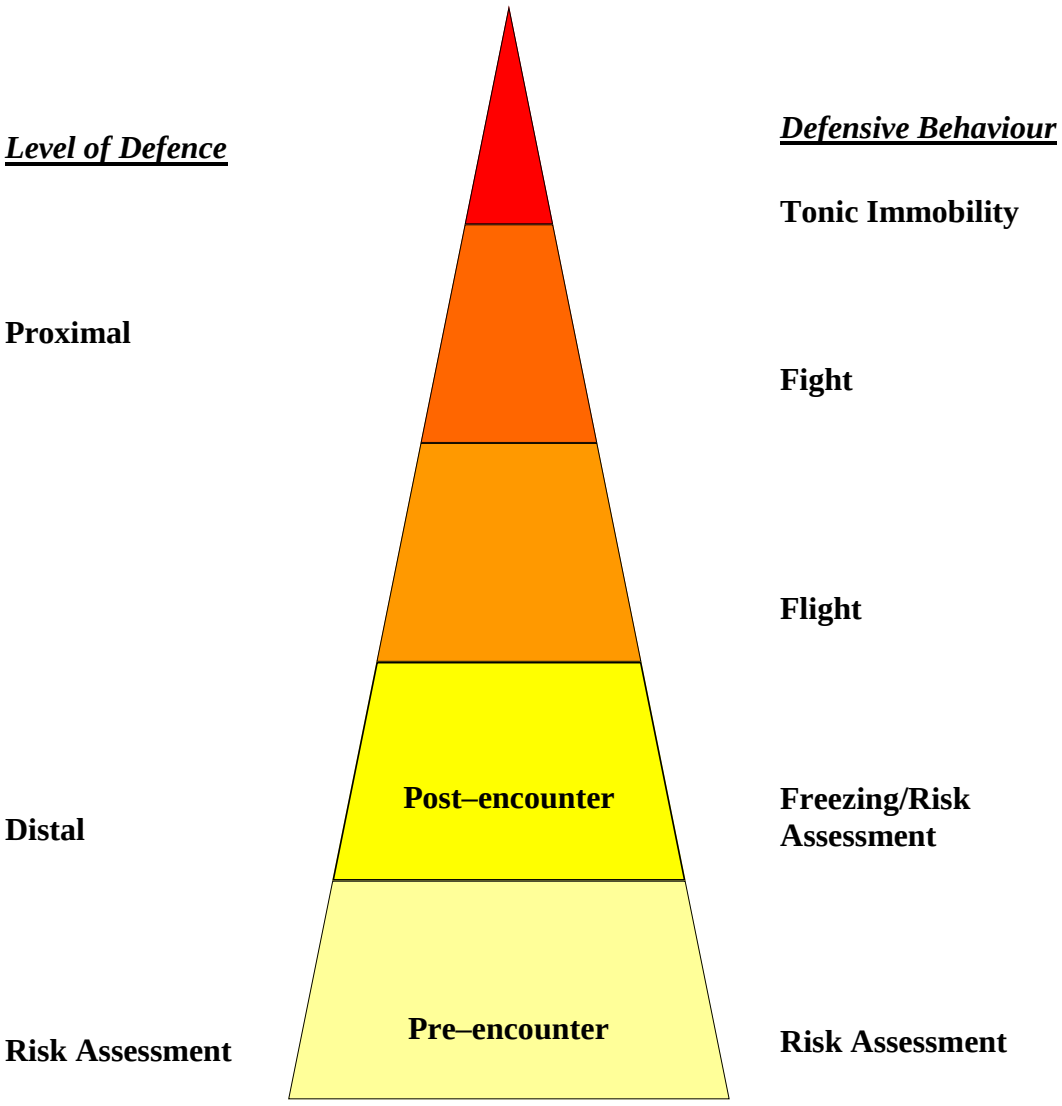

Figure 2: Relationship between levels of defence and defensive behaviour. Figure is based on the ethological studies of Robert and Caroline Blanchard and colleagues (e.g., Blanchard & Blanchard, 1988; 2008).

2.4.2 Human Behavioural Findings

To determine the relevance of the above ethologic findings to human defensive responding, several recent studies investigated behavioural responses to imagined threat scenarios in healthy subjects (Blanchard *et al.* 2001b; Perkins & Corr, 2003; Shuhama *et al.* 2008). In each study the scenarios were chosen to systematically manipulate contextual variables known to influence defensive responding in non–human mammals (e.g., threat magnitude, escapability and ambiguity; presence of a hiding place). The major difference between these studies and ethological studies was the nature of the threat. Whereas in animal studies this is typically a predator (Blanchard *et al.* 2001a), the threat stimulus in these human studies was in most instances an attacking conspecific. Taken together, the results of these three studies support the view that, despite the considerable level of behavioural flexibility of which humans are capable, the types of defensive behaviours and, moreover their patterning for comparable threat scenarios, is conserved across humans and non–human mammals (Blanchard *et al.* 2011).

However, one important difference between human and non–human animals in experimental research is the range of psychological factors that can influence the perception of threat imminence. For instance, human participants in laboratory studies of fear and anxiety may utilise prior knowledge about the nature of the research, including information gleaned from instructions and informed consent (Wilhelm & Roth, 2001; Grillon, 2002). Human participants in laboratory studies of fear and anxiety know that they can withdraw from the study at any time and that no actual harm will occur. According to Lang *et al.* (1997), non–anxiety disordered human research participants exposed to threatening stimuli respond in a post–

encounter manner, immobile and vigilant, analogous to a freezing rat. For these reasons it has been proposed that experimental studies of healthy subjects fail to measure intense fear (Lang *et al.* 1997). However, despite the lack of experimental evidence, there are anecdotal reports of tonic immobility from individuals who have survived intensely frightening life–threatening experiences coupled with some form of perceived restraint (e.g., sexual assault, attack by wild animals, plane crashes) (Heidt *et al.* 2005; Marx *et al.* 2008; Lima *et al.* 2010). In female survivors of sexual assault, tonic immobility was associated with depersonalisation and fear for one's life (Fúse *et al.* 2007). Taken together, the extant experimental and non–experimental evidence suggests that humans are capable or experiencing the full spectrum of defensive responses that are observed in other mammals.

2.4.3 Conditioning Studies

In parallel to the above basic and human literatures investigating defensive responses to innate threats, a separate literature has investigated defensive responses to conditioned stimuli (CSs). As the neural substrates supporting the acquisition and expression of conditioned fear have been conserved in evolution (LeDoux, 1995), much of this work has been conducted on rodents, with recent human findings supporting the validity of this translational approach (Davis *et al.* 2010). These studies have investigated the effect of a wide range of stimulus–related and individual–difference variables on defensive states, typically as indexed by startle reflex modulation (Davis, 1998; Walker *et al.* 2003; 2009).

For example, in cue conditioning studies, the predominant experimental paradigm of aversive conditioning, a discrete and specific CS (typically an auditory stimulus) is

repeatedly paired with an UCS (typically an electric shock) (Walker *et al.* 2003). Across conditioning trials the initially–neutral CS becomes strongly conditioned because its presence predictably signals the occurrence of the UCS, whereas its absence signals safety from that event (reviews Maren, 2005; Bishop, 2007). Subsequent presentations of the CS elicit a state of fear (Grillon, 2008). In contrast, the context, being a poor predictor of the occurrence of the aversive event, becomes relatively weakly conditioned (Grillon, 2002). The duration of fear is characteristically brief and is time–locked to the fear–inducing stimulus (Grillon, 2008). The rapid onset of fear in the presence of a fear stimulus reflects the evolutionary pressure to respond rapidly to threat (LeDoux, 1996; Öhman & Mineka, 2001), whereas its rapid offset reflects the discrete nature of fear cues (Grillon, 2002; Davis *et al.* 2010). In other words, once the immediate danger has passed, fear is normally quickly resolved.

By contrast, a variety of context conditioning paradigms model anxiety as opposed to fear (Walker *et al.* 2003; 2009; Davis *et al.* 2010). Anxiety is elicited in situations of potential threat in which, compared to fear, there is relatively less subjective certainty with regards the presence of threat (Barlow, 2000; Cannistraro & Rauch, 2003). Compared to fear, the situations that may elicit anxiety are relatively unpredictable, uncontrollable, novel, diffuse, non–specific and/or ambiguous, and with less obvious potential for harm (Blanchard & Blanchard, 1988; Barlow, 2000; Grillon, 2008; Walker *et al.* 2003; 2009). In the absence of a specific, discrete cue with which to predict the occurrence of an aversive event (again, typically an electric shock), the context becomes the best (albeit a poor) predictor of an aversive event and context conditioning is increased (Grillon, 2008; Fonteyne *et al.* 2009). Moreover,

manipulations that increase the temporal unpredictability of the UCS enhance context conditioning (Alvarez *et al.* 2008). In anxiety, there is the potential for harm, but no specific cue that would allow the individual to reliably predict or control the occurrence of an aversive event (Barlow, 2000; Grillon, 2008). Contextual cues are continuous reminders of danger, without signalling its time of occurrence (Grillon, 2008). The more sustained nature of anxiety relative to fear arises because, as situations of uncertain threat, by definition, do not clearly signal when a threat is, or is not, present (Eilam *et al.* 2011), the associated defensive state has no clear onset and offset (Grillon, 2008; Lang *et al.* 2009). In line, individuals who failed to learn the relationship between a CS and an UCS during aversive conditioning demonstrated a sustained CR throughout the entire testing session as they were unable to use the available information to predict the UCS occurrence (Baas *et al.* 2008).

Taken together, cue and context conditioning data demonstrate that relatively predictable aversive events produce a phasic defensive response (*i.e.* fear), whereas relatively unpredictable threats elicit a sustained defensive response (*i.e.* anxiety), and provide further robust support for the categorical distinction of fear and anxiety (Davis *et al.* 2010).

2.4.4 Human versus Non–Human Defensive Responses

Fear is a highly organised response that involves the rapid recruitment and coordination of multiple response–systems (Davis & Whalen, 2001; Hagemann *et al.* 2003; Blanchard & Blanchard, 2008). Given the imperative to respond quickly and appropriately when faced with imminent danger this response capacity is ‘hard–

wired' within phylogenetically ancient systems within the brain, and has been strongly selected and conserved by evolution (LeDoux, 1995; 2000; Davis & Whalen, 2001; Quinn & Fanselow, 2006). This results in a tendency for stereotyped, yet highly adaptive responses to imminent threat (Blanchard & Blanchard, 2008). However, given our species' capacity for behavioural flexibility, humans may sometimes inhibit the overt behavioural expression of fear (Lang *et al.* 1998; Panksepp, 2006). For example, an individual who experiences a panic attack may inhibit the urge to flee the situation (Craske & Barlow, 1988). On the other hand, there is evidence that tonic immobility, which is the defensive state associated with the greatest threat imminence, is non–volitional (Marx *et al.* 2008).

However, the differential attributes of anxiety as opposed to fear suggest greater scope for individual–related factors to contribute to anxiety, relative to fear (Belzung & Philippot, 2007; Shin & Liberzon, 2009). Anxiety–provoking situations, by definition, are characterised by the mere potential for harm, as opposed to the presence of a clear and present threat in fear (Barlow, 2000). Thus, anxiety requires the generation and maintenance of 'online' neural representations of possible future aversive events (Shin & Liberzon, 2009), which requires relatively advanced cognitive capacities, as compared to those required to respond to imminent threat (Belzung & Philippot, 2007; Hohoff, 2009). Whereas even the simplest animal such as protozoan are capable of responding to imminent threat stimuli (Belzung & Philippot, 2007), a trend for complexity gain in defensive responding may be observed in progressively higher phylogenetic levels (Mesulam, 1998; Porges, 2001; Belzung & Philippot, 2007). For example, in rodent species, which have been the primary animal models of defensive responses (Blanchard & Blanchard, 2001a;

Quinn & Fanselow, 2006), the nature of the eliciting situation is highly determinative of the animal's behaviour (Blanchard *et al.* 2001b; Blanchard & Blanchard, 2008). Yet humans and closely related primate species have a capacity for self–consciousness, which is one of the last cognitive capacities to develop in human ontogeny (Belzung & Philippot, 2007). This capacity in turn is central to episodic memory (Belzung & Philippot, 2007), which is the remembering of specific past experiences in which one was the subject of the experience, and the imagining of what future experiences would feel like (Tulving, 1984). As anxiety is a largely future–oriented emotion in which future aversive outcomes are anticipated, in part, on the basis of past experience (Barlow, 2000; Hofmann, 2008), the capacity for self–consciousness implies increased capacity for anxiety, in the sense of conscious anticipation of danger (LeDoux, 2000; Belzung & Philippot, 2007).

Humans, however, clearly differ from other mammalian species, even closely related primate species. Notably, humans have the capacity to express and experience anxiety in a manner that is unmatched in other species (Malizia & Nutt, 2008; Engel *et al.* 2009; Shin & Liberzon, 2009). For example, humans may elaborately imagine future threat scenarios, to verbally and otherwise symbolically transmit information to one another about potential dangers, and to worry and ruminate (Mathews, 1990; LeDoux, 2000; Grillon, 2002; Berkowitz, 2007; Engel *et al.* 2009). These unique capacities relate to features of the human brain that distinguish our species from even closely related primate species (Barton & Harvey, 2000), notably the disproportionate development of prefrontal cortical regions (Barton, 2006; Berkowitz, 2007; Shin & Liberzon, 2009), which permits greater flexibility in our behavioural repertoire (Mesulam, 1998; Panksepp, 2006; Thayer, 2006). It is

proposed, further, that this greater capacity of humans relative to non–human mammals for flexibility in defensive responding underpins uniquely human psychopathologies such as PD (Berkowitz, 2007; Shin & Liberzon, 2009). However, given the incremental nature of brain evolution, in which changes come to overlay and modify but not replace existing functions (Krubitzer & Kaas, 2005; Barton, 2006), the uniquely human elements of anxiety represent additional capacities, that extend rather than supersede the capacities for defensive responding of precursor hominids (Gardner & Wilson, 2004; Belzung & Philippot, 2007). Thus, human defensive responding comprises aspects that are both shared with other species and those which are unique (Panksepp, 2006; Belzung & Philippot, 2007; Hohoff, 2009).

2.4.5 Summary: Defensive Responses

Human anxiety and fear (including panic) responses are homologues of innate animal defensive responses – a set of distinct, pre–programmed preparatory states, each cued by different threat contingencies (Blanchard *et al.* 2001b). Anxiety and fear have many overlapping characteristics (Barlow, 2000), and are often conflated in the literature (Sylvers *et al.* 2011). For example, both anxiety and fear are complex responses comprising the coordinated activation of multiple response–systems (Davis & Whalen, 2001). Both represent evolutionary mechanisms that serve a vital protective function in that they increase the individual's capacity to survive or to cope with threat (Hohoff, 2009). Moreover, from an experiential perspective fear and anxiety may appear to differ only in intensity rather than kind; for panic disordered individuals, the distinction between the two emotions may further obscured by the linkage of somatic anxiety and panic attack cues via the process of interoceptive conditioning (Bouton *et al.* 2001).

Yet despite these similarities, converging data from different levels of analysis provide robust support for the conceptualisation of these patterns of defensive responding as qualitatively distinct phenomena. As reviewed, findings from ethological studies, human behavioural studies and aversive conditioning studies support the categorical differentiation of fear and anxiety, and show that fear and anxiety differ in several important respects. For instance, fear and anxiety differ in their eliciting cues and situations; whereas fear represents a response to imminent threat, anxiety is elicited by temporally uncertain danger. Additionally, anxiety and fear differ in their duration – whereas fear is a phasic response, anxiety is a more sustained state of distress (Walker *et al.* 2009). Further, fear and anxiety differentially engage the individual's attention. In fear, attention is focused on the specific threat stimulus (Grillon, 2002), whereas in anxiety the individual's attention is not focussed on any specific aspect of the environment, but is engaged in sustained vigilant scanning of the environment and its potential source/s of threat (Lang *et al.* 2000). For a list of the respective phenomenological properties of fear and anxiety, see Table 4.

Table 4: Phenomenological properties of fear and anxiety

	Fear	***Anxiety***
Eliciting Stimulus	Clearly defined, specific	Uncertain, ambiguous
Response Duration	Phasic	Sustained
Cognitive Focus	Present	Future
Defensive Direction	Avoidance	Avoidance/Approach conflict
Behaviours	Freezing, flight, fight, tonic immobility	Risk assessment

In summary, converging lines of human and non–human research support the categorical differentiation of fear and anxiety. As form shows a tight fit with function in evolved systems, fear and anxiety represent two functionally distinct classes of defensive responding (Tooby & Cosmides, 1990). The following section discusses maladaptive fear and anxiety within an evolutionary perspective.

2.5 Adaptive versus Maladaptive Human Fear and Anxiety

Emotional responses – which involve the coordinated activation of multiple response systems across multiple scales of function (e.g., physiology, cognition, behaviour, affect) (Barlow, 2000; Hoehn–Saric *et al.* 2004; Blanchard & Blanchard, 2008; Hohoff, 2009) – differ substantially between individuals in a given situation (Marwitz & Stemmler, 1998; Wilhelm & Grossman, 2010). For healthy individuals fear and anxiety are normal, adaptive emotional responses that prepare the individual to deal effectively threats, present or future (LeDoux, 1998). For such individuals, the intensity of the response is approximately commensurate with the objective level of existing or potential threat, facilitates the rapid detection of danger in the environment, and prompts an effective behavioural response that minimises harm (Hofmann, 2008). However, for individuals with anxiety disorders, these states are activated by stimuli or situations that are not realistically threatening, and the emotional response is thus maladaptive (Linden, 2008; Friedman & Kreibig, 2010). For anxiety disordered individuals, these emotions are excessive in intensity, frequency and/or duration, or occur in inappropriate situations (LeDoux 1998; Grillon, 2008; Hofmann, 2008). Panic attacks in PD, for instance, are elicited in situations that are not inherently dangerous or harmful, and elicit further, debilitating anxiety despite posing no real threat (Nesse, 1987; Maren, 2007). In other respects,

however, the expression of these defensive states in psychopathology is indistinguishable from normally expressed fear and anxiety, the difference being one of degree, not type (Blanchard & Blanchard, 2008; Linden, 2008). Pathologic fear and anxiety, which represent mismatches between the individual's defensive behaviour and the current environment demands (e.g., the occurrence of a panic attack in the presence of minimal or no objective threat, the persistence of anxiety despite no evidence of actual threat, the avoidance of situations that pose no real objective threat), may therefore be viewed as distortions of the threat imminence continuum (Nesse, 1987; Quinn & Fanselow, 2006). However, as fear and anxiety are evolved defences, it is to be expected that some individuals will occupy the tail ends of a Gaussian distribution, in terms of threat responding (Marks & Nesse, 1994). Moreover, this inter–individual variance is predicted by evolution theory, according to which, quantitative traits that provide a differential advantage in different contexts may be selected (Calvin, 1987; Marks & Nesse, 1994).

Nevertheless, mental illnesses including the anxiety disorders appear to defy natural selection in many respects. Firstly, anxiety disorders typically begin relatively early in life, yet are associated with reduced survival– and reproductive fitness (Uher, 2009). The peak age of onset for PD, for instance, is in the twenties (Kessler *et al.* 2005a) – in other words, early in the reproductive age. Additionally, the anxiety disorders are at least moderately heritable (Kendler *et al.* 2011); genetic epidemiological studies typically report moderate to large heritability estimates for a range of traits associated with proneness to fear and anxiety across development (Stein *et al.* 2008; Lonsdorf *et al.* 2009; Tambs *et al.* 2009; Domschke & Dannlowski, 2010; Domschke *et al.* 2010), and for anxiety disorder phenotypes

(Hettema *et al.* 2001; Mosing *et al.* 2009; Kendler *et al.* 2011). Moreover, anxiety disorders are highly prevalent across cultures (Kessler *et al.* 2004; Michael *et al.* 2007). In particular, the high, cross–cultural prevalence of PD (Weissman *et al.* 1997; Hinton *et al.* 2002) and its sub–diagnostic variants (Kessler *et al.* 2006; Batelaan *et al.* 2007a) point to a broad human vulnerability to these conditions. Further, the symptoms of the disorder (e.g., recurrent panic attacks in the absence of danger, chronic and debilitating anxiety and avoidance) impose a significant burden of dysfunction on the lives of sufferers (Olatunji *et al.* 2007). A challenge for such evolution–based disciplines, therefore, is to account for the persistence within the genome of liability for apparently sub–optimal traits and disorders that may be viewed as maladaptations (Nesse, 2005a).

In order to account for this apparent paradox, evolutionary perspectives consider not only proximate (*i.e.* individual–related) factors in psychopathology – as clearly not all individuals are equally affected by similar exposure to fear or anxiety stimuli – but also ultimate factors, and the interaction of the two (Panksepp, 2006; Gluckman *et al.* 2011). Nesse and others have been identified several major explanatory pathways by which natural selection and related processes make humans vulnerable to disease (*i.e.* ultimate explanations) (Nesse, 1987; Nesse & Williams, 1994; Nesse, 2005b; Nesse & Stearns, 2008; Gluckman *et al.* 2011). Two such pathways are central to evolutionary accounts of human vulnerability to anxiety disorders. These are, firstly, the apparently inappropriate regulation of defence mechanisms that were shaped by natural selection. The second proposed mechanism is a mismatch between the modern human environment and our bodies, which were designed for a very different environment. These two pathways are discussed.

2.5.1 Regulation of Defences

Consideration of the high cross–cultural prevalence of the anxiety disorders, which are associated with substantial suffering and impairment, suggests that fear and anxiety responses are expressed excessively in a significant proportion of humans. However, natural selection should, theoretically, shape defence mechanisms such that their expression is near optimal (Nesse, 2001; 2005b; Eilam *et al.* 2011). Nesse has proposed a theoretical framework that aims to resolve this apparent paradox. In the "smoke detector principle" (Nesse, 2001; 2005b), he applies signal detection theory to weigh the costs associated with false alarms against those associated with failing to defend against actual threats. Compared to the potentially catastrophic consequences of a single failure to respond to an actual threat, false alarm reactions – for instance, flight in the absence of an actual predator – are relatively inexpensive (Nesse, 2005b). According to the smoke detector principle, when defences protect against potentially catastrophic consequences, yet are relatively inexpensive, "selection will tend to shape a regulation mechanism that expresses at the least hint of the presence of the dangerous situation" (Nesse, 1999, p. 899).

The smoke detector principle particularly applies in the regulation of defences against severe threats that are hard to detect reliably (Nesse, 2005b). In the presence of subtle or indirect cues of potential threat, animals engage in risk assessment behaviours, which involve gathering information about potential threat in order to produce an appropriate response (Blanchard *et al.* 2011). In the absence of reliable signals of either danger or safety, the outcome of risk assessment is subjective and idiosyncratic (Eilam *et al.* 2011; Woody & Szechtman, 2011). In such circumstances, threat cues are typically only probabilistic indicators of the presence of threat and so the

expression of defence will deviate from the optimal level (Nesse, 2005b). On the whole, however, it is adaptive for threat detection and response mechanisms to tolerate a high rate of false alarms, and so risk assessment appears to be biased toward threat detection (Woody & Szechtman, 2011). For instance, ethological evidence suggests that vigilance is activated by relatively weak cues (Brown *et al.* 1999), and dissipates relatively slowly, even in the absence of confirmatory cues (Marks & Nesse, 1994). Thus, evolution has shaped threat detection and response mechanisms that may appear excessive or unnecessary in the individual instance, but are nonetheless adaptive overall (Stein & Nesse, 2011).

2.5.2 Environmental Mismatch

An evolutionary view considers that human fear and anxiety responses were well designed to facilitate survival in natural ancestral environments (Nesse, 1987; Tooby & Cosmides, 1990; Panksepp, 2006). Moreover, the high epigenetic prevalence of the anxiety disorders supports the view that these responses were adaptive in the past (Gardner & Wilson, 2004). The 'environment of evolutionary adaptedness' of early mammals, that is, the evolutionarily recurrent survival–relevant challenges which shaped fear and anxiety responses, was replete with danger which could quickly inflict harm, pain or death (Tooby & Cosmides, 1990). Within primitive ancestral environments, the most recurrent, potentially lethal threats encountered were animate (e.g., hunting predators and aggressive conspecifics) (Öhman & Mineka, 2001) and so animate dangers have been most influential in shaping mammalian defensive responses (Tooby & Cosmides, 1990; Blanchard *et al.* 2001a; Otto, 2002).

However, mechanisms that evolved for life in eras past may not be adaptive for the present modern human era (Tooby & Cosmides, 1990; Panksepp, 2006). According to 'environmental mismatch' theory (Glantz & Pearce, 1989), our behavioural, cognitive and affective predispositions are well adapted for the ancestral environment in which we evolved, but not for modern environments. Although it might have been adaptive in previous eras to attend to all potential threats and to interpret all ambiguous events as if threatening, this is no longer the case (Cosmides & Tooby, 2000; Bishop, 2007). In the modern information–saturated world in which we live, we are repeatedly exposed to vaguely menacing information from across the world regarding acts of violence and terrorism, natural disasters, medical threats, and of other cataclysmic events that threaten our selves, our society and our planet (Bishop, 2007). Although modern humans have less exposure than ancestral hominids to fear–eliciting cues (e.g., attack by predators or conspecifics) (Nesse, 2005b), and particularly those to which evolution has shaped our nervous systems to respond to most strongly (Merckelbach *et al.* 1988; Öhman *et al.* 2001; Otto, 2002), the presence of so many uncertain threats suggests that modern humans may be more susceptible to anxiety than our evolutionary forebears (Bishop, 2007). Moreover, as the modern human social environment is substantially more complex than the social environment of evolutionary adaptedness, it is conceivable that some forms of psychopathology arise because individuals are living in social environments that are beyond their evolved capacity to cope (Gluckman *et al.* 2011). Thus according to mismatch theory, although human minds and bodies were presumably were well suited to the ancestral environments which shaped them, they are less suited to certain elements of modern human environments.

2.6 Neural Organisation of Fear and Anxiety

2.6.1 Central Nervous System

Within the human brain, separate but partially overlapping neural networks organise the respective signs and symptoms of fear and anxiety (Walker *et al.* 2003; Graeff & Del–Ben, 2008; Davis *et al.* 2010). In each case, a distributed network of cortical, subcortical and brainstem structures are implicated as substrates for these emotions (Davis & Whalen, 2001; Walker *et al.* 2003). Key structures within these circuits include several regions within the prefrontal cortex (PFC), amygdala, hippocampus, hypothalamus, periaqueductal gray (PAG), and several brainstem nuclei (Cannistraro & Rauch, 2003; Graeff & Del–Ben, 2008). Given the heterogeneous clinical presentation of PD, different components of these networks are expected to be differentially involved in the disorder's different symptoms (e.g., spontaneous and cued panic attacks, anticipatory anxiety and avoidance) (Engel *et al.* 2009; Shin & Liberzon, 2009).

Current understanding of the neurocircuitry underpinning normal and pathological fear and anxiety is largely based on preclinical research findings, although these findings are increasingly being bolstered by research in both healthy and anxiety disordered subjects (Davis *et al.* 2010). Within the preclinical literature, a wide variety of experimental paradigms and research methodologies have been utilised to model fear and anxiety (Blanchard *et al.* 2001a; Hohoff, 2009). Notably, Walker, Davis, and colleagues (Davis, 1998; Walker *et al.* 2003; 2009; Davis *et al.* 2010) have conducted an extensive series of aversive conditioning studies in rodents in which they used startle reflex to index defensive states. Their findings show that phasic fear responses to imminent threat are mediated by the central nucleus of the

amygdala (CA), whereas sustained defensive responses to temporally unpredictable threat are mediated by the bed nucleus of the stria terminalis (BNST) (reviews Walker *et al.* 2009; Davis *et al.* 2010), a structure that is anatomically contiguous with the amygdala (Davis, 1998). The CA and the BNST have a distributed and largely overlapping set of effector targets in brainstem, subcortical and cortical loci which organise the various behavioural and physiological responses that characterise fear and anxiety (Davis & Whalen, 2001; Walker *et al.* 2003).

Common efferent targets of the CA and BNST include: (1) lateral hypothalamus (activates the sympathetic branch of the ANS, and is associated with fear–induced sympathetic changes such as increased sweating, blood pressure and heart rate, and tachycardia); (2) paraventricular nucleus of the hypothalamus (effects neuroendocrine and neuropeptide changes, in particular the release of corticosteroids; predominantly via BNST innervation); (3) parabrachial nucleus (increased respiration rate and dyspnoea); (4) ventral tegmental area, locus coeruleus, dorsal lateral tegmental area, and basal forebrain (increased behavioural and EEG arousal, increased vigilance and attention); (5) dorsal motor nucleus of the vagus (cardiovascular control) (Walker *et al.* 2003), and; (6) the midbrain PAG (active defensive responses to proximal threat) (Graeff *et al.* 1996; Walker *et al.* 2003; Graeff, 2004; Del–Ben & Graeff, 2009; Mobbs *et al.* 2009).

The hippocampus is another important structure in the neural control of normal and pathologic fear and anxiety (McNaughton & Corr, 2004; Ninan & Dunlop, 2005; Graeff & Del–Ben, 2008; Del–Ben & Graeff, 2009). The hippocampus transmits multimodal sensory information to the amygdala concerning the time and place of

aversive events (Fanselow, 2000; Maren, 2005), and animal data show that the hippocampus is essential for the acquisition of context conditioning (LeDoux, 1995). Similarly, human functional neuroimaging studies show that the hippocampus is specifically involved in contextual but not cue conditioning and, moreover, demonstrate a specific role of the right hippocampus in unpredictable aversive experience (Hasler *et al.* 2007; Alvarez *et al.* 2008; Marschner *et al.* 2008; Lang *et al.* 2009). The hippocampus also plays an important role in fear extinction in that it permits the learning of safe *vs.* dangerous contexts (LeDoux, 1998). Hippocampal abnormalities may contribute to pathologic anxiety states via overgeneralisation of fear learning (Cannistraro & Rauch, 2003). Abnormalities of metabolism or blood flow within the hippocampus and parahippocampal regions (and, particularly, the right hemisphere) have, to date, been the most consistent finding of functional neuroimaging studies of PD (reviews Del–Ben & Graeff, 2009; Engel *et al.* 2009).

Multiple prefrontal cortical regions are important components of the neurocircuitry of fear and anxiety. The amygdala shares extensive reciprocal projections with PFC regions including the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) (Kim *et al.* 2011). These pathways allow the PFC to exert top–down governance of fear, anxiety and other emotions (Charney, 2003). For instance, PFC regions exert tonic inhibitory control over the output of the CA (Shekhar *et al.* 2003; Thayer, 2006), modulate amygdala response to salient stimuli (Kent & Rauch, 2003) and mediate fear extinction (Sotres–Bayon *et al.* 2006). Metaphorically speaking, appropriate PFC modulation of subcortical threat circuitry provides the ‘brakes’ that prevent fear and anxiety reactions from being persistent, excessive, or inappropriate (Friedman, 2007). Functional neuroimaging studies show reduced activity in PFC

regions in panic disordered subjects relative to unaffected controls during symptom provocation procedures (review Cannistraro & Rauch, 2003). Prefrontal hypoactivity in the anxiety disorders results in inflexible defensive responding, as reflected in impaired habituation, a failure to recognise safety signals, a pre–attentive bias for threatening information, and negativity bias (Friedman, 2007). Finally, the insular cortex is an important component of the fear and anxiety circuitries that is of relevance to PD, given its prominent role in interoception and therefore anxiety sensitivity (Critchley *et al.* 2004; Paulus & Stein, 2006). Figure 3 shows some of the afferent and efferent pathways that mediate threat detection and response.

2.6.2 Autonomic Nervous System

Fear and anxiety are characterised by a wide range of physiological symptoms that reflect changes within many physiological response systems (Davies *et al.* 2010). For instance, 10 of 13 DSM–IV defined panic attack symptoms (APA, 1994) are somatic in nature, including palpitations, sweating, trembling, nausea and dizziness. These somatic panic symptoms reflect fear–related changes in the cardiovascular, electrodermal, and respiratory systems, amongst others (Wilhelm & Roth, 2001). Similarly, the diagnostic criteria for generalised anxiety disorder (GAD) include many somatic anxiety symptoms, including muscle tension, palpitations, sweating, nausea, and dizziness (Wilhelm & Roth, 2001). Further, meta–analyses of the physiological changes that occur during experimentally–induced fear and anxiety show that these emotions affect measurable change in most physiological response systems (Stemmler, 2004; Kreibig, 2010). These physiological changes are mediated, in large part, by the autonomic nervous system (ANS) (Belzung & Philippot, 2007).

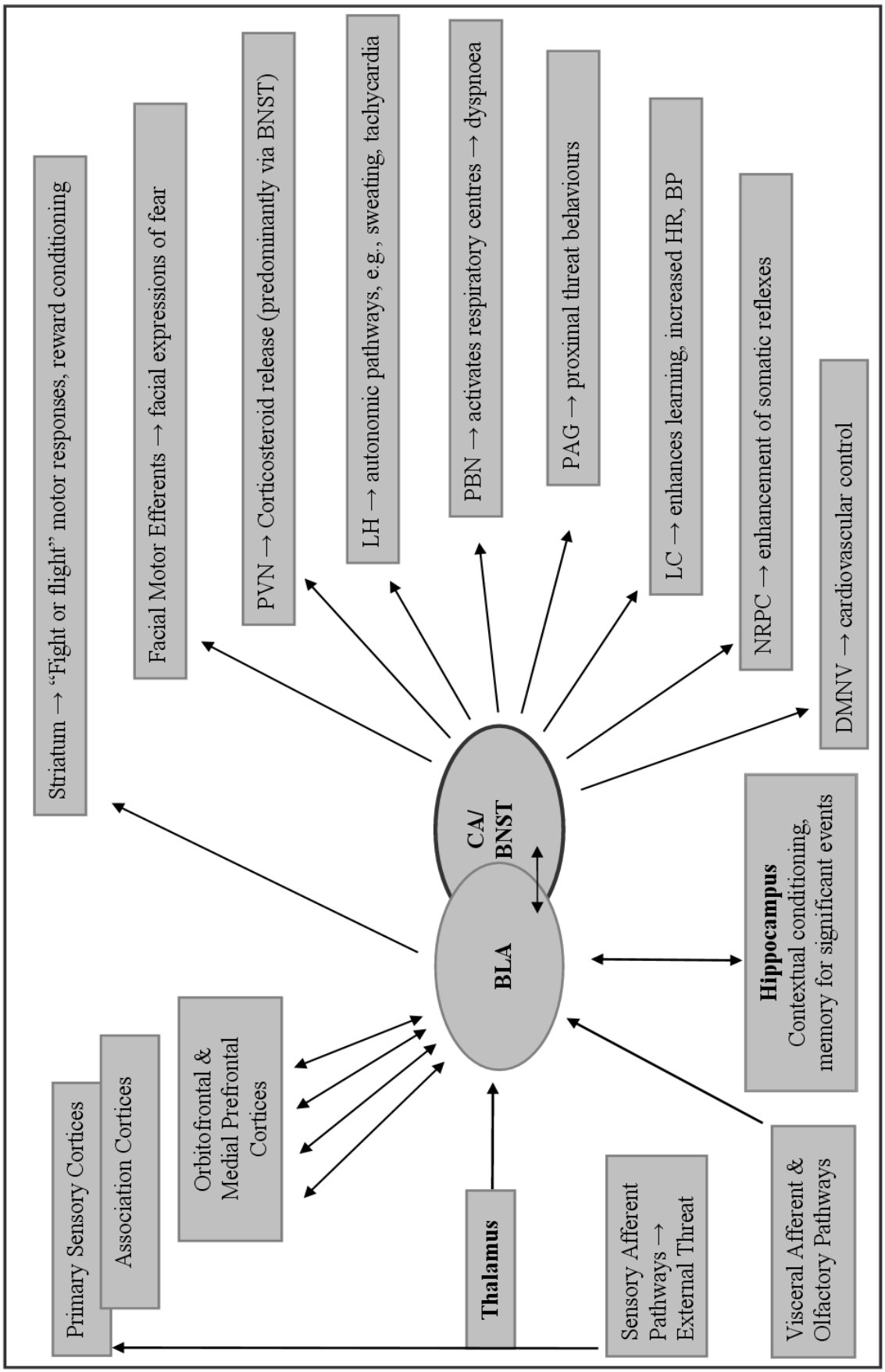

Figure 3: Central nervous system organisation of fear and anxiety (continued over page).

Figure 3: Central nervous system organisation of fear and anxiety. (continued). The central nucleus of amygdala (CA) and bed nucleus of the stria terminalis (BNST) receive projections from the basolateral amygdala (BLA). The CA and BNST, in turn, project to downstream effector targets that mediate the multiple components of fear and anxiety, respectively. PVN, paraventricular nucleus of hypothalamus; LH, lateral hypothalamus; PBN, parabrachial nucleus; PAG, periaqueductal gray; DMNV, dorsal motor nucleus of vagus; NRPC, nucleus reticularis pontis caudalis; LC, locus coeruleus. Figure based on Davis & Whalen (2001), Walker *et al.* (2003) and Ninan & Dunlop (2005).

The ANS is a phylogenetically ancient component of the nervous system (Belzung & Philippot, 2007) which comprises two major anatomic and functional subdivisions, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). In general, the SNS is activated in response to threat and facilitates the expenditure of energy in preparation for action (e.g., fight and flight responses) (Sequeira *et al.* 2008). In contrast, the PNS is involved in restorative functions and the conservation of energy (Porges, 1992). Thus, the two ANS branches serve largely complimentary roles in the maintenance of dynamic organism balance in the face of changing environmental demands (Thayer & Brosschot, 2005). However, in addition to its role in emotional processes, the ANS is involved in fine–tuning the organism's responses whenever stimuli of any functional significance or subjective salience are encountered (Öhman *et al.* 2000). More generally, the ANS mediates a wide variety of functions relating to bodily maintenance, digestion, effort and attention (Berntson & Cacioppo, 2000; Öhman *et al.* 2000).

The ANS has multiple, diverse somatovisceral targets that have specific roles in physiological and behavioural adaptation, including the heart and blood vessels, endocrine and exocrine glands, and sensory systems including the eyes and skin (Sequeira *et al.* 2008). Sympathetic outflow in response to threat induces changes in a range of effector targets, including vasoconstriction in the skin, vasodilation in the skeletal muscles, sweating and the release of adrenaline (Folkow, 2000). These physiological changes provide the organism with the metabolic/energetic resources needed to deal with environmental challenges (Belzung & Philippot, 2007). Although it was originally believed that the SNS operated in an all–or–none fashion on effector targets, it is now understood that pools of sympathetic neurons can be selectively activated, which allows for highly differentiated adjustments of effector targets (Folkow, 2000).

Whereas early accounts of ANS function presume that the system sustained physiologic stability (*i.e.* homeostasis), more recent accounts based on dynamic systems theory emphasise the importance of dynamically responding to changing environmental demands for physiologic health (Friedman, 2007). According to such accounts, when autonomic balance is chronically weighted in a sympathetic direction, adaptive flexibility is reduced (Friedman, 2007). Empirical evidence suggests that PD and other generalised anxiety disorders (*i.e.* GAD, PTSD) are associated with autonomic imbalance in the direction of sympathetic dominance, and diminished variability in physiologic responses (Thayer & Lane, 2000; Hoehn–Saric, 2007; Friedman, 2007). As sympathetic activation is metabolically taxing, chronic sympathetic activation leads to increased morbidity and mortality (Brook & Julius, 2000; Thayer & Lane, 2007).

The ANS is functionally integrated with all levels of the nervous system from the PFC, brainstem, and down to the spinal cord and the peripheral nervous system (Thayer & Lane, 2000; Kreibig, 2010). Within the CNS a distributed network of structures spanning the PFC, limbic, and brainstem regions form a functional network called the central autonomic network (CAN), which organises ANS output (Thayer & Lane, 2000). The components of the CAN are reciprocally connected, allowing information to flow bi–directionally between the lower and higher levels of the network (Thayer, 2007). Similarly, information flows bi–directionally between the CNS and the ANS effector targets, and the outcome of ANS–mediated innervation of effector targets, in addition to sensory information, continuously feeds back to the brain and regulates activity at all levels of the neuroaxis (Berntson *et al.* 2003; Thayer *et al.* 2009). This reciprocal connectivity allows the CAN to generate, receive and integrate information from the internal and external environment in support of goal–directed behaviour and adaptability (Thayer & Lane, 2000), and provides a crucial interface between the brain and the rest of the body (Niedenthal, 2007).

Despite over a century of debate and psychophysiological research there remains at present a lack of consensus regarding the exact role of the ANS in emotion (Stemmler, 2004). Over a century ago, William James controversially proposed that emotions are nothing more than sets of bodily changes that occur in response to emotive stimuli, and that it is the perception of those changes that evokes the feelings of an emotion (reviews Dalgleish, 2004; Friedman, 2010). James was a progenitor of the functionalist school of psychology, which is strongly guided by Darwinian principles (Friedman, 2010), and his ideas, which emphasise the embodiment of emotion, remain influential today (Dalgleish, 2004).

From an evolutionary perspective, the many ANS–mediated physiological changes that occur during fear and anxiety, for instance, represent responses that have been selected by evolution because they offered an increased survival/reproductive advantage in ancestral environments (Tooby & Cosmides, 1990). As form follows function in evolved systems, fear and anxiety, as two functionally distinct classes of defensive responding ought to differ in their peripheral physiological manifestations (Tooby & Cosmides, 1990). Thus, a corollary of James's theory is that different emotions ought to be associated with discrete somatic response patterns if they are to be differentiated (Friedman, 2010). However, empirical findings are yet to resolve whether different emotions have unique physiological signatures (Belzung & Philippot, 2007). A meta–analysis of emotion induction studies found only inconsistent evidence for autonomic specificity of emotions (including, but not limited to fear and anxiety) (Cacioppo *et al.* 2000a). One potential confound in these studies, given that ANS measures vary according to threat imminence (Lang *et al.* 1997), is that different forms of fear corresponding to different degrees of threat imminence were not differentiated. Additionally, joint consideration of multiple ANS measures may better support autonomic specificity of emotions, because different ANS measures typically correlate poorly (Mauss *et al.* 2005) and differ in their ability to discriminate different emotions (Blechert *et al.* 2007a). In line, a more recent review of 134 studies, some of which included a comprehensive array of physiological measures, found greater support for autonomic specificity (Kreibig, 2010). This review found that, independently of experimental paradigm, anxiety has almost unanimously been characterised by both sympathetic activation and parasympathetic deactivation, whereas the findings for fear point to broad sympathetic activation across multiple response systems.

2.7 Summary of Chapter

Chapter 2 discussed human fear, anxiety, and threat detection mechanisms from a broad evolutionary perspective. According to evolutionary accounts, these defence–related capacities have been selected and conserved by evolution because they confer a fitness advantage (Cosmides & Tooby, 2000; Öhman *et al.* 2000; Blanchard & Blanchard, 2008). Moreover, these evolved mechanisms are posited to underpin both normal and pathologic fear and anxiety (Nesse, 2005b; 2011). The distinction within evolution–based disciplines (*i.e.* evolutionary medicine, psychology and psychiatry) between ultimate and proximate explanations of a given trait or disorder was discussed. Whereas proximate explanations concern individual differences in disease liability, ultimate explanations concern the ways in which all members of a species share a vulnerability to a given disease (Nesse, 1999). In particular, two ultimate level explanations, which are proposed to account for our species' vulnerability to the anxiety disorders, were discussed. These were, firstly, the regulation of defences that were shaped by natural selection and apparently err on the side of caution (Nesse & Williams, 1994; Nesse, 2005b), and secondly, a mismatch between modern human environments, and our minds and bodies, which evolved to suit very different ancestral environments (Glantz & Pearce, 1989; Nesse & Williams, 1994; Nesse & Stearns, 2008). These ultimate–level explanations, when coupled with complementary insights from proximate levels of analysis, are viewed as essential for a comprehensive, integrative account of the anxiety disorders (Stein & Nesse, 2011).

The research conducted for this thesis, which constitutes the balance of this thesis, represents a proximate approach in that it aimed to identify differences between panic disordered and healthy matched control subjects.

Notes

1. Although Nesse and colleagues (e.g., Nesse & Williams, 1994; Nesse, 1999; 2011) uses the term 'evolutionary' in lieu of 'ultimate' explanations, the term 'ultimate' will be used herein to avoid confusion.

2. Although the terms 'defence' and 'defensive responses' apply to many organismic regulatory systems (Nesse, 2001), their use in this thesis is restricted to inducible responses to particular forms of potential threats.

Chapter 3

Research Background

3.1 Overview of Chapter

This thesis presents an integrative assessment of brain, body and cognitive function in panic disorder during the inter–panic interval. This research is presented as three separate studies: Study 1, Brain and Body Function 'at Rest' (Chapter 6); Study 2, Sensory Information Processing (Chapter 7), and; Study 3, Cognitive Function (Chapter 8). The empirical and conceptual background information of specific pertinence to each appears in the appropriate chapter. The present chapter, by contrast, discusses the present research and its empirical and conceptual context in necessarily broad terms.

The chapter begins by characterising, in general terms, the extant PD literatures. Specific findings from these literatures are not discussed in the present chapter. Those findings pertinent to the present series of studies are presented, as appropriate, in Chapters 6 – 8. Instead, the present chapter focuses on the limitations of extant PD investigations. This is followed by a brief introduction to the present research. The next major chapter section explicates the rationale for the present research, with reference to five key research features. Firstly, the rationale for a between–subjects design comparing clinical and healthy control participants, and the potential utility of findings of patient–control differences, are discussed. Secondly, a case is made for studying the tonic (*i.e.* inter–

panic) as opposed to the phasic (*i.e.* panic) manifestation of PD and, thirdly, for comparing panic disordered and healthy control participants in *weak situations*, that is, those situations with attributes conducive to evincing patient–control differences (Lissek *et al.* 2006). Weak situations, for the purpose of comparing individuals with differential threat reactivity, are defined by the presence of threat–related ambiguity or uncertainty (Lissek *et al.* 2006). Fourthly, the rationale for issues of sample selection (e.g., inclusion of patients with comorbidity) and subject numbers are discussed, followed by a discussion of the benefits of a relatively integrative research approach. The present research represents a novel approach to the study of PD, in that the research approach to date comprises a diverse array of studies that lack integration of multiple types of data.

3.2 The Extant Literatures

Extant, laboratory–based investigations of PD encompass a wide variety of research methodologies, experimental paradigms, outcome measures and theoretical rationales. In the aggregate, these various research approaches aim to identify how individuals with PD differ from healthy control subjects across one or more levels of function (e.g., central or peripheral physiology, behaviour, cognition, affect). The extant literatures of PD also include many psychophysiological and neuropsychological studies, including those that have employed similar testing paradigms to the present and are thus of obvious relevance to the present investigation. For example, the electrophysiological literature includes quantitative electroencephalography (QEEG) studies of brain function at rest (e.g., Newman *et al.* 1992; Knott *et al.* 1996; Dractu & Bond, 1998; Gordeev, 2008), and event–related potential (ERP) studies of the brain's response to non–threatening sensory stimulation in PD (e.g., Knott et al., 1991; Clark et al., 1996; Iwanami et al., 1997; Hanatani et al., 2005; Gordeev *et al.* 2006). Further, autonomic function in PD has been

investigated extensively (e.g., Hoehn–Saric *et al.* 1991; Cohen *et al.* 2000; Wilhelm *et al.* 2001; Blechert *et al.* 2007b). By contrast, a relatively small literature has investigated neuropsychological function in PD, using threat–neutral stimuli, as per the present research. Yet, although these literatures have yielded many important findings, these literatures to date are largely separate and lack interoperability. Moreover, several features of these literatures render many of their findings of indeterminate reliability and generality, and preclude attempts to link disparate research findings, both within and between these literatures.

A primary limitation of the extant literatures is their relative lack of data integration. Typically, the focus of these studies (each comprising unique patient samples) has been a restrictive set of levels of function. For example, only one published paper appears to have obtained psychophysiological and neuropsychological data from a common study sample (Dractu & Bond, 1998). Furthermore, within any given level of function few channels have been recorded. For example, psychophysiological investigations of PD have typically obtained measures of *either* central *or* peripheral function from a given study sample. A further methodological flaw of many of these literatures, especially the psychophysiology literatures, is the introduction of potential study confounds via the use of small subject samples. The problem with small datasets is that small *N*s preclude the possibility of quantifying the contribution of individual difference variables to outcome measures, such that the inter–subject variability, inherent in any measure of brain function, physiology or behaviour (Gordon *et al.* 2005), contributes unpredictably to the data. For example, distinctive patterns of brain function that were attributed to clinical status (*i.e.* PD diagnosis) have been based upon the contribution of as few as two outliers (e.g., Wang *et al.* 2003).

The aforementioned problems of minimal data integration and small *N*s are further exacerbated by the significant clinical heterogeneity within the panic disordered population. Clinical variability within PD is related to factors such as medication usage, and the extent of agoraphobic avoidance, comorbidity, functional impairment, panic frequency and depressive symptoms. However, significant between–studies clinical variance, in conjunction with the use of non–overlapping patient samples, thwarts attempts to directly compare results from separate studies. Furthermore, clinical data have not always been clearly reported, or their effects on the outcome measures of interest adequately addressed, yielding results of indeterminate generality. Some studies have aimed to reduce within–sample clinical variance by excluding patients with comorbid conditions. However, given the significant comorbidity typically observed in both community and clinical samples of PD patients (e.g., Kaufman & Charney, 2000; Brown *et al.* 2001a; Rodriguez *et al.* 2004), the selection of such 'pure' diagnostic groups will produce findings that do not generalize broadly within the panic disordered population (Charney, 2000; Kaufman & Charney, 2000). Further, as PD severity is typically greater within clinical compared to community settings (Rodriguez *et al.* 2004), the recruitment of clinical samples of convenience (*e.g.*, patients recruited exclusively via clinical practice or advertisement) may yield findings of limited generality (Rapaport *et al.* 1996).

Overall, the PD research approach to date comprises a disparate array of studies that lack an integration of diverse types of data, each utilizing different types of measures, testing paradigms, testing protocols, equipment, technical procedures, and methods of data analysis. The substantial clinical heterogeneity which is a characteristic of the disorder contributes further to inter– and intra–study variability. Importantly, unique – and typically small – study samples were used in different studies. Additionally, contextual

factors may represent a source of uncontrolled and unmeasured between–study variance in PD research (Dager, 2010). Taken together, the characteristics of the extant PD literatures preclude the generation of a coherent, integrative picture of inter–panic functioning in PD.

The present research aimed to overcome the identified limitations of the extant PD literatures whilst comparing panic disordered and healthy control subjects within a relatively integrative, multi–level assessment.

3.3 The Present Research

The present research entailed an integrative, laboratory–based assessment of panic disordered individuals (*n* = 53) and healthy matched–control subjects (*n* =106). The assessment encompassed multiple indices spanning multiple levels of function (e.g., central and peripheral physiology, behaviour, affect, cognition) and comprised a psychophysiological and a neuropsychological test battery, in addition to an extensive questionnaire battery. These were completed in an identical manner by patients and controls. Additionally, clinical data were obtained for panic disordered participants via questionnaires and structured interview.

Five key features of the present research may be delineated. The next major chapter section explicates the rationale for each of these research features, in turn. They are: 1) between–subjects design; 2) focus on tonic (*i.e.* inter–panic interval) as opposed to phasic (*i.e.* panic attack) PD; 3) comparison of PD and healthy controls in a weak situation; 4) subject selection and subject numbers, and 5); data integration.

3.4 Research Rationale

3.4.1 Between–Subjects Design

The present research, in common with the majority of clinical research (Nesse, 1999), is of between–subjects design. Primarily, analyses compared panic disordered patients and healthy matched controls. Given that data for patients and controls were collected at one time point, the present research – again, as per the majority of clinical research (Kraemer *et al.* 2000) – is cross–sectional. The common goal of between–subjects, cross–sectional clinical research, including the present, is to identify patient–control differences across one or more levels of function (e.g., central or peripheral physiology, behaviour, cognition, affect). Such patient–control differences are called 'disorder correlates', a term which encompasses a broad typology of factors which may or may not play a role in the disorder's aetiology (Kraemer *et al.* 1997; 2001). Another term that is sometimes used interchangeably with 'disorder correlate', and will be used as such herein, is '*disorder marker*' (e.g., biological or clinical marker) (e.g., Papakostas & Fava, 2008).

An important goal of clinical research is to distinguish different types of disorder markers, because the different types may differentially benefit clinical practice and research (Zvolensky *et al.* 2006c). For instance, as PD aetiology is poorly understood, yet believed to involve complex interactions of multiple factors (Klauke *et al.* 2010; Schumacher *et al.* 2011), the identification of multi–level causal risk factors and their interactions is an important goal in PD research (Zvolensky *et al.* 2005c; Clark & Beck, 2010). Increased knowledge of aetiological processes in PD may inform prevention programs (Zvolensky *et al.* 2006c), and facilitate development of novel diagnostic and treatment strategies (Glahn *et al.* 2007). Markers that are amenable to an intervention (*malleable* markers) may be the target of such treatments (Zvolensky *et al.* 2006c).

Similarly, *maintenance factors* (*i.e.* factors that predict persistence versus remission of the disorder over time; Stice *et al.* 2002) which are malleable are ideal targets for treatment interventions. Additionally, an array of multi–level markers including biological markers (biomarkers) and neuropsychological markers could potentially be utilized to predict how an individual with PD will respond to a given treatment and may ultimately inform treatment choice (Kraemer *et al.* 2006), whereas state–dependent markers may provide objective indices for monitoring treatment progress (Kraemer *et al.* 1994; Malhi & Lagopolous, 2008). Such indices are particularly needed to optimise treatment outcomes for individuals with treatment refractory PD (Diemer *et al.* 2010).

Intermediate phenotypes are one type of risk factor that has received much attention of late. Intermediate phenotypes are heritable and stable quantitative risk factors (Gould & Gottesman, 2006). The identification of intermediate phenotypes from among other disorder markers is an important goal for clinical research with many potential applications, such as to aid in classification, treatment, and the development of valid pre–clinical models (Gould & Gottesman, 2006; Panksepp, 2006). Intermediate phenotypes, being aetiologically 'downstream' of traits and 'upstream' of genes, are envisioned to involve fewer genes than complex psychiatric phenotypes (Gottesman & Gould, 2003). Larger effect sizes for intermediate phenotypes (e.g., neurophysiological, cognitive, neuropsychological) relative to behavioural phenotypes are expected, given their proximity to the consequences of genes (Green *et al.* 2008). In particular, as the brain is the obligatory genotype–behaviour intermediary, still larger effect sizes are expected for brain–based relative to behaviour–based intermediate phenotypes (Hamer, 2002). Additionally, as unaffected individuals may carry 'at–risk' polymorphisms, intermediate phenotypes may provide critical information about factors that either increase or decrease

risk for illness (Glahn *et al.* 2007). For these reasons the identification of intermediate phenotypes may simplify the task of clarifying the genetic basis of a complex phenotype, and assaying genome–to–phenotype aetiological pathways (Gould & Gottesman, 2006).

In sum, the identification of multi–level disorder markers may increase understanding of PD aetiology and pathophysiology, and has many potential clinical and research applications. However, it should be noted that cross–sectional research may not empirically demonstrate temporal and causal relationships, malleability, or disentangle state/trait aspects: these may be demonstrated by appropriately–designed research, or may be inferred where strong supporting evidence exists (Kraemer *et al.* 2001). Nevertheless, the identification of PD markers is an important step which may generate testable hypotheses, spur further research and ultimately benefit clinical practice and research (Zvolensky *et al.* 2006c).

3.4.2 Study of Panic Disorder in the Inter–Panic versus Panic State

In PD research, a broad distinction exists between studies of the tonic (*i.e.* inter–panic interval) versus phasic (*i.e.* panic attack) aspects of the disorder. A further distinction exists between studies of naturally–occurring and experimentally–provoked panic. The latter, in particular, is a fertile research area. Such studies have used chemical compounds with disparate mechanisms of action (e.g., sodium lactate, caffeine) and non–pharmacological procedures (e.g., CO_2 inhalation, voluntary hyperventilation) to induce physiological sensations, which trigger panic or anxiety reactions in susceptible individuals, notably individuals with, or at risk of PD (*i.e.* high anxiety sensitivity or a family history of PD) (Gorman *et al.* 1994; Charney, 2003; Gorman *et al.* 2004; Esquivel *et al.* 2008). By contrast, such procedures tend to be minimally anxiogenic for healthy

controls. Findings of abnormal psychological, biological or behavioural responses in panic susceptible individuals have informed cognitive–behavioural and biological models of PD (Roy–Byrne *et al.* 2006). Nevertheless, there are several advantages of studying PD during the inter–panic interval, as opposed to during panic attacks.

Firstly, naturally–occurring as opposed to experimentally–induced panic attacks in PD are relatively infrequent (Uhlenhuth *et al.* 2006) and unpredictable occurrences (Barlow, 2000; Bouton *et al.* 2001), making their investigation in the laboratory impractical (Goetz *et al.* 1993; Wilhelm & Roth, 2001; Wilhelm *et al.* 2001). Outside of the laboratory, however, some data may be obtained. The symptoms and antecedents of naturally–occurring panic episodes, for example, may be probed with either retrospective questionnaire measures or longitudinally with symptom diaries (Rapee *et al.* 1990; Mauss & Robinson, 2009). However, even for psychophysiological measures amenable to ambulatory monitor studies, it is impractical to undertake prolonged investigations extending across multiple panic episodes, and so only limited data may be obtained regarding naturally–occurring panic attacks (Wilhelm & Grossman, 2010).

Other concerns relate to experimentally–induced panic attacks, namely: (*i*) panic attacks are highly aversive experiences (McNally & Lukach, 1992; Bouton *et al.* 2001), the presence of which strongly predicts a range of psychopathologic conditions (Goodwin *et al.* 2004; Wittchen *et al.* 2008; Craske *et al.* 2010) and adverse outcomes (Goodwin & Hamilton, 2001; Bittner *et al.* 2004; Goodwin & Roy–Byrne, 2006; Kessler *et al.* 2006; Batelaan *et al.* 2007a), and so there are ethical objections (e.g. reducing distress, minimise harm) to their experimental induction (Linden, 2008), particularly in those at risk for panic but without a prior history of panic; (*ii*) the recruitment of anxiety

disordered patients for the study of such invasive and aversive procedures may result in sampling bias, and thereby generate findings which do not generalise across the spectrum of disorder severity, and; (*iii*) although experimentally–induced and naturally–occurring panic attacks are similar in terms of symptom profile (Schruers *et al.* 2004), their physiological covariance remains to be specified (Siepmann & Joraschky, 2007).

Despite the aforementioned concerns and impracticalities, research has typically focused on phasic as opposed to tonic PD (Grillon *et al.* 2008). Arguably, a bias exists because panic attacks are the eponymous feature of the disorder, and are the focus of inter–panic anticipatory anxiety. Nevertheless, the relative neglect of the inter–panic interval as a research focus is surprising as the inter–panic interval temporally represents the majority of panic disorder's course and is of intrinsic research interest. For instance, anticipatory anxiety is central to the differential diagnosis of PD: it is not the presence of panic attacks per se, but the development of sustained inter–panic anxiety which defines PD onset and continuance (Barlow *et al.* 1994; Craske *et al.* 2010). Moreover, various studies of 'baseline' function have demonstrated multi–level functional disturbances in PD during the inter–panic interval (reviews Lissek *et al.* 2005; Friedman, 2007; Hoehn–Saric, 2007; Grillon, 2002; 2008; Craske *et al.* 2009).

For the above reasons the present study focused on PD in the between–panic interval, although patients monitored their naturally–occurring panic attacks over a prolonged interval, so as to incorporate information about the disorder's phasic aspect. The next section discusses the rationale for comparing PD and control subjects in 'weak situations', that is, those contexts most conducive to eliciting patient–control differences (Lissek *et al* 2006).

3.3.3 The Strong/Weak Situation Distinction

As discussed, a common goal of much PD research, including the present, is to identify patient–control differences across one or more levels of function. In particular, given that PD symptoms represent threat imminence distortions (Blanchard & Blanchard, 2008), much experimental research has aimed to identify patient–control differences in reactivity to threatening procedures and stimuli that vary in their degree of aversiveness, imminence, ambiguity, and disorder–specificity (Lissek *et al* 2006). Increasingly, however, PD research has sought to identify patient–control differences during various 'baseline' states, and to systematically address the effects of the laboratory environment itself on baseline function (Dager, 2010). Overall, empirical findings show that threat imminence distortions in PD occur in a non–uniform, stimulus– and context–specific manner (reviews Friedman, 2007; Hoehn–Saric, 2007; Grillon, 2008; Craske *et al.* 2009).

The 'strong/weak situation' distinction (Lissek *et al.* 2006) is a theoretical framework which may account for this non–uniformity. It also provides a platform for designing PD research most conducive to eliciting patient–control differences. In their formulation, Lissek and colleagues distinguish between so–called '*strong situations'* and '*weak situations*', which attenuate and amplify the effect of individual differences, respectively. A *strong situation* is defined as a situation that provides "unambiguous stimuli that reliably predict or constitute hedonically salient events", and which "generally yield uniform reactions, expectancies, and response sets across individuals" (Lissek *et al.* p. 265). Strong situations are optimal when the effects of an experimental manipulation are paramount and individual differences represent a source of noise. *Weak situations*, by contrast, constitute less–defined events in which the situation or "experimental stimuli offer less predictive information and/or cue hedonic events of lower salience or

imminence" (Lissek *et al.* p. 265). In such situations, absent of reliable situational information, individual biases relating to prior expectations and personal beliefs emerge. In terms of threat situations and threat reactivity, strong situations are characterized by the presence of an unambiguous threat (*i.e.* fear) cue. Weak situations, by contrast, are characterized by the presence of ambiguous, potential or less predictable threat and are potentially anxiogenic. According to Lissek *et al.*, studies of defensive responding in threatening situations varying in aversiveness, imminence, and ambiguity show that strong situations evoke indistinguishable responses in those with and without anxiety disorders. However, by *weakening* the situation, that is, by reducing the salience or increasing the unpredictability of the situation, differential patient–control defensive responses may emerge due to increased reliance on idiosyncratic (*i.e.* biased) interpretations of uncertain/ambiguous events (see Figure 4).

In accordance with the above–described definition of a weak situation, the present studies used relatively low–threat, low–salience paradigms and procedures in order to increase the power to detect patient–control differences. Notably, the study did not involve deliberate manipulation of study participants' level of anxiety, fear or other emotions. Nor did the study investigate the processing of panic–related or otherwise emotional stimuli. Rather, measures of brain, body and cognitive function were obtained within normatively low–threat paradigms: sitting quietly in the laboratory 'at rest' (Study 1); processing simple, non–threatening sensory information (Study 2), and; performing cognitive tests comprising non–threatening stimuli (Study 3).

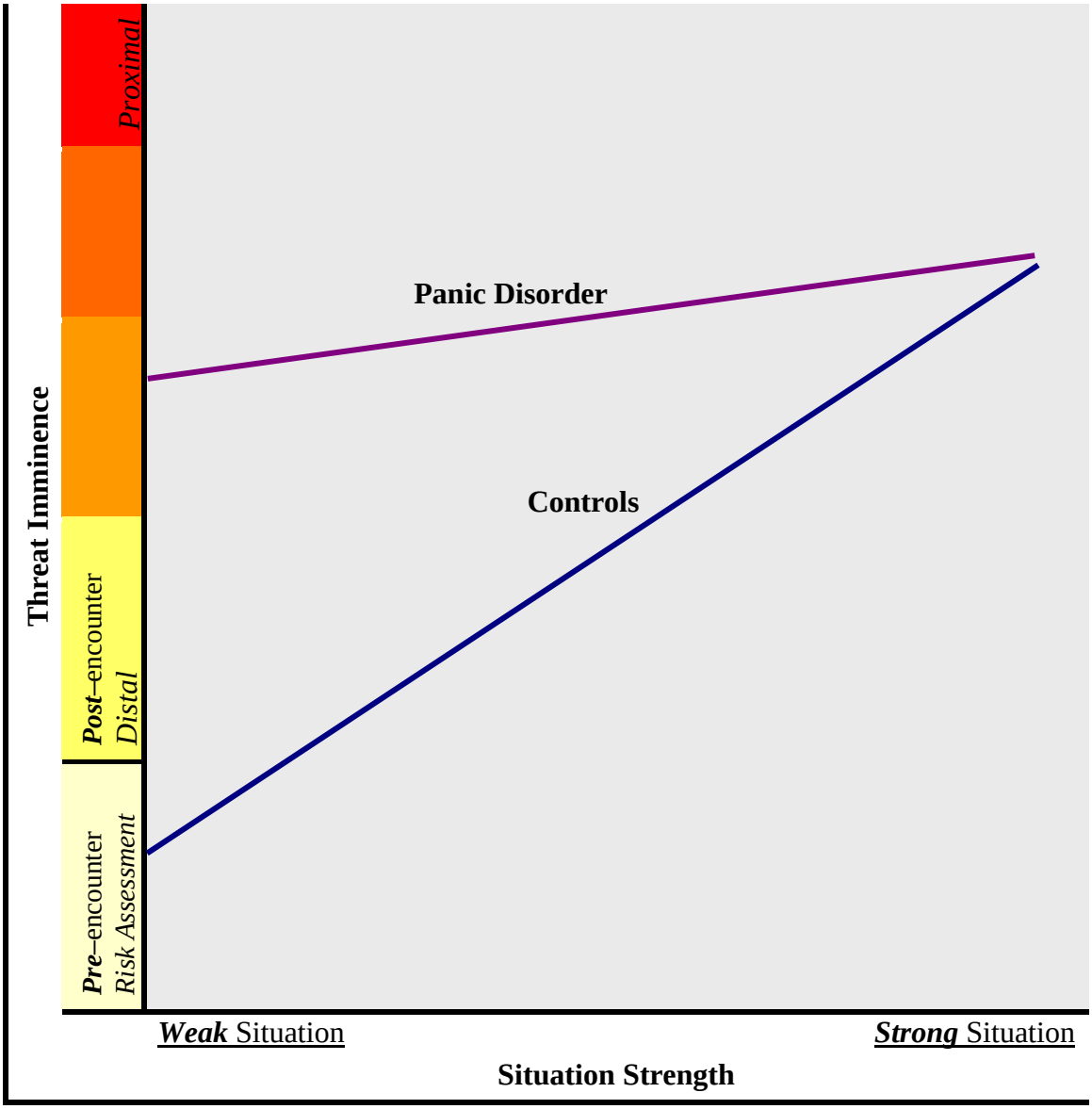

Figure 4: Hypothesised relationship between situation strength (Lissek et al. 2006) and threat imminence (Quinn & Fanselow, 2006) for PD and controls. Figure shows the two groups' respective responses to normatively low–threat *i.e. weak* situation (left). In weak situations, the two groups will show differential levels of perceived threat. Figure shows the two groups' respective responses to normatively high–threat *i.e. strong* situation (right). In strong situations, patients and controls will show near–identical responses, irrespective of threat imminence.

3.4.4 Subject Selection and Numbers

Clinical subjects were selected with view to being representative of the panic disordered population. In particular, given the high comorbidity of anxiety and mood disorders with PD (Kessler *et al.* 2006), individuals with these comorbidities were included. Additionally, patients were recruited from a variety of community and clinical sources (see 4.2.1.2 Recruitment of Clinical Participants) to minimize sample selection biases. The relatively large research samples will both increase the robustness of research findings (*i.e.* reduce the likelihood of Type I error), and increase the power of statistical analyses to detect patient–control differences (*i.e.* reduce the likelihood of Type II error). Additionally, the use of relatively large samples minimises such inter–subject variability unrelated to diagnosis (Pivik *et al.* 1993; Gordon *et al.* 2005). Moreover, the size of the clinical sample will permit within–group analyses of the clinical correlates of these differences. These analyses may help resolve some of the inconsistencies in the PD psychophysiological and neuropsychological literatures, as relate to clinical heterogeneity.

3.4.5 Data Integration

Extant PD research, as discussed, has yielded a vast array of separate findings that are rendered non–interoperable due to inter–study methodological differences. Many types of inter–study methodological differences (e.g., paradigm details, instructions, hardware, software, data analyses) may introduce an array of potential confounds, even across otherwise similar studies (Gordon *et al.* 2007). The use of separate study samples further limits attempts to pool separate findings.

The present research, by contrast, represents a relatively integrative approach to PD in that a common study sample completed a range of paradigms, and measures were obtained from multiple levels of function. The paradigms encompassed by the present research were selected to broadly tap core brain, body and cognitive functions (Gordon *et al.* 2005). Thus, psychophysiological tasks provided brain and body measures reflecting baseline function at rest (Study 1), and of the capacity to attend to relevant information, whilst ignoring irrelevant information (Study 2). Similarly, the neuropsychological test battery administered for Study 3 broadly spans five core cognitive domains of function (*i.e.* attention, working memory, language, executive function) (Paul *et al.* 2005). Overall, the present research integrated data from different states (e.g., resting state and task performance), levels of function (e.g., CNS, ANS, behaviour, cognition, and affect), and response systems (e.g. cardiovascular and electrodermal systems). Additionally, within any given response system, multiple measures were obtained. For instance, multiple electrodermal measures were obtained concurrently during Studies 1 and 2.

The potential benefits of an integrative approach to the study of PD are manifold. Firstly, the use of a common study sample and standardized data collection procedures eliminates many potential confounds (Gordon *et al.* 2007). These potential confounds relate to between–study methodological differences, uncontrolled contextual variables, and sample–related characteristics associated with both normal and clinical variance. Secondly, although brain, body and cognitive function are typically studied in isolation, they are functionally interdependent (Gordon *et al.* 2008; Critchley, 2009). For instance, body feedback to the brain is considered crucial for the affective component of emotions (Friedman, 2010), for regulating emotional and attentional processes (Thayer & Lane, 2009), and for 'higher' cognitive functions (Damasio, 1996; Bechara *et al.* 1999).

Therefore, somatic psychophysiological measures may complement CNS measures of a wide range of processes including emotion, attention, and decision–making (Öhman *et al.* 2000). However, only concurrent assessment of multiple levels of function can reveal these relationships (Cacioppo *et al.* 2000b; Berntson *et al.* 2007). Thirdly, many measures of brain and body function obtained during a baseline state (*i.e.* 'at rest') reflect the preparedness of the brain and body for subsequent information processing demands. Notably, individual differences in certain quantitative electroencephalography (QEEG) (Klimesch, 1999) and cardiovascular measures (Thayer *et al.* 2009) obtained at rest predict subsequent cognitive performance. However, these within–subject relationships may only be investigated within studies that incorporate both baseline and active task conditions.

A fourth benefit of data integration is that different measures typically correlate poorly in psychophysiological research (Fahrenberg & Foerster, 1982; Blechert *et al.* 2007a). Notably, correlations between subjective (self–report) and objective (physiologic) indices in anxiety disordered subjects states are frequently low (Mauss *et al.* 2005). Additionally, different measures of ANS activity can change independently or in opposition to each other, even within the same response system (Mataix–Cols & Phillips, 2007; Mauss & Robinson, 2009). For instance, non–covariance of cardiovascular and electrodermal indices, and of different electrodermal measures, has been reported in the PD (e.g., Hoehn–Saric *et al.* 1991; Cuthbert *et al.* 2003; Parente *et al.* 2005; Blechert *et al.* 2007b). Such observations highlight the importance of obtaining multiple measures, even within a single response system. Finally, by obtaining multiple psychophysiological and neuropsychological indices from the same subjects the relative utility of each in differentiating patients and controls may be determined (Falconer *et al.* 2008).

3.5 Summary of Chapter

The present chapter discussed the research conducted for this thesis in broad terms. Limitations that characterise the extant PD literature and strategies to be adopted by the present research for overcoming these limitations were discussed. Additionally, the discussion centred on explicating the rationale for several key research features. Whereas discussion of the present research thus far has been relatively general, the remainder of the thesis details the research. The next chapter (Chapter 4) describes the research methodology in detail.

Chapter 4

Overall Methodology

4.1 Overview of Chapter

This chapter describes the overarching methodology of the research conducted for this thesis. As this research is presented as three separate studies in later chapters (Chapters 6 – 8), and each of those chapters incorporates a Method section describing aspects of the research methodology of specific relevance to that study (e.g. data collection procedures, stimulus materials, statistical analyses), this chapter's description of the methodology is necessarily restricted to those elements that are common to all three studies.

The chapter begins with a description of the respective study criteria applied to clinical and control participants, and the methods of their recruitment. This is followed by a description of the overall data collection procedure, which comprised the following three components: (1) web–based questionnaires; (2) laboratory assessment, and; (3) clinical assessment. The latter component was undertaken only by clinical participants.

Next, stimulus materials of common relevance to each study are discussed. These materials include demographic measures and measures of patients' clinical severity. Finally, a description of the data cleaning and statistical analysis methodology that was applied across all three studies completes the chapter.

4.2 Participants

The study comprised two groups of participants, a clinical group of 53 patients with a positive diagnosis of current panic disorder, and 106 healthy control participants. Some 71.7% of each study sample were female (PD, n = 38; controls, n = 76). Control participants were matched to individual clinical participants as closely as possible for age, handedness and years of education. The inclusion of the larger control sample increased the statistical power of between–group analyses, and thereby diminished the likelihood of Type II error. All study participants were paid honoraria of $100 to reimburse them for travel costs and inconvenience.

4.2.1 Clinical Participants

4.2.1.1 Inclusion and Exclusion Criteria for Clinical Participants

The main inclusion criterion for clinical participants was a positive diagnosis of PD, with or without agoraphobia, according to the diagnostic criteria of DSM–IV (APA, 1994). Patients meeting criteria for other anxiety disorders and/or unipolar mood disorders, if secondary to PD, were included in the study. Further inclusion criteria were the presence of normal vision, hearing and dexterity, and speaking English as a first language. Patients who were using antidepressant medication, such as SSRIs and SRNIs were included in the study. Patients with ongoing use of other psychoactive medications including benzodiazepines were excluded.[1] Other exclusion criteria for clinical participants included: a personal or immediate family history of attention deficit hyperactivity disorder, bipolar disorders or schizophrenia, and; a personal history of neurological disorder, physical brain injury, serious medical problems (e.g., heart disease, thyroid disease, cancer, HIV), substance abuse or dependence. For the full list of selection criteria for clinical participants, see Appendix A.

4.2.1.2 Recruitment of Clinical Participants

Clinical participants were recruited from a range of clinical and community sources. Clinical sources included referrals from two outpatient anxiety clinics in Adelaide (Centre for Anxiety and Related Disorders, Centre for the Treatment of Anxiety and Depression). Another clinical source of participants was via referrals from psychiatrists, clinical psychologists and general practitioners in private practice. Additionally, a number of participants were recruited via notices placed on the noticeboards of hospitals, medical centres and anxiety clinics. Community sources included respondents to a local newspaper article about the study, and those who responded to notices placed on university and shopping centre noticeboards. Prospective clinical participants were sent a brief information sheet (Appendix B).

Clinical participants in current treatment for PD obtained a written referral from their treating clinician (*i.e.* psychiatrist, psychologist or general practitioner) indicating a primary diagnosis of PD. For the purpose of this referral, a primary diagnosis was defined as the disorder that was judged to interfere the most with the patient's overall functioning and/or that prompted the patient to seek treatment. All clinical participants, irrespective of referral status, were screened to confirm a positive, current diagnosis of PD with MINI International Neuropsychiatric Interview 5.0.0: Panic Disorder module, which is a short structured diagnostic interview (Sheehan *et al.* 2006). The diagnosis of PD was further verified upon administration of the Composite International Diagnostic Interview (CIDI–Auto 2.1) (World Health Organization, 1997) during the clinical assessment.

4.2.2 Control Participants

4.2.2.1 Inclusion and Exclusion Criteria for Control Participants

Inclusion criteria for healthy control participants were the presence of normal vision, hearing and dexterity, and speaking English as a first language. Exclusion criteria were: a personal or immediate family history of attention deficit hyperactivity disorder, bipolar disorders or schizophrenia, and; a personal history of neurological disorder, physical brain injury, serious medical problems, or substance abuse (Appendix C shows selection criteria for control participants). Scores on SPHERE, a mental health screening questionnaire of high sensitivity (Hickie *et al.* 2001), were used post–recruitment to exclude control subjects with likely anxiety or depressive disorders. As previously mentioned, control subjects were additionally selected on the basis of demographic criteria so that they matched individual clinical subjects on gender, and as closely as possible on age, handedness and years of education.

4.2.2.2 Recruitment of Control Participants

The control participants in the present study were obtained from the Brain Resource International Database (BRID: http://www.brainnet.net.org.au). BRID is an international research undertaking under the auspices of Brain Resource Company (http://www.brainresource.com). BRID data are collected in laboratories in the USA, United Kingdom, The Netherlands, South Africa and Australia (including Adelaide). The aim of BRID is to establish standardized, integrative databases of both normative and neuropsychiatric populations (Gordon, 2003; Gordon *et al.* 2005). Data acquired by the author of this thesis for panic disordered subjects generated the PD database, which was subsumed within BRID. Additionally, the author of this thesis collected data for approximately 200 BRID control subjects.

Although assessment of control subjects was undertaken internationally, a recent study of BRID data by Paul *et al.* (2007) revealed no significant site–related differences in cognitive performance or electrophysiology across three continents, reflecting the strict standardization[2] of BRID protocol across different sites (Gordon *et al.* 2005). BRID control participants were recruited in a number of ways, including word of mouth, media interviews, flyers on noticeboards, and notices in school newsletters.

4.2.3 Ethics Committee Approval and Informed Consent

Approval for the study was obtained from: Flinders Clinical Research Ethics Committee, Flinders Medical Centre, Adelaide, South Australia (separately for PD and control studies), and; the Central Northern Adelaide Health Service Ethics of Human Research Committee, Queen Elizabeth Hospital, Adelaide, South Australia (PD study). Furthermore, as normative data for BRID were acquired internationally, approval was obtained from the relevant institutional ethics committee/s, at each site.

As clinical and control participant groups in this study were recruited separately, and were subject to different ethics committees' requirements, the two groups received different information sheets and informed consent documents. Upon enrolling in the study clinical participants were provided with a Patient Information Sheet (Appendix D); whereas control participants at the Adelaide site received a Participant Information Sheet (Appendix E). Both forms, however, outlined the aims and requirements of the research, provided participants with information as to their rights as research participants, and provided contact details of persons to contact, should they require further information.

Upon arrival at the laboratory on the day of assessment, and after receiving a full description of the nature of the experimental procedures, all participants provided written informed consent for their involvement in the study. Clinical participants signed the informed consent document in Appendix F, whereas control subjects for whom data was collected in the Adelaide laboratory signed the form in Appendix G. Data acquired for normative and clinical BRID subjects must provide their explicit permission to add their delinked data to the brain database, and to use their data not only for the specified investigation, but also for other scientific investigations, or for commercial purposes such as providing control data for pharmaceutical treatment trials (Gordon *et al.* 2005).

4.3 Overall Procedure

The overall procedure consisted of three parts: (1) web–based questionnaires; (2) laboratory assessment, and; (3) clinical assessment. All research participants (*i.e.* both patients and controls) completed parts 1 and 2, whereas only patients completed the latter. Each of these components will now be discussed.

4.3.1 Overall Procedure: Web–based Questionnaires

Prior to attending their laboratory assessment each participant was provided with a unique 8–digit identification number. This identification number served to identify each participant's data, whilst maintaining the individual's anonymity in the 'delinked' database (no names are included in the database). They were subsequently asked to log on to a website to complete the web–based questionnaires. The 23 questionnaire items cover diverse topics including demography, personality, medical history and psychological symptoms (Appendix H). Of data acquired during

completion of these questionnaires, this thesis reports only demographic data, and scores on Depression Anxiety Stress Scales (DASS: Lovibond & Lovibond, 1995a; b).

4.3.2 Overall Procedure: Laboratory Assessment

Upon provision of informed written consent, all participants completed the following: (i) psychophysiological test battery, (ii) cognitive test battery, and (iii) personality questionnaire. Additionally, those participants who elected to provide a cheek swab for genetic analysis did so. Genetic data are not included in the present research and are, therefore, not discussed further. All participants completed this protocol in a highly standardised manner over a period of approximately three hours.

4.3.2.1 Psychophysiological Assessment

Immediately upon provision of informed written consent, participants were prepared for psychophysiological data collection. This involved being fitted with a QuickCap^{TM} (Neuroscan) for EEG recording, and the attachment of a strain gauge for respiration monitoring, and electrodes for electrocardiogram (ECG) and electrodermal activity (EDA) recording. Preparation time was approximately 50 minutes.

Whilst being prepared for psychophysiological assessment, participants completed two questionnaires on the computer in front of them. Firstly, the How Are You questionnaire obtained information pertaining to the participant's recent activities including recency of caffeine, nicotine, alcohol and recreational drug use. Secondly, participants completed the NEO Five Factor Inventory (Costa & McCrae, 2000). The results of these two questionnaires are not reported.

Psychophysiological assessment was performed in a sound and light attenuated room with an air–conditioned ambient temperature of 24±1^{O}C. Electroencephalographic and autonomic data were recorded simultaneously during the entire psychophysiology battery. The battery comprised 11 computer–administered tests and took approximately one hour to complete. The order of testing was as follows: Resting EEG (Resting Eyes Open; REO), Resting EEG (Resting Eyes Closed; REC), Auditory Habituation, Auditory Oddball, Go–NoGo, Visual Tracking, Continuous Performance Test, Executive Maze, Startle, Emotion Processing (Conscious), and Emotion Processing (Unconscious). Of these tests, this thesis reports data obtained during the five following psychophysiological tests.

Study 1 (Chapter 6), which investigated brain and body function at rest in PD, reports psychophysiological data obtained during the two periods of resting EEG: REO and REC. Details regarding the psychophysiology recording procedures, and artefact correction and data reduction procedures applied to psychophysiological data, are presented in Chapter 6.

Study 2 (Chapter 7), which investigated the processing of sensory information in PD, reports psychophysiological data obtained during the Auditory Oddball paradigm. Behavioral data arising from performance of this test of selective attention (*i.e.* response time and error rate) are also reported. Chapter 7 details this task's methodology.

Study 3 (Chapter 8), which investigated cognitive functioning in PD, incorporated performance data only (*i.e.* response time and error rate) from two

psychophysiological tests: a test of sustained attention (Continuous Performance Test) and a test of high level executive functions (Executive Maze). Psychophysiological data for these tests were not examined. Chapter 8 details relevant aspects of these paradigms' methodologies.

4.3.2.2 Cognitive Assessment

After completion of the psychophysiology battery participants undertook a computerized cognitive test battery comprising 10 tasks requiring touch–screen or verbal response. The cognitive test battery is part of the 'IntegNeuro' test battery (Paul *et al.* 2005; Williams *et al.* 2005; Clark *et al.* 2006), which is based on existing cognitive paradigms known to be sensitive measures of neuropsychological dysfunction (Paul *et al.* 2005). The tests are designed to tap the five core cognitive domains of attention, memory, sensory–motor–spatial function, language, and executive function (Paul *et al.* 2005). The tests have demonstrated convergent validity relative to established tests tapping equivalent domains of cognitive function, as well as divergent validity relative to tests tapping distinct domains of function (Paul *et al.* 2005), in addition to adequate test–retest reliability (~.70) (Williams *et al.* 2005). The battery took approximately 50 minutes to complete. Chapter 8 details the cognitive assessment methodology.

4.3.3 Overall Procedure: Clinical Assessment

Clinical participants, in addition to undertaking the above–described web–based questionnaires and laboratory assessment, completed a detailed clinical assessment comprising self–report and clinician–administered questionnaires, and a structured diagnostic interview. The clinical assessment generated detailed information about

patients' panic and related symptomatology, medication use and comorbidity. All patients undertook the following clinical assessment procedure in an identical manner.

Immediately following the laboratory assessment clinical participants completed the State–Trait Anxiety Inventory (STAI) State form (Spielberger *et al.* 1983), Panic Disorder Severity Scale (PDSS) (Shear *et al.* 1997), and Recent Medication Questionnaire (Appendix I). They were provided with a Panic Attack Diary (Appendix J), to record the occurrence of DSM–IV–defined panic symptoms over the following two weeks.

Within 24 hours of the laboratory assessment patients completed at their convenience: STAI Trait form (Spielberger *et al.* 1983), Beck Depression Inventory – Second Edition (Beck *et al.* 1996), Body Sensations Questionnaire (Chambless *et al.* 1984), Sheehan Disability Scale (Sheehan, 1983), and Sensory Gating Inventory (Hetrick *et al.* 2012). Finally, the Composite International Diagnostic Interview (World Health Organization, 1997) was administered within one month of assessment. Detailed information regarding each of the clinical assessment instruments is presented in the relevant section below.

4.4 Stimulus Materials

4.4.1 Stimulus Materials: Web–based Questionnaires

4.4.1.1 Handedness

Handedness was assessed using a questionnaire based on Annet (1970). Patients and controls were compared to ensure that they were well–matched for handedness. Respondents are asked to indicate which hand they predominantly use for 12 activities

(e.g., writing, throwing). Options are 'left', 'right', 'either', and 'don't know'. The questionnaire yields a continuous laterality quotient (*Handedness*) with scores ranging from –1 (extremely left–handed) to 1 (extremely right–handed).

4.4.1.2 Depression Anxiety Stress Scales (DASS)

A shortened version of DASS (DASS–21) (Lovibond & Lovibond, 1995a; b) assessed the core symptoms of depression, anxiety and stress in patients and controls. DASS–21 consists of 21 questions on three distinct yet correlated scales (Crawford & Henry, 2003), with seven questions for each state. Respondents indicate how much each statement applied to them over the past week on a four–point Likert–type scale. Scores on each scale (*Depression, Anxiety, Stress*) are derived by summing each scale.

4.4.2 Stimulus Materials: Laboratory Assessment

Details regarding the stimulus materials utilized in the psychophysiology and cognitive tasks are presented in the chapter reporting that task, that is, in either Chapter 6, 7 or 8.

4.4.3 Stimulus Materials: Clinical Assessment

4.4.3.1. Comorbidity

In addition to confirming PD diagnosis, the interviewer–administered CIDI–Auto (World Health Organization, 1997) provided information about the prevalence of patients' current and lifetime comorbid diagnoses.[3] CIDI–Auto provides psychiatric diagnoses according to the criteria of both DSM–IV (APA, 1994) and ICD–10 (World Health Organization, 1992), although only diagnoses meeting DSM–IV criteria are reported. The following interview sections were administered: Demographics; Phobic

and Other Anxiety Disorders; Depressive Disorders and Dysthymic Disorder; Eating Disorders; Alcohol Use Disorders; and Obsessive Compulsive Disorder and Post Traumatic Stress Disorder. The author of this thesis undertook training in the administration of CIDI–Auto prior to the commencement of this study.

Three comorbidity measures are reported in this thesis. Firstly, a categorical variable specified whether the subject met criteria for any current comorbid diagnosis (*Current Comorbidity*). As almost all patients met criteria for at least one current comorbid diagnosis when specific phobia diagnoses were taken into consideration, specific phobia diagnoses did not contribute to this variable. This was to maintain adequate power in analyses comparing patients with and without current comorbidity. Additionally, two continuous variables specifying the number of current and lifetime comorbid diagnoses, including specific phobias (*Current Comorbidities* and *Lifetime Comorbidities*) are reported. As DSM–IV codes PD according to the presence/absence of agoraphobia, but agoraphobia itself is not coded as a separate diagnosis (APA, 1994), a diagnosis of agoraphobia did not contribute to these comorbidity measures.

4.4.3.2 Medication Use

Details about patients' recent use of psychoactive medication were obtained via a brief questionnaire, Recent Medication Questionnaire (Appendix I).

4.4.3.3 Symptom Severity

4.4.3.3.1 Panic Disorder Severity Scale

The Panic Disorder Severity Scale (PDSS) (Shear *et al.* 1997) was used to provide a continuous measure of the current overall PD severity. The PDSS is a clinical

interview comprising seven items that assess the severity of core dimensions of PD and related symptoms: frequency and distress during panic attacks, severity of anticipatory anxiety, agoraphobic fear and avoidance, fear and avoidance of panic–related physical sensations, work and social impairment (Shear *et al.* 1997). PDSS questions are based directly on DSM–IV criteria for PD and agoraphobia (Shear *et al.* 2007). Symptoms ratings for the past month are made on a 5–point Likert–type scale from 0 (none or not present) to 4 (extreme, pervasive, near–constant symptoms, disabling, and incapacitating). Two PDSS scores are reported: total PDSS score (*PDSS*) and scores on the agoraphobic fear/avoidance item (Question 4; *AG Severity*). Additionally, PDSS total score was converted to a categorical measure of disorder severity, according to guidelines recommended by Furukawa *et al.* (2008).

4.4.3.3.2 State–Trait Anxiety Inventory

The State–Trait Anxiety Inventory (STAI) (Spielberger *et al.* 1983) was used to assess state and trait dimensions of anxiety in clinical participants. The STAI comprises separate self–report scales for assessing these two distinct manifestations of anxiety. The STAI state scale (STAI–S) evaluates current feelings of tension, nervousness and worry and comprises 20 statements that respondents are asked to rate ('how you feel *right* now, that is, *at this moment*'). State anxiety, in contrast to trait anxiety, fluctuates according to the stressors and threat perceived by an individual in a given situation (Spielberger *et al.* 1983; Barnes *et al.* 2002). Response options for STAI–S range from (1) 'not at all' to (4) 'very much so'. For the trait anxiety scale (STAI–T), respondents rate their frequency of feelings of anxiety ('how you *generally* feel'), for each of 20 statements. Response options range from (1) 'almost never' to (4) 'almost always'. Approximately one half of statements on both scales reflect the absence of anxiety

(e.g., 'I feel calm'), which must be reverse–scored prior to calculating a total for each scale. Total scores for each scale (*STAI–S* and *STAI–T*) are obtained by tallying the item scores.

4.4.3.3.3 Beck Depression Inventory–Second Edition

The Beck Depression Inventory–Second Edition (BDI–II) (Beck *et al.* 1996), which consists of 21 groups of statements, indexed the severity of patients' depressive symptoms. Respondents indicate which statement best describes their feelings of the past two weeks. The depressive symptoms assessed by BDI–II were selected to be consistent with DSM–IV criteria for major depression. BDI–II items include the following: sadness, loss of pleasure, guilt, irritability, agitation and changes in appetite. Each item is rated from 0 to 3, and a total score (*BDI*) is obtained by summing ratings.

4.4.3.3.4 Body Sensations Questionnaire

The Body Sensations Questionnaire (BSQ) (Chambless *et al.* 1984) provided a measure of fear elicited by bodily sensations associated with autonomic arousal. BSQ lists 17 such bodily sensations and respondents must indicate how afraid they are of those feelings (e.g., 'heart palpitations', 'feeling short of breath'). Response options range from (1) 'not frightened or worried by this sensation' to (5) 'extremely worried by this sensation'. A total BSQ score (*BSQ*) is obtained by tallying each score.

4.4.3.3.5 Sheehan Disability Scale

The Sheehan Disability Scale (Sheehan, 1983) comprises three questions, and provided information about the impact of patients' emotional symptoms on three key

areas of functioning within the past month. Responses are indicated on a visual analog scale with anchor points ranging from (0) 'Not at all' to (10) 'Extremely'. Total score (*SDS*) and scores for each question (*Work, Social, Family*) are reported.

4.4.3.3.6 Sensory Gating Inventory

The recently developed Sensory Gating Inventory (Hetrick *et al.* 2012) is a 36–item self–report instrument that aims to measure perceptual phenomena purportedly associated with disturbances of sensory gating and attention. Four factors may be identified: Perceptual Modulation (16 items; e.g., "At times I have a feeling of being flooded by sounds"); Distractibility (8 items; e.g., "At times I have trouble focusing because I am easily distracted"); Over–Inclusion (7 items; e.g., "I always seem to notice when automatic appliances turn on and off (like the refrigerator or the heating and cooling system)"), and; Fatigue–Stress Vulnerability (5 items; e.g., "When I am tired the brightness of light bothers me"). Response options range on a 6 point scale from (0) 'Never True' to (5) 'Always True'. A total score (*SGI*), derived by summing all item responses, is reported.

4.4.3.3.7 Panic Attack Diary

The Panic Attack Diary (unpublished; see Appendix J) yielded information about the frequency with which clinical participants experienced panic attacks and LSA, as defined by DSM–IV criteria. For a two week period patients were asked to register each episode 'as soon as practical after its occurrence' by recording which of 13 listed symptoms they had experienced. Continuous monitoring of panic attacks is more accurate than retrospective estimates (Rapee *et al.* 1990) and is thus recommended

(Shear & Maser, 1994; Shear *et al.* 1998). The number of panic attacks experienced in the two week period (*Panic Frequency*) is reported.

The diary also provided information about the frequency with which specific symptoms were experienced. Two variables relating to depersonalization and derealisation[4] were calculated: the percentage of panic episodes (panic attacks and LSA) during which these symptoms were present (*Depersonalization Frequency*), and; a categorical variable (*Depersonalization*) distinguishing patients with and without these symptoms.

4.5 Data Cleaning

Prior to statistical analysis, all variables were assessed for the presence of missing data and univariate outliers. For demographic data, missing values were not replaced. For all other data, the method for identifying and treating missing values and outliers proceeded as follows. Firstly, variables with a known, finite range were inspected for the presence of erroneous data. Data errors were checked against the original data source and corrected. Secondly, the distribution of each variable was visually inspected independently for each group to be compared (e.g. PD, controls) in order to identify outliers that appeared to represent measurement error rather than true individual differences, in accordance with the recommendation of Tabachnick and Fidell (2007). Then extreme outliers, defined as data values that markedly distorted the group's distribution, were deleted and group means were then recalculated. Randomly–missing values, as defined by Tabachnick and Fidell (2007), were replaced with group means. Finally, outliers deviating more than three standard deviations (*SD*) from the group mean were replaced with mean $\pm$ 3*SD*, as a conservative method of

maintaining subjects' ranking within the distribution (Evans, 1982; Leonowicz *et al.* 2005). Altered outliers and missing values together constituted less than 5% of the cases, for each group's data, for any given variable. In instances where >5% of cases represented outliers or missing data, additional missing values were not replaced, and subject numbers for these analyses are reported. Exact percentages of altered data are reported within the Data Cleaning section of the relevant chapter.

Prior to conducting statistical analyses, the distributions of all variables were visually inspected to determine if they complied with the assumption of normality of distribution, a requirement of parametric statistical analyses. Visual inspection of the distribution as opposed to inferential tests to identify deviations from normality is recommended for large samples (Tabachnick & Fidell, 2007). Variables that violated this assumption were transformed to normalise their distributions, according to recommended procedures (Gasser *et al.* 1982; Tabachnick & Fidell, 2007). In cases where transformation did not adequately normalise the data, non–parametric analyses were conducted, as indicated in the text.

4.6 Data Reduction

Because of the inherent problem of multiple comparisons associated with the study's integrative design, several data reduction strategies were adopted in order to reduce the probability of Type I error. Firstly, variables were aggregated for statistical analyses, where such a loss of information was not detrimental to the study objectives, or where empirical evidence suggests data redundancy. For instance, in Chapter 8 multiple measures of cognitive function were aggregated into empirically–based domains of cognitive function, thereby reducing the number of statistical analyses

performed. Secondly, omnibus analyses were conducted where feasible. In such cases, follow–up tests were only conducted in the presence of significant main effects or interactions of relevance to the study aims and hypotheses. For instance, in Chapter 6 an initial omnibus ANOVA incorporating multiple measures of electrical brain activity was performed, followed by post hoc tests, as justified. And thirdly, repeated–measures analysis of variance (RM–ANOVA) was performed, where possible, to reduce the number of statistical analyses performed.

4.7 Statistical Analyses

Prior to conducting parametric statistical analyses, data were inspected to ensure they met assumptions for such analyses. As physiological data (e.g., EEG data from multiple sites) rarely satisfy the independence assumption for parametric tests such as repeated–measures ANOVA (Kaiser, 2000), yet the Greenhouse–Geisser (G–G) correction is both theoretically and empirically conservative and often results in Type II errors (Klimesch *et al.* 1990), the Huynh–Feldt (H–F) correction was used for such analyses, and G–G correction for was used for non–physiological data. In all cases, the corrected significance level (p) and the appropriate ε statistic are reported. Corrected degrees of freedom and significance values reported upon violation of the equality of variance assumption in *t*–tests (Levine's correction). Tests for other assumptions of parametric statistical analyses were conducted as required, and the results of these analyses are indicated within the text.

Bonferroni–corrected p is reported in the Results section, as appropriate, otherwise alpha for significance testing was $p < .05$. Effect sizes for ANOVA are reported as partial eta squared ($\acute{\eta}_p^2$) (Cohen, 1988). Effect sizes were interpreted according to

Cohen's guidelines, according to which $\acute{\eta}_p^2$ = .01 signifies a small effect size, medium = .06, and large = .16 (Cohen, 1988). For *t*–tests, Cohen's *d* is reported to indicate the effect size, where 0.2 is indicative of a small effect, 0.5 a medium and 0.8 indicates a large effect size (Cohen, 1992).

Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago) was used for all analyses.

4.7.1 Statistical Analyses: Chapter 5

In Chapter 5 there were three types of statistical analyses. Firstly, there were between–group comparisons of patients and controls on demographic and DASS measures. The between–group demographic comparisons ensured that patients and controls were well–matched on those demographic measures (*i.e.* age, years of education, handedness, BMI) which represented potential confounds for later between–group comparisons. Secondly, statistical analyses extracted descriptive statistics from patients' responses on the above–described questionnaire and diagnostic interview measures. These descriptive statistics served to characterize the clinical sample in terms of morbidity and comorbidity. And thirdly, subgroup analyses examined clinical heterogeneity within the panic disordered sample. Seven mixed–model RM–ANOVAs compared patient subgroups on overall clinical severity. In each model, a demographic or clinical measure (*i.e.* gender; age; presence of agoraphobia; medication status; presence of comorbidity; presence of depersonalization, or; PD duration) defined the between–subjects factor. These analyses served to identify which demographic and/or clinical factors represented markers of disorder severity in the clinical sample.

4.7.2 Statistical Analyses: Chapters 6 – 8

Studies 1 – 3 (Chapters 6 – 8) report, predominantly, two types of statistical analyses. Firstly, between–group analyses compared patients and controls on measures of brain, body and cognitive function. The majority of these analyses were conducted as mixed–model RM–ANOVAs and, where possible, as an omnibus analysis incorporating multiple measures. And, secondly, standard multiple regression analyses examined the within–subject relationship (in patients) of a select subset of clinical measures with psychophysiological or neuropsychological measures. To reduce the number of such analyses, multiple regression analyses were only conducted for psychophysiological or neuropsychological measures distinguishing patients and controls. The clinical measures incorporated in these analyses were: state anxiety (STAI–S), PD severity (PDSS), PD duration (after controlling for age), current medication use, current comorbidity, and lifetime alcohol abuse or dependence.

All further details of the statistical analyses conducted are presented in the Statistical Analyses sections of later chapters, as appropriate.

4.8 Summary of Chapter

Chapter 4 described the overarching methodology for the present research, including details of subject selection criteria and recruitment, stimulus materials and procedures, and details relating to data cleaning and statistical analyses. Methodological details of specific relevance to Studies 1 – 3 are presented in later chapters, as appropriate. The next chapter presents demographic data for patients and controls and clinical data for patients. Within–group analyses comparing PD subgroups on clinical severity are also presented.

Notes

1. The exclusion of clinical participants with ongoing benzodiazepine use reflects the fact that both acute and long–term use of benzodiazepines alters many of the brain and cognitive function measures of interest in the experimental chapters (Urata *et al.* 1996; Johannes *et al.* 2001; van Laar *et al.* 2002; Barker *et al.* 2004; Fukami *et al.* 2010). Nevertheless, as experimental manipulation of brain serotonin and norepinephrine may also show behavioural and brain function effects (review: Kenemans & Kähkönen, 2011), the effect of SSRI and SNRI use on measures of brain, body and cognitive function in PD will be examined in experimental chapters.

2. BRID standardization encompasses: paradigms; data acquisition, analysis and quality control; the physical testing environment (e.g., lighting, ambient temperature); hardware (e.g., computers, amplifiers, electrodes, recording caps), software, and consumables (Gordon *et al.* 2005).

3. The term 'current', in the context of comorbidity, will denote diagnoses that were positive within the month prior to clinical assessment.

4. As per DSM–IV panic attack criteria, the Panic Attack Diary measured the frequency of depersonalization *and* derealisation, without distinguishing between the two. Moreover, there is no conclusive evidence that derealisation is an independent phenomenon (Sierra & Berrios, 2010). Therefore, unless specifically indicated the generic term 'depersonalization' will be used throughout to denote depersonalization and/or derealisation.

5. Depersonalization (as opposed to other panic attack symptoms) was selected for sub–group analyses because depersonalization during panic may represent a marker of disorder severity in PD (Cassano *et al.* 1989; Ball *et al.* 1997; Segui *et al.* 2000; Marquez *et al.* 2001; Mendoza *et al.* 2010).

Chapter 5

Demographics & Clinical Severity

5.1 Overview of Chapter

Overall, there were two objectives of this chapter – to present demographic and Depression Anxiety Stress Scales (DASS) data for patients and controls, and to present clinical data for panic disordered participants. Section 5.2 presents data cleaning statistics (e.g., number of missing values and outliers) and details of transformations applied to variables used in this chapter's analyses. Section 5.3 lists the statistical analyses that are reported in this chapter. Section 5.4 presents demographic data for patients and controls. Patients and controls were compared to determine whether they were appropriately matched on demographic variables that might conceivably influence measures of brain, body or cognitive function. Thus, the respective groups were compared on age, years of education, body mass index (BMI) and handedness. Additionally, the two groups were compared on DASS (Lovibond & Lovibond, 1995a), as the only measure of anxiety and depression symptoms obtained from controls.

Section 5.5 concerns patients' clinical severity. Firstly, descriptive statistics are presented for all clinical severity dimensions relating to PD, including overall PD severity, state and trait anxiety, panic frequency, impairment in function, and

comorbidity. Secondly, in order to assess within–group clinical heterogeneity, subgroup analyses were conducted. Seven patient subgroup pairs, identified on the basis of either demography or clinical status, were compared on measures of clinical severity. Comparisons were made between: (1) males/females, (2) younger/older patients, (3) PDA/PD without agoraphobia, (4) medicated/unmedicated PD, (5) PD with/without current comorbidity, (6) PD with/without depersonalization, and (7) shorter/longer PD duration. Overall, these clinical data served to characterise patients according to responses on questionnaire, diary and clinical interview measures. Furthermore, these data were used to determine the extent to which patients are clinically representative of the wider panic disordered population, and to aid interpretation of later analyses of brain, body and cognitive function in PD. Chapter 4 described the method of defining this chapter's data variables.

5.2 Data Cleaning

Prior to conducting statistical analyses, all reported demographic, DASS and clinical variables were inspected for the presence of missing data, outliers, and deviations from normality of distribution, according to the previously–described methodology (see Section 4.5).

5.2.1 Demographic Data

The only missing demographic data were for BMI (PD = 2; controls = 6). These missing data were not replaced. There were no outlier values for any demographic variable. As both groups' distribution for Handedness did not meet the assumption of normality required for parametric statistical analysis, and were not improved by transformation, Handedness scores were compared non–parametrically.

5.2.2 DASS Data

No missing data or outliers were identified in clinical participants' DASS data. Approximately 4% of controls' DASS data were missing from each scale, and approximately 1% represented outliers (total 4.7%). Logarithmic transformations ($Ln_{10}(x + 1)$) were applied to normalise DASS distributions.

5.2.3 Clinical Data

There were no missing clinical data. One outlier each for Panic Frequency, PD duration and PD age of onset were replaced ($M \pm 3SD$). There were no other clinical data outliers. As the distributions for PD duration, Panic Frequency and Depersonalization Frequency were positively skewed, the median and standard error of mean (*SEM*) are reported in the text. Panic Frequency data were logarithmically transformed ($Ln_{10}(x + 1)$) for inferential testing.

5.3 Statistical Analyses

5.3.1 Demographic Data

Independent–samples *t*–tests compared patients and controls on age, years of education and BMI. Handedness scores were compared with Mann–Whitney *U*–test.

5.3.2 DASS Data

A mixed–model RM–ANOVA with *Scale* (Depression, Anxiety, Stress) as within–subjects factor and *Group* (PD, controls) as the between–subjects factor compared patients and controls on DASS.

5.3.3 Clinical Data

Seven separate mixed–model RM–ANOVAs assessed the effect of select demographic and clinical measures on overall clinical severity in PD, with one of the following between–subjects factors per model: *Gender* (males, females); *Age* (younger/older patients, median split); *Agoraphobia* (PD with/without agoraphobia); *Medication* (medicated/unmedicated patients); *Comorbidity* (patients with/without current comorbidity); *Depersonalization* (presence/absence of depersonalization), and; *Duration* (shorter/longer PD duration, median split).

Within each model up to eight clinical severity measures represented levels of the within–subjects factor Severity. The number of dependant variables (DVs) per model varied as comorbidity measures could not serve as both independent and dependent variables in a given model. To do so would increase Type I error risk. Therefore, the ANOVA with Comorbidity as between–subjects factor included no comorbidity indices as DVs. For each measure, higher values indicate greater clinical severity. The eight measures were: PDSS, STAI–S, STAI–T, BDI, SDS, Panic Frequency, Current Comorbidities, and Lifetime Comorbidities.

5.4 Results: Comparison of Patients and Controls

5.4.1. Demographics Check

The two groups were well–matched for age (t_{157} = 0.14, p = .887), years of education (t_{157} = 0.36, p = .716) and Handedness (U = 25.3, p = .251), although there was a trend for higher BMI in PD (t_{149} = 1.83, p = .070) (see Table 5).

Table 5: Demographic data for panic disorder (n = 53) and healthy control participants (n = 106)

	Panic Disorder	Controls		
	***M* (*SD*)**	***M* (*SD*)**	***t***	***p***
Age	35.3 (13.3)	35.0 (13.1)	0.14	.887
Education (years)	14.4 (2.63)	13.9 (2.42)	1.00	.332
BMI [a]	26.0 (5.45)	24.4 (4.89)	1.83	.070
Handedness [b]	0.70 (0.56)	0.72 (0.58)	25.3	.251

[a] BMI, body mass index (PD, $n = 51$; controls, $n = 100$). [b] Mann–Whitney *U*–test.

5.4.2 Depression Anxiety Stress Scales (DASS)

As expected, patients had higher DASS scores (Group $F_{1, 157} = 161.5$, $p < 6.84E{-}27$, $\acute{\eta}_p^2 = .507$). There was a significant Group*Scale interaction ($F_{2, 314} = 9.15$, $p < .001$, $\acute{\eta}_p^2 = .052$, $\varepsilon = .972$), the between–group difference being most pronounced for Stress and Anxiety, but with very large patient–control differences on each scale (Table 6).

*Table 6: Depression Anxiety Stress Scales (DASS) data for panic disorder and healthy control participants**

	PD	**Controls**			
	(*n* = 53)	**(*n* = 106)**	***F***	***p***	**$\acute{\eta}_p^2$**
Group			161.5	6.84E–27	.507
Group*Scale			9.15	.0002	.055
	***M* (*SD*)**	***M* (*SD*)**	***t***	***p***	***d***
Depression	2.44 (0.83)	1.19 (1.01)	8.35	.00001	1.21
Anxiety	2.56 (0.49)	0.76 (0.82)	17.2	.00001	1.61
Stress	2.74 (0.45)	1.50 (0.98)	10.88	.00001	1.12

*Transformed distributions ($Ln_{10}(x + 1)$) and Levene's test corrected *p* reported.

5.5 Results: Clinical Severity

5.5.1 Descriptive Statistics

5.5.1.1 PD Diagnosis

Mean age of PD onset was 21.5±11.3 years (range 5 – 55), and median PD duration was 9±1.62 years (range 1 – 50). Thirty–four (64.2% of sample) met criteria for PDA, including 68.4% of females (*n* = 26) and 53.3% of males (*n* = 8).

5.5.1.2 Panic Frequency and Panic Symptoms

Patients reported a median of 3±0.59 panic attacks across the two week recording period, with depersonalization present during 17±5.12% of panic episodes. A substantial minority of patients (45%) reported no symptoms of depersonalization during panic, whereas a lesser number (13%) reported experiencing depersonalization during each episode. Depersonalization frequency was calculated across both panic attacks and LSE. Therefore, these data are available for all subjects, including those (17%; *n* = 9) who reported no full panic attacks within the recording period. Table 7 shows descriptive statistics for questionnaire and diary measures of clinical severity.

5.5.1.3 Clinical Severity Questionnaires

Patients' PDSS scores – the measure of overall PD severity – were (mean±*SD*) 11.8±4.2. Additionally, PDSS scores were converted to categories of PD disorder severity according to evidence–based guidelines provided by Furukawa *et al.* (2009). Categories range from 'Normal' to 'Among the most severely ill'. The category to which a patient is assigned differs according to whether agoraphobia is present or absent (see Table 8).

Table 7: Descriptive statistics for clinical participants' (n = 53) scores on questionnaire and diary measures of clinical severity.

Questionnaire	*M* (*SD*)	Median	Range
PDSS	11.8 (4.23)	12.0	5 – 20
STAI–S	44.6 (11.4)	45.0	21 – 69
STAI–T	54.7 (9.22)	55.0	27 – 73
BDI	22.3 (10.2)	20.0	4 – 50
BSQ	44.7 (13.4)	46.0	19 – 80
SGI	77.6 (31.6)	78.0	3 – 134
SDS	15.2 (6.31)	16.0	0 – 27
Panic Frequency [a]	3.92 (4.40)	3.00	0 – 20
Depersonalization Frequency [b]	30.8 (37.3)	17.0	0 – 100

PDSS, Panic Disorder Severity Scale; STAI, State–Trait Anxiety Inventory; BDI, Beck Depression Inventory; BSQ, Body Sensations Questionnaire; SGI, Sensory Gating Inventory; SDS, Sheehan Disability Scale. [a] Number of panic attacks recorded in Panic Attack Diary over two weeks. [b] Percentage of panic attacks and LSE during which symptoms of depersonalization and/or derealisation present.

Table 8: Number (%) of clinical participants with PDA (n = 34) and PD without agoraphobia (n = 19) in each category of disorder severity.

	PD *with* Agoraphobia *n* (%)	**PD *without* Agoraphobia *n* (%)**
Normal	0 (0)	0 (0)
Borderline ill	4 (11.8)	0 (0)
Slightly ill	7 (20.6)	6 (31.6)
Moderately ill	15 (44.3)	9 (47.3)
Markedly ill	2 (5.9)	1 (5.3)
Among the most severely ill	6 (17.6)	3 (15.8)

Patients' scores on other clinical severity measures were: STAI–S (state anxiety) 44.6±11.4; STAI–T (trait anxiety) 54.7±9.22; BSQ (fear of bodily sensations) 44.7±13.4; BDI (depression symptoms) 22.3±10.2; SGI (perceptual difficulties) 77.6±31.6, and; SDS (overall impairment) 15.5±6.63. On SDS, patients rated social function as most greatly impaired (Social, 5.60±2.50), followed by Family (5.11±2.61) and Work (4.79±2.65); ratings of 1 – 3, 4 – 6, 7 – 9, and 10, represent 'Mildly', 'Moderately', 'Markedly', and 'Extremely' disrupted (Sheehan, 1983) (Figure 5).

5.5.1.4 Comorbidity

Mean (±*SD*) Current Comorbidities was 2.32±1.59 (median 2, range 0 – 6) and Lifetime Comorbidities was 4.25±2.37 (median 4, range 0 – 9). As previously indicated, these variables include the number of specific phobia diagnoses. Specific phobia was the most common current comorbid diagnosis, followed by social phobia, obsessive–compulsive disorder (OCD), PTSD, MDD, and generalised anxiety disorder (GAD). Specific phobia was also the most common lifetime comorbid diagnosis, followed by MDD, social phobia, and equally alcohol abuse and/or dependence, and PTSD. Table 9 shows the frequencies of each comorbid diagnosis.

5.5.1.5 Medication

Thirty–four clinical participants had used no psychotropic medication for at least six months prior to their involvement in the study. Of the remaining participants, 12 were taking SSRIs, four were taking SNRIs, and three were using tri–cyclic or monoamine oxidase inhibiting antidepressants at the time of the study. Because of the small number of participants using non–SSRI psychotropic medication, participants using any psychotropic medication were aggregated for later analyses.

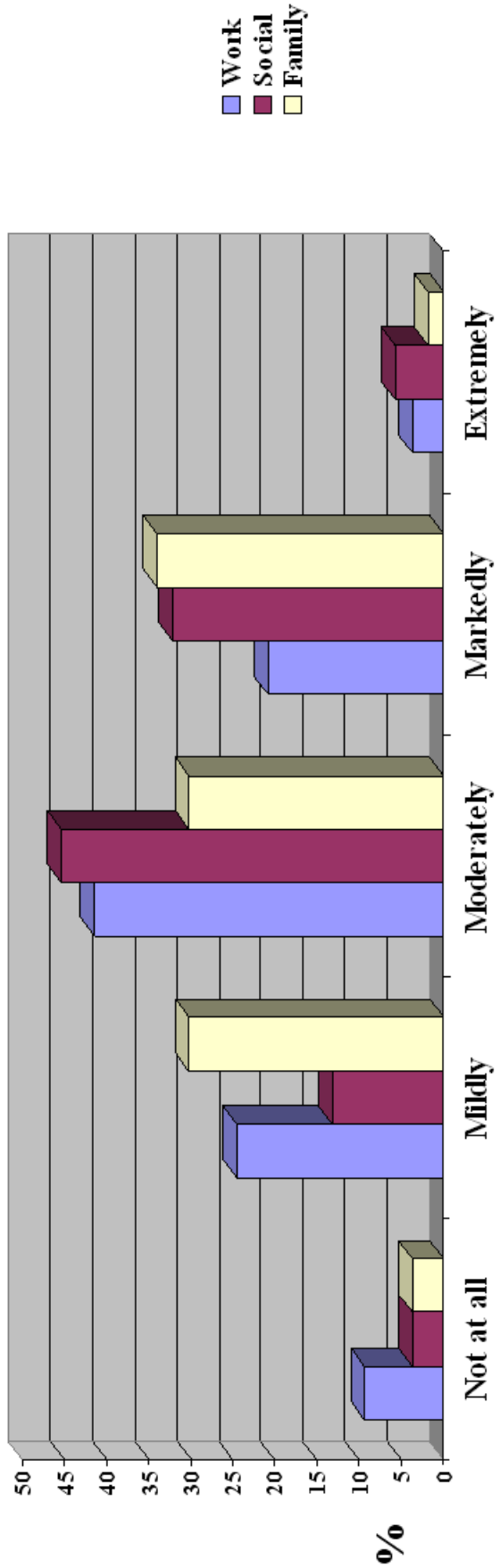

Figure 5: Clinical Participants' Self-Reported Impairment in Work, Social, and Family Scales of SDS (Sheehan, 1983)

Table 9: Number (%) of clinical participants meeting DSM–IV criteria for each comorbid diagnosis (current and lifetime)

	Current (1–month) Comorbidity	Lifetime Comorbidity
Diagnosis	***n* (%)**	***n* (%)**
Specific Phobia [a]	33 (62.3)	37 (69.8)
Social Phobia	23 (43.4)	27 (50.9)
OCD	16 (30.2)	20 (37.7)
PTSD	12 (22.6)	21 (39.6)
MDD	8 (15.1)	33 (62.3)
GAD	6 (11.3)	10 (18.9)
Dysthymic Disorder	3 (5.7)	11 (20.8)
Alcohol [b]	0 (0.0)	21 (39.6)
Bulimia Nervosa	0 (0.0)	4 (7.5)

[a] Patients meeting criteria for ≥1 specific phobia. [b] Alcohol abuse and/or dependence

5.5.1.6 Summary: Descriptive Statistics

Overall these data indicate that clinical participants in the present study suffer a substantial burden of panic and associated symptoms including depressive symptoms, impaired functioning, situational and trait anxiety, and past and present comorbidity. For example, on the basis of overall PD severity ratings (PDSS score), approximately two–thirds of patients with or without agoraphobia were at least 'moderately ill' at the time of assessment (Table 8), and a similar percentage were at least moderately impaired in the areas of social, work and family functioning (SDS scores, Figure 5).

The present data, moreover, are broadly consistent with reported norms for PD, where available. Thus the present sample conformed to typical population–based estimates of

PD age of onset, percentage of PD complicated by agoraphobia, and ratio of affected males to females (APA, 2000; Goodwin *et al.* 2005; Kessler *et al.* 2005a; b; 2006), in addition to PD severity in treatment–seeking outpatients (Shear *et al.* 1997; 2001), suggesting that the present sample is representative of the broader panic disordered population, at least on these parameters. Similarly, the present findings of substantial comorbidity (particularly mood and anxiety disorders) accord with previous findings of multi–comorbidity in both clinic– and community–based PD samples (Kaufman & Charney, 2000; Rodriguez *et al.* 2004; Goodwin *et al.* 2005; Kessler *et al.* 2006; Michael *et al.* 2007), although the latter did not report the actual number of comorbid conditions, limiting comparisons. The data also indicate significant clinical heterogeneity within the patient sample across the many dimensions of symptom severity assessed. The next section examined this within–group heterogeneity.

5.5.2 Comparison of Patient Subgroups

5.5.2.1 Comparison 1: Males vs. Females with PD

Male (n = 15) and female (n = 38) patients had comparable scores on all clinical indices: Gender main effect ($F_{1, 51}$ = 1.60, p = .211, $\acute{\eta}_p^2$ = .030) and Gender*Severity interaction ($F_{7, 357}$ = 0.94, p = .424, $\acute{\eta}_p^2$ = .018, ε = .448) (see Table 10).

5.5.2.2 Comparison 2: Younger vs. Older PD

Younger (n = 26) and older patients (n = 27, median split) had similar scores on all clinical severity measures: Age main effect ($F_{1, 51}$ = 0.18, p = .674, $\acute{\eta}_p^2$ = .003); Age*Severity ($F_{7, 357}$ = 0.15, p = .937, $\acute{\eta}_p^2$ = .003, ε = .442) (see Table 11).

Table 10: Clinical severity comparison: males vs. females with PD

	Males (*n* = 15)	**Females** (*n* = 38)	***F***	***p***	$\acute{\eta}_p^2$
Gender			1.60	.211	.030
Gender*Severity			0.94	.424	.018
	***M* (*SD*)**	***M* (*SD*)**			
PDSS	12.2 (4.52)	12.3 (5.01)			
STAI–S	42.5 (11.3)	46.0 (11.8)			
STAI–T	51.8 (4.36)	56.1 (10.1)			
BDI	20.5 (7.88)	23.3 (10.6)			
Sheehan	13.9 (6.88)	16.1 (6.51)			
Panic Frequency	*3.13* 1.02 (0.90)	*4.32* 1.36 (0.82)			
Current Comorbidities	2.27 (1.58)	2.34 (1.62)			
Lifetime Comorbidities	4.13 (2.23)	4.29 (2.45)			

Table 11: Clinical severity comparison: younger vs. older PD

	Younger (*n* = 26)	**Older (*n* = 27)**	***F***	***p***	$\acute{\eta}_p^2$
Age			0.18	.674	.003
Age*Severity			0.15	.937	.003
	***M*. (*SD*)**	***M*. (*SD*)**			
PDSS	11.9 (5.10)	12.7 (4.61)			
STAI–S	45.1 (10.3)	44.9 (13.0)			
STAI–T	54.9 (8.35)	54.9 (9.81)			
BDI	22.0 (9.24)	23.1 (10.7)			
Sheehan	15.3 (5.56)	15.7 (7.62)			
Panic Frequency	*3.46* 1.30 (0.66)	*4.48* 1.23 (1.00)			
Current Comorbidities	2.04 (1.54)	2.59 (1.62)			
Lifetime Comorbidities	3.46 (2.30)	5.00 (2.22)			

Panic Frequency (both tables) reported as Mean $_{\text{untransformed}}$ (in italics), Mean $_{\text{transformed}}$ (*SD*)

5.5.2.3 Comparison 3: PDA vs. PD without Agoraphobia

As an initial validity check, the extent of current agoraphobic fear/avoidance (AG Severity) was compared in patients with and without lifetime agoraphobia according to CIDI. Interestingly, the two groups did not differ in current agoraphobia, with similar scores in PDA (n = 34; 1.68±1.09) and PD uncomplicated by agoraphobia (n = 19; 1.42±1.22) (t_{51} = –0.78, p = .437). For subsequent analyses the dimensional measure was used. The RM–ANOVA compared patients with *Lower* (0 – 1; n = 26) and *Higher* (2 – 4; n = 27) AG Severity score (between–subjects factor Agoraphobia). The within–subjects level PDSS score was adjusted ($PDSS_{total} - PDSS_{Question\ 4}$) to reduce Type I error risk. The main effect and interaction were non–significant ($F_{1, 51}$ = 2.54, p = .117, $\acute{\eta}_p^2$ = .048; $F_{7, 357}$ = 1.31, p = 273, $\acute{\eta}_p^2$ = .025, ε = .419) (see Table 12).

Table 12: Clinical severity comparison: lower vs. higher agoraphobic severity

	Lower Agoraphobia (n = 26)	**Higher Agoraphobia** (n = 27)	***F***	***p***	$\acute{\eta}_p^2$
Agoraphobia			2.54	.117	.048
Agoraphobia*Severity			1.31	.273	.025
	***M* (*SD*)**	***M* (*SD*)**			
PDSS	8.54 (2.92)	12.8 (3.91)			
STAI–S	45.2 (11.8)	44.9 (11.3)			
STAI–T	54.2 (9.73)	55.6 (8.44)			
BDI	21.5 (10.7)	23.6 (9.25)			
Sheehan	13.0 (6.23)	17.9 (6.21)			
Panic Frequency	*2.50* 0.97 (0.77)	*5.41* 1.55 (0.83)			
Current Comorbidities	2.08 (1.62)	2.56 (1.55)			
Lifetime Comorbidities	3.38 (2.52)	5.07 (1.92)			

Panic Frequency data reported as $Mean_{untransformed}$ (in italics), $Mean_{transformed}$ (*SD*)

5.5.2.4 Comparison 4: Medicated vs. Unmedicated PD

Medicated (n = 20) and unmedicated (n = 33) patients had similar scores on all clinical severity indices. The main effect ($F_{1, 51}$ = 0.43, p = .515, $\acute{\eta}_p^2$ = .008) and interaction ($F_{3.07, 157}$ = 1.77, p = 154, $\acute{\eta}_p^2$ = .034) were non–significant (Table 13).

Table 13: Clinical severity comparison: medicated vs. unmedicated PD

	Medicated (n = 19)	**Unmedicated** (n = 34)	***F***	***p***	$\acute{\eta}_p^2$
Medication			0.43	.515	.008
Medication*Severity			1.77	.154	.034
	***M* (*SD*)**	***M* (*SD*)**			
PDSS	12.2 (4.53)	12.3 (5.06)			
STAI–S	43.7 (9.97)	45.7 (12.6)			
STAI–T	56.2 (9.17)	54.2 (9.01)			
BDI	26.1 (8.27)	20.6 (10.3)			
Sheehan	15.8 (5.05)	15.3 (7.43)			
Panic Frequency	*3.89* 1.30 (0.82)	*4.03* 1.24 (0.87)			
Current Comorbidities	2.32 (1.49)	2.32 (1.67)			
Lifetime Comorbidities	4.63 (2.54)	4.03 (2.28)			

Panic Frequency data reported as Mean $_{\text{untransformed}}$ (in italics), Mean $_{\text{transformed}}$ (*SD*)

5.5.2.5 Comparison 5: Patients with vs. without Current Comorbidity

Patients with current comorbidity (Current Comorbidity $\geq$1; n = 37) had higher scores on all clinical measures compared to those without (Current Comorbidity = 0; n = 16). The main effect for Comorbidity was significant ($F_{1, 51}$ = 22.0, p < .0001, $\acute{\eta}_p^2$ = .301), as was the interaction ($F_{5, 255}$ = 5.24, p < .002, $\acute{\eta}_p^2$ = .093, ε = .623). The difference was significant for all measures except Panic Frequency (trend; see Table 14).

Table 14: Clinical severity comparison: patients with vs. without current comorbidity

	Current Comorbidity (*n* = 37)	***No* Current Comorbidity** (*n* = 16)	***F***	***p***	**$\acute{\eta}_p^2$**
Comorbidity			22.0	.0001	.301
Comorbidity*Severity			5.24	.002	.093
	***M* (*SD*)**	***M* (*SD*)**	***t***	***p***	***d***
PDSS	13.4 (5.05)	9.81 (3.25)	–2.58	.013	0.73
STAI–S	47.9 (11.7)	38.4 (8.64)	–2.89	.006	0.81
STAI–T	57.6 (8.68)	48.7 (6.56)	–3.67	.001	0.99
BDI	26.1 (9.17)	14.4 (6.35)	–4.60	.001	1.17
Sheehan	17.1 (6.42)	11.8 (5.62)	–2.90	.005	0.81
Panic Frequency	*4.65* 1.41 (0.84)	*2.44* 0.93 (0.78)	–1.95	.057	0.57

Panic Frequency data reported as Mean $_{\text{untransformed}}$ (in italics), Mean $_{\text{transformed}}$ (*SD*)

5.5.2.6 Comparison 6: Patients with vs. without Depersonalization

Patients with depersonalization during panic (*n* = 29) scored higher on all measures, relative to those without (*n* = 24). The main effect was significant ($F_{1, 51}$ = 4.83, *p* = .033, $\acute{\eta}_p^2$ = .086), the interaction was not ($F_{7, 357}$ = 2.27, *p* = .079, $\acute{\eta}_p^2$ = .043, ε = .448) (see Table 15).

5.5.2.7 Comparison 7: Shorter vs. Longer PD Duration

Patients with shorter *vs.* longer PD duration (median–split; 4.52±2.64 years *vs.* 22.7±10.3 years) were compared. Longer PD duration was associated with greater disorder severity ($F_{1, 51}$ = 11.1, *p* = .002, $\acute{\eta}_p^2$ = .181; interaction trend $F_{7, 350}$ = 2.55, *p* = .056, $\acute{\eta}_p^2$ = .048, ε = .442) (see Table 16). Although the two subgroups differed in age (t_{51} = 3.34, *p* = .002), age itself was not associated with clinical severity [1] (Table 11).

Table 15: Clinical severity comparison: PD with vs. without depersonalization

	PD *with* Depersonalization (n = 29)	**PD *without*** (n = 24)	***F***	***p***	$\acute{\eta}_p^2$
Depersonalization			4.83	.033	.086
Depersonalization*Severity			2.27	.079	.043
	***M* (*SD*)**	***M* (*SD*)**	***t***	***p***	***d***
PDSS	13.3 (5.22)	11.0 (4.09)	–1.73	.089	0.47
STAI–S	48.5 (11.6)	40.8 (10.5)	–2.49	.016	0.66
STAI–T	55.7 (10.2)	54.0 (7.50)	–0.69	.493	0.19
BDI	24.1 (11.0)	20.7 (8.31)	–1.23	.224	0.34
Sheehan	17.2 (7.13)	13.5 (5.41)	–2.12	.039	0.56
Panic Frequency	*5.21* 1.52 (0.85)	*2.50* 0.96 (0.74)	–2.53	.015	0.66
Current Comorbidities	2.55 (1.64)	2.04 (1.52)	–1.17	.249	0.32
Lifetime Comorbidities	4.59 (2.72)	3.83 (1.83)	–1.20	.237	0.32

Table 16: Clinical severity comparison: shorter vs. longer PD duration

	Shorter (n = 27)	***Longer*** (n = 26)	***F***	***p***	$\acute{\eta}_p^2$
Duration			11.5	.001	.184
Duration*Severity			2.51	.058	.045
	***M.* (*SD*)**	***M.* (*SD*)**	***t***	***p***	***d***
PDSS	10.4 (3.76)	14.2 (1.15)	–3.04	.004	0.78
STAI–S	42.1 (11.4)	48.1 (11.4)	–1.92	.060	0.51
STAI–T	51.8 (9.40)	58.1 (7.54)	–2.69	.010	0.70
BDI	19.6 (9.34)	25.7 (9.75)	–2.33	.024	0.61
Sheehan	13.0 (5.58)	18.1 (6.75)	–2.97	.005	0.76
Panic Frequency	*2.85* 1.17 (0.61)	*5.15* 1.36 (1.04)	–0.82	.416	0.23
Current Comorbidities	1.74 (1.29)	2.92 (1.67)	–2.89	.006	0.74
Lifetime Comorbidities	3.59 (2.52)	4.92 (2.04)	–2.11	.040	0.56

Panic Frequency (both tables) reported as Mean $_{\text{untransformed}}$ (in italics), Mean $_{\text{transformed}}$ (*SD*).

5.5.2.8 Summary: Patient Subgroups

Panic disorder is a complex disorder comprising multiple, varied symptoms and impairments. The present subgroup analyses used multiple indices of disorder morbidity and comorbidity in order to better capture this complexity, in accordance with recommendations for PD research (Shear *et al.* 2007). Overall, these analyses show that three clinical factors were significant predictors of greater disorder severity on multiple illness dimensions: the presence of current comorbidity, presence of depersonalization symptoms during panic, and longer illness duration (after controlling for age). In contrast to these positive findings, gender, age, current agoraphobic fear/avoidance, and current medication usage did not predict illness severity. Conceivably, the choice of both independent and dependent variables for these analyses could have affected the results. However, with the exception of the null finding for agoraphobia, these results are consistent with the extant literature.

The present positive findings accord with robust findings linking adverse clinical outcomes in PD with comorbidity (Brown *et al.* 1995; Baldwin *et al.* 1998; Kaufman & Charney, 2000; Roy–Byrne *et al.* 2000; Kessler *et al.* 2005b; Kroenke *et al.* 2007), depersonalization during panic (Cassano *et al.* 1989; Ball *et al.* 1997; Segui *et al.* 2000; Marquez *et al.* 2001; Mendoza *et al.* 2010), and longer illness duration (Slaap & den Boer, 2001). However, given the cross–sectional nature of the present findings, the causal directions of these associations are unclear. Theoretically, there are many possible explanations for diagnostic comorbidity (Maj, 2005; Widiger & Samuel, 2005; Hyman, 2007) and thus for the observed association between PD morbidity and comorbidity. Similarly, the causal relationship between disorder severity and depersonalization remains to be specified (Mendoza *et al.* 2010). With regards illness

duration, bidirectional causal pathways are plausible. Assuming, as per the 'symptom progression model', a developmental sequence of PD evolving into PDA (Klein *et al.* 1987; Barlow, 2002), and a temporal accumulation of comorbidities (e.g., depression and substance use disorders) secondary to PD (Wittchen *et al.* 1998), greater morbidity and comorbidity could be a consequence of prolonged illness. Conversely, as greater disorder severity predicts poor prognosis, in terms of remission (Batelaan *et al.* 2010a; b) and response to treatment (Haby *et al.* 2006; Chavira *et al.* 2009), greater disorder severity could cause illness prolongation.

On the basis of the extant literature, the null finding for gender was not unexpected; Although population estimates consistently suggest a female preponderance of PD and, particularly, PDA (Weissman *et al.* 1997; Goodwin *et al.* 2005; Kessler *et al.* 2006; Michael *et al.* 2007), and there is some evidence for a specific association of female gender and agoraphobic severity (Starcevic *et al.* 1998; Turgeon *et al.* 1998; Yonkers *et al.* 1998; Schmidt & Koselka, 2000), a consistent association between gender and overall disorder severity has not emerged. By contrast, the present null finding for agoraphobic severity (agoraphobia item on PDSS) was unexpected as the presence of agoraphobia and, in particular, agoraphobic severity are associated with a range of disorder severity indices (e.g., panic–related measures, impairment, comorbidity) (reviews Schmidt & Cromer, 2008; Wittchen *et al.* 2010). However, PDSS's agoraphobia item was recently found to have poor discriminant validity, being equally correlated with questionnaire measures of agoraphobia and other, dissimilar constructs (Wuyuk *et al.* 2011). Therefore, psychometric issues may account for the latter null finding, and for the lack of association between categorical and dimensional measures of agoraphobia. Finally, there was no reason a priori to expect an association

between patients' medication use and disorder severity. Although successful pharmacotherapy with commonly prescribed antidepressants may ameliorate all of the main symptom components of PD (Seddon & Nutt, 2007), medicated patients' baseline (*i.e.* pre–medication) clinical status was unknown. Such interactions are opaque to cross–sectional analyses.

5.6 Summary of Chapter

The present chapter examined demographic and clinical variables in patients and controls. Patient–control comparisons determined that patients and controls were demographically well–matched, notwithstanding a trend for higher BMI in PD. Patients' clinical data were characterised at the group level, and within–group heterogeneity examined. Three clinical variables – presence of current comorbidity, presence of depersonalisation, and longer PD duration – were associated with greater overall clinical severity. In sum, the clinical findings were broadly consistent with the literature, with the exception of a null finding for agoraphobic severity. The latter inconsistency, as explained, may relate to psychometric issues. More generally, however, between–study clinical variance may be due to the substantial clinical heterogeneity within the panic disordered population. Relatively integrative research designs may avoid the potentially confounding effect of clinical variance, by utilising a common study sample for a range of experimental procedures (Gordon *et al.* 2005). The following three chapters (Chapters 6 – 8) present Studies 1 – 3 which, together, form an integrative, psychophysiological and neuropsychological assessment of PD.

Notes

1. As it would be statistically inappropriate to covary age, given that age is associated with the grouping variable (*i.e.* PD duration; see Miller & Chapman, 2001), a separate ANOVA compared illness severity in younger and older PD patients.

Chapter 6

Study 1: Brain & Body Function 'at Rest'

6.1 Overview of Chapter

This chapter describes Study 1[1], an integrative psychophysiological investigation of brain and body function in panic disorder, whilst nominally 'at rest'. Central (QEEG) and peripheral autonomic (cardiovascular and electrodermal) psychophysiological indices were recorded simultaneously during two periods of sitting quietly in the laboratory; a Resting Eyes Open (REO) and a Resting Eyes Closed (REC) paradigm.

The chapter begins by describing the psychophysiological techniques used to derive indices of brain and body resting state function for Study 1. This is followed by a brief review of relevant (QEEG, cardiovascular and electrodermal) resting state findings for PD. Then, because a range of contextual elements and individual difference factors and their interactions determine an individual's perception of threat, even in the absence of experimentally–imposed task requirements (*i.e.* at rest) (Lang & Davis, 2006; Wilhelm & Grossman, 2010), the chapter then considers those factors that may differentially bear upon panic disordered and healthy control subjects' perception of threat during these paradigms. The balance of the chapter describes Study 1 with regards its aims and hypotheses, its methodology and results, and concludes with a discussion of the possible interpretations and implications of the Study's results.

6.2 Study Background

6.2.1 Psychophysiological Measures

The present study obtained concomitantly–recorded CNS and ANS resting state indices from individuals with PD and healthy matched–control subjects. This section describes the psychophysiology techniques from which these indices of brain and body function were derived, with reference to the type of information that such measures yield.

6.2.1.1 Quantitative Electroencephalography

Electroencephalogram (EEG) recording allows the extraction of multiple, precisely quantified indices of electrical brain activity, which, in turn, reflect the dynamic functional state of the brain (Kutas & Federmeier, 1998). Scalp–recorded EEG currents largely consist of the summed electrical potentials of large populations of synchronously firing neurons – specifically, the post–synaptic potentials of pyramidal cells in the neocortex (Niedermeyer, 2005). Quantitative EEG (QEEG) involves the use of computer systems for the quantitative analysis and imaging of multi–lead EEG (Van Cott & Brenner, 1998; Coburn *et al.* 2006). Whereas the raw EEG signal appears largely aperiodic, QEEG spectral analysis extracts a number of fundamental EEG rhythms from the signal (Hughes & John, 1999). This is achieved through the application of a series of frequency filters to brief segments (*i.e.* epochs) of the digitized EEG signal, which decomposes the signal into its constituent periodic components (Pivik, 1993; Kaiser, 2000). Commonly investigated frequency bands include theta (θ: ~4 – 7.5 Hz), alpha (α: ~8 – 13 Hz), and beta (β: ~14.5 – 30 Hz) (Kaiser, 2000).

Spectral power, typically as absolute power (*i.e.* square of the amplitude, expressed in μV^2), is the main metric of waveform amplitude (Pivik, 1993). Spectral power is

computed at each electrode site within each frequency band of interest by averaging across multiple epochs (Allen *et al.* 2004a). Spectral analysis thus extracts and reduces the information in an apparently aperiodic EEG signal to precisely quantified indices of its periodicity (Gruzelier *et al.* 2002). Because complicated homeostatic mechanisms regulate synchronized neural activity (Hughes & John, 1999; John & Prichep, 2006), normative QEEG parameters such as spectral power show high within–subjects stability over time (Kondacs & Szabo, 1999; Hagemann & Naumann, 2009). This stability, and the high heritability of resting EEG spectral power (Smit *et al.* 2005; Zietsch *et al.* 2007), supports the notion that spectral power reflects a trait characteristic of individuals. These properties of spectral power (*i.e.* precisely quantifiable, test–retest stability) permit precise quantitative comparisons of normative and patient QEEG samples (Prichep, 2005), and deviations from normative values may delineate different clinical populations with high specificity (Hughes & John, 1999).

Alpha frequency activity is the most prominent EEG rhythm in awake adults at rest, and is generally understood to signify a state of relaxed wakefulness (Niedermeyer, 2005). The alpha rhythm is most prominent over posterior scalp sites when subjects close their eyes, and is attenuated with visual stimulation (e.g., REO *vs.* REC) (Klimesch, 1999). Whereas large scale alpha synchronization serves to block information processing, alpha desynchronization, in contrast, reflects actual information processing as different neuronal networks oscillate independently at different frequencies and phases (Kropotov, 2009). As alpha attenuates it is supplanted by a desynchronised low–voltage EEG pattern (Pfurtscheller *et al.* 1996). Recent fMRI/EEG co–registration studies suggest that scalp–recorded alpha–frequency oscillatory activity is associated with reduced cortical metabolic activity, in line with conceptualisations of alpha as an

inverse index of cortical activation (Laufs *et al.* 2003; de Munck *et al.* 2007). Conventionally, alpha synchronisation has been considered a marker of cognitive inactivity, (*i.e.* 'cortical idling') (Pfurtscheller *et al.* 1996). However, more recent conceptualisations assign spontaneous alpha an active role in the inhibition of non–task relevant cortical areas (review Klimesch *et al.* 2007).

Within the alpha band at least two functionally and topographically distinct spectral parameters may be distinguished, which may be denoted *alpha–1* [2] (~8 – 11 Hz) and *alpha–2* (~11 – 13 Hz) (Goncharova & Davidson, 1995; Petschke *et al.* 1997; Klimesch, 1999). Non–clinical findings have shown that changes in alpha–1 spectral power reflect tonic and phasic changes in aspects of attention (unspecific 'alertness' and/or 'expectancy'), wherein increased attentional demand is associated with a selective alpha–1 desynchronization, as indexed by reduced spectral power (review Klimesch, 1999). In a series of studies, Wolfgang Klimesch and colleagues manipulated subjects' attention via, for instance, the use of a warning signal prior to the presentation of a to–be–recalled verbal stimulus, resulting in alpha–1 attenuation (Klimesch, 1996; 1999; Klimesch *et al.* 1998; 2007). Alpha–1 desynchronization is topographically widespread and has been observed across diverse experimental paradigms in response to both non–task and non–stimulus specific factors encompassed by the term 'attention' (Klimesch, 1999). By contrast, alpha–2 synchronization is topographically restricted and is positively associated with capacity for semantic memory performance (Klimesch, 1999).

The spatial resolution of scalp–recorded EEG, relative to its superior temporal resolution, is poor (Kutas & Federmeier, 1998). Therefore, topographical analyses

typically contrast activation in relatively large regions (Mauss & Robinson, 2009). Notably, frontal alpha asymmetry (FAA) analyses contrast alpha spectral power at right and left hemisphere prefrontal sites (Coan & Allen, 2003). As substantial evidence supports the differential lateralisation of approach– and withdrawal–related prefrontal cortex circuitry, FAA analysis provides a biologic assay of the relative engagement of approach (left) *vs.* withdrawal (right) circuitry (Davidson, 2004).

6.2.1.2 Autonomic Measures

6.2.1.2.1 Cardiovascular Measures

The heart is dually innervated by the sympathetic and parasympathetic branches of the ANS, which largely control heart rate (HR) and rhythm (Thayer & Lane, 2009). Whereas increased cardiac sympathetic innervation increases the HR, parasympathetic cardiac innervation via the vagus cranial nerve tonically inhibits HR (Uijtdehagge & Thayer, 2000). Via their interplay, the heartbeat is dynamically and continuously adjusted to meet the individual's current needs; under resting conditions, energy conservation via vagal cardiac inhibition prevails (Thayer & Lane, 2007).

The electrocardiogram (ECG) yields multiple indices of HR and heart rhythm dynamics (Malik *et al.* 1996). Time–domain ECG–derived measures of HR reflect an admixture of SNS and PNS influences, yet provide a rough estimate of sympatho–vagal balance (Thayer & Brosschot, 2005). In addition to HR average measures, the HR time series shows substantial beat–to–beat variability (*i.e.* heart rate variability; HRV) (Thayer & Lane, 2007). Although variously operationalised, HRV is defined as variance in the interval between consecutive normal heartbeats (Malik *et al.* 1996). There are multiple time– and frequency–domain indices of HRV (Malik *et al.* 1996). In the frequency–

domain, spectral analysis of the ECG permits the differentiation of intrinsic sources of HR variance, which occur at different frequencies (Beauchaine, 2001). Spectral analysis of the ECG reveals 3 peaks: very low frequency (VLF), low frequency (LF) and high frequency (HF) (Yeragani *et al.* 2004). As HRV is largely modulated by HF spectral power (~0.15 – 0.4 Hz) (Malik *et al.* 1996), which is under is parasympathetic control, HRV measures index cardiac vagal control (Friedman & Thayer, 1998a; Friedman *et al.* 2002a).

Higher cardiac vagal tone facilitates orienting to discrete environmental stimuli, whereas poorer cardiac vagal tone is associated with poorer attention to and discrimination among environmental stimuli (Friedman & Thayer, 1998b). Thus HRV, as an index of vagal tone, is considered an important marker of the individual's capacity for adaptive environmental engagement (Friedman, 2007). In accordance with the view that healthy physiological systems show high levels of adaptive variability, whereas pathological states are typified by extreme predictability (Thayer & Lane, 2000; Thayer & Friedman, 2002), low HRV has been linked with manifold psychopathological and medical conditions (Friedman *et al.* 2002a; Thayer & Lane, 2007).

6.2.1.2.2 Electrodermal Measures

Psychophysiological assessment of electrodermal activity (EDA) measures psychologically–induced changes in the level of sweat in eccrine sweat glands, which are most densely distributed on the palmar surfaces (Dawson *et al.* 2000). Changes in the level of sweat are positively associated with changes in the skin's electrical conductivity which, in turn, is measured as changes in EDA (Siepmann & Joraschky, 2007). Although stress and anxiety may produce noticeable sweatiness of the hands,

relatively mild emotions and even cognitive processes may activate the sweat glands at a level which is not consciously perceived by the individual, but which is nevertheless detectable by EDA recording devices (Grillon & Ameli, 2005). Unlike the heart, which receives dual sympathetic and parasympathetic innervation, EDA is mediated by cholinergic fibres which are entirely under sympathetic control (Critchley, 2002). EDA measures, therefore, provide indices of SNS activity unconfounded by PNS function (Gruzelier *et al.* 2002).

EDA comprises both slow and relatively rapid, transient changes in skin conductivity (tonic and phasic EDA, respectively). Tonic EDA can be measured as skin conductance level (SCL), which is the absolute level of skin conductance at a given time, or alternatively, the rate of decrement of SCL over time (*i.e.* habituation) (Boucsein, 1992). Phasic EDA, by contrast, refers to transient increases in skin conductivity called skin conductance responses (SCRs) (Dawson *et al.* 2000). Skin conductance responses are sensitive markers of events having particular significance for an individual and thus are related to emotional, novelty or attentional fields (Öhman *et al.* 2000; Critchley, 2002; Barry, 2004; Dindo & Fowles, 2008). However, SCRs can also occur in the absence of any apparent eliciting stimulus (e.g., during resting states) and are called *non–specific SCRs* (NS.SCRs) (Boucsein, 1992). EDA is considered to be a relatively stable trait that is related to behavioural and psychological individual differences (Dawson *et al.* 2000). Accordingly, test–retest correlations for EDA parameters recorded in normal subjects are high (Schell *et al.* 2002). However, correlations between different electrodermal parameters are not high (Fowles, 1980; Dawson *et al.* 2000), reflecting the differential validity of different EDA measures and thus the non–redundancy of electrodermal measures (Boucsein, 1992).

6.2.2 Resting State Findings

6.2.2.1 QEEG Findings

The association of reduced alpha–1 power with increased attentional and information processing demands suggests the possibility of a specific disturbance of this spectral parameter in PD. This is because, as discussed, individuals with PD may find the laboratory environment for resting state psychophysiological assessment anxiogenic (Wilhelm & Grossman, 2010), and distal threats elicit vigilance as a component of the anxiety response (Blanchard & Blanchard, 2008). However, only one study appears to have investigated alpha–1 spectral power at rest in PD (Newman *et al.* 1992), finding globally reduced alpha–1 power in an eyes–closed baseline condition (prior to caffeine challenge), in PD relative to unaffected controls. By contrast, patients and controls did not differ in alpha–2 power (Newman *et al.* 1992). Other resting state findings for PD relate to the broader alpha frequency band. Findings include a topographically–widespread reduction in alpha power that was particularly apparent in PDA (Gordeev, 2008), and a negative correlation of alpha power and self–reported anxiety (Knott, 1990). In contrast to these findings, both increased alpha power in PD (Knott *et al.* 1996) and null findings (Dractu & Bond, 1998) have been reported. No pattern is evident in the literature for the other commonly–investigated broad frequency bands, theta and beta.

In addition to these global alterations in basal cortical activity, there were several region–specific findings within frontal and temporal cortices. These include a greater frontal EEG asymmetry (R<L alpha power) in PD compared to controls during resting phases and when viewing anxiety–relevant stimuli, but not during an emotionally–neutral 'distraction' condition (Wiedemann *et al.* 1999). According to the authors,

resting phases may be experienced by panic disordered individuals as unpleasant, as they offer no distractions from their negative thoughts. Other findings show reduced inter–frontal and intra–temporal functional connectivity (Hanaoka *et al.* 2005), and decreased relative alpha power in the temporal region (Bystritsky *et al.* 1999) in PD.

Thus QEEG findings, although equivocal, suggest that PD during the inter–panic interval may be associated with both global alterations in cortical stability, and region–specific abnormalities in frontal and temporal cortices. However, various methodological and sample–selection issues preclude the integration of this literature, and cast doubt on the reliability of some of its findings. These issues include, importantly, sample size. Alpha–1 power, for example, shows marked inter–individual variability (~90–fold) (Chen *et al.* 2008). The single above–reported finding of reduced alpha–1 power in PD (Newman *et al.* 1992) would therefore need replication with greater subject numbers. Additionally, patients' medication status and comorbidity varied between studies and has not always been addressed statistically. Methodological issues include inconsistency in the recording condition (*e.g.*, REC *vs.* REO *vs.* pre–activation challenge). Also, given empirical evidence of two orthogonal components within the extended alpha range, the analysis of a broad alpha frequency band may obscure frequency–specific effects (Klimesch, 1999). Given the relative dearth of QEEG studies of PD, the interpretive challenge presented by this literature, and its inconsistent findings, there remains a need to investigate basal cortical function in PD during the inter–panic interval.

6.2.2.2 Autonomic Findings

In parallel to the QEEG literature, a largely separate literature has investigated ANS

function during various resting states in PD. Findings for resting HR in PD are equivocal. Although many studies reported increased resting HR (Hoehn–Saric *et al.* 1991; Roth *et al.* 1992; Cohen *et al.* 2000; Cuthbert *et al.* 2003; Blechert *et al.* 2007b; Garakani *et al.* 2009), there have been null findings (Dractu & Bond, 1998; Larsen *et al.* 1998; Parente *et al.* 2005; Lambert *et al.* 2006). However, as these physiologic baseline conditions varied markedly and often preceded challenge procedures, these results were likely influenced by the specificity of the test situation (Wilhelm & Roth, 2001; Hoehn–Saric, 2007). By contrast, findings for HRV in PD are relatively consistent, with robust evidence of tonically reduced HRV in PD relative to healthy controls across a wide variety of conditions (review Friedman, 2007). Additionally, increased tonic and phasic EDA, as increased SCL, less variable SCL, reduced SCL habituation and more frequent NS.SCRs, have often been reported (Roth *et al.* 1990; Hoehn–Saric *et al.* 1991; Braune *et al.* 1994; Roth *et al.* 1998; Parente *et al.* 2005), although there have been null findings (e.g., Jensen *et al.* 1996).

Taken together, resting state autonomic findings for PD (increased HR and EDA, and reduced HRV and habituation) reflect a weighting of ANS function balance in the direction of SNS as opposed to vagally–mediated PNS function (Friedman & Thayer, 1998b). However, the findings do not support a global increase in sympathetic activation. For instance, cardiovascular and electrodermal measures of arousal in PD often correlate poorly (e.g., Hoehn–Saric *et al.* 1991; Cuthbert *et al.* 2003; Parente *et al.* 2005; Blechert *et al.* 2007b). Additionally, different measures within the same response system may dissociate. For example, non–covariance of EDA measures occurs in PD (Parente *et al.* 2005), and more broadly (Fowles, 1980; Boucsein, 1992). Moreover, the presence of null findings is inconsistent with global SNS activation.

6.2.3 Defining 'at rest'

Psychophysiological *resting state* paradigms are defined by the absence of experimentally–imposed task requirements (Rauch *et al.* 2003). In such paradigms, research participants simply remain still whilst psychophysiological measures are obtained. Historically, PD research has assumed that resting state measures index a symptom–free baseline state, and have typically contrasted these measures with those obtained during active (*i.e.* symptom–manipulation) states (Wilhelm & Grossman, 2010). However, despite the absence of task demands, resting state paradigms do not index a universal, threat–neutral baseline – indeed, no such baseline exists (Wilhelm & Roth, 2001; Blackhart *et al.* 2002; Hagemann *et al.* 2005; Dager, 2010). On the contrary, a range of contextual and individual difference factors interact to determine an individual's perception of threat imminence in a given situation, including at rest (Wilhelm & Roth, 2001; Lang & Davis, 2006; Wilhelm & Grossman, 2010). Within the PD literature of late there is increasing acknowledgement that the psychophysiological assessment environment may exert a differential effect on panic disordered and healthy control subjects (Lissek *et al.* 2005; Grillon, 2008; Dager, 2010). In short, available evidence (see below) suggests that the experience of sitting quietly in an unfamiliar laboratory environment, with barriers to escape, etc., would represent a mildly anxiogenic situation for unaffected controls, and a relatively aversive, threatening situation for individuals with PD. Hence, the inverted commas around "at rest" in the chapter title allude to the disjunction between the operational definition of resting state and the anxious state that such an environment may engender.

Typical psychophysiology assessment rooms comprise numerous contextual elements which are inherently (*i.e.* normatively) anxiogenic or otherwise of negative valence and

thus significant. For instance, laboratories typically comprise many novel, unfamiliar and potentially threatening elements (e.g., unfamiliar rooms, apparatus and procedures) (Wilhelm & Grossman, 2010). Novel situations elicit hypervigilance, increased alertness, and a range of physiologic changes, including increased cortical activity (Stapleton *et al.* 1997; Dietl *et al.* 2004; Lang & Davis, 2006; Blanchard *et al.* 2011). Additionally, psychophysiology assessment rooms are typically confined spaces in which research subjects are physically tethered to several recording devices (Wilhelm & Grossman, 2010). Self–report and psychophysiological evidence suggests that these elements (*i.e.* confinement and physical restraint) are anxiogenic for many healthy subjects (Argyle, 1991). Restraint is also implied by the presence of surveillance equipment and laboratory staff for monitoring performance (Lang *et al.* 1997). Moreover, psychophysiology preparation and acquisition protocols (e.g., restriction of movement for prolonged intervals, preparation and fitting of EEG cap) are often physically uncomfortable and unpleasant (Wilhelm *et al.* 2001; Blackhart *at al.* 2002). Finally, as unpredictable/uncontrollable aversive events are anxiogenic (Fonteyne *et al.* 2009), insofar as laboratory procedures are perceived as unpredictable/uncontrollable and adverse they may elicit anxiety (Grillon, 2008).

However, available evidence suggests that people with PD show exaggerated responses to each of these contextual parameters. For instance, heart rate data demonstrate increased response to novel situations in PD relative to controls (Larsen *et al.* 1998). Additionally, evidence suggests that individuals with PD show exaggerated physiological arousal and subjective anxiety during conditions of distal, but not proximal threat (Craske & Waters, 2005; Grillon, 2008). Furthermore, self–report data suggest that individuals with PD frequently report phobic responses to physical

sensations of restriction or entrapment (Cassano *et al.* 1999; Rucci *et al.* 2009), and find confined spaces more anxiogenic than controls (Argyle, 1991). Physical restraint, which represents a barrier to escape, may be especially anxiogenic for patients with more severe agoraphobia (Roth *et al.* 1986; Jones *et al.* 1996; Burkhardt *et al.* 2010). More generally, a range of physical sensations may elicit anxiety in PD (Bouton *et al.* 2001; Schmidt *et al.* 2006a; Lissek *et al.* 2010). Additionally, as fears of social evaluation are an important theme in PD catastrophic cognitions (Raffa *et al.* 2004; Hicks *et al.* 2005), panic disordered individuals may be particularly sensitive to being observed and monitored. Finally, resting state paradigms may be anxiogenic for individuals with PD because they provide minimal distraction from panic–related events (e.g., bodily sensations, thoughts and imagery) (Wiedemann *et al.* 1999; Wilhelm *et al.* 2001). Accordingly, REC conditions may be particularly anxiogenic because competition from environmental cues is further reduced (Pennebaker, 2000). Overall, the resting state psychophysiological assessment environment constitutes a 'weak situation' in terms of threat, and thus is ideal in order to elicit patient–control differences (Lissek *et al.* 2006).

6.3 The Present Study

In contrast to previous resting state studies of PD, the present study is of relatively integrative design in that central and peripheral measures were concomitantly–recorded. Moreover, multiple measures of brain or body function were obtained from each psychophysiological channel (QEEG, ECG and EDA). Study 1 encompassed two resting conditions: REO and REC. QEEG spectral power was examined within four frequency bands (theta, alpha–1, alpha–2 and beta), and FAA was examined within two alpha bands. Additionally, alpha peak amplitude and alpha peak frequency (APF) were computed. Alpha peak amplitude is defined as the maximal peak within the alpha

frequency range and is thus a measure of EEG magnitude, whereas APF is the discrete frequency which at which this peak occurs (Klimesch, 1999; Angelakis *et al.* 2004). Although Newman *et al.* (1992) investigated the effect of caffeine on EEG measures, including APF, but they did not report the baseline APF. Previous research has shown that individual differences in resting state APF are positively associated with cognitive performance, particularly memory performance (Klimesch, 1997; Angelakis *et al.* 2004; Clark *et al.* 2004).

Cardiovascular measures were: mean RR interval (an inverse index of HR) (Pan & Tompkins, 1985), standard deviation of the RR interval, and LF:HF ratio, which represent measures of mean HR, HRV, and strength of SNS relative to PNS cardiac influences, respectively (Malik *et al.* 1996). Tonic and phasic EDA were indexed by SCL habituation and NS.SCR frequency, respectively. Additionally, the effects of medication use, comorbidity and several other clinical parameters on brain and body function in PD were examined.

Specific aims of Study 1 were to replicate the earlier finding for alpha–1 frequency spectral power (Newman *et al.* 1992) with a larger sample, and to determine the specificity of this finding in relation to other frequency bands. Study 1 also aimed to replicate the finding of frontal alpha asymmetry in PD (Wiedemann *et al.* 1999) and extend this finding with analysis of narrower alpha frequency bands, as previous research has indicated that asymmetry effects are more prominent in the lower alpha band (Goncharova & Davidson, 1995; Davidson *et al.* 2000b; Wacker *et al.* 2003).

The rationale pertinent to this study's hypotheses derives from several different literatures that to date have been largely unintegrated. Nevertheless, on the basis of the foregoing it was predicted that individuals with PD, relative to healthy matched controls, would show:

1) Reduced alpha–1 spectral power;

2) Increased alpha–1 frontal asymmetry (R<L power);

3) Reduced RR interval (*i.e.* increased HR);

4) Reduced HRV;

5) Increased LF:HF ECG spectral power;

6) Increased tonic EDA (*i.e.* reduced SCL habituation), and;

7) Increased phasic EDA (*i.e.* more frequent NS.SCRs).

6.4 Method

6.4.1 Participants

The patient and control samples for Study 1 comprised 52 participants with a primary diagnosis of PD (37 females) and 104 age, gender, handedness and education–matched controls (74 females). Details regarding the recruitment of patients and controls, and study criteria were presented in Chapter 4. Additionally, as demographic and clinical data for all subjects were reported in Chapter 5, this chapter does not report these data, given the near identical subject numbers comprising the Study 1 samples.

6.4.2 Stimulus Materials and Procedure

Study 1 reports the results of two paradigms: Resting Eyes Open (REO) and Resting Eyes Closed (REC). These two resting EEG tests are the first two tests in the psychophysiological battery comprising 11 tests.

After being prepared for psychophysiological recording (Section 4.3.2.1) participants were seated in a sound– and light–attenuated room directly in front of a computer monitor, at a distance of 60 cm, so that their eyes were aligned with the centre of the screen. Standardized pre–recorded task instructions were delivered binaurally via headphones using computer .wav files. Test instructions were also presented visually on the computer screen. Participants were instructed to minimize their movement during each test. For the REO condition participants were asked to focus their eyes on a red dot at the centre of the computer screen for the test duration. For REC they were asked to sit with their eyes closed, and were told that they would be informed when the test was complete. For each test, participants were informed that the test duration was 3 minutes, although the actual recording time is 2 minutes. At the time of undertaking these tests participants had been in the laboratory for approximately one hour.

6.4.3 Psychophysiology Data Acquisition, Artefact Correction and Data Reduction

Measurement of brain (EEG) and body (heart rate, EDA) function were recorded concurrently and continuously throughout the tests. Electrooculogram (EOG) and electromyography (EMG) data were also recorded continuously throughout, for offline removal of eye movement and muscle artefact, respectively.

6.4.3.1 Electroencephalography

A QuickCap (Neuroscan) was used to acquire EEG data from 26 cephalic sites, according to the 10–20 International system (Jasper, 1958). These sites were Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (see Figure 6 for a depiction of cephalic sites). Data were recorded relative to the average of A1 and A2 (mastoid) electrode sites, with a forehead ground.

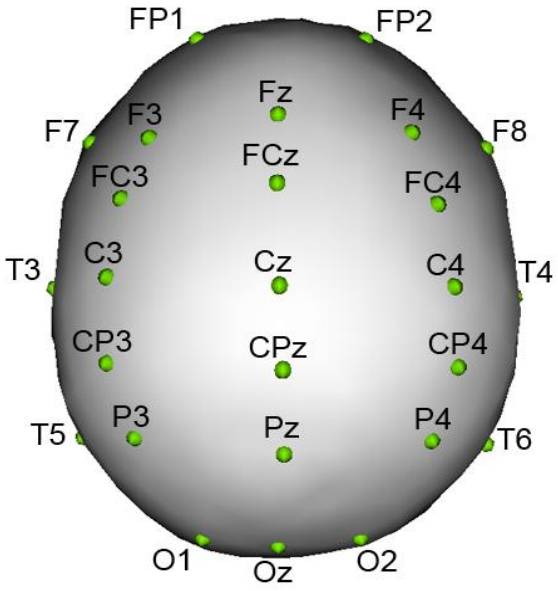

Figure 6: Electrode location. Figure shows location of 26 cephalic sites as bird's–eye view of head (nose at top of image).

Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded from electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye–lid. Electromyography data were recorded continuously with an electrode positioned over the right mastoid muscle. Figure 7 shows the placement of the electrode cap for psychophysiology recording.

Skin resistance was kept below 5 kΩ. Scalp, EOG and EMG potentials were amplified and digitized continuously by a system (NuAmps, SCAN 4.3) having a frequency response from DC to 100 Hz (above which attenuating 40 dB per decade), and a sampling rate of 500 Hz.

NOTE:
This figure is included on page 172 of the print copy of the thesis held in the University of Adelaide Library.

Figure 7: Placement of electrode cap for recording. Photograph reproduced from Brain Resource Ltd. materials.

EEG data were screened both visually and automatically for artefact. Three methods of artefact correction were applied to the EEG data. Firstly, an eye–blink correction algorithm took continuous EEG and performed offline artefact correction, similar to the Gratton method (Gratton *et al.* 1983). In contrast to the Gratton method, however, correction coefficients were calculated for both vertical and horizontal EOG data, and the algorithm was applied to continuous data, not separate epochs. Secondly, an epoch rejection algorithm identified channels exceeding a given voltage threshold. When three or more channels exceeded this threshold, the epoch was rejected. For most channels, the specified threshold was 100μV. If more than 50% of a subject's epochs were rejected, the subject's EEG data were rejected. Finally, manual rejection of individual channels or entire EEG datasets occurred when data were marked as 'bad' by a technician blinded to group status. Manual rejection could occur due to the presence of visible muscle artefact, or other 'noise' in the signal (Pivik *et al.* 1993).

For each resting EEG task average power spectra were computed for 28 epochs. Two minutes of EEG were divided into adjacent intervals of 4 s. Spectral power analysis was performed on each epoch by applying a Welch window to the data and then performing a Fast Fourier Transform. Spectral power, reported as μV^2, was aggregated across frequency bins to yield absolute power data for the following frequency bands: theta (4 – 7.5 Hz), alpha–1 (8 – 11 Hz), alpha–2 (11 – 13 Hz), and beta (14.5 – 30 Hz), at each electrode position, in each condition. Only absolute as opposed to relative power measures are reported, in accordance with recommendations (Klimesch, 1999; Pivik *et al.* (1993). Absolute spectral power values reflect the overall electrophysiological activity at a given electrode within a given frequency band (Klimesch, 1996). Spectral EEG data analyses were based on data acquired from 16 scalp sites: 3 each frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital sites (O1, Oz, O2), and 4 temporal sites (T3, T4, T5, T6). These sites were chosen to permit the assessment of both global and region–specific scalp topography of QEEG parameters in PD. (Note, topographical maps and statistical probability maps, which are for illustrative purposes only, depict electrocortical activity at all 26 sites, to illustrate spectral topography.)

In addition to average spectral power measures, alpha peak amplitude and APF values were computed. Alpha peak amplitude was defined as the maximal amplitude within the broad alpha frequency range (8 – 13 Hz), whereas the frequency at this peak was designated APF.

6.4.3.2 Electrocardiography

Electrocardiogram recording was obtained throughout each test from an electrode positioned at the radial pulse, on the inside of the left wrist and referenced for analysis

by two non–cephalic sites: Erbs point (located above the clavicle) and C7 (the 7th cervical vertebra). The ECG recording channel was sampled at 500 Hz, with 22–bit resolution digitization. A low pass filter was applied prior to digitization with a cutoff starting at 100 Hz. The reported time–domain measures were mean RR and standard deviation of the RR interval for each condition (*RR* and *HRV*, respectively). Within the frequency–domain, a Welch window was applied to the interpolated RR series and low frequency (LF: 0.04 – 0.15 Hz) and high frequency (HF: 0.15 – 0.4 Hz) spectral power density for each condition was calculated (reported as *LF:HF*). The following criteria resulted in rejection of all the ECG data for a given paradigm: (1) <40 beats per minute, (2) tacho series standard deviation >12 or, (3) a gap in the series of >2.5 s.

6.4.3.3 Electrodermal Activity

Electrodermal activity was recorded with the aid of a traducer (Grass, SCA1), via a pair of silver–silver chloride electrodes with 0.05M NaCl gel, which were placed on the medial phalanges of digits II and II of the non–dominant hand. A constant voltage of 0.5V excited the electrode pair, and the current proportional to conductance was converted to a voltage, which was digitised by the same hardware and software as was used for EEG. After digitization, EDA data were stored on magnetic media and numerically analysed offline. As per EEG data, EDA recordings were screened visually for artefacts and variants by a technician blinded to group status.

EDA recordings were decomposed into tonic and phasic measures of EDA: SCL as a function of time served as the index of tonic EDA, whereas NS.SCR frequency indexed phasic EDA. Although SCL average is the most common tonic EDA measure (Dawson *et al.* 2000), SCL could not be used directly due to some uncertainty regarding the DC

offsets in some control subjects' recordings. Instead, the slope of the skin conductance level within each test, as microSiemens/second (μS/s), was estimated. This measure was calculated by fitting an exponential curve to the EDA time series and then taking the initial slope of the fit as characterising the rate of change of the exponential baseline. This measure (*SCL–GRAD*) thus represented the systematic decrement in SCL over time. The frequency of NS.SCRs was quantified using a method that enables overlapping SCRs to be separated (Alexander *et al.* 2005). Individual NS.SCRs were scored if the amplitude of response exceeded 0.02 μS. The number of NS.SCRs occurring within each paradigm is reported (*NS.SCR*).

6.4.4 Data Cleaning

Prior to statistical analysis, all variables were assessed for the presence of missing data and outliers, in accordance with the method described in Section 4.5. As a substantial proportion of one patient's EEG data was missing in a non–random manner, all of that subject's data were excluded from Study 1 analyses, in accordance with the recommendations of Tabchnick and Fidell (2008). Consequently, data for two matched control subjects were also removed.

Overall, altered outliers and missing data constituted l.1% of patients' EEG data and 1.2% of controls' EEG data; the corresponding figures for autonomic data were 3.1% and 2.4%. Unless otherwise stated, the subject numbers for the clinical and control samples are (n = 52) and (n = 104), respectively. To normalize their distributions, logarithmic transformations were applied to all EEG spectral power data (Ln_{10}x), HRV (Ln_{10}x) and NS.SCR (Ln_{10}(x + 1)) data.

6.4.5 Statistical Analyses

An omnibus mixed–model ANOVA of spectral power data was conducted with the within–subjects factors *Condition* (REC, REO), *Band* (theta, alpha–1, alpha–2, beta) and *Site* (absolute power at 16 sites), and the between–subjects factor *Group* (PD, controls). This initial analysis tested for global and/or regional between–group differences in spectral power, and identified whether such differences were selectively related to spectral frequency and/or condition. A significant Group main effect and several interactions of relevance to the study hypotheses and aims necessitated further analyses, as detailed in Section 6.5.1.1.

A mixed–model ANOVA (*Site* and *Group* factors) examined alpha peak amplitude. APF data for REC condition only were compared with between–groups *t*–test, due to excessive missing data in REO. An omnibus mixed–model ANOVA compared the groups for FAA. Within–subjects factors were *Condition* (REO, REC), *Band* (alpha–1, alpha–2) and *Hemisphere* (absolute power at F3, F4), with *Group* (PD, controls) as the between–subjects factor. Bilateral power data were used for the assessment of FAA, as opposed to the computation of asymmetry metrics, to retain information about frontal brain activity within each hemisphere (Davidson, 2004). This analysis also determined whether FAA group differences were specific to a narrow alpha frequency band. Significant Group*Hemisphere interactions were followed by paired–samples *t*–tests, to compare the extent of alpha asymmetry within each group.

Separate mixed–model ANOVAs (*Group* and *Condition* factors) were conducted for all autonomic variables except SCL–GRAD. Due to the presence of substantial missing

SCL–GRAD data during REC, only data from the REO test were used. Independent–samples *t*–tests compared the two groups on the latter.

Finally, standard multiple regression analyses examined the relationship between clinical measures and psychophysiological measures distinguishing patients and controls, in patients.

6.5 Results

6.5.1 Panic Disorder vs. Matched Controls

6.5.1.1 Spectral Power

The initial omnibus mixed–model ANOVA incorporating all spectral power data revealed several significant main effects and interactions of relevance to the study aims and hypotheses. A significant main effect for Group ($F_{1, 152} = 6.68$, $p = .011$, $\acute{\eta}_p^2 = .042$) reflected reduced spectral power in PD ($n = 50$) relative to controls ($n = 104$) at almost every electrode position, within each frequency band and condition. The Group main effect was qualified by significant Group*Band ($F_{3, 456} = 3.70$, $p = .012$, $\acute{\eta}_p^2 = .024$) and Group*Condition ($F_{1, 152} = 5.94$, $p = .016$, $\acute{\eta}_p^2 = .038$) interactions, which reflected a more prominent reduction of spectral power in PD within alpha–1 band, and REC condition, respectively.

As these interactions required more detailed analyses, separate mixed–model ANOVAs were conducted for each frequency band within each condition, with Site (absolute power at 16 sites) as the sole within–subjects factor and Group (PD, controls) as the between–subjects factor. Main effects for Site are not reported due to the high predictability of spectral EEG parameters, including topography, within normative

populations (Hughes & John, 1999). Significant Group main effects and Group*Site interactions were explored post hoc with independent–samples *t*–tests.

6.5.1.1.1 Spectral Power Summary Data

Group mean spectral power for the four frequency bands at midline sites Fz, Cz, Pz, and Oz are shown in Table 17 (REO) and Table 18 (REC). Group mean continuous power spectra for the 5 – 20 Hz frequency range at sites Fz and Pz are shown in Figures 8 (REO) and 9 (REC).

6.5.1.1.2 Theta

Patients and controls did not differ in theta power ($p \geq .436$) or topography in either condition, despite a significant Group*Site interaction in REC ($F_{15, 2310} = 2.29$, $p = .038$, $\acute{\eta}_p^2 = .015$; $\varepsilon = .392$). The latter positive result was not associated with any clear topographical difference between patients and controls.

6.5.1.1.3 Alpha–1

A trend for reduced alpha–1 in patients during REO, particularly at frontal sites, did not attain statistical significance (Group main effect $F_{1, 154} = 2.46$, $p = .119$, $\acute{\eta}_p^2 = .016$). During REC, however, alpha–1 was greatly reduced in PD (Group $F_{1, 154} = 14.0$, $p < .001$, $\acute{\eta}_p^2 = .083$), and post hoc *t*–tests for all sites were significant (non–occipital $p < .001$, occipital $p < .05$). Group*Site interactions in both conditions were non–significant ($p \geq .131$). Figure 10 shows group mean alpha–1 spectral power averages for frontal, central, temporal, parietal, and occipital regions during REC. Figure 11 shows spectral power topographic maps and statistical probability map for alpha–1 during REC.

Table 17: Spectral Power for Panic Disorder (n = 52) and Controls (n = 104) During Resting Eyes Open: 4 Frequency Bands, 4 Midline Sites.

Resting Eyes Open	Fz	Cz	Pz	Oz
Theta				
PD	*11.49* 2.32 (0.51)	*13.02* 2.48 (0.43)	*9.81* 2.17 (0.50)	*6.43* 1.71 (0.55)
controls	*12.51* 2.44 (0.46)	*13.67* 2.48 (0.53)	*9.90* 2.16 (0.52)	*6.55* 1.69 (0.63)
Alpha-1				
[a] PD	*7.02* 1.80 (0.54)	*9.78* 2.10 (0.61)	*11.46* 2.16 (0.75)	*10.35* 1.97 (0.61)
controls	*10.34* 2.12 (0.68)	*11.95* 2.20 (0.75)	*16.20* 2.35 (0.93)	*12.81* 2.07 (1.00)
Alpha-2				
PD	*2.98* 0.93 (0.55)	*3.71* 1.14 (0.58)	*4.95* 1.35 (0.72)	*4.52* 1.22 (0.75)
controls	*3.70* 1.13 (0.62)	*4.25* 1.26 (0.64)	*5.65* 1.46 (0.76)	*4.77* 1.24 (0.84)
Beta				
PD	*10.04* 2.19 (0.48)	*11.60* 2.35 (0.48)	*10.31* 2.24 (0.45)	*9.72* 2.17 (0.46)
controls	*11.59* 2.33 (0.52)	*12.70* 2.39 (0.57)	*11.39* 2.29 (0.58)	*9.61* 2.09 (0.60)

Untransformed and transformed (Ln_{10}x) spectral power descriptive statistics reported as: $M_{\text{untransformed (in italics)}}$ $M_{\text{transformed}}$ $SD_{\text{transformed (in brackets)}}$. Untransformed means are for illustrative purposes only. [a] $n = 50$

Table 18: Spectral Power for Panic Disorder (n = 52) and Controls (n = 104) During Resting Eyes Closed: 4 Frequency Bands, 4 Midline Sites.

Resting Eyes Closed	Fz	Cz	Pz	Oz
Theta				
PD	*14.92* 2.56 (0.54)	*17.70* 2.75 (0.48)	*16.22* 2.57 (0.66)	*11.26* 2.15 (0.76)
controls	*16.77* 2.69 (0.53)	*18.04* 2.72 (0.60)	*15.59* 2.54 (0.66)	*10.80* 2.13 (0.73)
Alpha–1				
PD	*22.51* 2.78 (0.85)	*28.18* 3.01 (0.84)	*42.91* 3.30 (1.03)	*56.61* 3.38 (1.27)
controls	*40.24* 3.41 (0.84)	*46.04* 3.53 (0.87)	*85.37* 3.95 (1.11)	*75.57* 3.80 (1.12)
Alpha–2				
PD	*4.67* 1.34 (0.65)	*6.16* 1.60 (0.68)	*8.28* 1.84 (0.75)	*7.44* 1.73 (0.74)
controls	*5.32* 1.50 (0.59)	*6.83* 1.70 (0.70)	*11.09* 2.10 (0.82)	*9.84* 1.93 (0.86)
Beta				
PD	*11.46* 2.34 (0.45)	*14.55* 2.57 (0.47)	*13.71* 2.52 (0.45)	*12.73* 2.44 (0.45)
controls	*14.42* 2.54 (0.52)	*17.00* 2.68 (0.56)	*17.05* 2.67 (0.58)	*14.32* 2.50 (0.59)

Untransformed and transformed (Ln_{10}x) spectral power descriptive statistics reported as: $M_{\text{untransformed (in italics)}}$ $M_{\text{transformed}}$ $SD_{\text{transformed (in brackets)}}$. Untransformed means are for illustrative purposes only.

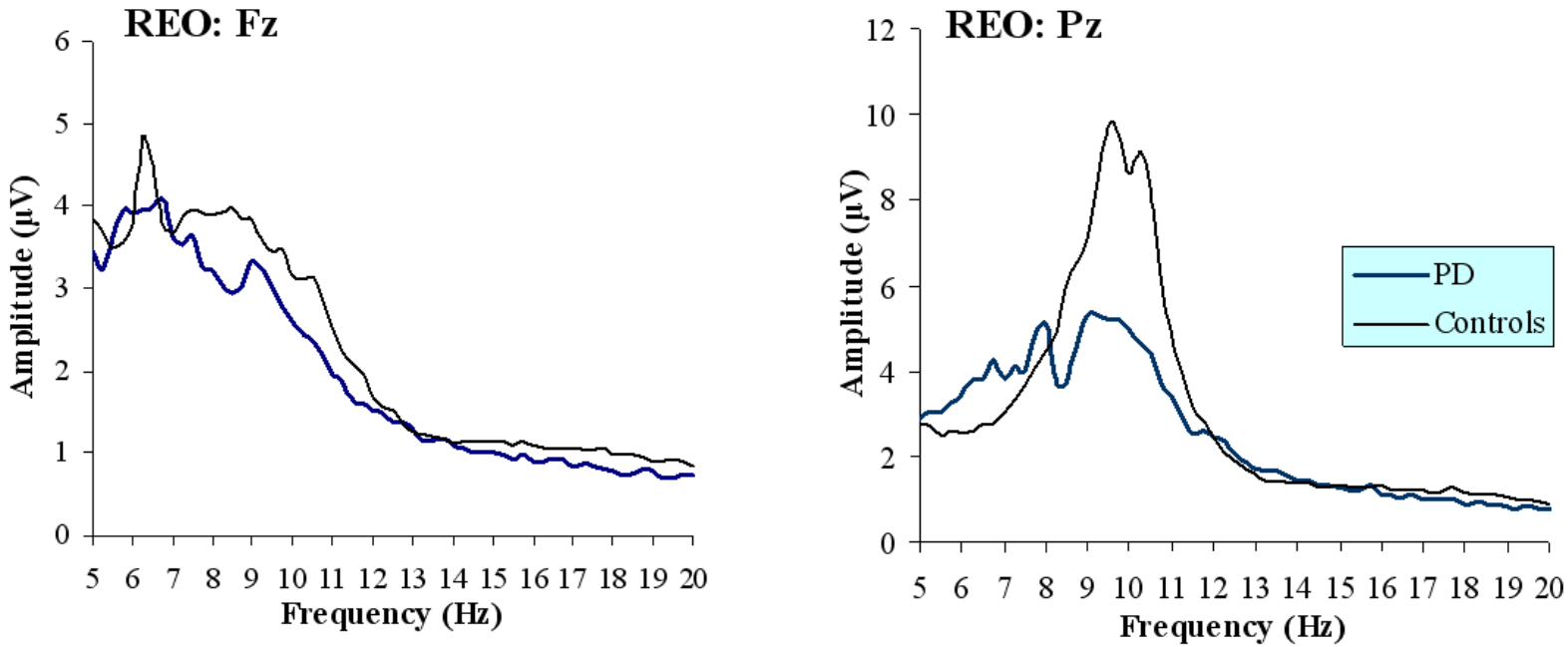

Figure 8: Group Mean Continuous Power Spectra for REO (5 – 20 Hz Frequency Range, 0.25 Hz Sampling). Left panel shows spectral power at midline frontal site Fz, right panel shows spectral power at midline parietal site Pz. Graphs show raw, untransformed spectral power data for PD (n = 49) and control (n = 105) participants. In contrast, inferential tests use *Ln*-transformed spectral power data.

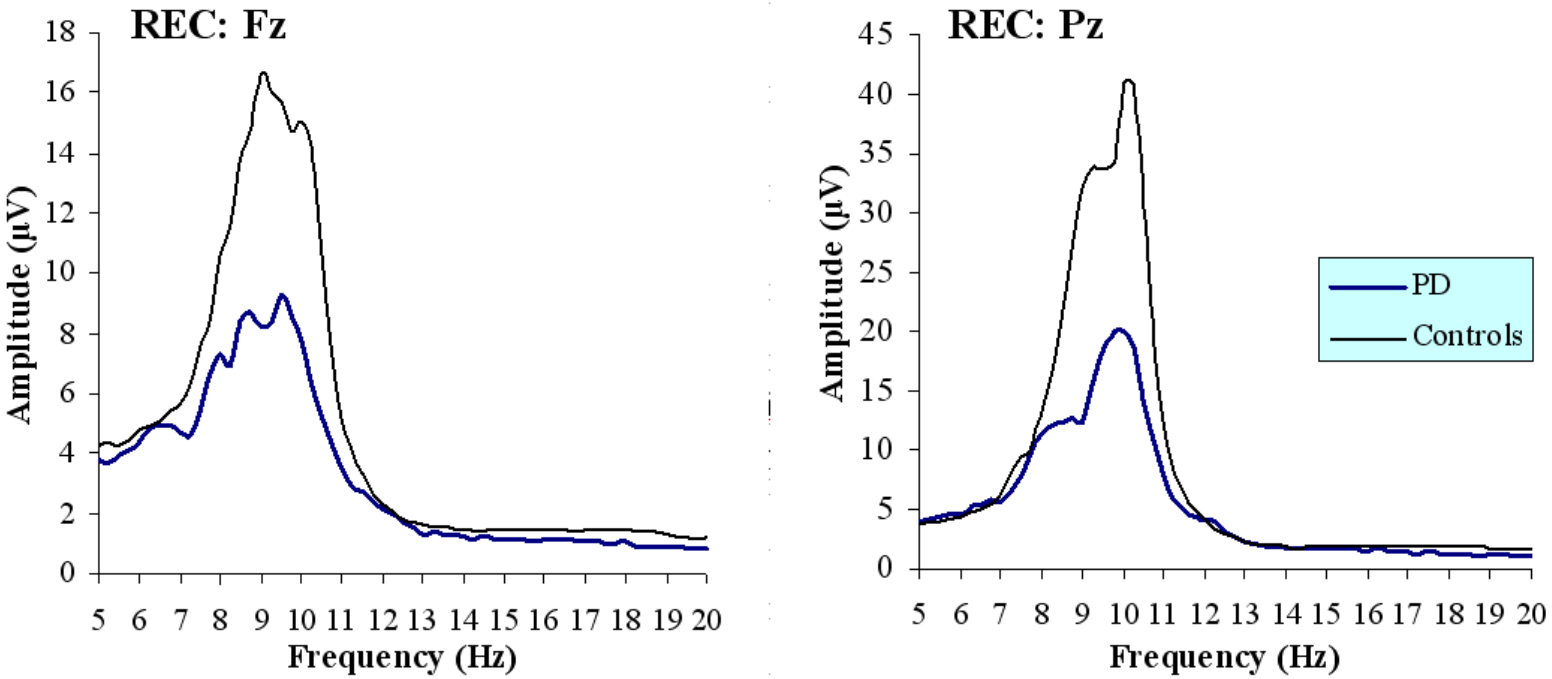

Figure 9: Group Mean Continuous Power Spectra for REC (5 – 20 Hz Frequency Range, 0.25Hz Sampling). Left panel shows spectral power at midline frontal site Fz, right panel shows spectral power at midline parietal site Pz. Graphs show raw, untransformed spectral power data for PD (n = 49) and control (n = 105) participants. In contrast, inferential tests use *Ln*-transformed spectral power data.

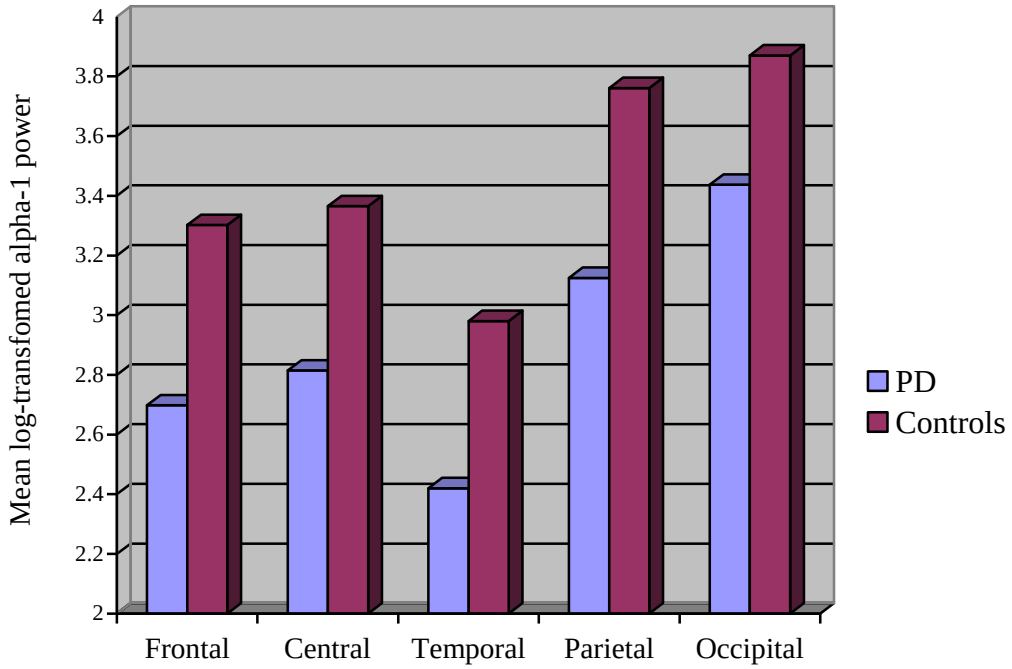

Figure 10: Group mean alpha–1 spectral power during REC by region. Figure shows mean log–transformed alpha–1 power (μV^2) for PD (n = 52) and controls (n = 104) during REC for frontal (av. F3, Fz, F4), central (av. C3, Cz, C4), temporal (av. T3, T4, T5, T6), parietal (av. P3, Pz, P4) and occipital (av. O1, Oz, O2) regions.

6.4.1.1.4 Alpha–2

During REO patients (n = 50) and controls (n = 104) did not differ in alpha–2 spectral power (Group $F_{1, 152}$ = 1.54, p = .217, $\acute{\eta}_p^2$ = .010) or its topography (Group*Site $F_{15, 2310}$ = 1.77, p = .102, $\acute{\eta}_p^2$ = .012, ε = .398). Similarly, during REC the main effect for Group was non–significant ($F_{1, 154}$ = 2.16, p = .144, $\acute{\eta}_p^2$ = .014), as was the Group*Site interaction (p = .707).

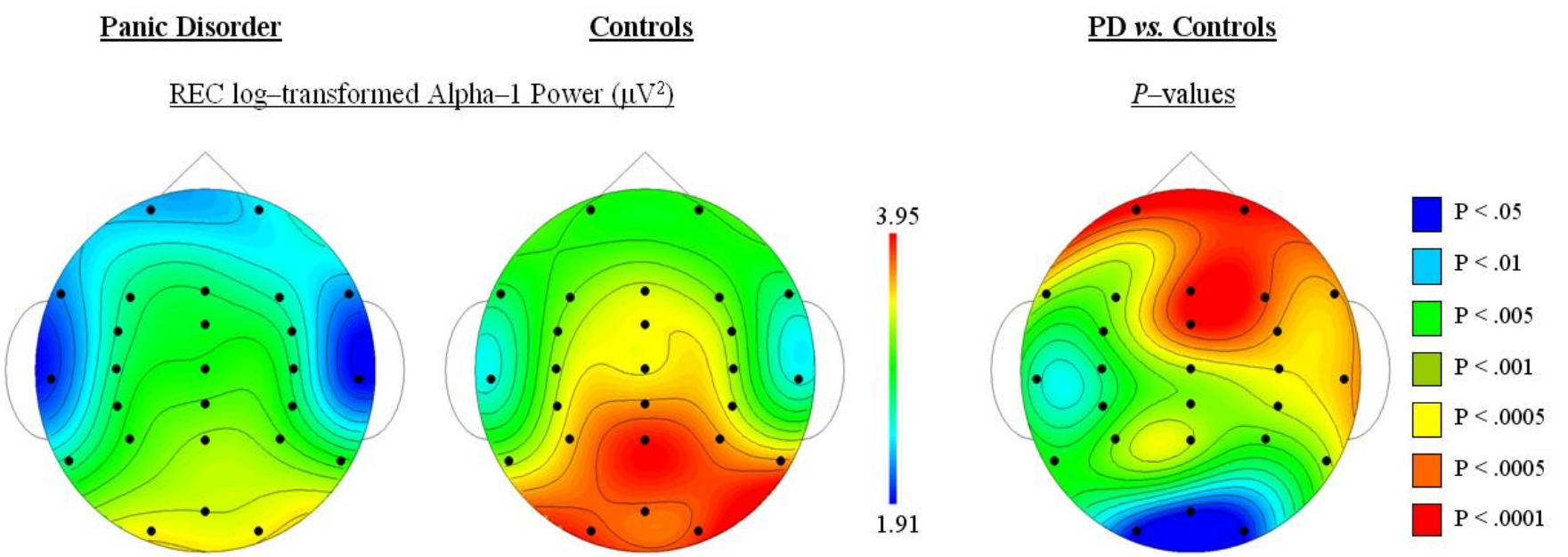

Figure 11: Spectral Power Topographic Maps and Statistical Probability Map for Alpha–1 during REC. Topographic maps (bird's–eye view, nose at top of image) show clinical (n = 52) and healthy control (n = 104) participants' mean log–transformed alpha–1 power during REC (at left), and significance level of between–group t–tests at 26 scalp sites (at right). Repeated–measures ANOVA showed significant Group main effect.

6.4.1.1.5 Beta

Patients showed a region–specific reduction in beta power during REO. The Group main effect was non–significant ($F_{1, 154}$ = 1.74, p = .190, $\acute{\eta}_p^2$ = .010), but the Group*Site interaction attained significance ($F_{15, 2310}$ = 3.97, p < .001, $\acute{\eta}_p^2$ = .025; ε = .362). Post hoc *t*–tests showed that beta power was attenuated at F4 (p = .014) and all temporal sites in PD (p < .05). Figure 12 shows topographic maps and statistical probability map for REO beta power. During REC, patients showed a scalp–wide reduction in beta spectral power, as reflected in the main effect trend ($F_{1, 154}$ = 3.27, p = .072, $\acute{\eta}_p^2$ = .021), and non–significant interaction ($F_{15, 2310}$ = 1.45, p = .202, $\acute{\eta}_p^2$ = .009).

6.5.1.2 Alpha Peak Amplitude

Alpha peak amplitude was reduced in PD (n = 43) compared to controls (n = 100) during REC, particularly at anterior sites (Group $F_{1, 141}$ = 15.0, p < .001, $\acute{\eta}_p^2$ = .096; Group*Site trend $F_{4.09, 577}$ = 2.10, p = .077, $\acute{\eta}_p^2$ = .015). Post hoc *t*–tests for all non–occipital sites were significant at p < .001, and occipital sites were significant at p < .05. Figure 13 shows REC alpha peak amplitude topographic maps and statistical probability map. Figure 14 shows REC group mean alpha peak amplitudes at aggregated frontal, central, temporal, parietal and occipital sites.

6.5.1.3 Alpha Peak Frequency

Patients (n = 49) and controls (n = 100) did not differ on alpha peak frequency or its topography (Group main effect and Group*Site interaction: $p \geq .399$).

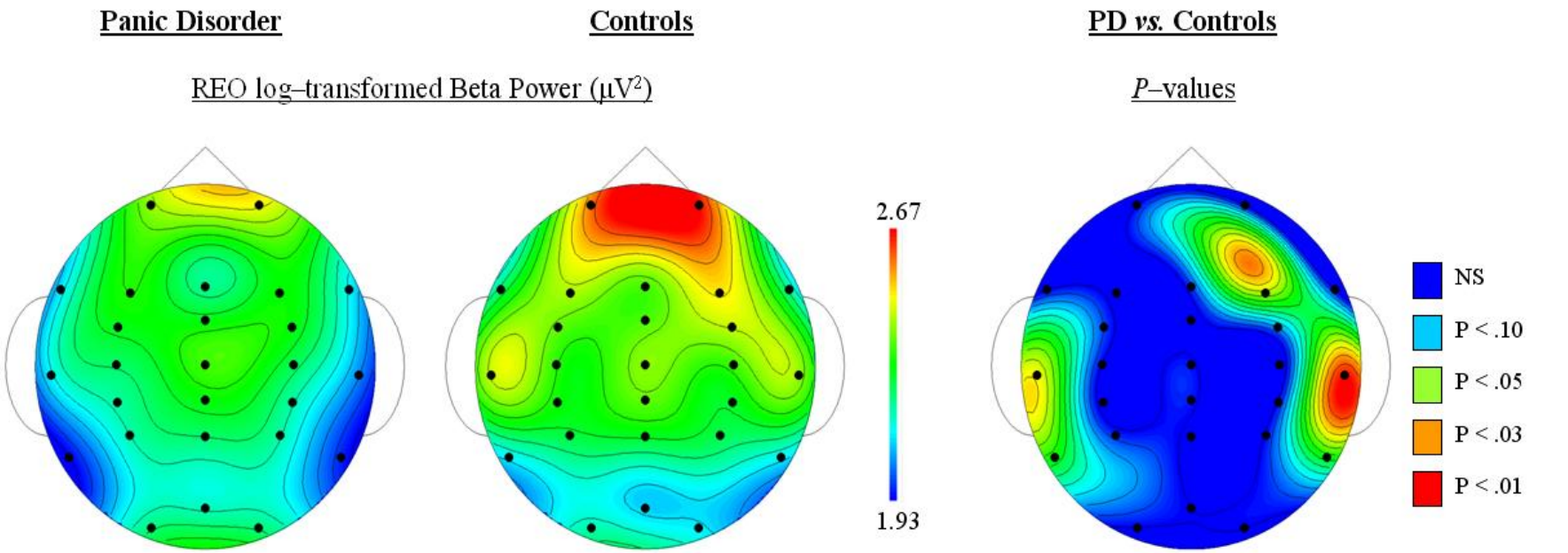

Figure 12: Spectral Power Topographic Maps and Statistical Probability Map for Beta during REO. Topographic maps (bird's–eye view, nose at top of image) show clinical (n = 52) and healthy control (n = 104) participants' mean log–transformed beta power during REO (at left), and significance level of between–group t–tests at 26 scalp sites (at right). Repeated–measures ANOVA showed a significant Group*Site interaction.

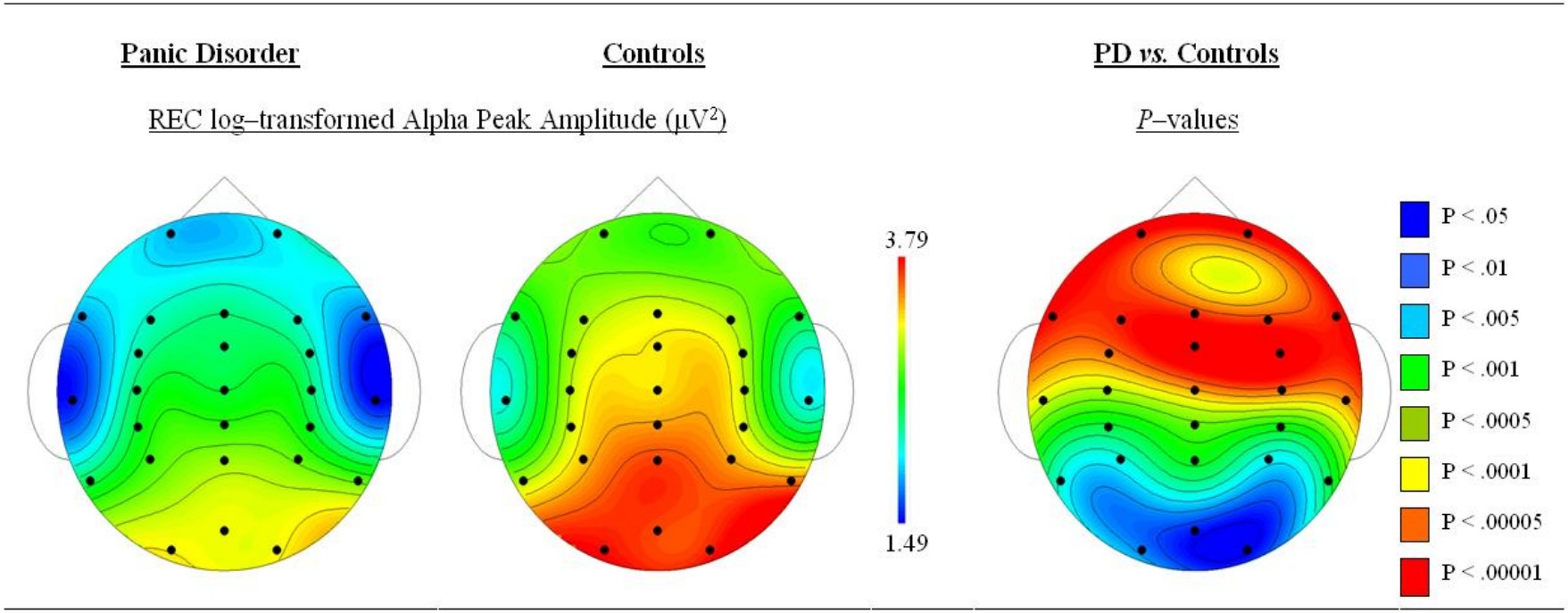

Figure 13: Spectral Power Topographic Maps and Statistical Probability Map for Alpha Peak Amplitude during REC. Topographic maps (bird's–eye view, nose at top of image) show clinical (n = 52) and healthy control (n = 104) participants' mean log–transformed alpha peak amplitudes during REC (at left), and significance level of between–group t–tests at 26 scalp sites (at right). Repeated–measures ANOVA showed significant Group main effect.

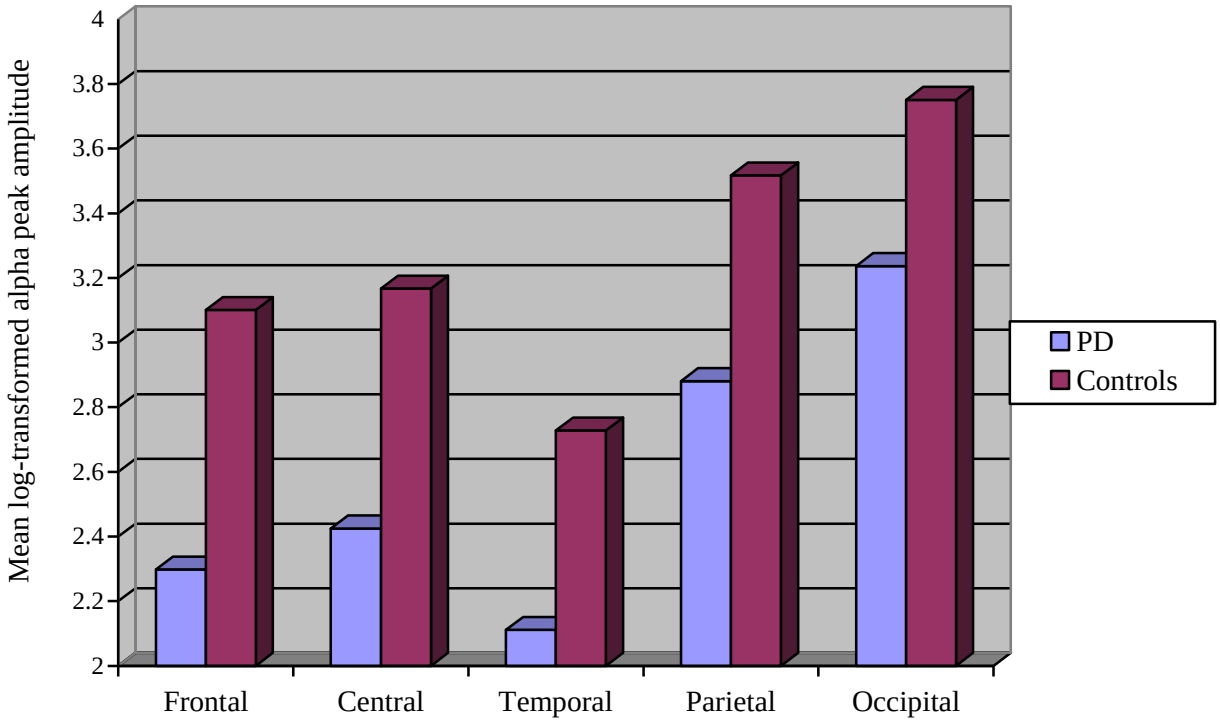

Figure 14: Group mean alpha peak amplitude during REC by region. Figure shows mean log–transformed alpha peak amplitude (μV) for clinical participants (n = 43) and controls (n = 100) during REC for frontal (av. F3, Fz, F4), central (av. C3, Cz, C4), temporal (av. T3, T4, T5, T6), parietal (av. P3, Pz, P4) and occipital (av. O1, Oz, O2) regions.

6.5.1.4 Frontal Alpha Asymmetry

The omnibus ANOVA showed several significant interactions of relevance to the study hypotheses and aims, including Group*Band*Condition ($F_{1,\ 154}$ = 11.3, p < .001, $\acute{\eta}_p^2$ = .069) and Band*Condition*Hemisphere interactions ($F_{1,\ 154}$ = 2.48, p < .05, $\acute{\eta}_p^2$ = .025). Therefore, separate ANOVAs were conducted for each alpha band and condition, resulting in four ANOVAs, each with *Hemisphere* (F3, F4) and *Group* (PD, controls) factors. Only alpha–1 power during REC showed a significant Group*Hemisphere

interaction ($F_{1,\ 154}$ = 7.46, p = .007, $\acute{\eta}_p^2$ = .046). Paired–sample t–tests showed a significant frontal alpha–1 asymmetry in PD (t_{51} = 2.77, p = .008), that was not evident in controls (t_{103} = –0.33, p = .745). Figure 15 shows alpha–1 spectral power at left (F3) and right (F4) frontal sites.

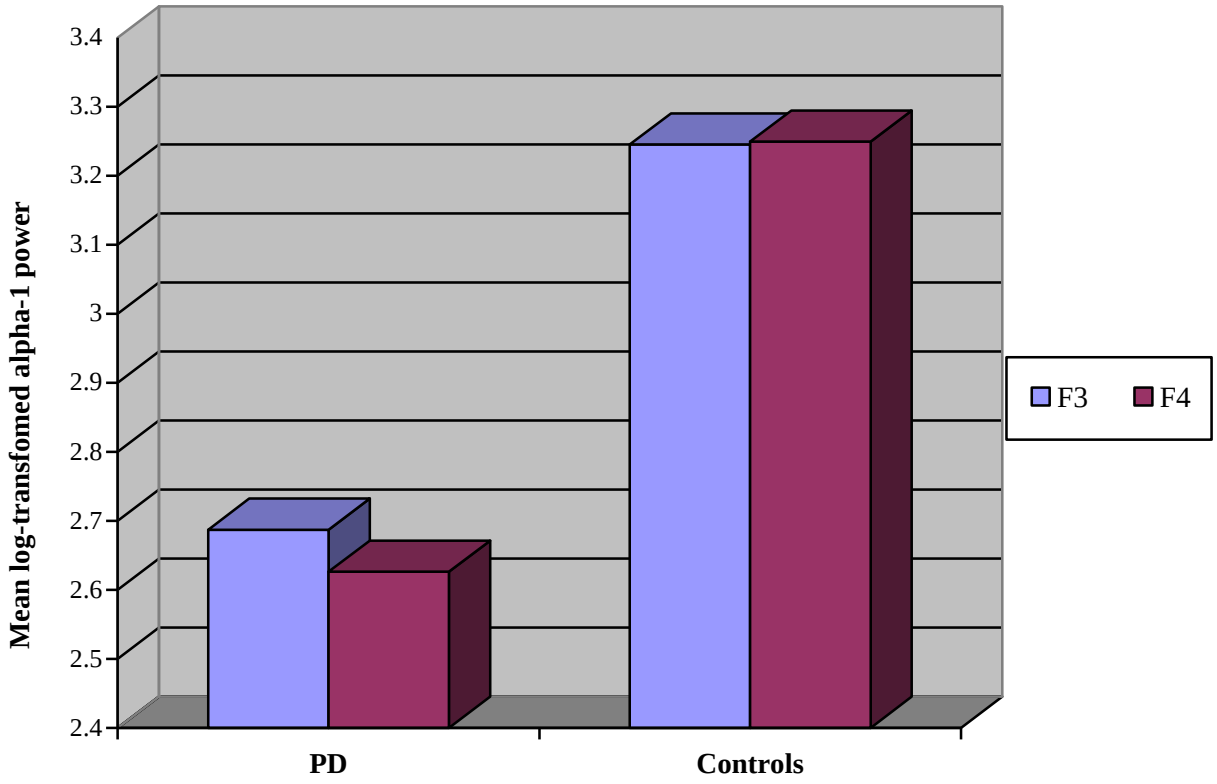

Figure 15: Group mean alpha–1 power at left (F3) and right (F4) frontal sites. Figure shows R<L alpha–1 power in PD, which represents greater right frontal activation. By contrast, controls show almost identical values for left and right frontal alpha–1.

6.5.1.5 Autonomic Function

As predicted, mean RR interval was lower in PD (n = 50) than controls (n = 104) (Group $F_{1,\ 152}$ = 6.97, p = .009, $\acute{\eta}_p^2$ = .044). Also, both groups' mean RR intervals were reduced during REC relative to REO (Condition $F_{1,\ 152}$ = 8.86, p = .003, $\acute{\eta}_p^2$ = .055;

Group*Condition p = .532). HRV was lower in PD (n = 51) compared to controls (n = 102) (Group $F_{1, 151}$ = 5.30, p = .023, $\acute{\eta}_p^2$ = .034), but the Condition main effect and Group*Condition interaction were non–significant ($p \geq .354$). Additionally, LF:HF ratio was higher in patients (n = 50) compared to controls (n = 100) (Group $F_{1, 148}$ = 6.63, p = .011, $\acute{\eta}_p^2$ = .043), but the Condition main effect and Group*Condition interaction were non–significant ($p \geq .712$). Post hoc independent samples t–tests were significant for all cardiovascular measures, within both conditions. For cardiovascular descriptive statistics and t–test results see Table 19.

Contrary to prediction, patients (n = 38) showed fewer NS.SCRs than controls (n = 72) (Group $F_{1, 108}$ = 12.8, $p < .001$, $\acute{\eta}_p^2$ = .106). Post hoc independent–samples t–tests were significant for both tests. Also, both groups showed fewer NS.SCRs during REO (Condition $F_{1, 108}$ = 9.23, p = .003, $\acute{\eta}_p^2$ = .079). The Group*Condition interaction was non–significant (p = .667). SCL–GRAD during REO was significantly lower in PD (n = 49) than controls (n = 95) (t_{142} = 2.95, p = .004, d = .038) (corrected t and p). For EDA descriptive statistics and t–test results see Table 20.

6.5.2 Relationship of Clinical and Psychophysiological Measures

Standard multiple regression analyses examined the relationship between measures of clinical severity and psychophysiology, in patients. Six psychophysiological measures differentiating patients and controls were entered simultaneously as predictor measures in two separate models. The predictor measures were: REC frontal alpha–1 power (av. F3, Fz, F4); REO temporal beta power (av. T3, T4, T5, T6); REC FAA (Ln_{10} (alpha–1 at F4) – Ln_{10} (alpha–1 at F3)) (Coan & Allen, 2004); REO SCL–GRAD; and RR and HRV during REC. Other variables, which would have violated the assumption of

multicollinearity (e.g., alpha peak amplitude, LF:HF), were not included as a predictor variables. Outcome variables for the two models were STAI–S and PDSS score. Additionally, a hierarchical model was conducted with PD duration as the outcome measure, with age entered in step 1. The same six psychophysiological variables served as predictors in this model. The selected psychophysiological variables were not significant predictors of STAI–S ($F_{6, 41} = 1.10$, $p = .380$), PDSS score ($F_{6, 42} = 0.73$, $p = .628$) or PD duration after controlling for age (F change $_{6, 41} = 1.45$, $p = .220$).

A second set of regression analyses was conducted to determine the extent to which patients' comorbidity and medication use contributed to these six psychophysiological measures. In these models, continuous psychophysiological measures served as the outcome variables, rather than predictors. This was because the comorbidity and medication measures, being categorical, were unsuitable as outcome measures. In each model Medication (Medicated/Unmedicated), Current Comorbidity (Yes/No), and Alcohol (lifetime alcohol abuse or dependence: Yes/No) were entered simultaneously as predictor variables. The combined effect of patients' medication status and comorbidity did not significantly predict the following (above–defined) measures: frontal alpha–1 power ($F_{3, 48} = 0.22$, $p = .886$); temporal beta power ($F_{3, 47} = 1.18$, $p = .329$); FAA ($F_{3, 48} = 1.64$, $p = .192$), SCL–GRAD ($F_{3, 45} = 1.04$, $p = .385$), or RR ($F_{3, 48} = 1.18$, $p = .326$). However, the combined model for HRV was significant ($F_{3, 47} = 4.09$, $p = .012$). Patients' comorbidity and medication use accounted for 20.7% of HRV variance. Medication status was the only (borderline) significant unique predictor of HRV (*Beta* = –.388, $p = .055$). Post hoc tests revealed lower HRV in medicated compared to unmedicated patients ($t_{49} = 3.63$, $p < .001$). HRV was not lower in unmedicated patients ($n = 31$) compared to matched controls ($n = 64$) ($t_{93} = –1.49$, $p = .140$).

Table 19: Descriptive and inferential statistics for cardiovascular measures

RR						
Group $F_{1, 152} = 6.97, p = .009, \acute{\eta}_p^2 = .044$						
Condition $F_{1, 152} = 8.86, p = .003, \acute{\eta}_p^2 = .055$						
		PD	***Controls***	***t***	***p***	***d*** [a]
	[b] REO	818.0 (106.7)	871.5 (120.8)	–2.79	.006	0.45
	REC	807.7 (107.2)	862.0 (115.4)	–2.85	.005	0.47
HRV [b]						
Group $F_{1, 151} = 5.30, p = .023, \acute{\eta}_p^2 = .034$						
		PD	***Controls***	***t***	***p***	***d*** [a]
	[c] REO	*44.42* 3.64 (0.47)	*53.17* 3.89 (0.44)	–3.17	.002	0.52
	[c] REC	*42.38* 1.56 (0.22)	*52.35* 1.67 (0.20)	–3.19	.002	0.52
LF:HF						
Group $F_{1, 148} = 6.63, p = .011, \acute{\eta}_p^2 = .043$						
		PD	***Controls***	***t***	***p***	***d*** [a]
	REO	1.13 (0.33)	1.04 (0.21)	2.25	.026	0.35
	[b] REC	1.13 (0.29)	1.04 (0.19)	2.05	.044	0.39

[a] Cohen's *d* (Cohen, 1992). [b] Levene's test corrected *t* and *p* values. [c] Reported as: $M_{\text{untransformed (in italics)}}$ $M_{\text{transformed}}$ $SD_{\text{transformed (in brackets)}}$. Untransformed means are for illustrative purposes only. Only significant ANOVA main effects and interactions are shown.

Table 20: Descriptive and inferential statistics for electrodermal measures

ns–SCR

Group $F_{1, 108} = 12.8, p < .001, \acute{\eta}_p^2 = .106$

Condition $F_{1, 108} = 9.23, p = .003, \acute{\eta}_p^2 = .079$

	PD	***Controls***	***t***	***p***	***d*** [a]
[b] [c] REO	*2.01* 0.84 (0.78)	*6.45* 1.44 (1.12)	–3.42	.001	0.55
[b] REC	*2.26* 0.61 (1.00)	*4.01* 1.11 (1.01)	–2.46	.015	0.48
SCL–GRAD					
[c] REO	–0.0063 (0.0081)	–0.0174 (0.0347)	2.95	.004	0.38

[a] Cohen's *d* (Cohen, 1992). [b] Reported as: $M_{\text{untransformed (in italics)}}$ $M_{\text{transformed}}$ $SD_{\text{transformed (in brackets)}}$. Untransformed means are for illustrative purposes only. [c] Levene's test corrected *t* and *p* values. Only significant main effects and interactions are shown.

6.6 Discussion

Study 1 investigated psychophysiological indices of brain and body function during a nominal resting state in panic disorder, in the main finding support for study hypotheses. Patients showed a frequency–specific reduction in alpha–1 spectral power, relative to controls, region–specific reductions in spectral power at frontal and temporal scalp sites, and greater relative right hemisphere frontal activation, which manifested as an alpha–1 asymmetry, which was not evident in controls. In addition to these findings of altered CNS function in PD, ANS findings indicated that patients had reduced RR interval (*i.e.* increased HR), reduced HRV, and a higher LF:HF ratio, relative to controls. The latter two findings reflect reduced parasympathetically–mediated HF influence on the heart rate time series. Further, patients showed reduced SCL habituation. These findings, which were predicted from the earlier QEEG and autonomic literatures (e.g., Hoehn–Saric *et al.* 1991; Newman *et al.* 1992; Roth *et al.* 1992; Cohen *et al.* 2000; Hoehn–Saric *et al.* 2004; Parente *et al.* 2005), provide an important replication within a relatively large, single sample. Additionally, the findings suggest that patients' medication use and comorbidity did not contribute significantly to any of the CNS measures, but that medication use was a significant predictor of patients' reduced HRV. Study 1's main findings will now be discussed in detail.

6.6.1 Study Findings

6.6.1.1 Spectral Power

Spectral power was somewhat attenuated in PD across a broad frequency range, as indicated by the omnibus Group main effect for spectral power (section 6.5.1.1 Spectral Power). A tendency for reduced spectral power in PD was evident across the broad alpha band and beta, but did not extend into the slower (*i.e.* theta) range (see Tables 17 and 18).

This reduction in intrinsic cortical synchronization showed global as well as region–specific characteristics, and was most prominent in the alpha–1 frequency band and during REC.

6.6.1.2 Alpha–1 Spectral Power

Previous studies in non–clinical samples show that changes in alpha–1 spectral power reflect tonic and phasic changes in aspects of attention (unspecific 'alertness' and/or 'expectancy'), and that baseline alpha–1 spectral power is positively associated with capacity for attentional allocation (review Klimesch, 1999). The findings for alpha–1, therefore, suggest that panic disordered patients compared to unaffected controls may have been relatively alert and that their attention was more engaged during the REC period of sitting quietly in the laboratory. Given the absence of task–imposed attentional demands, patient–control differences in attentional allocation may reflect differences in task–unrelated attentional processes. Research participants typically experience ongoing spontaneous cognition (*i.e.* 'stimulus–independent thought') during resting state paradigms (Mason *et al.* 2007). However, for panic disordered subjects, a period of sitting without distraction within an unfamiliar laboratory environment would likely represent a relatively threatening, anxiogenic situation (Grillon, 2008; Fonteyne *et al.* 2009). For example, compared to healthy controls, individuals with PD are more likely to rate a confined laboratory environment as anxiety provoking (Argyle, 1991) and, when anxious, are especially prone to become hypervigilant for bodily sensations that may signify impending panic (Barlow, 2002; Beck & Clark, 1997; Khawaja & Oei, 1998). As somatic and environmental cues vie for limited attention and neural processing resources (Pennebaker, 2000), somatic cues during REC may have more successfully engaged patients' attention given the absence of visual competition.

Additionally, in a hypervigilant state and with their eyes closed patients may have become more attentive to sounds within the unfamiliar environment. In line with this suggestion, a recent combined fMRI/EEG study found that auditory information was more negatively appraised and was associated with increased activity in the amygdala and associated threat–processing circuitry, during a REC compared to REO condition (Lerner *et al.* 2009).

Given the clinical phenomenology of the disorder, the idea that attenuated alpha represents an anxiety–related response to the testing environment has intuitive appeal. However, given the design of the study, it is unclear whether low–voltage EEG (especially alpha–1 power) represents a state, trait or risk marker for PD. In non–clinical samples absolute spectral power shows high within–subjects stability over time (Hughes & John, 1999; Hagemann & Naumann, 2009), even several years (Kondacs & Szabo, 1999), suggesting that these measures reflect trait characteristic of individuals. Moreover, Schmidt *et al.* (in press) reported that high test–retest stability for resting state spectral power in generalized SAD. Therefore, future studies are needed in order to directly test the extent to which reduced alpha–1 power represents a state–related or enduring characteristic of PD.

6.6.1.3 Beta Spectral Power

Compared to controls, individuals with PD showed reduced beta spectral power during REO at bilateral temporal and right–frontal scalp sites. In addition, there was a scalp–wide trend for reduced beta spectral power during REC. Increased fast frequency beta activity is prominent when individuals are alert and attentive (Niedermeyer, 2005) and has traditionally been associated with states of increased subjective and behavioural arousal

(Knott *et al.* 1997). In healthy adults, alpha frequency activity predominates the awake resting state EEG, followed by beta activity and minimal delta and theta (Miller, 2007). In the eyes closed state, the alpha rhythm is enhanced (Niedermeyer, 2005), but upon eye opening (or other sensory stimulation) alpha desynchronises, and activity in other frequency bands is enhanced (Klimesch *et al.* 1997), reducing the dominance of alpha (Rowe, 2005).

The functional significance of beta has not been studied as extensively as alpha. Recently, however, several combined functional neuroimaging/EEG studies have investigated intrinsic brain activity, that is, activity not directly related to identifiable sensory or motor events (Raichle & Snyder, 2007). This methodology combines the superior spatial resolution of functional neuroimaging technologies with the excellent temporal resolution of EEG (Menon & Crottaz–Herbette, 2005) in order to better characterize the spatial–temporal pattern of brain activity at rest. These studies reflect increased interest of late in intrinsic brain activity, and linked to it, the extent to which this neurophysiological baseline constrains subsequent sensory–, cognitive–, or motor–driven activity (Thut & Miniussi, 2009). Much research and debate on intrinsic brain activity followed the publication of a seminal paper by Raichle and colleagues (2001), who presented positron emission tomography evidence of a specific neural network that is maximally active in the eyes open and eyes closed resting state, and which decreases in activity in response to a wide variety of tasks – a so–called 'default–mode network'. Since then, multiple other highly specific functional anatomical neural networks have been documented by functional neuroimaging studies (review Laufs, 2008). These networks have been referred to collectively as either resting state networks (Mantini *et al.* 2007) or intrinsic function connectivity networks (Sadaghiani *et al.* 2010).

Of relevance to the present study, the resting state networks associated with beta frequency EEG oscillations have recently been investigated. For instance, Mantini *et al.* (2007) recently investigated intrinsic brain activity in a combined fMRI/EEG co–registration study, using used a completely data–driven approach. The resting state networks they identified were very similar in topographical distributions to previous reports. However, they assessed electrocortical activity in multiple frequency ranges, in contrast to most such studies, which only examined the spatial distribution of networks correlated with alpha power. They found that intrinsic beta activity was positively correlated with EEG spectral power in the broad alpha band, which accords with the present finding of reduced power across this frequency range. In regards the association of hemodynamic and electrocortical oscillations, they found that alpha and beta spectral power at rest was positively correlated with neuronal metabolism in a network largely overlapping with the default–mode network, which is putatively associated with internal processing, and with activity within a network that is putatively related to self–referential mental activity (Mantini *et al.* 2007). By contrast, alpha and beta spectral power was negatively correlated with activity in the dorsal attention network, which was previously shown to mediate goal–directed response selection (Mantini *et al.* 2007). Specifically, a reduction of alpha and beta power at rest was associated with increased activity within this network. Similarly, Laufs *et al.* (2003) found a negative correlation between resting state alpha activity and a network similar to the dorsal attention network and a positive association between beta power and a network similar to the default–mode network. Taken together, the findings of these resting state studies suggest panic disordered individuals at rest show decreased activity within the default–mode and self–referential resting state networks and increased activity within the dorsal attention network, in comparison to healthy controls. Additionally, the differential findings for alpha and beta frequency spectral activity, in terms of their respective

topographic distributions and condition effects, could be due to differences between these frequency bands in their global spatial characteristics and response to visual stimulation (Chen *et al*. 2008).

Although the exact functional significance of resting state networks and associated electrocortical activity is not known, one proposal is that activity in resting state networks represents a neurophysiological baseline of activity from which task–networks are dynamically assembled according to need (Mantini *et al.* 2007). A more expanded view proposes that intrinsic brain activity "instantiates the maintenance of information for interpreting, responding to and even *predicting* environmental demands" (Raichle & Snyder, 2007, p. 1087, italics in original). In the context of the present EEG findings, these views imply that individuals with PD differ from healthy controls in their respective baselines of electrocortical activity that prepare the brain for upcoming information processing demands. However, the actual function and clinical significance of these deviations remain to be elucidated.

6.6.1.4 Frontal Alpha Asymmetry

Another significant between–group finding was a frontal alpha–1 spectral power asymmetry (R<L power) that was present in PD, but not controls, during REC. A large corpus of animal and human data shows that the PFC hemispheres are differentially lateralised for approach and withdrawal motivational tendencies and emotions (Davidson, 1992; 2002; 2004; Davidson *et al.* 2000a). Specifically, the left PFC is part of the neural circuitry that mediates appetitive approach, whereas the right PFC forms part of the circuitry that mediates defensive withdrawal (Miskovic & Schmidt, 2010). Relative right frontal activation has previously been reported in PD. Wiedemann *et al.*

(1999) reported that individuals with PD showed greater relative right frontal activation (*i.e.* R<L alpha power) both when viewing anxiety–relevant stimuli and during resting phases, but not during an emotionally–neutral distraction condition. The authors proposed that resting phases as opposed to distraction conditions may be experienced by individuals with PD as unpleasant and thus engage withdrawal circuitry. In broad agreement with this interpretation, patients with several other anxiety disorders showed increased right anterior activation upon disorder–specific symptom provocation but not in emotionally–neutral baseline conditions (Rauch *et al.* 1997; Davidson *et al.* 2000b).

6.6.1.5 Autonomic Findings

Overall, the majority of autonomic findings were in line with previous reports of increased HR, reduced HRV, and elevated tonic EDA, during resting state in PD (e.g., Hoehn–Saric *et al.* 1991; Roth *et al.* 1992; Friedman & Thayer, 1998a; Cohen *et al.* 2000; Friedman, 2007). In particular, reduced HRV has been observed in PD across a wide variety of conditions and is a robust finding (review Friedman, 2007). Each of these findings suggests a weighting of ANS in the direction of sympathetic as opposed to vagally–mediated PNS function (Friedman & Thayer, 1998b). These cardiac findings, in particular, are important because autonomic imbalance in cardiac control, specifically chronic dominance of the sympathetic branch of the ANS, is a significant risk factor for cardiac morbidity and mortality, as indicated by studies comprising both cardiovascular patients and unselected samples (reviewed by Thayer & Lane, 2007). Worldwide, cardiovascular disease (CVD) is the leading cause or morbidity and mortality (Yusef *et al.* 2001), and people with PD are at increased incidence of CVD and sudden cardiac death (Coryell *et al.* 1982; Gomez–Caminero *et al.* 2005; Smoller *et al.* 2007; Chen *et al.* 2009; Goodwin *et al.* 2009; Vogelzangs *et al.* 2010). Reduced

HRV, which is indicative of reduced vagally–mediated tonic cardiac inhibitory control (Malik *et al.* 1996; Friedman & Thayer, 1998b), is a powerful independent predictor of CVD and cardiac death (Molgaard *et al.* 1991; Bigger *et al.* 1992; Driefus *et al.* 1993; Tsuji *et al.* 1994; Dekker *et al.* 1997; Liao *et al.* 1997; Gerritsen *et al.* 2001; Camm *et al.* 2004; Evrengul *et al.* 2006). Reduced HRV is also independently associated with all of the established and emerging risk factors for CVD (reviews Malik *et al.* 1996; Brook & Julius, 2000; Thayer & Lane, 2007; Thayer *et al.* 2010). Moreover, several large studies encompassing over 30,000 subjects found a dose–response relationship between resting HR and all–cause mortality (review Habib *et al.* 1999). Finally, the HRV finding also has important implications for cognitive function in PD, as Hansen and colleagues demonstrated in a series of studies in healthy individuals that resting state HRV is longitudinally and positively associated with performance on tasks of sustained attention (Hansen *et al.* 2003; 2004; 2009).

The finding of slower SCL decline in PD follows earlier reports of delayed electrodermal habituation in PD (Roth *et al.* 1990; Birket–Smith *et al.* 1993; Roth *et al.* 1998). Habituation, which is the waxing of a response to a non–significant stimulus, is a ubiquitous and adaptive process (Dawson *et al.* 2000). In contrast, the observed reduction in NS.SCR frequency in PD, indicative of less frequent spontaneous sympathetic discharges (Lindberg & Wallin, 1981), appears anomalous as both tonic and phasic EDA are associated with emotional arousal (Dawson *et al.* 2000; Lang & Davis, 2006). One possible explanation of fewer NS.SCRs in conjunction with delayed SCL habituation is that PD is associated with tonically elevated but phasically dampened EDA. This would parallel the findings within the cardiovascular system of tonically elevated HR, but diminished phasic modulation (*i.e.* reduced HRV, and higher

LF:HF ratio). Moreover, this interpretation is consistent with reduced autonomic flexibility in PD (Hoehn–Saric, 2007; Friedman, 2007). According to this view, individuals with chronic as opposed to episodic anxiety disorders show a reduction in the adaptive ability to modulate their response to normal everyday minor stressors, but an exaggerated response to disorder–specific threat cues (Hoehn–Saric, 2007; Friedman, 2007). However, an alternative explanation that cannot be ruled out because absolute SCL data could not be used, is that reduced phasic sweat gland activity in PD might represent a ceiling effect relating to skin hydration (Fowles, 1980). In general, a pattern of non–covariance of different EDA measures is not uncommon (Dawson *et al.* 2000), and demonstrates the functional independence of sympathetic nervous system sub–divisions, even within the electrodermal system (Boucsein, 1992; Critchley *et al.* 2000). Moreover, the results underscore the importance of obtaining multiple measures simultaneously.

6.6.1.6 Clinical Severity and Psychophysiology

In the first set of multiple regression analyses no significant association between the selected psychophysiological variables and the clinical outcome measures was found. As there is no reason to assume a priori that a complex clinical phenotype such as PD would faithfully conform to underlying pathophysiological fault–lines, this was unremarkable. Although in general there is typically a low concordance of self–reported clinical measures (e.g., state anxiety) and psychophysiological indices (Wilhelm & Roth, 2001; Mauss *et al.* 2005), the fact that patients' ratings of state anxiety (STAI) were not obtained until the end of the assessment, would have lessened the ability to detect a relationship between self–reported anxiety and psychophysiological measures.

The findings that HRV was lower in medicated compared to unmedicated patients, and did not significantly differ between unmedicated patients and healthy matched controls, were unexpected. Reduced HRV is a robust finding for PD in both medicated and unmedicated patient samples (reviews Friedman & Thayer, 1998b; Friedman, 2007: Garakani *et al.* 2009). Although some findings indicate that tricyclic anti–depressant use has a HRV lowering effect in PD (Yeragani *et al.* 1992; 1994) and in MDD (Kemp *et al.* 2010), only 16% (n = 4) of patients who were undertaking pharmacotherapy at the time of the assessment were using tricyclic anti–depressants, and the remaining 84% (n = 16) were using either SSRIs or SNRIs. However, findings on the effect of serotonergic medications on HRV in PD are mixed. For instance, some findings suggest that SSRI medication may have a normalising effect on resting HRV in PD (Tucker *et al.* 1997; Yeragani *et al.* 2000; Sullivan *et al.* 2004), whereas Garakani *et al.* (2009), by contrast, found that 12 weeks of treatment with sertraline (a SSRI) in combination with CBT did not significantly alter HR or HRV in PD. Recently, moreover, a large study in the Netherlands found that anti–depressant use was longitudinally associated with a lowering of HRV in adults with anxiety disorders (including, but not limited to PD) and/or MDD (Licht *et al.* 2010). This study, which has been criticised on several methodological grounds (see Kemp *et al.* 2010), reported that HRV decreased significantly in individuals who commenced anti–depressant treatment within the two years following the baseline assessment, with the largest effect size associated with TCA use, followed by SNRIs, then SSRIs (S–M effect size). Conversely, individuals who ceased pharmacotherapy within this period showed a trend for increased HRV. According to the authors, these longitudinal findings provide support for a causal role of anti–depressants in lowering cardiac vagal control.

Several possible explanations for the present association between medication use and HRV are plausible. For instance, individuals with more severe PD may have lower HRV and be more amenable to pharmacotherapy. Alternatively, SSRI treatment may have a causal effect of lowering HRV, as suggested by Licht *et al.* However, given the inconsistent results from the above–cited longitudinal studies, and the cross–sectional nature of the present study, one cannot determine the nature of this association.

6.6.2 Study Limitations

A limitation of this study is that it was not possible to compare absolute SCL in patients and controls. Absolute SCL is the most commonly used measure of tonic EDA (Boucsein, 1992) and is reliably and positively associated with self–reported anxiety and fear (reviews Kreibig *et al.* 2007; Kreibig, 2010). For instance, Blechert *et al.* (2007a) compared the relative utility of an extensive range of psychophysiological parameters in differentiating neutral (*i.e.* resting state) and anxiety (*i.e.* threat of shock) states in healthy subjects, finding the largest effect sizes for electrodermal measures including SCL and NS.SCR frequency. Nevertheless, the current finding of slower decline of the SCL in PD compared healthy controls accords with previous findings for PD (Roth *et al.* 1998; Parente *et al.* 2005), and PTSD (Falconer *et al.* 2008), and indicates elevated tonic EDA (Boucsein, 1992).

A second possible limitation of Study 1 is that the recording duration for REO and REC conditions, at 2 minutes, is at the lower end of that recommended for spectral analysis of the ECG (Malik *et al.* 1996). At least 2 minutes of recording, which is more than 10 times the wavelength of the lower bound of the LF range (0.04–0.15HZ), is required for reliable estimation of this component (Malik *et al.* 1996). However, as patients and

controls were assessed in standardised conditions the recording duration could not account for between–group HRV differences.

6.6.3 Conclusions and Future Directions

Study 1 examined resting state brain and body function in PD with concomitantly recorded measures of central– and autonomic nervous system function. The study results indicate that, under nominally resting conditions while sitting quietly in the laboratory, individuals with PD show extensive deviations from normative function on multiple measures of brain and body function. The QEEG findings included a global reduction in alpha–1 frequency spectral power, and greater relative right frontal activation within the same frequency band. Spectral power at rest is proposed to signify the preparedness of different oscillating circuits for specific types of information processing (Başar, 1998), and predicts subsequent cognitive and perceptual ability in a frequency–specific manner (Klimesch, 1999; Thatcher *et al.* 2005). Specifically, reduced alpha–1 frequency electrocortical activity has previously been linked to a reduced capacity for task–related attentional allocation (Klimesch, 1999). Panic disorder patients' relative desynchronization of this circuitry, therefore, implies a lack of neural preparedness for attention–demanding information processing. Concomitant ECG recordings showed that this pattern of tonic electrocortical activity in PD was associated with reduced HRV and RR interval, which reflect a reduction of parasympathetic relative to sympathetic control of the heart (Friedman & Thayer, 1998b). Electrodermal findings for PD included delayed SCL habituation, which reflects SNS activity unconfounded by PNS influence (Gruzelier *et al.* 2002).

Psychophysiological measures obtained during resting states have traditionally been assumed to index a symptom–free baseline (Wilhelm & Grossman, 2010), and are thus taken as trait markers of function (e.g., Linden & Fallgatter, 2009). However, psychophysiological measures never truly measure traits, but traits as they interact with the specific experimental procedures and context (Blackhart *et al.* 2002; Hagemann *et al.* 2005). As discussed, even in the absence of experimentally–imposed task demands, a range of contextual and individual difference factors interact to determine an individual's state during laboratory assessments (Wilhelm & Roth, 2001; Lang & Davis, 2006; Wilhelm & Grossman, 2010). Therefore, it remains to be determined to what extent the present CNS and ANS findings for PD are stable trait–like disorder–related differences, and to what extent the findings represent a state–like response of the individual to the particular laboratory environment. It remains to be determined, moreover, whether these deviations from normative function temporally precede PD onset and whether they are malleable. These are questions that have important implications for both research and clinical practice in PD. The research and clinical implications of the present results, in conjunction with the results of Studies 2 and 3, are discussed further in Chapter 9.

6.7 Summary of Chapter

Study 1 examined brain and body function at rest in PD. The study encompassed multiple concomitantly–recorded indices of brain and body function which were recorded in two resting states. Overall, the findings both in terms of electrocortical activation and peripheral measures of ANS function, are consistent with the view that the experience of sitting quietly in the laboratory was relatively anxiogenic for panic disordered compared to healthy subjects[3].

The brain and body are never truly at rest, and some of the resting state psychophysiological indices included in the present study provide important information about the preparedness of the individual for subsequent information processing. Previous research findings, for instance, indicate that resting state measures of EEG spectral power predict subsequent cognitive performance in a frequency–specific manner (review Klimesch, 1999). On the basis of this literature, the present QEEG finding of reduced alpha–1 spectral power in PD suggests a diminished cortical preparedness for meeting upcoming information processing demands on tasks that require attention and alertness for their effective execution. By contrast, the null finding for alpha–2 predicts normative performance in PD on tasks of semantic memory. Further, the present finding for reduced HRV in PD suggests that clinical participants in the present study will show impaired performance on tasks of sustained attention, given previous findings in healthy samples (Hansen *et al.* 2003; 2004; 2009).

Studies 2 and 3 therefore aimed to test these predictions, but with quite different research methodologies – Study 2 via psychophysiological assessment, and Study 3 via neuropsychological assessment. Specifically, Study 2 employed an event–related potential (ERP) paradigm to examine the electrocortical response to different types of auditory stimuli within a task of sustained attention. Whereas resting EEG reflects intrinsic brain activity, ERP analysis extracts and quantifies electrocortical signals specifically associated with the processing of stimulus events (Key *et al.* 2005), and may index specific cognitive operations that are not measureable by behavioural measures alone (Gruzelier *et al.* 2002), although ERP measures were complemented by concomitantly–recorded electrodermal and behavioural measures.

Notes:

1. The results of this study have previously been reported in the literature (Wise *et al.* 2010, see Appendix L).

2. Although alpha sub–bands are sometimes denoted 'lower alpha' and 'upper alpha' (e.g., Klimesch, 1999), the terms alpha–1 and alpha–2 will be used throughout for consistency.

3. It should be noted, however, that one cannot definitively infer a psychological state from a pattern of psychophysiological activation (Berntson *et al.* 2007). Therefore, alternative interpretations for the present psychophysiological findings cannot be ruled out. Stronger support for the present interpretation requires experimental manipulation in multivariate, multi–level research (see Berntson *et al.* 2007).

Chapter 7

Study 2: Sensory Information Processing

7.1 Overview of Chapter

Study 2 examined sensory information processing in panic disorder using an auditory oddball task.[1] The auditory oddball task is a simple auditory discrimination paradigm that is commonly performed as an event–related potential (ERP) paradigm (Reinvang, 1999). The oddball task provides multiple indices of the brain's response to stimuli of varying significance. Two–tone oddball tasks, such as that used in the present study, provide ERP indices of the brain's response to two types of stimuli: infrequent target tones and frequent standard tones. These ERP measures were complemented in the present study with electrodermal and behavioural measures of the response to significant target tones.

The chapter begins by discussing sensory gating, that is, those mechanisms which allow the brain to modulate its response to incoming stimuli as a function of its significance (Boutros & Belger, 1999). This is followed by discussions of the auditory oddball task and the ERP methodology. Next, the discussion turns to empirical findings of relevance to Study 2, including previous ERP findings for PD and findings from Study 1. Finally, the remainder of Chapter 7 is devoted to describing Study 2 in terms of its methodology, results and the implications of these results.

7.2 Study Background

For humans to function adequately in complex environments, it is necessary for the brain to appropriately modulate its response to environmental events (Jääskeläinen *et al.* 2004). Due to the capacity limits of higher perceptual centres, only a subset of the environmental information that impinges upon the senses is selected for further processing (Escera *et al.* 2000; Öhman *et al.* 2000). Selective attention mechanisms determine which portion of environmental information gains access to higher centres, and which portion is inhibited (Compton, 2003). Stimuli which are significant within a given spatiotemporal context are selected for preferential processing (Öhman *et al.* 2000), with significance being determined on the basis of the dynamic interaction of multiple 'bottom–up' and 'top–down' factors (Compton, 2003). For instance, novel sounds need to be rapidly differentiated from background noise and gated to awareness (Opitz *et al.* 2002), as do stimuli that are relevant to current goals (Bishop, 2007). By contrast, stimuli of low informational content such as repetitive, goal–irrelevant stimuli are discarded relatively early in the information processing stream, in order to reduce the flow of environmental information (Boutros & Belger, 1999).

The ability of the brain to modulate its sensitivity to incoming sensory input is referred to as '*sensory gating*' (Boutros & Belger, 1999). This definition of gating incorporates both capacities to reduce or cease responding to incoming irrelevant stimuli ('gating out' or 'filtering out'), and to respond to relevant stimuli ('gating in') (Boutros & Belger, 1999). Deficits in sensory gating mechanisms, particularly those early in the information processing stream, may lead to cognitive or behavioural disturbances (Grunwald *et al.* 2003; Geyer, 2006). The auditory oddball task provides ERP measures of both types of gating mechanisms.

7.2.1 Auditory Oddball Task

The auditory oddball task is a simple auditory discrimination paradigm that assesses attentional modulation and, to a lesser extent, impulsivity (Riccio *et al.* 2002). Oddball tasks are simple exemplars of the continuous performance test (CPT), a group of paradigms that have the common property of requiring subjects to continuously monitor a rapid sequence of stimuli in order to identify and respond to infrequent 'target' stimuli (Reinvang, 1999). Oddball tasks, as per all CPTs, are of relatively long duration (the present task was 6 minutes), and are considered tasks of sustained attention (Borgaro *et al.* 2003). Sustained attention, which refers to one's readiness to detect and respond to rarely and unpredictably occurring signals over prolonged intervals, is a fundamental component of attention which determines the efficiency of other aspects of attention (e.g., selective attention, divided attention) and of cognitive capacity more generally (Sarter *et al.* 2001). Tasks of sustained attention require the capacity to deliberately modulate alertness and maintain selective attention or vigilance to non–arousing but goal–relevant stimuli (Robertson *et al.* 1997).

Standard two–tone oddball tasks, such as that used in the present study, provide ERP indices of the brain's response to two types of stimuli: infrequent target tones and frequent 'standard' tones. The task also provides electrodermal and behavioural indices of responses to target stimuli. The ANS plays an important role in modulating the individual's response to significant stimuli (Öhman *et al.* 2000). Stimuli that are in some respect significant but not threatening may elicit a complex biobehavioural response called the 'orienting reflex' (OR), the electrodermal component of which is a SCR (Öhman *et al.* 2000; Dindo & Fowles, 2008). Findings from integrative ERP–EDA analyses reveal that stimuli that elicit an OR are allocated relatively more neural

processing resources (Bahramali *et al.* 1997; 2001; Williams *et al.* 2000). Measures of SCR frequency to significant stimuli (e.g., oddball target stimuli) thus index stimulus significance and attention allocation (Dawson *et al.* 2000). Behavioural measures derived from the oddball task include several measures of sustained attention (reaction time, RT; RT variability; errors of omission), and a measure of impulsivity (errors of commission) (Riccio *et al.* 2002).

7.2.2 Event–related Potentials

Event–related potentials (ERPs) are transient changes in the continuous EEG signal that are time–locked to and triggered by discrete events (e.g., auditory stimuli) (Key *et al.* 2005). ERPs have a temporal resolution in the millisecond timescale and reflect the transmission of sensory information through successive levels of information processing (Hansenne, 2006). Typically, multiple EEG segments from identical time–locked events are signal–averaged to increase the signal–to–noise ratio (Fabiani *et al.* 2000). Subsequently, a series of polarity deflections (*i.e.* components) may be identified in the signal–averaged waveform (Menon & Crottaz–Herbette, 2005). Component amplitude – defined as the voltage difference between a component's peak and a pre–stimulus baseline (Polich, 1998) – is understood to reflect the extent of neural 'resources' allocated to a particular type of stimulus (Kok, 1997). By contrast, component latency is understood to reflect the speed of information processing at respective stages of information processing (Hansenne, 2006).

Conveniently, ERP components are divided into two types. Early 'sensory' components are considered exogenous in that their characteristics are largely determined by the physical properties of the eliciting stimulus (Reinvang, 1999). By contrast, later

'cognitive' components (e.g., N2 and P3) [2] are considered endogenous in that their properties are determined by the cognitive state of the individual (Reinvang, 1999). For instance, elicitation of the oddball P3 requires active discrimination of target stimuli from standard stimuli (Braff & Light, 2004). However, components N1 and P2, which are elicited by oddball target and standard stimuli, are relatively late sensory components that are both sensitive to the physical properties of the eliciting stimulus as well as the nature of the interaction between the subject and the event (e.g., whether or not the event is attended) (Boutros *et al.* 2000; Fabiani *et al* 2000). Auditory evoked potentials from the oddball task span a continuous window of information processing from the early–attentive (N1) to attentive (P3) latency range (Reinvang, 1999).

The N1 ERP component and several other auditory evoked potentials (e.g., P2 and N2) have the common property of decreasing in amplitude with repetition at short intervals (Fruhstorfer *et al.*1970; Budd *et al.* 1998; Sambeth *et al.* 2004). N1 attenuation upon repetition is an important process in filtering out behaviourally–irrelevant stimuli (Boutros *et al.* 1999), and underlies pre–attentive gating of novel sounds to awareness (Jääskeläinen *et al.* 2004). Therefore, these auditory–evoked components, when elicited by repetitive stimuli such as oddball standard tones, provide a method for examining the ability of the brain to inhibit irrelevant sensory input (Boutros *et al.* 2000). Conversely, as oddball target stimuli typically elicit a robust P3, given the heightened significance in context of designated target stimuli (Ilardi *et al.* 2007), oddball P3 amplitude provides a metric of the amount of attentional resources allocated to task–relevant stimuli (Polich & Comerchero, 2003). Oddball P3 is very well–characterised (Hansenne, 2006) and conditions that affect attention allocation influence P3 measures by reducing P3 amplitude and/or increasing P3 latency (Polich, 1998).

7.2.3 Empirical Findings

7.2.3.1 ERP Findings

Several studies have investigated sensory information processing in PD using variants of an auditory oddball task, or other ERP paradigms. Increased N1 amplitude to standard tones in an oddball task stimuli (Iwanami *et al.* 1997; Ogura, 1995), and to repeated auditory stimuli in a passive listening task (Knott *et al.* 1991) have been reported. These findings suggest a reduced ability to discard stimuli of low significance in PD. However, other investigators found no group effect for N1 (e.g., Clark *et al.* 1996; Wang *et al.* 2003). With regards P3, decreased P3 amplitude to target tones within two–tone oddball tasks were reported (Gordeev *et al.* 2003; 2006; 2008). Additionally, a three–tone oddball task elicited a fronto–centrally enlarged P3 component to rare target and distractor tones in PD (Clark *et al.* 1996). This component was regarded as P3a, a component which reflects passive reorientation of attention to physical change in the environment, not stimulus significance (Clark *et al.* 1996). Frontal P3a may be observed when the subject's attention has been directed away from the oddball series (Goldstein *et al.* 2002). The findings for P3 and P3a amplitudes, therefore, suggest disturbances in active and passive attentional mechanisms in PD, respectively (Muller–Gass & Campbell, 2002). Furthermore, both reduced (Hanatani *et al.* 2005) and prolonged (Turan *et al.* 2002) P3 latencies have been reported, suggesting abnormal speed of information processing in PD. Related findings for PD include inadequate pre–attentive sensory gating (Ghisolfi *et al.* 2006) and sensorimotor gating mechanisms, as indexed by attenuation of the acoustic startle reflex in the presence of a pre–stimulus warning (Ludewig *et al.* 2002; 2005).

Taken together, ERP and related findings for PD are equivocal, which likely reflects

issues of sample selection (e.g., small study samples, within– and between–sample clinical heterogeneity) and methodology (e.g., paradigm differences, reporting results only for components of interest). Despite inconsistencies, these findings suggest the presence in PD of deficits in the ability to filter out irrelevant stimuli at early information processing stages, and reduced allocation of attentional resources to task–relevant stimuli later in the information processing stream.

7.2.3.2 Study 1 Findings

Two Study 1 findings bear upon the present study. Firstly, as previous findings show that baseline spectral power predicts subsequent capacity for task–related desynchronization and cognitive performance in a frequency–specific manner (review Klimesch, 1999), the finding of reduced resting alpha–1 spectral power in PD suggests reduced capacity for alpha–1 desynchronization and allocation of attention to task–relevant oddball stimuli. Notably, baseline alpha–1 power is positively associated with capacity for attentional allocation (Klimesch, 1999; Dockree *et al.* 2007).

Secondly, the finding in Study 1 of reduced HRV in PD, which is now a robust finding (review Friedman, 2007), suggests impaired capacity for sustained attention in PD. This is because HRV is associated with a range of cognitive and psychological correlates, including sustained attention (Beauchaine, 2001; Thayer *et al.* 2009). During sustained attention there is a marked phasic suppression of HRV (Porges, 1992; Thayer *et al.* 2009). Therefore, the finding of low HRV in PD reflects diminished capacity for adaptive HRV modulation in response to current goals (Friedman & Thayer, 1998b; Friedman, 2007). Specifically, in the context of the present study low HRV in PD suggests impaired ability to sustain attention in a goal–directed manner.

Taken together, the Study 1 findings of reduced alpha–1 spectral power and reduced HRV in PD suggest that individuals with PD will show reduced ability to modulate and sustain their attention in a goal–directed manner. In the context of the oddball task, reduced attention to task–relevant stimuli may present as reduced P3 amplitude and increased P3 latency (Polich, 1998), fewer SCRs (Öhman *et al.* 2000), longer and more variable reaction time, and more errors of omission (Riccio *et al.* 2002).

7.2.3.3 Depersonalization

Depersonalization is one of 13 DSM–IV panic attack symptoms (APA, 1994). Depersonalization is a complex phenomenon comprising a range of symptoms which alter the individual's perception of themselves or their external world (Sierra & Berrios, 2001). Depersonalization is defined as a feeling of detachment or estranged from one's self (APA, 1994). Derealisation – an aspect of depersonalization (Sierra & Berrios, 2001) – is defined as an alteration in the perception or experience of the external world so that is seems strange or unreal (APA, 1994). The experience of depersonalization may occur independently of panic and, indeed, spans a continuum from transient symptoms in healthy individuals to chronic and unremitting symptoms, in the case of depersonalization disorder (Hunter *et al.* 2004). Depersonalization during panic and depersonalization disorder are both common in PD (Mendoza *et al.* 2010). The presence of depersonalization during panic is associated with agoraphobic severity, a high prevalence of comorbidity, treatment resistance and disorder chronicity in PD (Cassano *et al.* 1989; Ball *et al.* 1997; Bovasso & Eaton, 1999; Segui *et al.* 2000; Marquez *et al.* 2001; Gulsun *et al.* 2007; Mendoza *et al.* 2010), and was associated with greater disorder severity in the present sample (see Section 5.5.2.5).

The phenomenology of depersonalization, which includes sensory anesthesia and other perceptual distortions (Sierra & Berrios, 2001), suggests aberrant sensory processing. In line, a functional neuroimaging study revealed altered brain metabolism in multiple cortical areas involved in the processing of somatosensory and exteroceptive sensory information in individuals with depersonalization disorder (Simeon *et al.* 2000). Additionally, two EEG studies have compared the electrophysiological response of panic disordered individuals with and without depersonalization symptoms to sensory stimulation. Notably, EEG measures were obtained during the inter–panic interval, not during depersonalization. Firstly, in a temporal region of interest study Locatelli *et al.* (1993) found that patients with depersonalization, relative to those without and healthy controls, responded to odour stimulation with an abnormal increase in slow wave activity.

More recently, Hayashi *et al.* (2010) found that depersonalization symptoms significantly predicted abnormal EEG responses (most commonly theta waves) to photic stimulation and hyperventilation. However, this study finding was based on non–quantitative EEG analysis, which has low reliability for evaluation of non–epileptiform abnormalities (Thatcher, 2010). Moreover, as ERP waveforms reflect the change in electrophysiological signal associated with sensory events (Key *et al.* 2005), ERP as opposed to EEG analysis may better probe the electrophysiological correlates of depersonalization. In one such study, healthy subjects with transient depersonalization showed reduced P3 amplitudes to frequent auditory tones signaling the start of a working memory task (Papageorgiou *et al.* 2002). To date, however, the ERP correlates of depersonalization in PD do not appear to have been investigated.

7.2.3.4 Sensory Gating and Perceptual Phenomena

Sensory gating deficits have been identified in a number of psychiatric disorders, including PD (Grunwald *et al.* 2003). In general, it is assumed that sensory gating deficits will be clinically meaningful and have clear relationships with symptoms, neuropsychological function and real–world functioning (Braff & Light, 2004). In particular, sensory gating deficits are assumed to underpin anomalies of attention and perception (Freedman *et al.* 2002). According to Stewart and White (2008, p. 38), individuals with sensory filtering deficits report "being bothered by sounds and light, and feeling easily distracted by sensory events such as machine noises in the environment that usually go unnoticed by others." Such deficits may contribute to negative outcomes in stimulus–rich environments, such as academic and social settings, and may be detrimental to higher cognitive operations, such as attention and working memory (Stewart & White, 2008).

However, the assumed relationship between purportedly sensory gating–related behavioural phenomena and ERP indices of sensory gating had not until recently been tested (Hetrick *et al.* 2012). Jin *et al.* (1998) found that ERP and self–report indices of sensory gating did not correlate in individuals with schizophrenia, although this null finding may reflect the limits of self–report in individuals who lack insight and self–awareness (Light & Braff, 2000). By contrast, Kisley *et al.* (2004) found that several ERP and self–report measures of sensory gating were correlated in a sample of healthy adults. In this study they used the self–report instrument SGI which indexes different phenomenological aspects of sensory gating (Hetrick *et al.* 2012). Previous research had found that approximately 25% of healthy subjects endorse sensory gating–like anomalies of perception and attention (Bunney *et al.* 1999). Notably, they found that a

measure of N1 attenuation negatively correlated with the Over–Inclusion factor of SGI, but not other factors (Kisley *et al.* 2004). Over–Inclusion items index anomalies of radial attention arising from low stimulus perception threshold (Hetrick *et al.* 2012).

In PD, separate literatures have reported either electrophysiological findings of sensory gating disturbances or behavioural phenomena which are broadly consistent with deficient gating mechanisms. For instance, previous research has identified sensory gating deficits, or ERP abnormalities consistent with deficient sensory gating mechanisms, at various stages of information processing spanning the pre–attentive to attentive spectrum, in individuals with PD (Knott *et al.* 1991; Ogura, 1995; Iwanami *et al.* 1997; Ludewig *et al.* 2002; 2005; Ghisolfi *et al.* 2006). Behavioural phenomena include the common clinical observation that individuals with PD frequently experience heightened anxiety and panic in complex environments of particularly high sensory load such as supermarkets, shopping malls and crowds (Street *et al.* 1989; Sadock & Sadock, 2005). Additionally, findings that agoraphobics' self–reported anxiety and heart rate were specifically associated with repetitive visual stimuli, such as conventional, imperceptibly flickering fluorescent lighting (Watts & Wilkins, 1989; Hazell & Wilkins, 1990), are also consistent with gating deficits. However, the relationship between these behavioural difficulties and electrophysiological indices of sensory gating has not, to date, been tested for PD.

7.3 The Present Study

The present study investigated sensory information processing in PD using a standard two–tone auditory oddball task. In the task, subjects were presented with two types of easily distinguishable auditory stimuli differing in acoustic frequency: infrequent target

tones, and frequent standard tones. Whereas target tones required a behavioural response (button press), subjects were instructed to ignore standard tones. Trials for target stimuli were signal–averaged to yield N1, P2, N2 and P3 ERPs, whereas N1 and P2 peaks were calculated for standard tone trials. The analysis of all components elicited by oddball target and standard stimuli will help clarify the extent of auditory information processing disturbances in PD. In the present study, ERP indices were complemented with electrodermal and behavioural measures of significance processing (*i.e.* responses to target stimuli). The electrodermal measure, SCR frequency, indexes stimulus significance and attention allocation (Dawson *et al.* 2000). The behavioural measures were RT, RT variability, errors of omission and errors of commission. In comparison to previous studies, the present study comprised relatively large research samples. Additionally, the clinical correlates of any observed information processing disturbances were examined. As PD is a highly heterogeneous disorder these analyses may help resolve discrepancies in previous findings. In particular, the association of patients' comorbidity and medication use and oddball task measures was examined. Finally, the association of depersonalisation and information processing was examined, as was the relationship between ERP and behavioural measures of sensory gating.

On the basis of the foregoing it was predicted that patients compared to healthy matched controls would show:

1. Increased N1 amplitude to standard tones;

2. Reduced P3 amplitude and prolonged P3 latency to target tones;

3. Reduced SCR frequency;

4. Increased and more variable RT, and more errors of omission, and;

5. Negative correlation of N1 amplitude (standards) and SGI Over–Inclusion factor.

7.4 Method

7.4.1 Participants

The patient and control samples for Study 2 comprised 50 participants with a primary diagnosis of PD (35 females) and 98 age, gender, handedness– and education–matched controls (69 females), respectively. Details regarding the recruitment of patients and controls, and their respective study criteria were presented in Chapter 4. Demographic and clinical data for all subjects were reported in Chapter 5.

7.4.2 Stimulus Materials and Procedure

Study 2 reports the results obtained during performance of the Auditory Oddball task, which is the fourth–presented psychophysiological test. The test is preceded by the two Resting EEG periods (Chapter 6) and an Auditory Habituation task. At the time of undertaking the Oddball task subjects had been in the laboratory for just over one hour.

As described in Section 4.3.2.1, psychophysiology tests were conducted in a sound and light attenuated room, with the participant seated directly in front of a computer screen. Standardized pre–recorded task instructions and auditory stimuli were presented binaurally via headphones. Test instructions were also presented visually on the computer screen. In the oddball task the participant was presented with a series of series of differing auditory tones, and was required to ignore the frequent, low–pitched tones (standard tones; 500 Hz), and respond only when they heard the infrequent high–pitched tones (target tones; 1000 Hz). Prior to performing the task, participants completed a brief practice trial to clarify the distinction between the two stimulus types. For the test duration participants were asked to focus their eyes on a red dot at the centre of the computer screen and to minimize their movements. They were asked to respond to the

target tones by pressing buttons with the index fingers of each hand, but to not respond to the frequent, low–pitched tones. Speed and accuracy of the response were equally stressed. Both stimulus types were presented at 75 dB, and the two were easily distinguishable. Duration of each stimulus was 50 ms, with an ISI of 1 s, and rise and fall times of 5 ms. 280 standard tones and 60 target tones were presented in a quasi–random order, with the only constraint being that two targets never occurred consecutively. The task duration was approximately 6 minutes.

7.4.3 Data Acquisition, Artefact Correction, and Data Reduction

Psychophysiological measures of brain (EEG) and body (EDA) function were recorded concurrently and continuously throughout the test. Event–related potentials for each stimulus type (*i.e.* target and standard tones) were extracted from the continuous electroencephalographic recording. Electrooculogram (EOG) and electromyography (EMG) data were used for offline correction for eye movement and muscle artefact. Performance measures relating to the speed and accuracy of subjects' response to target tones were also calculated.

7.4.3.1 EEG Recording

A QuickCap was used to acquire continuous EEG data from 26 cephalic sites, EOG and EMG data, in the manner described in Section 6.4.3.1. The artefact correction procedures applied to all EEG data were also described in that section.

7.4.3.2 ERP Measurement

Prior to signal averaging, each single–trial waveform was filtered with a low–pass Tukey filter function that attenuates frequencies above 25 Hz. A cosine ramp from 1

down to 0.5 between 25 Hz and 35 Hz was used as an envelope on the Fast Fourier Transform data in the Tukey filter. The single–trial waveforms were then signal–averaged to form conventional ERPs for each stimulus type, at each scalp site. Only target stimuli with a correct button press were included in target averages. The average of the pre–stimulus period (–300 to 0 ms) was subtracted from the ERP data. For target stimuli waveforms, the peaks (amplitude and latency) of the N1, P2, N2 and P3 components were identified. For standard stimuli, the N1 and P2 component peaks were identified. ERPs were scored using an automated algorithm and then visually validated (Haig *et al.* 1995). The algorithm used the following pre–determined latency windows as a guide to determining component peaks: N1 (70 – 140 ms), P2 (120 –220 ms), N2 (140 – 300 ms), and P3 (220 – 550 ms).

Statistical analyses were based on data acquired from sites Fz, Cz, and Pz to best represent the components of primary interest (*i.e.* N1 and P3), for consistency with the ERP literature (Polich, 2007), and to minimize Type I errors arising from the analysis of multiple recording sites. Topographical and statistical probability maps, however, depict electrocortical and statistical data for all 26 scalp sites for illustrative purposes.

7.4.3.3 Electrodermal Activity

Electrodermal activity was recorded continuously during the task, in the manner described in Section 6.4.3.3. However, the measure of phasic EDA obtained during the oddball task (*i.e.* the number of specific SCRs elicited by target tones) differed from that used in Study 1. In the present study, SCRs were defined as unambiguous increases in EDA of $\geq$ 0.05 μS, with respect to each pre–stimulus baseline**,** the onset of which occurring 1 – 3 s post–stimulus. The total number of SCRs (*SCR–FREQ*) is reported.

7.4.3.4 Performance Measures

Mean reaction time (*RT*) and intra–individual RT variability (standard deviation of RT: *RT–SD*) of correct responses were calculated for each participant. Additionally, the number of incorrect responses (*False Positives*) and missed responses (*False Negatives*) are reported.

7.4.4. Data Cleaning

Prior to statistical analysis, all variables were assessed for the presence of missing data and outliers, and dealt with according to the methodology described in Section 4.5. As electrophysiological data for three patients and eight controls were either substantially or entirely missing, those subjects were excluded from this chapter's analyses. Overall, altered outliers and missing data constituted 2.0% of patients' and 2.3% of controls' ERP data; the corresponding figures were 2.0% and 4.5% for electrodermal data, and 3.1% and 2.5% for performance data. In instances where >5% of cases represented outliers or missing data, the subject numbers for these analyses are reported. Otherwise, the subject numbers for clinical and control samples are (n = 50) and (n = 98), respectively. The distribution of each variable was visually inspected (separately for each group) to assess for normality. SCR–FREQ, False Positives and False Negatives data required transformation ($Ln_{10}(x + 1)$) to normalize their distributions.

7.4.5 Statistical Analyses

Separate mixed–model ANOVAs with *Site* (Fz, Cz, Pz) as within–subjects factor and *Group* (PD, controls) as between–subjects factor were conducted for each component's peak amplitude and latency. Significant Group main effects were explored with independent–samples *t*–tests, whereas significant Group*Site interactions were explored

with paired–samples *t*–tests, to determine each group's scalp distribution for that component. Significant Site main effects were not explored as the topography of each component, independent of diagnosis was not a focus of Study 2.

Independent–samples *t*–tests compared patients and controls on autonomic and performance measures.

Several statistical analyses examined the relationship between PD clinical measures and oddball task measures. Firstly, standard multiple regression analyses examined the relationship between clinical measures and, respectively, oddball psychophysiological and performance measures distinguishing patients and controls. Secondly, Spearman correlation analyses examined the relationship between depersonalization (DD Percentage) and ERP measures distinguishing patients and controls. This non–parametric test was used because DD Percentage did not meet the assumption of normality required for parametric statistical analyses. Finally, Pearson correlation analyses (one–tailed) examined the relationship between N1 amplitude to standard stimuli and the SGI Over–Inclusion factor.

7.5 Results

7.5.1 Event–Related Potentials

7.5.1.1 ERP Summary Data

Group mean amplitudes for all ERP components (midline sites Fz, Cz, Pz and Oz) are shown in Table 21 (targets) and Table 22 (standards). Corresponding data for ERP latencies are shown in Table 23 (targets) and 24 (standards). Grand averaged ERP waveforms for each group are shown in Figures 16 (Fz), 17 (Cz) and 18 (Pz).

Table 21: ERP group mean amplitudes for target tones at sites Fz, Cz, and Pz.

Amplitudes (μV) [a]	Group Mean (*S.D.*) Amplitudes		
	Fz	*Cz*	*Pz*
N1 [b]			
PD	–6.82 (2.82)	–8.19 (3.25)	–6.07 (2.69)
controls	–7.26 (3.16)	–7.71 (2.95)	–5.13 (2.21)
P2			
PD	2.45 (3.92)	1.90 (4.71)	2.51 (3.16)
controls	1.63 (4.60)	1.57 (4.76)	2.71 (3.45)
N2			
PD	–5.08 (4.53)	–5.83 (5.23)	–2.48 (4.50)
controls	–4.87 (5.14)	–5.48 (6.44)	–1.86 (4.75)
P3 [c]			
PD	5.90 (6.23)	7.10 (6.79)	11.24 (6.12)
controls	7.70 (5.99)	10.11 (6.83)	14.98 (6.50)

[a] Subject numbers indicated in the text. [b] Group main effect significant ($p < .05$). [c] Group*Site interaction significant ($p < .05$).

Table 22: ERP group mean amplitudes for standard tones at sites Fz, Cz, and Pz.

Amplitudes (μV) [a]	**Group Mean (*S.D.*) Amplitudes**		
	Fz	***Cz***	***Pz***
N1 [b]			
PD	–4.90 (2.61)	–6.30 (3.17)	–4.74 (2.71)
controls	–4.97 (2.06)	–5.22 (2.17)	–3.53 (1.66)
P2			
PD	2.53 (2.76)	4.12 (3.27)	2.82 (2.26)
controls	2.25 (2.32)	3.96 (2.40)	2.75 (1.79)

[a] Subject numbers for each component are indicated in the text. [b] Group main effect significant ($p < .05$).

Table 23: ERP group mean latencies for target tones at sites Fz, Cz, and Pz.

Latencies (ms) [a]	**Group Mean (*S.D.*) Latencies**		
	Fz	***Cz***	***Pz***
N1			
PD	115.5 (9.5)	115.3 (9.3)	115.0 (9.9)
controls	111.7 (11.8)	113.8 (13.1)	114.1 (14.8)
P2			
PD	187.0 (21.2)	180.8 (23.8)	183.0 (25.8)
controls	187.6 (23.2)	181.3 (23.2)	185.5 (24.3)
N2			
PD	245.8 (29.7)	232.2 (32.3)	231.1 (29.4)
controls	238.0 (28.3)	231.6 (27.9)	231.7 (29.4)
P3 [b]			
PD	333.8 (27.2)	332.5 (31.0)	345.2 (31.5)
controls	347.4 (31.3)	347.0 (34.3)	357.3 (31.0)

[a] Subject numbers indicated in the text. [b] Group main effect significant ($p < .05$).

Table 24: ERP group mean latencies for standard tones at sites Fz, Cz, and Pz.

Latencies (ms) [a]	Group Mean (*S.D.*) Latencies		
	Fz	*Cz*	*Pz*
N1			
PD	118.4 (11.1)	119.2 (11.1)	117.1 (11.4)
controls	116.7 (15.6)	119.0 (14.9)	116.4 (17.0)
P2			
PD	232.7 (31.7)	231.0 (30.3)	234.7 (33.2)
controls	232.1 (33.4)	233.3 (27.6)	238.4 (32.1)

[a] Subject numbers indicated in the text.

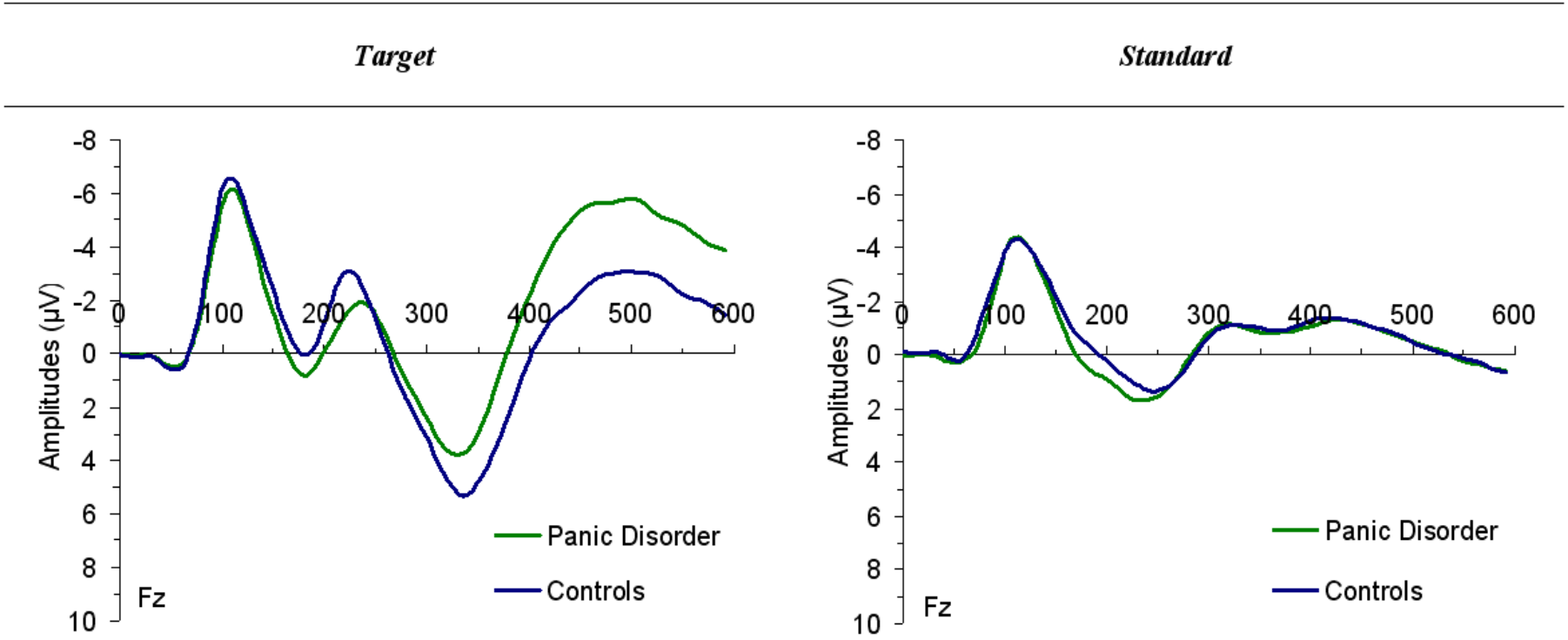

Figure 16: Group Grand Averaged ERP Waveforms to Target and Standard Tones at Site Fz. Figures show group grand averaged ERP waveforms (0 – 600 ms post–stimulus) for PD ($N = 45$) and control ($N = 96$) subjects. These figures represent raw data, without replacement of missing values.

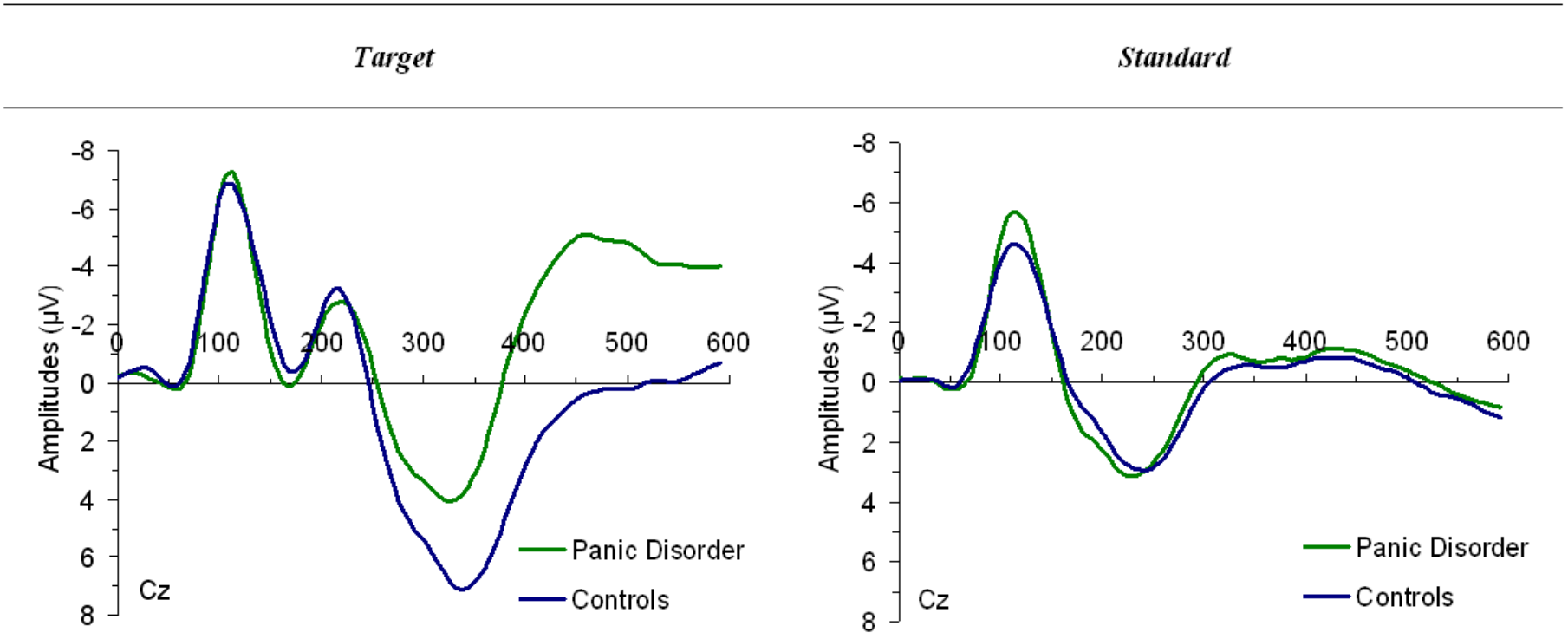

Figure 17: Group Grand Averaged ERP Waveforms to Target and Standard Tones at Site Cz. Figures show group grand averaged ERP waveforms (0 – 600 ms post–stimulus) for PD ($N = 45$) and control ($N = 96$) subjects. These figures represent raw data, without replacement of missing values.

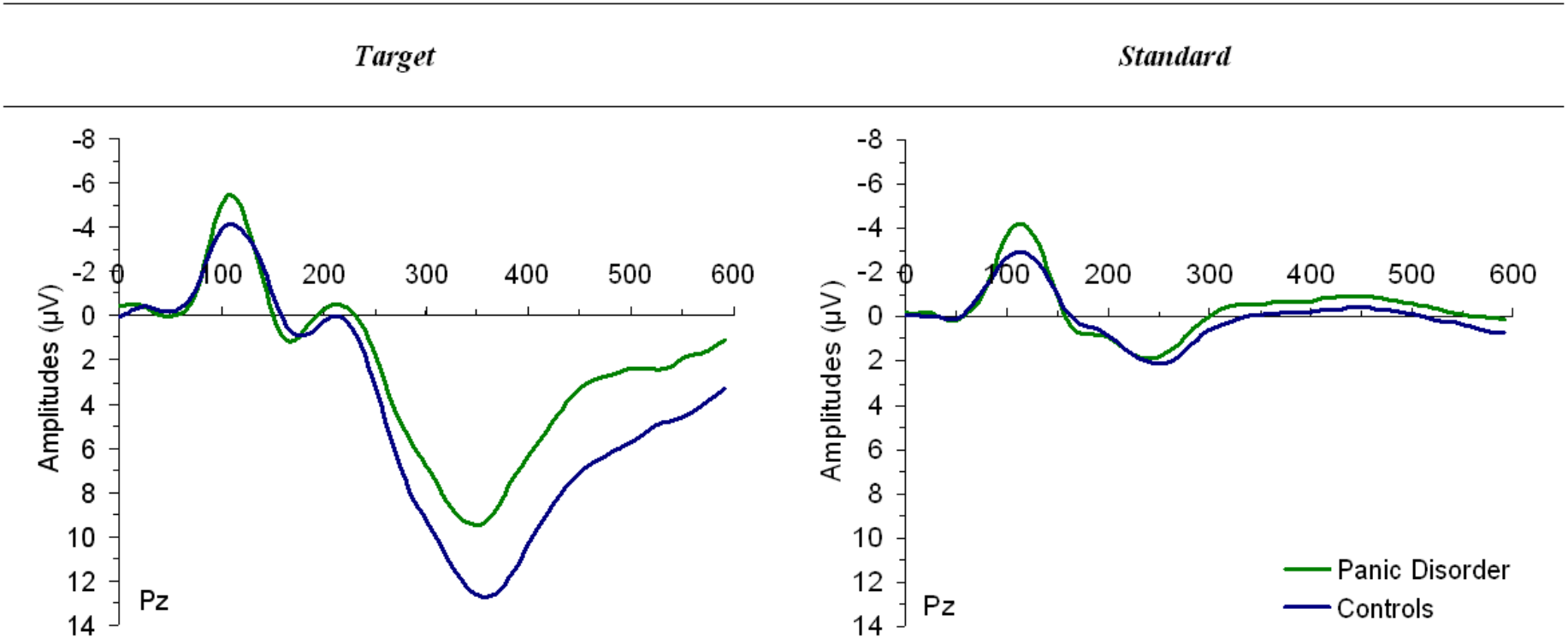

Figure 18: Group Grand Averaged ERP Waveforms to Target and Standard Tones at Site Pz. Figures show group grand averaged ERP waveforms (0 – 600 ms post–stimulus) for PD ($N = 45$) and control ($N = 96$) subjects. These figures represent raw data, without replacement of missing values.

7.5.1.2 N1

Patients (n = 50) and controls (n = 94) did not differ significantly on N1 amplitude for target stimuli (Group $F_{1, 142}$ = 0.52, p = .470). However the Group*Site interaction was significant ($F_{2, 284}$ = 7.25, p = .002, $\acute{\eta}_p^2$ = .049; ε = .822). Inspection of the group mean amplitude plot (Figure 19) suggested that this interaction was due to a relatively strong centralization of N1 target amplitudes in PD, compared to controls. Paired–samples *t*–tests confirmed this impression: Although N1 amplitude was significantly larger at Cz relative to Fz in both groups, the effect size was medium in patients (t_{49} = 6.25, p = 9.68E–8, d = .45) and small in controls (t_{93} = 2.37, p = .020, d = .15). There was no group difference for N1 target latency (Group main effect and Group*Site interaction $p \geq .225$).

For standard stimuli, patients (n = 50) and controls (n = 96) differed significantly on N1 amplitude (Group main effect ($F_{1, 144}$ = 3.91, $p < .050$, $\acute{\eta}_p^2$ = .026). This component was larger in PD compared to controls at sites Cz (t_{144} = –2.17, p = .033, d = .41) and Pz (t_{144} = –2.88, p = .005, d = .55) (corrected t and p values). The Group*Site interaction was also significant ($F_{2, 288}$ = 15.26, $p < .001$, $\acute{\eta}_p^2$ = .096; ε = .828). As per target stimuli, N1 amplitude for standards was relatively centralized in PD (see Figure 20). N1 amplitude was significantly larger at Cz relative to Fz in both PD (t_{49} = 6.64, p = 2.39E–8, d = .49) and controls (t_{95} = 2.13, p = .036, d = .12), representing medium and small effect sizes, respectively. The two groups did not differ in N1 latency for standard stimuli (Group main effect and Group*Site interaction $p \geq .691$). Topographical maps and statistical probability maps for N1 amplitudes are shown in Figures 21 (target stimuli) and 22 (standard stimuli).

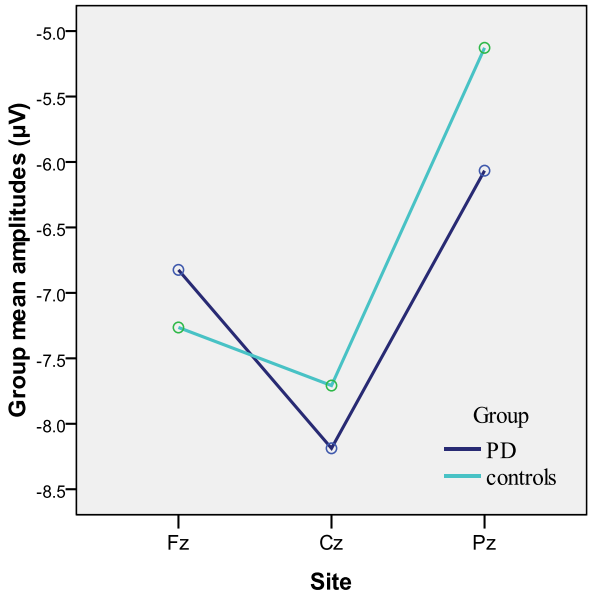

Figure 19: Group mean N1 amplitudes to target stimuli at sites Fz, Cz and Pz. Graph shows ERP mean N1 amplitudes for PD (*n* = 50) and controls (*n* = 94).

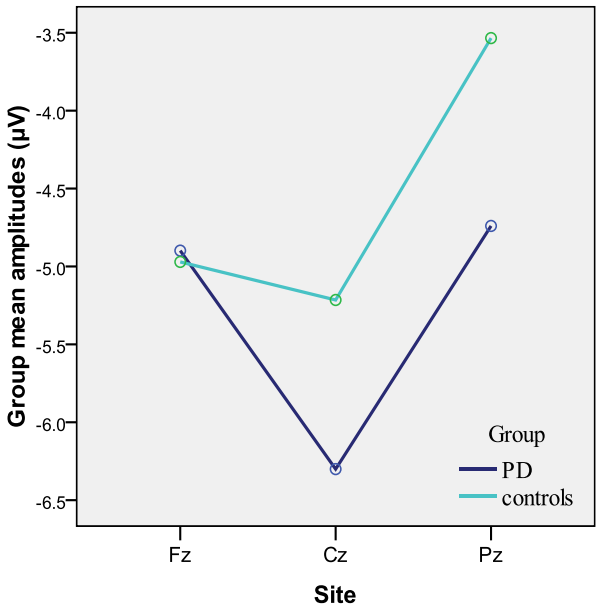

Figure 20: Group mean N1 amplitudes to standard stimuli at sites Fz, Cz and Pz. Graph shows ERP mean N1 amplitudes for PD (*n* = 50) and controls (*n* = 96).

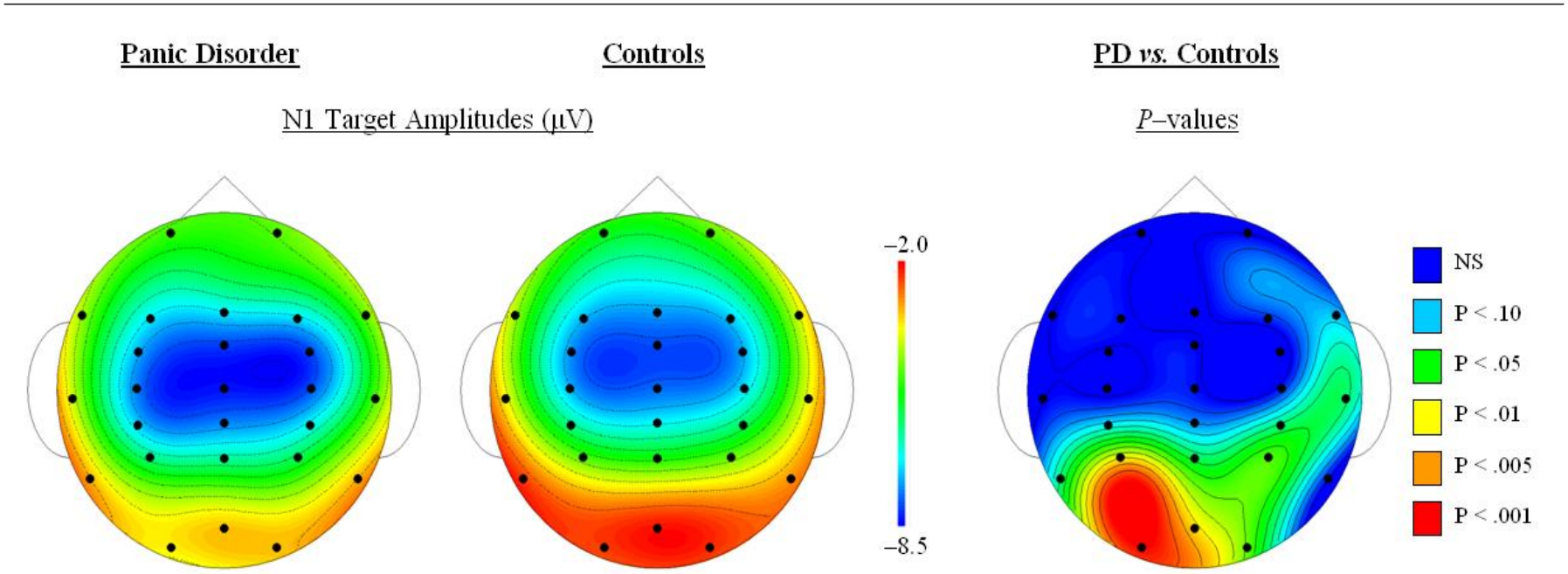

Figure 21: Group Mean Topographic Maps and Statistical Probability Map for N1 Target Amplitudes. Topographic maps (bird's–eye view, nose at top of image) show group mean N1 target amplitudes (left) and significance level of between–group *t*–tests at 26 scalp sites (right). Amplitude values reflect site maxima, independent of component latency.

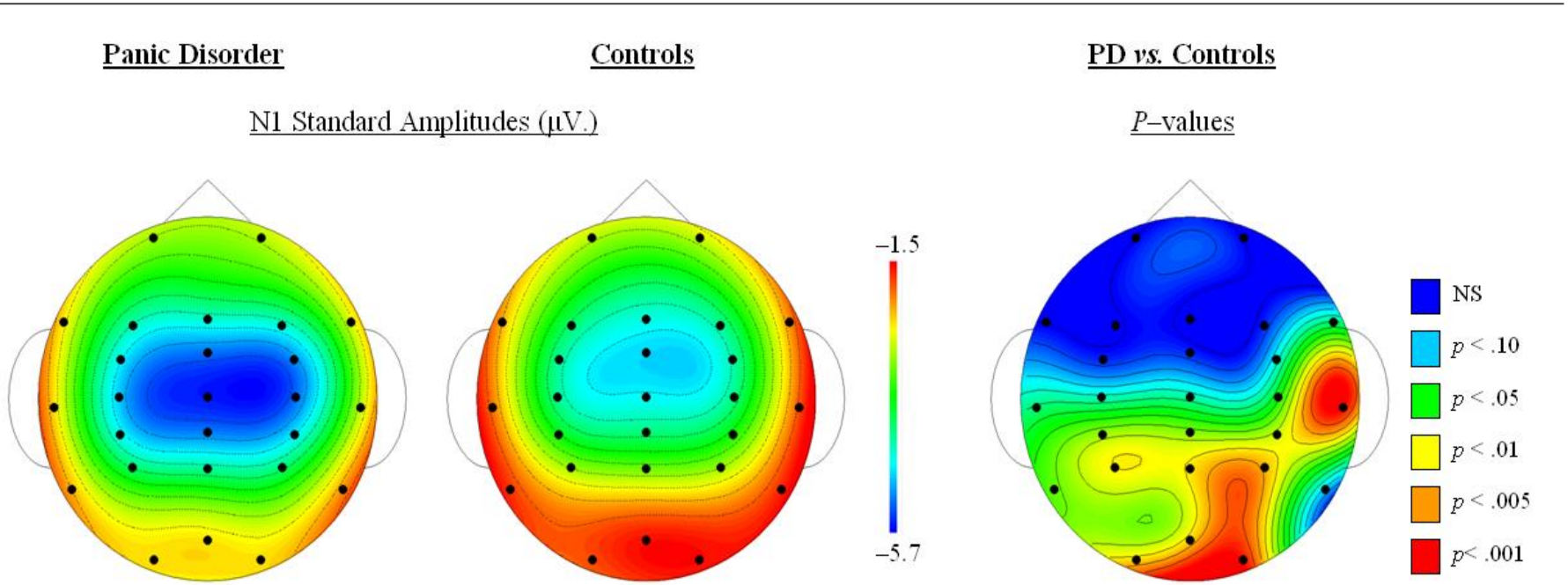

Figure 22: Group Mean Topographic Maps and Statistical Probability Map for N1 Standard Amplitudes. Topographic maps (bird's–eye view, nose at top of image) show group mean N1 standard amplitudes (left) and significance level of between–group *t*–tests at 26 scalp sites (right). Amplitude values reflect site maxima, independent of component latency.

7.5.1.3 P2

The two groups did not differ in their response to target stimuli at P2 (Group main effects and Group*Site interactions: amplitude $p \geq .252$; latency $p \geq .457$). Similarly, the Group main effects and Group*Site interactions were non–significant for standard stimuli (amplitude $p \geq .659$; latency $p \geq .244$).

7.5.1.4 N2

Patients and controls did not differ in N2 amplitude or its topography (Group main effect and Group*Site interaction $p \geq .518$). For N2 latency the Group main effect was non–significant ($p = .500$), but there was a significant Group*Site interaction ($F_{2, 258} = 6.42$, $p = .004$, $\acute{\eta}_p^2 = .047$; $\varepsilon = .813$). Inspection of the group mean N2 plot indicated that this interaction was due to a trend for attenuated N2 amplitude in PD at Fz ($t_{141} = 1.56$, $p = .121$), but not other sites.

7.5.1.5 P3

P3 amplitude was attenuated in PD ($n = 50$) compared to controls ($n = 91$) at all sites (Group $F_{1, 139} = 7.92$, $p = .006$, $\acute{\eta}_p^2 = .054$; Group*Site $F_{2, 278} = 2.25$, $p = .114$; $\varepsilon = .895$), significantly so at Cz ($t_{142} = –2.53$, $p = .013$, $d = .88$) and Pz ($t_{139} = –3.33$, $p < .001$, $d = .59$). Also, P3 latencies were shorter in PD ($n = 50$) compared to controls ($n = 92$) at all sites (Group $F_{1, 140} = 7.32$, $p = .008$, $\acute{\eta}_p^2 = .050$), significantly so at Fz ($t_{142} = –2.59$, $p = .011$, $d = .43$), Cz ($t_{142} = –2.49$, $p = .014$, $d = .44$) and Pz ($t_{140} = –2.21$, $p = .029$, $d = .38$). The Group*Site interaction was non–significant ($F_{2, 280} = 0.26$, $p = .730$; $\varepsilon = .828$). Group mean plots (Figures 23 and 24) show uniformly attenuated P3 amplitudes and reduced P3 latencies in PD across the 3 midline sites. Topographic maps and statistical probability maps for P3 amplitudes and latencies are shown in Figures 25 and 26.

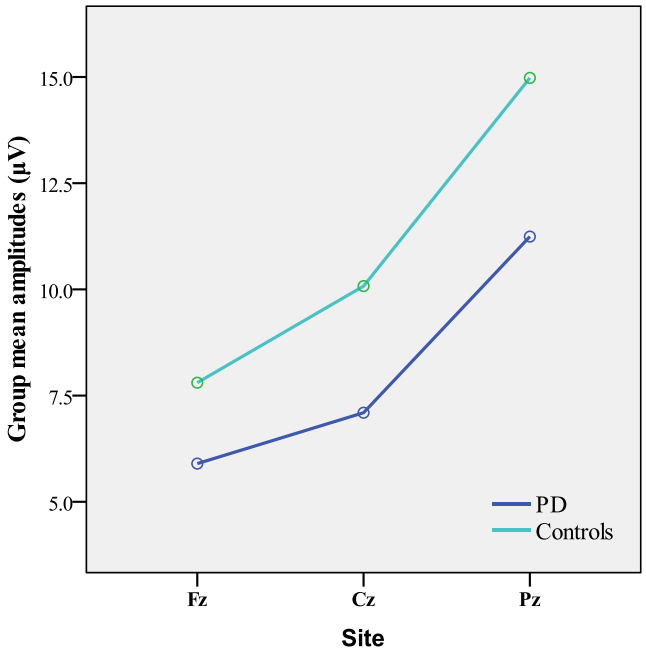

Figure 23: Group mean P3 amplitudes at sites Fz, Cz and Pz. Graph shows ERP mean P3 amplitudes for PD (*n* = 50) and controls (*n* = 91).

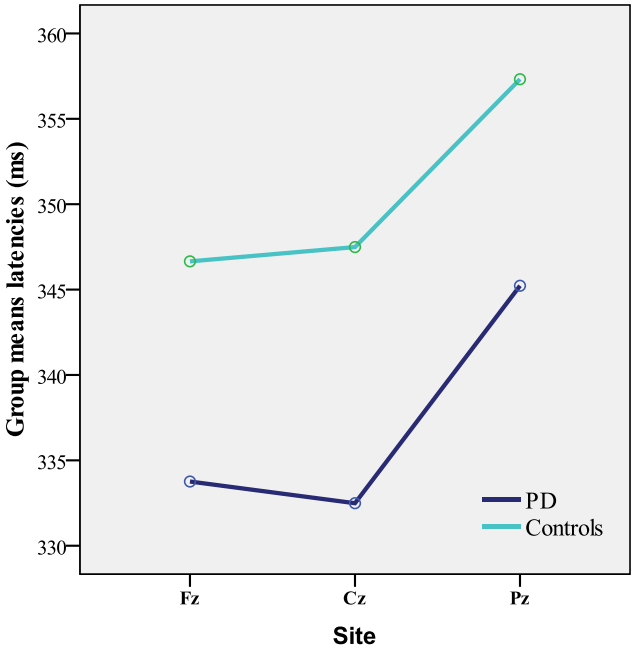

Figure 24: Group mean P3 latencies at sites Fz, Cz and Pz. Graph shows ERP mean P3 latencies for PD (*n* = 50) and controls (*n* = 92).

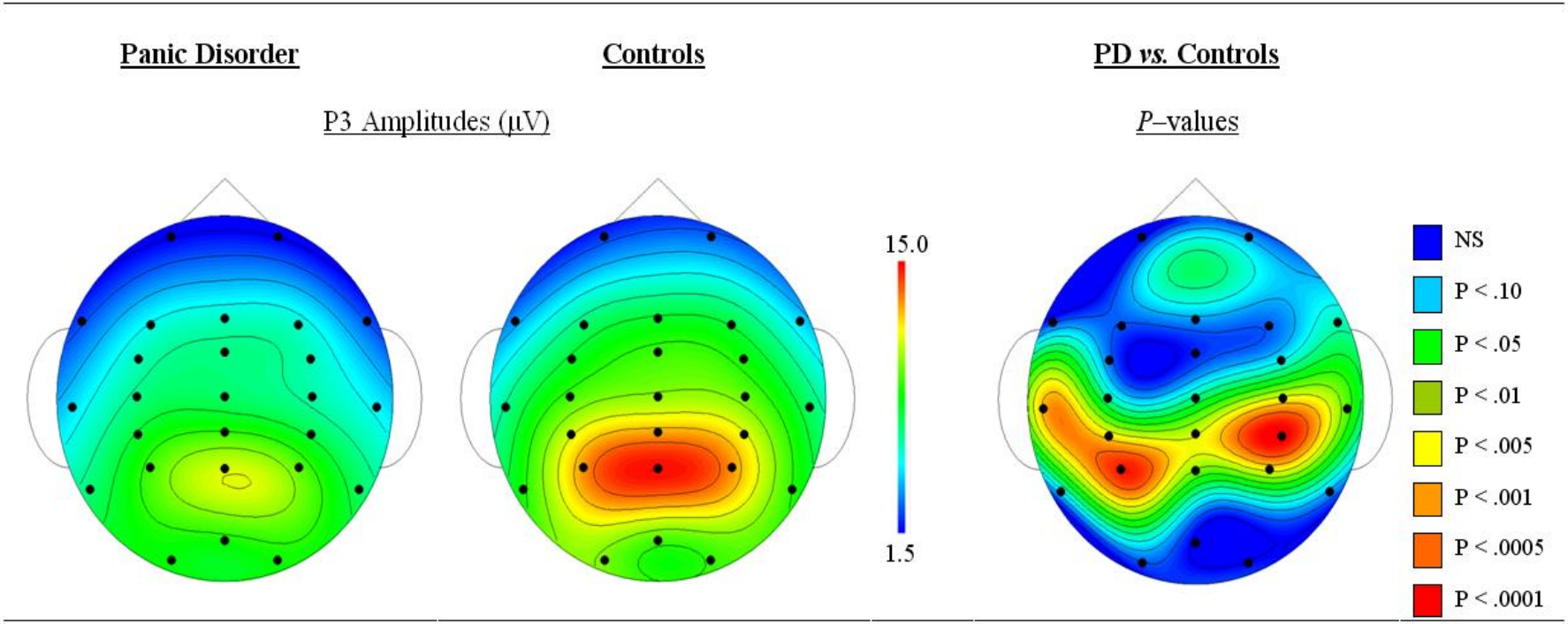

Figure 25: Group Mean Topographic Maps and Statistical Probability Map for P3 Amplitudes. Topographic maps (bird's–eye view, nose at top of image) show group mean P3 amplitudes (left) and significance level of between–group *t*–tests at 26 scalp sites (right). Amplitude values reflect site maxima, independent of component latency.

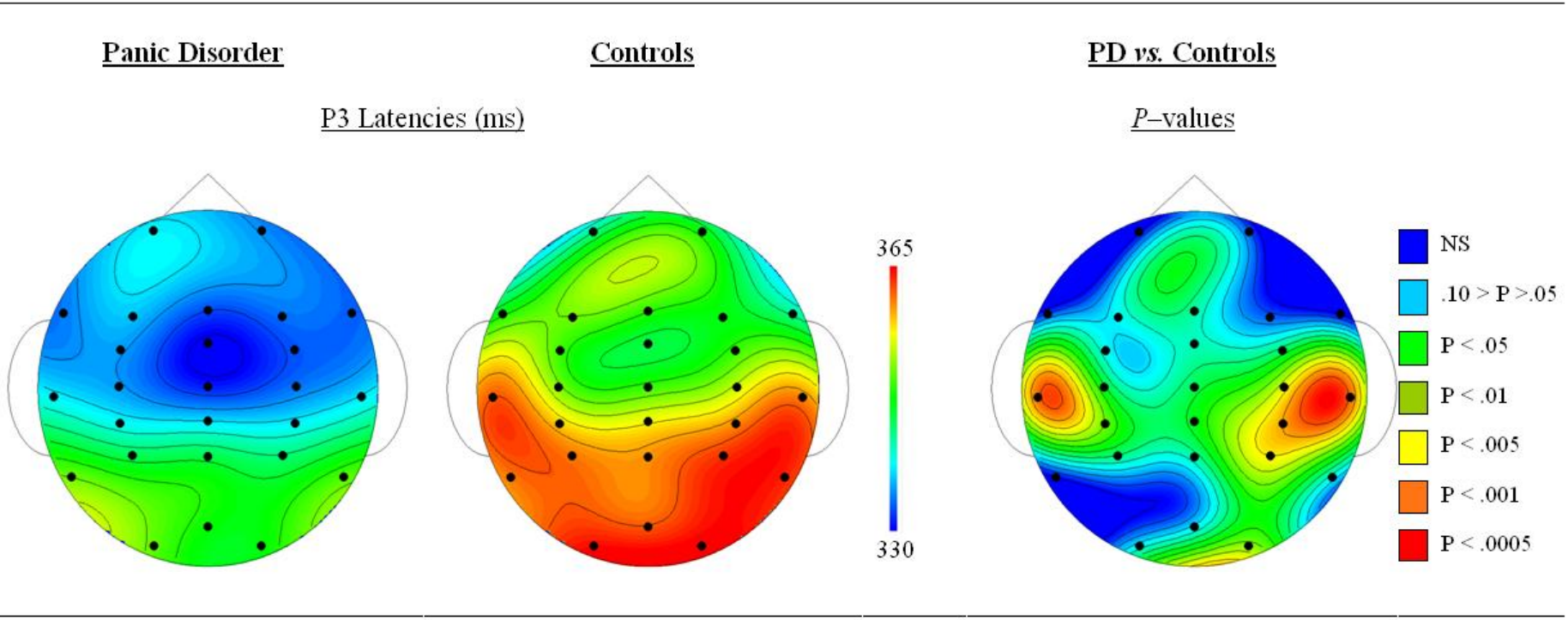

Figure 26: Group Mean Topographic Maps and Statistical Probability Map for P3 Latencies. Topographic maps (bird's–eye view, nose at top of image) show group mean P3 latencies (left) and significance level of between–group *t*–tests at 26 scalp sites (right).

7.5.2 Electrodermal Activity

Patients showed a trend for fewer SCRs than controls (t_{140} = –1.76, p = .081, d = –0.31). Descriptive statistics are shown in Table 25.

Table 25: Descriptive statistics for SCR frequency during auditory oddball task.

	PD	***Controls***
SCR–FREQ [a]	*6.18* 1.16 (1.29)	*7.55* 1.55 (1.21)

[a] Reported as: $M_{\text{untransformed (in italics)}}$ $M_{\text{transformed}}$ $SD_{\text{transformed (in brackets)}}$. Untransformed means are for illustrative purposes only.

7.5.3 Performance Measures

Mean RT was longer (t_{139} = 3.63, p < .001, d = 0.61), and more variable (t_{139} = 3.33, p < .001, d = 0.61, corrected t and p) in PD, compared to controls. Patients showed a trend for more frequent errors of commission than controls (False Positives t_{141} = 1.78, p = .079, d = 0.35, corrected t and p). The two groups did not differ on errors of omission (False Negatives t_{141} = –0.33, p = .740, d = –0.06). Descriptive statistics are shown in Table 26.

7.5.4 Relationship of Clinical Measures with Auditory Oddball Measures

7.5.4.1 Clinical Severity

Standard multiple regression analyses examined the relationship between patients' clinical severity and electrophysiological and behavioural measures. Five oddball task measures differentiating patients and controls were entered simultaneously as predictors

Table 26: Descriptive and inferential statistics for performance measures.

	PD	Controls
Speed (ms)		
RT	376.8 (54.5)	344.7 (47.7)
RT–SD	73.2 (27.1)	58.6 (20.2)
Accuracy		
False Positives [a]	*0.79* 0.37 (0.60)	*0.34* 0.20 (0.39)
False Negatives [a]	*0.10* 0.07 (0.21)	*0.15* 0.09 (0.27)

[a] Reported as: $M_{\text{untransformed (in italics)}}$ $M_{\text{transformed}}$ $SD_{\text{transformed (in brackets)}}$. Untransformed means are for illustrative purposes only.

in two separate models. The predictor measures were: N1 standard amplitude at Cz; P3 amplitude at Pz; P3 latency at Pz; RT, and; RT–SD. Outcome variables for the two models were STAI–S and PDSS score. Additionally, a hierarchical model was conducted with PD duration as the outcome measure, with age entered in step 1. The same five psychophysiological variables served as predictors in this model. The selected variables did not predict STAI–S ($F_{5, 44} = 0.10$, $p = .991$), PDSS ($F_{5, 44} = 1.02$, $p = .416$) or PD duration after controlling for age (F change $_{5, 43} = 0.52$, $p = .758$).

7.5.4.2 Comorbidity and Medication

A second set of regression analyses determined the extent to which patients' comorbidity and medication use contributed to the five above–defined oddball task measures. Comorbidity and medication measures served as predictors in these models as, being categorical, they were unsuitable as outcome measures. In each model

Medication (Medicated/Unmedicated), Current Comorbidity (Yes/No), and Alcohol (lifetime alcohol abuse or dependence: Yes/No) were entered simultaneously as predictor variables. The combined effect of patients' medication status and comorbidity did not predict any of the outcome measures: N1 standard amplitude at Cz ($F_{3, 46} = 0.76$, $p = .522$); P3 amplitude at Pz ($F_{3, 46} = 1.28$, $p = .292$); P3 latency at Pz ($F_{3, 46} = 0.59$, $p = .622$); RT ($F_{3, 46} = 0.80$, $p = .503$), or; RT–SD ($F_{3, 46} = 0.06$, $p = .980$).

7.5.4.3 Depersonalization and Event–Related Potentials

Spearman correlations examined the association between frequency of depersonalization (DD Percentage) and three ERP measures most strongly distinguishing patients and controls. ERP measures were: N1 standard amplitude at Cz; P3 amplitude at Pz; P3 latency at Pz. DD Percentage was negatively correlated with P3 latency (Spearman's *rho* = –0.33, $N = 48$, $p = .022$), but not the amplitude measures ($p \geq .400$). A post hoc independent–samples *t*–test comparing P3 latencies of patients who reported no depersonalization ($n = 23$) and matched controls ($n = 46$) was non–significant ($t_{67} = 0.33$, $p = .742$), reflecting near–identical mean P3 latencies. In contrast, P3 latencies of patients who reported depersonalization ($n = 25$) were significantly briefer than those of respective matched controls ($n = 50$: $t_{73} = 2.60$, $p = .011$, $d = 0.64$).

7.5.4.4 Sensory Gating

Pearson correlations examined the association of N1 amplitude to standard tones at Cz and the SGI Over–Inclusion factor (*OI*). Because of group differences in N1 topography – N1 amplitude was relatively centralized in PD compared to controls (see Figure 20) – a metric of N1 topography (Fz:Cz ratio) was calculated to examine the association of N1 topography and OI. Given that N1 was relatively centralized in PD, this measure

was considered an index of N1 centralization. Patients' scores on the OI factor were correlated with N1 topography (r = –.37, n = 49, p = .005, one–tailed) but not amplitude (r = .14, n = 49, p = .164).

7.6 Discussion

7.6.1 Study 2 Findings

The results identify disturbances in PD of several ERP indices of elementary sensory information processing. The findings of increased N1 amplitude to standard stimuli and reduced P3 amplitude in PD compared to healthy controls were predicted on the basis of the extant literatures, whereas the findings of reduced P3 latency and altered N1 topography to both stimulus types were unexpected. Other significant between–group differences were as predicted findings of increased and more variable RT in patients, in addition to and an unexpected trend for more errors of commission in PD. Analyses indicate that none of these positive findings could be accounted for by patients' medication use or comorbidity. Contrary to prediction, patients did not make more of errors of omission than controls, nor was the prediction of fewer SCRs to significant target stimuli in PD supported, although the results showed a non–significant trend in the predicted direction.

Analyses examining the association of clinical and psychophysiological measures showed that reduced P3 latency in PD was associated with the presence of depersonalization during panic. Finally, an association between neural and behavioural sensory gating measures was observed, but not as predicted. There were no other positive findings of associations between patients' clinical status and oddball task–derived measures. The study's main findings will now be discussed in more detail.

7.6.1.1 N1 Amplitude and Topography

N1 amplitude rapidly decreases with stimulus repetition, which either reflects refractoriness of the neural generators of N1 or a process of habituation (Budd *et al.* 1998; Sambeth *et al.* 2004). Current theory ascribes an important role of N1 attenuation with repeated stimulation in the ability to detect and gate novel sounds to awareness (Grunwald *et al.* 2003; Jääskeläinen *et al.* 2004). Thus the finding of increased N1 amplitude to standard tones in an oddball task in PD, particularly in the context of reduced P3 to infrequent target stimuli, may reflect an impaired ability to filter out insignificant stimuli early in the information processing stream. As impaired stimulus filtering mechanisms are believed to contribute to anxiety disorder patients' difficulties in stimulus–rich environments (Stewart & White, 2007), a sensory–gating interpretation of this finding is also consistent with behavioural evidence of sensory gating–like phenomena in PD. These include, for example, increased incidence of panic and anxiety symptoms in stimulus–rich environments in PD (Street *et al.* 1989; Watts & Wilkins, 1989; Sadock & Sadock, 2005). Impaired stimulus filtering functions are believed to leave the individual exposed to an excess of sensory information which overwhelms limited–capacity higher cortical centres (Freedman *et al.* 2002). The absence of a correlation of N1 amplitude and a measure of sensory gating phenomena (Over–Inclusion factor of SGI; OI) does not necessarily rule out a sensory gating interpretation for increased N1 in PD. Although an earlier study found that an index of N1 sensory gating specifically correlated with OI in healthy subjects (Kisley *et al.* 2004), and the present study found that OI correlated with N1 topography in PD, increased N1 amplitude to repetitive stimuli in PD could correlate with other, as yet untested, sensory gating measures.

There is, however, one caveat regarding a sensory gating interpretation for increased N1 amplitude in PD – this finding was based on the signal–averaged N1 across all trials of oddball standard tones, whereas N1 indices of sensory gating are typically derived from a paired–click paradigm and reflect N1 change across pairs of clicks (Boutros *et al.* 2004). An alternative explanation of increased N1 to oddball standard tones of increased dishabituation to the first standard stimulus in each train and intact N1 decrement across trials could be excluded with future single–trial ERP analysis studies. Alternatively, future analysis of N1 responses within a paradigm that yields an index of N1 amplitude change may clarify whether sensory gating for auditory stimuli is deficient at the early–attentive stage of information processing in PD.

N1 amplitudes in both conditions showed distinct central scalp maxima in PD, in contrast to a less localized N1 response in controls. Altered N1 topography may reflect the differential activation of distinct neural generators sub–serving different psychophysiological functions in the two groups (Näätänen & Picton, 1987). The finding of an association in patients between N1 amplitude topography for standard tones and a behavioural measure of sensory gating disturbances, although requiring replication, suggests that altered N1 scalp topography in PD is functionally significant. Nevertheless, further research is required to separate N1 component processes and determine the significance of altered N1 topography in PD.

7.6.1.2 P3 Amplitude and Latency

Oddball P3 is a very well–researched ERP measure (Reinvang, 1999; Hansenne, 2006). P3 amplitude is proportional to the attentional resources devoted to a given stimulus type and therefore provides a direct CNS measure of the degree to which incoming

sensory information is processed (Polich & Comerchero, 2003). In the present study, P3 amplitudes were smaller in PD compared to healthy matched controls, replicating earlier reports (Gordeev, 2008; Gordeev *et al.* 2003; 2006). Attenuated P3 to salient oddball target stimuli is generally considered indicative of impaired attentional function (Illardi *et al.* 2007). According to Polich and Herbst (2000) any neuropsychiatric disorder that affects the allocation of attention will show reduced P3 amplitudes and/or increased latencies – although the present findings of reduced P3 amplitude *and* latency defy that generalization.

The present finding for P3 amplitude, which indicates reduced allocation of attentional resources to affectively–neutral yet task–relevant stimuli in PD, is however, consistent with a wealth of behavioural evidence for attentional disturbances in PD. These data suggest that panic disordered individuals maintain an excessively self–focused attention and are preoccupied with disorder–related thoughts and imagery, while showing a concomitant reduction of attention to their external environment (Ottaviani & Beck, 1987; Watts, 1989; Schmidt *et al.* 1997; Khawaja & Oei, 1998; Wells & Papageorgiou, 1999; Hayward *et al.* 2000). For example, Hayward *et al.* (2000) found that PD patients, because of their inability to override their tendency for self–focused attention, were incapable of complying with experimental instructions to externally focus their attention. Several clinical interventions for PD, specifically aiming to exert control of the locus of attention in order to facilitate anxiety reduction, have been described (e.g., Wells *et al.* 1997; Kallai *et al.* 1999; Mobini & Grant, 2007). Such attentional interventions might benefit from the use of precise psychophysiological measures such as P3 amplitude to both predict and gauge treatment response.

Although P3 amplitude reduction is observed in numerous neuropsychiatric disorders (Polich & Herbst, 2000; Hansenne, 2006), the present result could not be attributed to patients' comorbidity. However, given inconsistencies in P3 findings for PD, the present finding requires replication. Previously, for instance, there have been both positive (Gordeev *et al.* 2003; 2006; 2008) and null findings (e.g., Iwanami *et al.* 1997; Turan *et al.* 2002; Wang *et al.* 2003; Hanatani *et al.* 2005), although the latter studies, which typically comprised small samples, may have been inadequately powered to detect group differences for P3. Moreover the inclusion of patients with current use of benzodiazepines may have confounded these results.

The finding of P3 latency reduction accords with an earlier finding by Hanatani *et al.* (2005). Although the earlier study did not specify the clinical characteristics of patients with latency reduction, in the present study P3 latency reduction was accounted for by patients who frequently experienced depersonalization during panic. Whereas other DSM–IV panic attack symptoms signify autonomic (Roth, 2005), hyperventilation–related (Meuret *et al.* 2009) or cognitive (Beck & Clark, 1997) disturbance, the phenomenology of depersonalization (altered perception of body) and derealisation (altered perception of surroundings) implicate aberrant sensory information processing (Sierra & Berrios, 1998). The finding linking depersonalization with P3 latency reduction follows earlier reports of altered sensory information processing in PD patients with relative to without depersonalization (Locatelli *et al.* 1993; Hayashi *et al.* 2010), and extends those findings to specifically implicate altered information processing speed.

P3 latency is understood to represent the speed of stimulus classification (Polich, 2007)

and is considered to be independent of behavioural reaction time (Verleger, 1997). In healthy subjects, individual differences in P3 latency are correlated with cognitive performance, such that shorter latencies are related to superior cognitive performance, with the strongest correlations being observed for task measures that assess how rapidly subjects can allocate attentional resources (Reinvang, 1999; Polich, 2007). However, P3 latency is typically inversely related to P3 amplitude (Polich, 2007). Therefore a combination of reduced P3 latency and reduced P3 amplitude is unusual, and suggests speeded but impoverished processing of salient environmental cues in a subgroup of individuals with PD. Reduced P3 latency in PD could, conceivably, have resulted from the superimposition of increased late negativity in PD, relative to controls (see Figures 16 – 18). To rule out this explanation, the grand mean waveforms of patients without depersonalization (n = 18) and those with frequent depersonalization (n = 13; depersonalization during $\geq$ 60% panic episodes) were plotted (see Appendix K). Inspection of these waveforms indicates no enhanced late negativity in patients with frequent depersonalization, arguing against P3 latency reduction as an artifact of superimposed late negativity.

7.6.1.3 N2 and P2

No between–group differences were apparent for either N2 or P2. Oddball N2 reflects the detection of a mismatch within a stimulus stream (Folstein & van Petten, 2008). Although reduced oddball N2 amplitude in PD was previously reported (Wang *et al.* 2003), the small number of patients showing that ERP abnormality renders the finding unreliable. Interpretations of P2 include attentional modulation of standard stimuli (Novak *et al.* 1992) and stimulus classification (Garcia–Larrea *et al.* 1992), and the component is believed to represent a functionally discrete stage of neural processing

(Crowley & Colrain, 2004). In healthy subjects, increased scalp–recorded negativity and reduced P2 amplitude during an oddball task were associated with novelty stress, that is, physiological arousal associated with unfamiliar environments (Dietl *et al.* 2004). Although HR data suggest that individuals with PD may be more susceptible to novelty stress (Larsen *et al.* 1998), the absence of group differences for P2 in the present study argues against novelty–related cortical arousal. The absence of N2 and P2 group differences suggests that sensory information processing at these latencies is not disturbed in PD, at least not when easily–discriminated auditory stimuli are used.

7.6.1.4 Electrodermal and Behavioural Findings

Patients compared to controls showed a trend for fewer SCRs to oddball target stimuli. The SCR represents the electrodermal component of the OR (Öhman *et al.* 2000) and reflects the personal salience of stimuli (Dindo & Fowles, 2008). The SCR finding, therefore, provides support (albeit limited, given the non–significant result) of reduced orienting to and attentive processing of salient environmental stimuli. The findings of increased RT in conjunction with reduced processing speed (*i.e.* decreased P3 latency) suggest that response–related factors underlie patients' delayed behavioural response. Increased and more variable RT during an oddball task reflect inattention to the task (Riccio *et al.* 2002). In performing tasks that are prolonged and repetitive in nature, such as CPTs, the challenge is to maintain focused attention to the task and to ignore potentially interfering task–unrelated distractors (e.g., thoughts, sensations) (Smallwood *et al.* 2004). According to biased competition models of selective attention, frontal control mechanisms support the processing of task–related stimuli in the presence of potential distractors (Desimone & Duncan, 1995). Such models predict that the outcome of attentional competition between affectively–neutral task–related stimuli and task–

unrelated threat stimuli will be determined by the relative strength of prefrontal cortex and amygdala (Bishop, 2007). Indeed, the frequency of task–unrelated thoughts during tests of sustained attention varies as a function of the salience of one's current concerns (Smallwood *et al.* 2004). Given that potentially panic–associated cues are ubiquitous (Lissek *et al.* 2010) and perceived as threatening in PD (Craske & Waters, 2005), it is possible that ongoing processing of disorder–related cues contributed to impaired task performance on measures of speed. However, the two groups did not differ in terms of accuracy. This could reflect a ceiling effect, given that target and standard tones were easily distinguishable.

7.6.2 Study Limitations

The uncertain significance of the findings for phasic EDA in the present study (and Study 2) is a limitation of these studies. Study 1 found fewer non–specific SCRs (NS.SCRs) in patients compared to controls, and Study 2 found a trend for fewer SCRs in PD compared to controls. Stimuli that are in some sense significant elicit a SCR (Dindo & Fowles, 2008), which represents the electrodermal component of the orienting reflex (Öhman *et al.* 2000). In both clinical and healthy samples, auditory oddball target stimuli that elicit a SCR are associated with a larger P3 amplitude relative to those that do not elicit a SCR (Bahramali *et al.* 1997; 2001). Although it was predicted that patients would show fewer SCRs than controls during the oddball task the unexpected Study 1 finding of fewer NS.SCRs in PD raised the possibility that both findings represented ceiling effects in terms of skin hydration. However, because it was not possible to quantify absolute SCL, this explanation could be neither supported nor refuted.

Another limitation of Study 2, given the large number of statistical analyses conducted, is the possibility of Type I error. Nevertheless, it should be noted that the majority of positive findings in Study 2 were predicted on the basis of the extant literature. There were only two positive findings that were not predicted. These were reduced P3 latency in PD (the opposite was predicted), and a correlation between P3 latency and depersonalization in patients. The latter finding in particular, which was based on exploratory analyses, requires replication within an independent sample.

A final limitation of Study 2 relates to the between–group finding for N1 amplitude. One interpretation of this finding, given that N1 amplitude decrement with stimulus repetition is considered an important stage of sensory gating (Jääskeläinen *et al.* 2004), is that N1 attenuation was reduced in PD. However, the fact that this finding was based on the signal–averaged N1 across trials precluded the possibility of ruling out alternative explanations for this finding. Although the auditory oddball task is not specifically deemed a test of sensory gating, future single–trial ERP analyses, even of oddball ERPs, are needed to clarify the nature of increased N1 amplitude to repetitive stimuli in PD.

7.6.3 Conclusions and Future Directions

Increased N1 to standard stimuli suggests a reduced ability to discard stimuli of low significance, whereas P3 amplitude attenuation suggests an inability to appropriately allocate limited neural resources to selected stimuli. Reduction of the N1 wave due to stimulus redundancy and elicitation of the P3 in response to stimulus relevance may be viewed as complementary neural functions, both of adaptive value in the allocation of attention: the filtering of background stimuli and the allocation of attention to relevant

stimuli, respectively (Jääskeläinen *et al.* 2004). These ERP disturbances, affecting different stages of attentive sensory information processing, reflect a disturbance in appropriate signal to noise discrimination (Gordon *et al.* 2007) within the context of a very basic auditory discrimination task. It is expected that this pattern of impaired stimulus processing would contribute to the excessive reactivity of PD patients in complex environments of high sensory load. However, cross–sectional investigations, such as the present study, may not determine the causal direction between the observed central and peripheral nervous system abnormalities and the clinical manifestations of the disorder. Appropriate analyses are needed to determine the nature of the association between PD and these disorder markers.

7.7 Summary of Chapter

Several disturbances of attentive sensory information processing were evident in PD in a simple auditory discrimination task utilizing non–threatening stimuli. The main ERP findings were increased amplitude to repetitive, irrelevant tones (standards), and reduced P3 amplitude and latency to infrequent, salient tones (targets). Given the purported functional significance of these ERP components, these results are broadly consistent with the clinical phenomenology of the disorder in which patients frequently experience increased symptoms of panic and anxiety in environments of particularly high sensory load, and poorly attend to their surroundings.

Considered together, a number of the findings of Studies 1 and 2, including several measures of intrinsic and evoked electrocortical activity and HRV, indicate either impaired attentional processing or diminished capacity for attentional processing in PD. By contrast, several of the Study 1 findings for intrinsic brain activity support the

prediction of normative performance on tests of memory in PD. Study 3 therefore sought to elucidate the nature and extent of any impairment in cognitive function in PD, using an extensive neuropsychological test battery encompassing several tests of attention, memory and other core cognitive domains of function.

Notes

1. The results of this study have previously been reported in the literature (Wise *et al.* 2009, see Appendix M).
2. ERP components are named for their polarity (P for positive, N for negative), and either their ordinal position after stimulus (e.g., P1, P2) or their latency in ms after stimulus onset (e.g., P300) (Menon & Crottaz–Herbette, 2005). For consistency, the former nomenclature will be used throughout. As P3 is considered a multi–component phenomenon (Polich, 2007) the generic term P3 will be used throughout to denote the P3b component, to distinguish it from the earlier fronto–centrally maximal P3a (Goldstein *et al.* 2002).

Chapter 8

Study 3: Cognitive Function

8.1 Overview of Chapter

Study 3 examined neuropsychological performance in PD using tests spanning the cognitive domains of attention, memory, executive function, language, and sensory–motor function. The tests provide measures of cognitive functioning such as the ability to selectively attend to stimuli, sustain focused attention, maintain representations in working memory, learn new information, and long–term memory – all of which are important in the regulation of behaviour in daily life. Although an extensive literature has examined cognitive biases for disorder–specific threat stimuli, which are proposed to play a key role in the development and maintenance of PD (Clark, 1986; McNally, 2002; Benítez, 2009), there is a relative paucity of studies that have addressed general cognitive function in PD with affectively–neutral stimuli (Dupont *et al.* 2000). The aim of Study 3, therefore, was to elucidate the nature and extent of any impairment in cognitive function in PD.

The chapter begins by defining the major cognitive domains encompassed by the present neuropsychological assessment. This is followed by a review of empirical findings of relevance to the present study. As there have been few neuropsychological studies of PD and the findings of this literature are equivocal, this review encompasses pertinent literatures other than neuropsychological studies

of PD. Notably, given the integrative nature of the present research several predictions for the present study were derived from the psychophysiological findings of Study 1 and 2. Following this background information, the present research and its results are presented.

8.2 Study Background

8.2.1 Cognitive Domains

Neuropsychological studies of PD have typically examined functioning within the broad domains of attention, memory, and executive functions. Each of these is discussed.

8.2.1.1 Attention

Attention refers to a set of capacities or processes that underlie our awareness of the world and the voluntary regulation of our thoughts, feelings and behaviours (Posner & Rothbart, 2007). A salient feature of information processing within the human brain is its limited capacity (Marois & Ivanoff, 2005). According to Escera *et al.* (2000, p. 151), "The human brain does not have a sufficient capacity to allow the conscious processing of all stimulus information that simultaneously impinges upon the various senses. Therefore, following an initial survey of the sensory input, only a part of the incoming information gains access to consciousness." Selecting which stimuli to respond to in a complex and changing environment is one of the key functions of attention (Öhman *et al.* 2000).

Since William James, a broad distinction has been drawn between two types of attentional process that determine entry of information to the limited capacity system

and thus consciousness – *passive* (reflexive or automatic) *attention* and *voluntary* (active) *attention* (Öhman *et al.* 2000). Passive attention is a bottom–up (*i.e.* stimulus–driven) process whereby stimuli that are in some sense interesting automatically capture one's attention (Öhman *et al.* 2000). Involuntary attentional capture draws the individual's focus of attention to potentially significant events so that they may be further evaluated (Sussman *et al.* 2000). Voluntary attention, by contrast, is a top–down (*i.e.* knowledge–driven) process that involves the intentional selection of channels of information for enhanced processing (Sarter *et al.* 2001). Increased *distractibility*, that is, the extent to which one is subject to involuntary redirection of attention from goal–focussed behaviour, implies reduced top–down control of attention (Escera *et al.* 2000).

In addition to the broad distinction between passive and voluntary attention, models of attention typically distinguish several other components or processes of attention. These include: 1) attentional capacity; 2) selective attention; 3) sustained attention; 4) divided attention, and; shifting attention (Lezak *et al.* 2004). *Attentional capacity* refers to the amount of information that can be grasped at once and is considered an integral component of attention (Lezak *et al.* 2004). Attentional capacity – also called working memory capacity (Howieson & Lezak, 2002) – is measured by span tests such as Digit Span (Lezak *et al.* 2004). *Selective attention* is defined as those processes that allow a subset of information from the environment to be selected for further, more elaborated processing (Behrmann *et al.* 2004). Definitions of selective attention also encompass the capacity to inhibit the processing of potentially distracting irrelevant stimuli (Lavie, 2005). Other terms which are sometimes used interchangeably with selective attention are focussed attention and concentration

(Lezak *et al.* 2004). *Sustained attention* (or vigilance), as previously defined, refers to the capacity to detect infrequent and unpredictable signals over a prolonged interval (Sarter *et al.* 2001). *Divided attention* and the overlapping construct *shifting attention* refer to the capacity to engage in more than one task–related activity, and to shift the focus of attention between tasks or mental sets (Strauss *et al.* 2006).

8.2.1.2 Memory

Memory refers to a set of processes whereby the individual encodes, stores and retrieves information (Strauss *et al.* 2006). Although many models of memory systems have been proposed, a broad distinction exists between working memory and long–term memory (LTM). *Working memory*, according to Miyake and Shah (1999, p. 450), is defined as those "mechanisms or processes that are involved in the control, regulation, and active maintenance of task–relevant information in the service of complex cognition". The working memory system is closely linked with LTM, as the contents of working memory include representations of currently activated LTM items and external sensory events (Miyake and Shah, 1999). According to the influential multi–component model of working memory by Baddeley and Hitch (Baddeley, 1986), working memory comprises three components, two of which are specialised for the short–term storage and maintenance of information: one for verbal material (the phonological loop) and one for visuospatial material (the visuo–spatial sketchpad). The third component, the central executive, is considered responsible for the control and regulation of cognitive processes (*i.e.* executive functions) (Baddeley, 1986). However, as the content of the stores are subject to decay, an important aspect of working memory is that working memory representations must be actively maintained (*i.e.* rehearsed) if

they are to remain in memory (Baddeley, 2010). Thus, effective working memory function requires the capacity to sustain attention to the mental representations active in working memory (Baddeley, 1999). The ability to "keep things in mind" in working memory via executive control (Baddeley, 2010) is considered essential for many complex cognitive tasks, such as language processing, decision making, reasoning, problem solving, planning, learning, and selective attention (Baddeley, 1986; 1992; 2010; Miyake & Shah, 1999).

Long–term memory, by contrast, refers to the permanent or relatively stable storage of memories and is typically divided into several functionally distinct subsystems (Strauss *et al.* 2006). Within LTM, two long–term storage and retrieval systems may be distinguished: *declarative memory* and *non–declarative memory* (Squire and Knowlton, 2000). Declarative or explicit memory is memory for facts or events that requires conscious, effortful recollection (Graf & Schacter, 1985). It is typically measured by tests of verbal recall and recognition (Golier & Yehuda, 2002) and is strongly influenced by the degree of attention at the time of encoding (Danckwerts & Leathem, 2003). Implicit or procedural memory, on the other hand is not conscious. Yet, implicitly recalled information may influence current behaviour in the absence of recollection of the prior occurrence (Danckwerts & Leathem, 2003).

8.2.1.3 Executive Functions

The executive functions do not constitute a discrete cognitive domain, per se (Lezak *et al.* 2004). Rather, the term *executive functions* denotes a set of 'higher–level' cognitive functions that control and regulate 'lower–level' cognitive processes to enable performance of complex cognitive tasks and goal–directed behaviour

(Alvarez & Emory, 2006). Therefore, executive functions necessarily manifest in the context of other cognitive processes (Miyake *et al.* 2000). Although consensus is lacking regarding which mental processes constitute the executive functions (Alvarez & Emory, 2006), processes that are commonly conceived as executive functions include: attention (selective, sustained, divided, and shifting); working memory (maintenance, monitoring and updating); inhibition of dominant or prepotent responses, and; planning a sequence of sub–tasks to achieve a goal (Barkley, 1996; Denckla, 1996; Smith & Jonides, 1999; Miyake *et al.* 2000; Shimamura, 2000).

8.2.2 Neuropsychological Assessment

Neuropsychological assessment provides objective, standardised and well–validated measures of brain dysfunction by delineating those cognitive domains that are disrupted from those that are intact within a given disorder (Ritchie & Richards, 2002). Information derived from neuropsychological assessment has many potential applications for research and clinical practice. Potential clinical applications include the monitoring of cognitive changes in the course of treatment, prediction of treatment response and assessment of treatment efficacy, and the identification of cognitive dysfunction as targets for cognitive therapy (Ritchie & Richards, 2002). Within a research framework, objective indices of cognition may further understanding of the psychopathologic processes underlying the overt clinical symptoms (Williams *et al.* 2010) and provide sensitive and objective intermediate phenotypes that are aetiologically more proximal to the underlying brain basis of a psychiatric disorder than top–level symptoms (Gould & Gottesman, 2003). Further, neuropsychological tests help describe the consequences of pathology, particularly in terms of the real–life impact for the individual (Ritchie & Richards, 2002). As

cognitive disturbances may have wide–ranging consequences for the individual in terms of their quality of life, employability, ability to study, and to perform everyday tasks (Fujii *et al.* 2002; Chamberlain & Sahakian, 2005; Castaneda *et al.* 2008), accurate assessment of cognitive function is important.

Computerized administration of neuropsychological tests offers several advantages over standard "paper–and–pencil" formats (Bauer *et al.* 2012). Firstly, computerized assessment permits greater standardization in comparison to non–computerized assessment, in that the tests are delivered and the performance is measured the same way every time (Clark *et al.* 2006; Woo, 2008). Secondly, computerized assessment is advantageous because it permits measurement of aspects of performance not possible with standard paper–and–pencil testing, such as RT latency and variability (APA, 1987). Increased precision in the measurement of time–sensitive measures is another advantage of computerized assessment (Bauer *et al.* 2012). Finally, computerized assessment reduces in significant measure the interaction between the examiner and the examinee (Lezak *et al.* 2004; Leposavić *et al.* 2010). This is important because neuropsychological performance may be adversely affected by the presence of an observer, and this effect may be moderated by individual differences in state anxiety (Horwitz & McCaffrey, 2008). As laboratory environments typically elicit greater state anxiety in panic disordered relative to unaffected subjects (Dager, 2010), and individuals with PD frequently endorse specific fears relating to behavioural loss of control, social catastrophe and social evaluation (Ottaviani & Beck, 1987; Breitholtz *et al.* 1998; Chambless *et al.* 2000; Raffa *et al.* 2004; Hicks *et al.* 2005), computerized neuropsychological assessment may be preferable for PD research in that it entails less potential for performance observation.

8.2.3 Empirical Findings

Information about cognitive function in clinical populations is derived from several sources, including: 1) neuropsychological studies; 2) psychophysiological studies, and; 3) clinical observations and patients' self–reports of everyday difficulties with cognitive function (e.g., concentration, memory) (Danckwerts & Leathem, 2003). Accordingly, the following sections review neuropsychological, psychophysiological, and clinical empirical findings relating to neuropsychological function in PD. Psychophysiological findings are derived from Studies 1 and 2.

8.2.3.1 Neuropsychological Findings

In comparison to other anxiety disorders relatively few studies have investigated cognitive function in PD (Castaneda *et al.* 2008). Further, in comparison to the sizeable literature that has investigated cognitive function in PD with threat stimuli few studies have investigated cognitive function in PD using standardised neuropsychological tests comprising threat–neutral stimuli (Dupont *et al.* 2000). In particular, given considerable experimental evidence of attentional biases for disorder–related threat stimuli in PD (reviews McNally, 1998; Bar–Haim *et al.* 2007; Mobini & Grant, 2007; Craske *et al* 2009), and that affectively–neutral task stimuli and threat–related but task–irrelevant stimuli effectively vie for limited attention (Bishop, 2007), the relative paucity of studies that have investigated attentional processing using threat–neutral stimuli is surprising. The present study therefore investigated neuropsychological function in PD with a computer–administered cognitive test battery that tapped multiple aspects of attention (attentional capacity; selective, sustained and shifting attention), memory (verbal and visual working memory, verbal learning and LTM), executive functions, language, and sensory–

motor function. Findings on tests similar to those administered in the present study are reviewed.

Several studies have investigated neuropsychological performance in PD on tasks that tap different aspects of attention. These tests were either administered as part of a neuropsychological test battery, or as a primary research focus. Dupont *et al.* (2000) examined visuospatial attention in PD using a simple target discrimination task. Studies that use visual search to detect salient target features assess passive as opposed to voluntary aspects of attention (Maruff & Pantelis, 1999). They hypothesised that individuals with PD would poorly attend to the affectively–neutral task stimuli and would show impaired performance, because of automatic attentional biases for disorder–related threat. They did not find support for this hypothesis. Instead they found that patients were more likely than controls to detect a target stimulus, whether or not it was present. In other words, patients made fewer errors of omission and more errors of commission than controls. They interpreted this finding as indicative of increased perceptual sensitivity due to hypervigilance in PD.

Lautenbacher *et al.* (2002) assessed selective and divided attention in PD. They argue that previous neuropsychological investigations of PD had not previously tested the limits of attentional capacity with higher loads, but had instead used simple tests which focus on psychomotor speed and selective attention. Clinical participants in this study were inpatients with relatively severe PD. They found that RT was greater in PD compared to controls within a dual–task paradigm, but not in a single–task selective attention task. Performance on dual–task divided attention paradigms tax the executive functions of inhibition and switching (Strauss *et al.* 2006).

Kampmann *et al.* (2002) and van den Heuvel *et al.* (2005) compared performance of individuals with PD and healthy controls on the emotional Stroop paradigm. This task is the most commonly used task for assessing attentional biases in anxiety disorders (Kolassa *et al.* 2005). Task performance requires the executive function of actively inhibiting an automatic response (word reading) in favour of a slower voluntary response (colour naming) (Williams *et al.* 1996). Colour–naming latency for emotional relative to neutral stimuli is typically reported, and is taken as a measure of attentional bias (McNally, 1998). However, Kampmann *et al.* and van den Heuvel *et al.* both reported that colour–naming latencies in PD were prolonged, irrespective of the valence of the stimuli.

Several studies assessed declarative memory in PD. The parahippocampal region within the medial temporal lobe (MTL) is a key region in the neurocircuitry that subserves declarative memory formation (Tranel & Damasio, 1995; Squire & Knowlton, 2000; Shu *et al.* 2003; Moscovitch *et al.* 2005). Specifically, converging data from lesion, preclinical, and neuroimaging studies indicate that left and right MTL structures mediate verbal and visual memory, respectively (Geschwind & Galaburda, 1985; Preston & Gabrieli, 2002). However, parahippocampal structures are also important neuroanatomical substrates for anxiety (Gray & McNaughton, 2000; Charney, 2003; Lang *et al.* 2009), and both function and structural abnormalities – particularly, the right hemisphere – are a consistent finding of neuroimaging studies of PD (reviews Cannistraro & Rauch, 2003; Engel *et al.* 2008; Shin & Liberzon, 2009). As cognitive performance may suffer as a consequence of neural competition between task–relevant cognition and anxiety–related activation (Lavric *et al.* 2003; Shackman *et al.* 2006), LTM deficits might be observed in PD.

Lucas *et al.* (1991) used a battery of tests to assess different aspects of verbal and visual memory and learning in PD. They found that patients performed worse than controls on measures of visual learning and memory, although the former was not significant after controlling for state anxiety. By contrast, patients and controls did not differ on performance of tests of verbal memory. Verbal memory measures included Digit Span test, which indexes working memory capacity (Groth–Marnet & Baker, 2003), and Reverse Digit Span which places great demands on working memory in that it not only requires the short–term retention of information, but the executive function of manipulating that information (Ramsay & Reynolds, 1995).

On the contrary, Asmundson *et al.* (1994) reported no impairment in performance on a measure of immediate visual memory in PD, but found impaired performance on measures of immediate and short–delay recall on California Verbal Learning Test (CVLT). CVLT assesses the ability to learn and remember new verbal information (Crossen & Wiens, 1994) and the use of semantic associations to aid learning (Lezak *et al.* 2004). They also reported null findings for both parts of Trail Making Test (TMT). TMT measures attention and psychomotor speed, although the second part (Part B) involves additional cognitive processes including the executive function of switching attention between mental sets (O'Donnell *et al.* 1994).

Dractu and Bond (1998) also found a selective impairment in PD of performance on a verbal learning task, on measures of immediate and long–delay (30 minutes) recall. In contrast, they found no group differences for Digit Span test or on tests of psychomotor speed. This was a relatively integrative study which encompassed neuropsychological assessment and electrophysiological (EEG and ERP) recording.

Airaksinen *et al.* (2005) examined cognitive function in different anxiety disorders, using a population–based sample. Subjects completed three neuropsychological tests: verbal learning, verbal (phonological) fluency, and TMT. Compared to controls, individuals with PD recalled fewer words on the verbal learning task, and took longer to complete TMT Part B, although the latter finding was non–significant after controlling for comorbid alcohol dependence/abuse. Patients and controls did not differ in verbal fluency. Verbal fluency tasks are taxing on a range of executive abilities (Henry & Crawford, 2004) including self–monitoring responses to prevent errors, inhibiting previous responses, and actively retrieving items from long–term memory (Azuma *et al.* 2004).

Castaneda *et al.* (2011) also conducted a population–based study of neuropsychological function in different anxiety disorders. The clinical group comprised 75 young adults with an anxiety disorder (age range 22 – 35), of whom 17 met criteria for PD. The neuropsychological test battery encompassed tests of verbal and visual working memory (Digit Span, Visual Span), verbal learning and long–term memory (CVLT), attention, psychomotor processing speed, and executive function (TMT). Individuals with PD performed worse than controls on a strategy measure, which was one of eight performance measures derived from CVLT, but not on CVLT measures of learning or memory, or on other tests. Across anxiety disorders they found that a measure of psychosocial function in conjunction with psychotropic medication use predicted performance on multiple tests.

Deckersbach *et al.* (2011) aimed to disentangle the potentially confounding effects of chronic benzodiazepine use and PD diagnosis by comparing memory performance in

chronically benzodiazepine–medicated and benzodiazepine–free PD patients. The neuropsychological assessment encompassed multiple tests of verbal and non–verbal memory. Overall, medicated and unmedicated patients had comparable neuropsychological performance, with both groups showing a specific impairment relative to controls on select measures of non–verbal short–term memory. Chronic benzodiazepine use was associated with worse performance on one of these measures. By contrast, both patient groups showed normative performance on tasks including a non–verbal analogue of Digit Span, Digit Span, CVLT, and Controlled Oral Word Association test (COWA), a test of phonological fluency.

Other studies have reported null findings. Gladsjo *et al.* (1998) administered a relatively extensive neuropsychological test battery to a large PD sample (n = 69). The battery encompassed tests from multiple cognitive domains, and included CVLT, TMT, Digit Span, a test of phonological and semantic verbal fluency and a visual learning task. They found no evidence for neuropsychological impairment in PD after covarying estimated intelligence quotient (IQ), which was significantly lower in PD relative to healthy controls. Similarly, Galderisi *et al.* (2008) conducted a relatively comprehensive neuropsychological assessment of PD and found no significant group differences after covarying estimated intelligence. However, as discussed by Dennis *et al.* (2009), IQ does not meet the requirements for a covariate in neuropsychological studies comprising non–randomly assigned groups, as it is inappropriate to remove variance associated with a covariate when it is an attribute of the disorder under investigation (Miller & Chapman, 2001). Since the null findings of the Gladsjo *et al.* and Galderisi *et al.* studies likely represent Type I error, they will not be discussed further.

Finally, given the considerable comorbidity of MDD and PD (Kessler *et al.* 2006), Kaplan *et al.* (2006) compared cognitive function in primary PD with and without comorbid MDD on a battery of tests that included several tests of visuospatial memory. They found no evidence of neuropsychological impairment in PD uncomplicated by MDD, although inadequate power may have contributed to this result, given the small sample size (n = 11). By contrast, patients with comorbid MDD performed more poorly than healthy matched controls, on several tasks including a CPT (prolonged RT), and a delayed matching to sample task that assesses non–verbal learning. Deficits in sustained attention, as indexed by CPT performance, have previously been observed in MDD (reviews Maruff & Pantelis, 1999; Chamberlain & Sahakian, 2005).

Overall, reported neuropsychological findings for PD within the broad cognitive domain of attention have been mixed. Firstly, Dupont *et al.* (2000) found that individuals with PD showed a response bias on a target detection task. Such tests index passive aspects of attention (Maruff & Pantelis, 1999). By contrast, there have been several null findings on Digit Span (Lucas *et al.* 1991; Dractu & Bond, 1994; Castaneda *et al.* 2011; Deckersbach *et al.* 2011), and Visual Span test (Castaneda *et al.* 2011; Deckersbach *et al.* 2011), suggesting that attentional capacity for verbal and visual material is intact in PD. Moreover, there have been null findings for TMT test Part A (Asmundson *et al.* 1994; Airaksinen *et al.* 2005; Castaneda *et al.* 2011), which taps psychomotor speed and attention to a simple task (O'Donnell *et al.* 1994), and a null finding for performance on a task of selective attention (Lautenbacher *et al.* 2002). With regards attention switching, there have been null findings for TMT Part B (Asmundson *et al.* 1994; Castaneda *et al.* 2011), and the one positive finding

was no longer significant after controlling for comorbid alcohol–related disorders (Airaksinen *et al.* 2005). In regards divided attention, Lautenbacher *et al.* (2002) reported impaired performance in PD on a dual–task paradigm. Such tasks incorporate executive elements of inhibition and switching (Strauss *et al.* 2006). There is also some evidence of impaired performance on taxing tests of sustained attention, but this may be limited to patients with comorbid MDD (Kaplan *et al.* 2006). Thus it seems that for certain aspects of attention (*i.e.* attentional capacity; passive, selective or shifting attention) there is no evidence of impaired performance in PD. In contrast, on tests that tap more demanding, effortful aspects of attention (*i.e.* sustained or divided attention) there is some evidence of impaired performance, although the effect of comorbidity needs to be considered. Finally, there have been null findings for psychomotor speed (Asmundson *et al.* 1994; Dractu & Bond, 1998; Airaksinen *et al.* 2005; Castaneda *et al.* 2011).

Findings within the broad cognitive domain of memory are inconsistent. Although there have been reports of impaired performance in PD on tests of verbal learning and memory (Asmundson *et al.* 1994; Dractu & Bond, 1998; Airaksinen *et al.* 2005), there have been null findings (Lucas *et al.* 1991; Castaneda *et al.* 2011; Deckersbach *et al.* 2011). Similarly, while there have been reports of specific deficit in PD on tasks of visual memory (Lucas *et al.* 1991; Deckersbach *et al.* 2011), there were null findings (Asmundson *et al.* 1994; Kaplan *et al.* 2006) including the aforementioned findings for visual span tests (Castaneda *et al.* 2011; Deckersbach *et al.* 2011).

Neuropsychological findings in regards the executive functions are mixed. In addition to the aforementioned findings for attention–related executive processes,

there is some evidence of a deficit in inhibition (Kampmann *et al.* 2002; van den Heuvel *et al.* 2005). By contrast, the extant findings do not support a deficit of working memory maintenance and updating, as indicated by the null finding for Reverse Digit Span (Lucas *et al.* 1991). Additionally, there were null findings for verbal fluency (Airaksinen *et al.* 2005; Deckersbach *et al.* 2011), which taps a range of executive abilities (Henry & Crawford, 2004).

In summary, many of the neuropsychological findings for PD to date have been either inconsistent or contradictory, and a clear picture of cognitive function in PD is yet to emerge. Presumably some of this inconsistency is attributable to the aforementioned issues of inadequate sampling and inappropriate statistical analyses, which may have produced Type I and II errors. Further, between–study clinical differences (e.g., comorbidity, medication use and disorder severity), appears to have contributed to variable findings (Airaksinen *et al.* 2005; Kaplan *et al.* 2006; Castaneda *et al.* 2011). These factors, in addition to methodological issues (e.g., computer administration versus paper–and–pencil format, the assessment of different cognitive functions, use of different tests), render between–study comparisons problematic.

8.2.3.2 Study 1 Findings

Given the integrative nature of the present research, several psychophysiological findings from Study 1 bear upon the present study. These findings (reduced alpha–1 spectral power; normative alpha–2 and theta spectral power; normative APF, and; reduced HRV, in panic disordered relative to healthy matched–control subjects) each suggest testable hypotheses regarding cognitive function in PD.

Previous research in healthy subjects shows that resting state alpha–1 and alpha–2 spectral power predict capacity for task–related desynchronization and cognitive performance in a frequency–specific manner: Whereas alpha–1 desynchronization reflects phasic changes in alertness and/or expectancy, alpha–2 desynchronization correlates with declarative memory performance (review Klimesch, 1999). The Study 1 finding for alpha–1 therefore suggests that neuropsychological performance on tests that tap general alertness and/or expectancy may be worse in the present PD sample relative to healthy matched–controls, whereas the null finding for alpha–2 spectral power suggests normative performance on tasks of declarative memory.

Work by Klimesch and colleagues has shown that alpha and theta respond in opposite ways to task demands: whereas alpha typically desynchronises as a function of task demands, theta synchronises with increasing task demands, specifically on tasks that require encoding of new information into declarative memory (review Klimesch, 1999). As resting state theta power predicts the capacity for task–related synchronisation (Klimesch, 1999) the Study 1 finding for theta power supports a prediction of normative performance in the present PD sample on neuropsychological tests that require successful mnemonic encoding into LTM.

The null finding for alpha peak frequency (APF) also supports the prediction of normative memory performance in PD. Previous research has consistently found that individual differences in resting state APF predict performance on tasks of both working memory and LTM, such that higher APF is associated with superior performance (review Klimesch, 1997: Angelakis *et al.* 2004; Clark *et al.* 2004). Individual differences in APF are proposed to reflect the speed of firing in thalamo–

cortical feedback loops, which in turn corresponds with the speed of access to encoded information (Klimesch, 1997). Regarding working memory, for instance, resting state APF significantly predicted performance on Digit Span tests (Angelakis *et al.* 2004; Clark *et al.* 2004), with the strongest association between APF and Reverse Digit Span (Clark *et al.* 2004). The present finding for APF, therefore, suggests normative performance in PD on such tasks.

Finally, the Study 1 finding of lower HRV in PD compared to controls has implications for the present study. Individual differences in HRV have been linked to performance on tasks that involve high mental workload. For instance, in a series of studies in military personnel, Hansen and colleagues showed that resting HRV predicted cognitive performance, specifically on tasks that tax executive functions, but not non–executive tasks (Hansen *et al.* 2003; 2004; 2009). In each study, subjects performed CPT variants, some requiring executive functions, others not. They found that low HRV subjects performed worse than high HRV subjects on two *n*–back CPTs (*1*–back, *2*–back), but did not differ on non–executive function CPTs (simple RT, choice reaction time). *N*–back tasks are very demanding and tax the executive functions of working memory monitoring, manipulating and updating, and sustained attention (Borgaro *et al.* 2003; Harvey *et al.* 2004; Owen *et al.* 2005). These findings suggest that these executive functions in the context of sustained attention might be compromised in PD.

8.2.3.3 Study 2 Findings

Several findings from Study 2 (reduced P3 amplitude, prolonged and more variable RT) bear upon the present study. These findings indicate impaired performance in

PD on a very simple test of sustained attention. Although patients and controls did not differ in target detection accuracy, the oddball paradigm comprised easily distinguishable auditory stimuli and an invariant target stimulus. It remains to be tested, however, whether a reduced ability to sustain task–focussed attention in PD would affect accuracy in addition to speed on more cognitively demanding tasks. In particular, performance decrement might be observed on *n*–back tasks, which place considerable demands on working memory processes in comparison to the oddball task (Owen *et al.* 2005).

8.2.3.4 Clinical Observations and Self–Reports

Clinical observations suggest that individuals with PD have a specific cognitive deficit within the broad domain of attention. For example, it is a common clinical observation that individuals with PD are constantly vigilant for somatic changes that might signify an impending panic attack (Barlow, 2002). Clinical observations also suggest that individuals with PD pay little attention to environmental cues when in anxiety–provoking situations, presumably because they are so preoccupied with their own bodily sensations (Watts, 1989). Alternatively, they may engage in subtle avoidance behaviours in order to reduce anxiety and the likelihood of panic (White *et al.* 2006). Psychometric data indicate that self–focused attention in PD compared to other anxiety disorders is relatively context–invariant (Schmidt *et al.* 1997; Wells & Papageogiou, 1999). Further, evidence suggests that individuals with PD are incapable of correcting their self–focussed attention at will: Hayward *et al.* (2000) aimed to investigate the effect of self–focussed versus outwardly–directed attention on symptom reporting in PD, but found that patients were incapable of complying with experimental instructions to externally focus their attention.

Additionally, because the comorbidity rate in PD is so substantial and may common comorbidities of PD are associated with neuropsychological impairment, cognitive function in PD may covary with the type and severity of comorbid symptoms and diagnoses. For instance, MDD, which is the single most common comorbidity associated with PD (Roy–Byrne *et al.* 2000), is associated with a range of cognitive disturbances, particularly of psychomotor speed, executive functions, and memory (Egeland *et al.* 2005). Moreover, cognitive deficits are integral to MDD classification in that DSM criteria for MDD include diminished ability to concentrate (APA, 1994). Ball *et al.* (1995) examined the prevalence of MDD symptoms in outpatients with a primary diagnosis of PD, and found that inability to concentrate was one of the most frequently endorsed MDD symptoms in PD patients with or without current MDD. In their sample 20% of patients without MDD and 95% of those with current MDD reported impaired concentration meeting DSM criteria for diagnostic significance, in terms of pervasiveness, duration and for severity.

8.2.3.5 Empirical Findings: Summary

As reviewed, neuropsychological findings for PD are mixed. The extant literature provides some evidence of cognitive deficits within each of the broad functional domains of attention, memory and executive functions. However, a clear picture of cognitive dysfunction in PD is yet to emerge, given that the reported positive findings are either qualified by null findings or require replication. As discussed, a number of between–study differences relating to sample selection and methodology likely contributed to the inconsistency of findings. Therefore, the present study's predictions relating to cognitive function in PD are based, in part, on the findings of Studies 1 and 2.

Several Study 1 findings support predictions in relation to memory performance. These predictions are based on previous research in healthy subjects linking resting EEG parameters with memory performance. Specifically, alpha–2 and theta spectral power (Klimesch, 1999) and APF (Klimesch *et al.* 1993; Angelakis *et al.* 2004; Clark *et al.* 2004) predicted subsequent performance on a range of tests of verbal working memory and LTM. Taken together, the null findings for these EEG measures in PD, support the prediction of normative performance on tests of verbal memory, both short–term and long–term.

Several findings from Studies 1 and 2 support predictions in relation to attentional processes. Firstly, as alpha–1 spectral power at rest is positively associated with neuropsychological performance on tests of alertness and/or expectancy (Klimesch, 1999) the finding of reduced alpha–1 power in PD supports that prediction of impaired performance on such tests in PD. Secondly, previous research in healthy subjects has linked reduced HRV with a specific performance deficit on *n*–back tasks (Hansen *et al.* 2003; 2004; 2009), which tax the executive functions of working memory updating in the context of sustained attention (Borgaro *et al.* 2003; Harvey *et al.* 2004; Owen *et al.* 2005). The Study 1 finding for HRV therefore supports the prediction of poor performance on this or similar tasks. In line, several findings from Study 2 reflect an impaired ability to sustain task–focussed attention in PD.

In sum, the findings from Studies 1 and 2 support a relatively specific deficit within the cognitive domain of attention and associated executive functions in PD, but normative performance on tests of learning and memory. Clinical observations and patients' self–reports also support a cognitive deficit within the domain of attention.

8.3 The Present Study

The present study investigated cognitive function in PD using a computerized test battery that indexed a broad range of cognitive functions. The battery encompassed tests that indexed multiple aspects of attention (attentional capacity; selective, sustained and switching attention), memory (verbal and spatial working memory; verbal learning and LTM), executive functions (working memory monitoring and updating; inhibition; shifting, and; planning), psychomotor speed, and verbal ability (phonological and semantic fluency; vocabulary). These tests were based on existing and commonly–used pencil–and–paper tests. The present study also examined the relationship between patients' neuropsychological performance and clinical measures. Given that neuropsychological performance in PD may vary as a function of comorbidity (Airaksinen *et al.* 2005; Kaplan *et al.* 2006), clinical severity and medication use (Castaneda *et al.* 2011), these clinical variables were the focus of data analyses. Moreover, it is expected that the present study, in contrast to some previous studies, will be adequately powered to detect group differences.

On the basis of extant empirical findings, it was predicted that PD patients compared to healthy controls would show:

1. Normative performance on tests several aspects of attention (attentional capacity, selective attention, switching attention);
2. Normative performance on all tests of memory (verbal and spatial working memory, verbal learning and long–term working memory);
3. Normative performance on all tests of psychomotor speed and verbal ability;
4. Impaired performance on tests of sustained attention, and;
5. Impaired performance on tests of the executive function inhibition.

8.4 Method

8.4.1 Participants

The study samples comprised 53 clinical participants with a diagnosis of PD and 106 age, gender, and education–matched healthy controls. Patients' and controls' respective selection criteria and recruitment methods were detailed in Chapter 4. Clinical and demographic data for the two samples were presented in Chapter 5.

8.4.2 Procedure

The neuropsychological assessment incorporated measures of cognitive function derived from two sources. Firstly, cognitive performance measures were derived from the cognitive test battery. And secondly, behavioural measures obtained during performance of two psychophysiological test battery tasks (Continuous Performance Test and Executive Maze) provided additional measures of cognitive function.

The cognitive test battery comprised 10 tasks. It was presented on a touch–screen computer and took approximately 50 minutes to complete. For the duration of the tasks participants were seated in front of the touch–screen (NEC MultiSync LCD 1530V) in a sound and light–attenuated room with an ambient temperature of approximately 24^{O} C. The touch–screen was positioned on a desk directly in front of participants such that the screen subtended an angle of 15^{O} (see Figure 27), and received standardized pre–recorded task instructions and materials. These were delivered visually on the screen and concurrently via headphones as .wav audio files. The touch–screen was used to record most answers, and verbal responses were recorded via .wav files. Practice trials ensured that participants understood the task requirements prior to undertaking the task proper.

Figure 27: The cognitive test battery touch–screen.

The psychophysiological test battery comprises 11 tests which were presented on a computer monitor in a sound and light attenuated room. Continuous Performance Test and Executive Maze are the seventh and eighth tests, respectively. Psychophysiological and behavioural (error rate and RT) measures were recorded simultaneously. Pre–recorded task instructions and stimuli were delivered both visually on the screen and binaurally as .wav files via headphones. Responses for the two tasks are made by pressing response buttons in front of the computer screen with the index fingers of each hand. Each test is preceded by a brief practice trial.

Overall procedures relating to the laboratory assessment, including administration of the cognitive and psychophysiological test batteries were described in Chapter 4 (4.3.2 Overall Procedure: Laboratory Assessment).

8.4.3 Stimulus Materials

The tests comprising the cognitive test battery were administered in the following order: Tapping Test; Choice Reaction Time; Timing Test (results not reported in this study); Verbal Learning Part 1; Span of Visual Memory; Digit Span; Verbal Interference; Spot the Real Word; Switching of Attention; Verbal Learning Part 2, and; Word Generation. The following sections describe each of these tests, followed by descriptions of Continuous Performance Test and Executive Maze.

8.4.3.1 Tapping Test

This test is a variation of the Finger Tapping test (Lezak *et al.* 2004). The test assesses basic motor function, hand–eye coordination, fine movement speed and manual dexterity – skills which are required for everyday tasks such as typing and writing (Gill *et al.* 1986). In addition to direct motoric effects, tapping speed and pacing may also by moderated by non–specific factors such as the subject's level of alertness, and his/her ability to focus and maintain attention (Lezak *et al.* 2004). Participants were required to tap a circle on the touch–screen with their index finger as fast as possible for 30 s. This is repeated for both hands. Tapping variability from the dominant and non–dominant hands is reported separately (standard deviation of inter–tap interval; *TAP–D* and *TAP–ND*). Inter–tap variability as opposed to mean RT is considered a more sensitive measure (MacDonald *et al.* 2006).

8.4.3.2 Choice Reaction Time (CRT)

Participants attended to the computer screen as one of four target circles was illuminated in a pseudorandom sequence. Immediately following presentation the participant has to touch the illuminated circle as quickly as possible. There are 20

trials, and the task lasts approximately 3 minutes. Mean RT across trials (ms) is reported (*CRT*). Although the task is simple, performance is understood to be a multi–stage process involving stimulus detection and evaluation, and response selection and mobilization (Finkel & McGue, 2007). CRT assesses basic sensory–motor functions, visuomotor coordination, and information processing speed (Adam *et al.* 1999). Appropriate RT time is crucial to many everyday activities, notably driving (Hindmarch, 1999).

8.4.3.3 Verbal Learning

Verbal learning test is an analogue of Rey Auditory Verbal Learning and Memory task (Rey, 1964 in Clark *et al.* 2006) and is similar to CVLT (Crossen & Wiens, 1994). In this test participants are required to recall a set of words after various time intervals and later recognize the words from a list of repeated and new words. Subjects verbally answer recall components of the test, whereas responses for the recognition component are indicated via touch–screen. The test provides indices of auditory–verbal learning, recall and recognition, and also the executive function verbal self–monitoring (Crossen & Wiens, 1994). Four measures are reported: *Total Recall Score* (the mean number of correctly recalled words across 4 trials); *Short Delay Recall* (recall of word list after approximately 6 min); *Long Delay Recall* (recall of word list after approximately 25 min) and; *Recognition Accuracy*.

8.4.3.4 Span of Visual Memory

This visual span test is a computerized adaptation of the Corsi Block–tapping task (Kessels *et al.* 2000). Nine squares on the touch–screen light up in a pseudo–random order. After a delay of 4 s, the subject is required to press the squares in the order in

which they previously lit up. The sequence length increases from two to nine across trials, and the longest sequence length correctly completed twice is reported (*SVM*). Visual span tests index visuospatial working memory capacity (Howieson & Lezak, 2002).

8.4.3.5 Digit Span

The Digit Span task consists of two parts. In each part of the test a series of digits appears briefly on the screen and the subject is asked to immediately enter the digits on a key–pad on the screen, either in the order presented (Forward Digit Span) or in reverse order (Reverse Digit Span). The number of digits in each trial increases from 3 to 9 and the longest sequence length correctly completed twice is reported for each task. The reported measures *Forward Digit Span* indexes working memory capacity (Groth–Marnet & Baker, 2003) and attentional capacity (Lezak *et al.* 2004) and *Reverse Digit Span*, which places additional, executive function demands on working memory due to the requirement to mentally transform the digit set (Lezak, 2004).

8.4.3.6 Verbal Interference

This task consists of two parts and is a computerized adaptation of the classic Stroop test (Golden, 1978 in Paul *et al.* 2005). In each part a colour word (red, yellow, green or blue) is presented on the screen. In each trial the word's colour contrasts with the word itself. In Part 1 the subject is required to indicate the word that is written (and not the incongruent 'ink' colour that the word is written in) whereas in Part 2 the subject is required to name the 'ink' that the word is written in (and not read the actual word). Responses are made by pressing the appropriate tab on the screen. Performance measures are word–naming score (*Word Naming*) and colour–naming

score (*Colour Naming*). Part 1 measures reading speed and accuracy, whereas the second part measures the executive ability to inhibit inappropriate, well–learned automatic responses (MacLeod, 1991). In Part 2 the 'Stroop interference' effect occurs because reading is a well–learned response that occurs automatically unless suppressed through sustained attention (Pardo *et al.* 1990). Performance data will test the hypothesis of impaired performance on a test of inhibition (Hypothesis 5).

8.4.3.7 Spot the Real Word

This task is a computerized adaptation of Spot the Word test (Baddeley *et al.* 1993). In each trial, a valid English word is presented simultaneously with a pseudo–word on the screen, and the participant is required to indicate via the touch–screen, which of the pair is the valid word. The number of words correctly selected is reported (*SRW*). Spot the Word test has been found to provide a valid and reliable measure of pre–morbid intellectual functioning (Baddeley *et al.* 1993; Lucas *et al.* 2003). The test is thought to be relatively resilient to various forms of brain dysfunction because numerous strategies may be employed in lexical decision (Baddeley *et al.* 1993).

8.4.3.8 Switching of Attention

This test is a computerized adaptation of TMT (Reitan, 1958). In Part A the participant is required to touch an array of numbers on the screen in ascending numerical sequence, and in Part B they must touch numbers and letters, alternately, in ascending sequence. Although both parts measure attention and psychomotor speed, Part B involves additional executive processes including switching attention between mental sets (O'Donnell *et al.* 1994). Time to completion for each part in seconds is reported (*SoA–1* and *SoA2*).

8.4.3.9 Word Generation

This test comprises two parts. In Part 1, which is a variant of COWA (Benton & Hamsher, 1989), the participant is required to say as many words as possible that begin with specific letters (F, A, S) within the given time (60 s per letter). Proper nouns are not allowed. A composite score, which is the mean number of novel, correct words generated across the three letters is reported (*FAS*). In Part 2, the participant is required to name animals as quickly as possible for 60 s. The outcome measure is total number correct (*Animals*). Letter and category fluency tasks assess phonological and semantic fluency, respectively (Tombaugh *et al.* 1999). "Animals" is the most common category on tests of semantic fluency (Strauss *et al.* 2006).

8.4.3.10 Continuous Performance Test (CPT)

This test is an *n*–back test, which is a particular type of CPT (Owen *et al.* 2005). *N*–back tests, as per all CPTs, assess the ability to sustain attention over an extended period (Riccio *et al.* 2002). However, unlike certain CPTs that have invariant target stimuli (e.g., oddball tasks), in *n*–back tests the target stimulus is constantly changing (Borgaro *et al.* 2003) and subjects respond whenever a stimulus is the same as the one presented *n* trials previously (Owen *et al.* 2005). *N*–back test performance therefore imposes additional cognitive demands in terms of on–line monitoring, updating and manipulating information in working memory (Owen *et al.* 2005). A series of letters (B, C, D or G) were presented briefly on the computer screen. If the same letter appeared twice in a row (*i.e. 1*–back), the participant was required to press the response keys as fast and accurately as possible. The response box was positioned on the table directly in front of the computer screen. There were 125 stimuli comprising 85 background letters and 20 pseudo–randomly presented target

letters. The task duration was 8 min. The reported performance variables are RT (*CPT–RT*) and errors of omission (*CPT–EO*), which are considered measures of attention to the task (Riccio *et al.* 2002). CPT performance measures will test the hypothesis of impaired performance in PD on a test of sustained attention (Hypothesis 4). A novelty task, in which a checkerboard pattern flashes upon the screen, is embedded within this task. Novelty task measures are not reported.

8.4.3.11 Executive Maze

This task is a computerized adaptation of the Austin Maze (Bowden, 1989). Maze learning tasks assess high level executive functions, such as the ability to plan, strategise and implement complex tasks using visuospatial information (Bowden, 1989). These cognitive abilities are considered of fundamental importance in the ability to navigate through the physical world (Van Horn *et al.* 1998). The objective is to identify a fixed, hidden path through an 8*8 matrix of circles on the computer screen. The participant must navigate through the maze from a beginning circle to the end circle, by pressing the directional keys on the response button box. The task ends once the participant has completed the maze twice without error, or after 7 minutes, whichever comes first. The number of overrun errors (*Overruns*), and time to task finish in seconds (*Maze Completion*) are reported.

8.4.4 Data Cleaning

Overall, altered outliers and replaced missing data constituted 2.3% of patients' and 2.1% of controls' cognitive performance data. Following visual inspection of cognitive performance variables, several were logarithmically transformed to normalise their distributions: CPT–EO (Ln_{10} (x+1)), TAP–D and TAP–ND (Ln_{10}x).

8.4.5 Statistical Analyses

To reduce the number of statistical analyses conducted, cognitive performance measures were aggregated into empirically–defined cognitive domains, as determined by principal components analysis (PCA) of normative data from BRID (Rowe *et al.* 2007). Rowe *et al.* found that a 7–factor solution provided the best fit to the data, and then named each factor according to the cognitive domain that best described its highest–loading measures. The 7 factors were: Information Processing Speed; Verbal Memory; Working Memory Capacity; Sustained Attention; Sensorimotor Function; Verbal Processing, and; Executive Function (Rowe *et al.* 2007). Table 27 shows the tasks that loaded most strongly on each factor. On the basis of this classification of cognitive measures, separate repeated–measures ANOVAs were conducted for each cognitive domain. In each model *Group* (PD/controls) was the between–subjects factor, whereas domain–matched performance measures constituted the levels of the within–subjects factor *Domain*. Because some of the cognitive tests yield many performance measures, and to reduce the likelihood of Type I error, only those performance measures that loaded onto PCA–defined factors were included in each ANOVA. Because measures derived from Timing Test did not load selectively any one PCA factor these measures were not included in analyses. For these analyses, cognitive test measures were reverse–scored as required so that lower values consistently represented inferior performance.

Independent–samples *t*–tests compared the two groups on Spot the Real Word test. Standard multiple regression analyses examined the relationship within patients between clinical measures, and cognitive performance measures distinguishing patients and controls.

Table 27: Principal components analysis–defined cognitive domains and tests

NOTE:
This table is included on page 286 of the print copy of the thesis held in the University of Adelaide Library.

Table shows cognitive domains and associated cognitive tests, as defined by principal components analysis of normative data by Rowe *et al.* (2007).

8.5 Results

8.5.1 Panic Disorder vs. Matched Controls

8.5.1.1 Information Processing Speed

For Information Processing Speed, the Group main effect and interaction term were non–significant ($F_{1, 140}$ = 0.39, p = .532; $F_{4, 560}$ = 0.32, p = .574). Table 28 shows descriptive statistics for Information Processing Speed measures.

Table 28: Descriptive statistics for Information Processing Speed measures

Performance Measure	***PD* (*n* = 53)**	***Controls* (*n* = 89)**
Word Naming	17.2 (3.55)	18.3 (2.67)
Colour Naming	10.5 (4.55)	11.0 (4.56)
SoA1 (s)	21.5 (5.68)	22.0 (6.36)
SoA2 (s)	47.8 (13.6)	46.4 (14.8)
CRT (ms)	748.9 (154.2)	733.8 (146.6)

8.5.1.2 Verbal Memory

For Verbal Memory, the Group effect was non–significant ($F_{1, 99}$ = 0.46, p = .498), as was the interaction term ($F_{3, 297}$ = 0.30, p = .652) (see Table 29).

Table 29:Descriptive statistics for Verbal Memory measures

Performance Measure	***PD* (*n* = 48)**	***Controls* (*n* = 53)**
Total Recall Score	33.4 (6.29)	33.2 (4.37)
Short Delay Recall	8.52 (2.33)	8.06 (2.18)
Long Delay Recall	8.29 (2.50)	7.68 (2.14)
Recognition Accuracy	11.2 (1.70)	11.2 (0.96)

8.5.1.3 Working Memory Capacity

Neither the Group main effect (Group $F_{1, 157} = 0.58$, $p = .447$) nor the interaction term ($F_{1, 157} = 0.64$, $p = .426$) was significant (see Table 30).

Table 30: Descriptive statistics for Working Memory Capacity measures

Performance Measure	***PD* (*n* = 53)**	***Controls* (*n* = 106)**
Forward Digit Span	7.00 (1.95)	7.42 (2.37)
Reverse Digit Span	4.30 (2.04)	4.38 (2.60)

8.5.1.4 Sustained Attention

The Group main effect for Sustained Attention was significant ($F_{1, 150} = 7.27$, $p = .008$, $\acute{\eta}_p^2 = .046$), as was the interaction term ($F_{1, 150} = 7.14$, $p = .008$, $\acute{\eta}_p^2 = .045$). Patients showed longer RT ($t_{150} = 2.68$, $p = .008$, $d = .46$) and made more errors of omission ($t_{150} = 2.67$, $p = .008$, $d = .49$) compared to controls during performance of CPT (see Table 31). Both between–group differences represent medium effect sizes.

Table 31: Descriptive statistics for Sustained Attention measures

Performance Measure	***PD* (*n* = 53)**	***Controls* (*n* = 99)**
CPT–RT (ms)	544.4 (96.2)	502.8 (88.3)
CPT–EO (*Ln* transformed)	0.79 (0.69)	0.51 (0.57)

8.5.1.5 Sensorimotor Function

Both the Group main effect ($F_{1, 134} = 1.67$, $p = .199$) and the interaction term ($F_{1, 134} = 0.88$, $p = .349$) for Sensorimotor Function were non–significant (see Table 32).

Table 32: Descriptive statistics for Sensorimotor Function measures

Performance Measure	***PD* (*n* = 53)**	***Controls* (*n* = 83)**
TAP–D	1.35 (0.19)	1.37 (0.21)
TAP–ND	1.45 (0,22)	1.54 (0.21)

8.5.1.6 Verbal Processing

The Group effect and interaction were non–significant ($F_{1, 157} = 0.83$, $p = .363$; $F_{1, 157} = 2.48$, $p = .117$) (see Table 33).

Table 33: Descriptive Statistics for Verbal Processing measures

Performance Measure	***PD* (*n* = 48)**	***Controls* (*n* = 53)**
FAS	14.7 (3.58)	14.7 (3.91)
Animals	24.8 (6.05)	23.4 (5.97)

8.5.1.7 Executive Function

Neither the Group effect nor the interaction term for Executive Function was significant ($F_{1, 143} = 0.30$, $p = .585$; $F_{2, 286} = 1.07$, $p = .307$) (see Table 34).

Table 34: Descriptive Statistics for Executive Function measures

Performance Measure	***PD* (*n* = 53)**	***Controls* (*n* = 92)**
SVM	7.45 (2.02)	7.77 (2.16)
Overruns	2.78 (0.38)	2.83 (0.68)
Maze Completion (s)	5.21 (0.52)	5.21 (0.57)

8.5.1.8 Estimated Intelligence

Patients and controls had similar scores on Spot the Real Word test (patients, n = 53; 48.9±4.25: controls, n = 104; 48.4±6.29). The between–group difference was non–significant (t_{155} = 0.48, p = .634).

8.5.2 Relationship of Clinical and Cognitive Function Measures

8.5.2.1 Clinical Severity

Standard multiple regression analyses examined the relationship between patients' cognitive performance and measures of clinical severity. The two cognitive performance measures differentiating patients and controls (CPT–RT and CPT–EO) were entered simultaneously as predictor measures in each of two models. The two selected clinical outcome measures were scores on STAI–S and PDSS. Neither model was significant: STAI–S (R^2 = .031; $F_{2, 50}$ = 0.80, p = .455); PDSS (R^2 = .031; $F_{2, 50}$ = 0.80, p = .455).

8.5.2.2 Comorbidity and Medication

A second set of standard multiple regression analyses determined the extent to which patients' comorbidity and medication use contributed to the above two Sustained Attention measures. In each model the following three dichotomous variables were entered simultaneously as predictors: Medication (Medicated/Unmedicated), Current Comorbidity (Yes/No), and Alcohol (lifetime alcohol abuse or dependence; Yes/No). Medication use and comorbidity did not contribute significantly to either CPT–RT (R^2 = .003, $F_{3, 49}$ = 0.05, p = .987) or CPT–EO (R^2 = .043, $F_{3, 49}$ = 0.73, p = .539).

8.6 Discussion

Study 3 Findings

Study 3 examined neuropsychological function in PD using a computer–administered battery of cognitive tests that indexed a broad range of cognitive functions. For between–group comparisons neuropsychological performance measures were aggregated into seven empirically–defined cognitive domains, as determined by prior research using principal components analysis (Rowe *et al.* 2007). However, the present findings support only a very specific cognitive deficit in PD within the Sustained Attention cognitive domain. This deficit could not be accounted for by patients' comorbidity or medication use. By contrast, individuals with PD showed normative performance on tests comprising each of the following cognitive domains: Information Processing Speed; Verbal Memory; Working Memory Capacity; Sensorimotor Function; Verbal Processing, and; Executive Function. Inspection of the descriptive statistics for cognitive performance measures that constituted each of these cognitive domains (Tables 27 – 29 and 31 – 33) shows modest patient–control differences, which suggests that these null findings are unlikely to represent Type II error. With the exception of the null finding for Verbal Interference task, the present findings were as predicted on the basis of the findings of Studies 1 and 2 and/or extant neuropsychological findings. Each of these findings are now discussed.

8.6.1.1 Information Processing Speed

Patients and controls did not differ in performance on tests comprising the factor Information Processing Speed (*i.e.*, Verbal Interference, Switching of Attention, and CRT). Although the null finding for Verbal Interference was contrary to prediction,

the findings for Switching of Attention and CRT were predicted on the basis of previous neuropsychological findings.

Switching of Attention is a computerized version of TMT (Reitan, 1958), and the present result replicates earlier null findings for TMT (Asmundson *et al.* 1994; Airaksinen *et al.* 2005; Castaneda *et al.* 2011). Although Airaksinen *et al.* found that individuals with PD took longer than controls to complete the more cognitively demanding TMT Part B, the finding was no longer significant upon controlling for alcohol–related comorbidities. The exclusion from the present study of patients with current alcohol–related comorbidities may have contributed to the null findings. The two parts of TMT index a range of cognitive processes including visual search, psychomotor speed, and set switching (O'Donnell *et al.* 1994). Taken together, past and present findings suggest that these processes are not impaired in PD per se.

Four–choice CRT is a commonly used test of psychomotor speed. Although the test is simple, task performance is a multi–stage process involving cognitive and motoric components (Finkel & McGue, 2007). The present null finding is consistent with previous reports of normative performance on tests of psychomotor speed in PD (Asmundson *et al.* 1994; Dractu & Bond, 1998; Airaksinen *et al.* 2005; Castaneda *et al.* 2011).

Because there were prior reports of impaired performance on variants of Stroop test in PD (Kampmann *et al.* 2002; van den Heuvel *et al.* 2005), it was predicted that patients would show impaired performance on Verbal Interference test, which is a computerized adaptation of the classic Stroop test (Golden, 1978 in Paul *et al.* 2005). However, there were substantial methodological differences between the present and

prior studies which could account for the discrepant findings. Firstly, whereas the emotional Stroop paradigm comprises predominantly threat–related verbal stimuli (McNally, 1998), paradigmatic Stroop tests comprise colour name (*i.e.* threat–neutral) stimuli (Lezak *et al.* 2004). Although van den Heuvel *et al.* administered both task types, the intermixing of threat and non–threat stimuli could conceivably have altered performance on the standard Stroop test. Another methodological difference is that whereas the duration of each part of Verbal Interference was one minute, the task duration in the earlier studies was considerably longer, and the number of presented stimuli, higher. Because longer Stroop test formats may be more sensitive to difficulties in maintaining focused attention over time (Lezak *et al.* 2004), task duration may have contributed to discrepant findings. Finally, the van den Heuvel study was a functional neuroimaging study. As the functional MRI scanner is a highly anxiogenic environment for individuals with PD (Giardino *et al.* 2007), elevated state anxiety (which is not reported) may have contributed to their positive findings. Therefore, these or other between–study methodological differences could account for the differential findings of the present and prior Stroop test studies.

It has been proposed that the ability to inhibit the Stroop interference effect may reflect a general ability to resist irrelevant information in the environment (Strauss *et al.* 2006), whereas greater interference is associated with impaired concentration and distractibility (Lezak *et al.* 2004). Thus the present null finding, although requiring replication, suggests that individuals with PD do not show a generalized inability to inhibit irrelevant, non–threatening information in the environment.

8.6.1.2 Verbal Memory

Individuals with PD showed normative performance in Verbal Memory, as indexed by measures derived from Verbal Learning test. This finding is consistent with some (Lucas *et al.* 1991; Castaneda *et al.* 2011; Deckersbach *et al.* 2011), but not all (Asmundson *et al.* 1994; Dractu & Bond, 1998; Airaksinen *et al.* 2005), previous findings for verbal memory in PD. However, there are numerous possible reasons for variable findings in regards this area of cognitive function in PD. Because efficient memory involves multiple cognitive operations, memory deficits may reflect either a primary dysfunction within the brain circuits that mediate memory function, or secondary deficits due to associated cognitive processes (Vasa *et al.* 2007). Thus impaired performance on neuropsychological tests of memory may reflect such diverse factors as state anxiety (Eysenck & Calvo, 1992), attention, information processing speed, strategy, effort and self–monitoring (Howieson & Lezak, 2002). Notably, poor performance on a test of memory may reflect impaired attentional control (Lezak *et al.* 2004), which prevents proper registration of the information to be learned and thus memory formation (Danckwerts & Leathem, 2003). Moreover, since impaired performance on tests of verbal memory have been reported in conditions that are common comorbidities of PD, such as MDD (Egeland *et al.* 2005) and other anxiety disorders (reviews Golier & Yehuda, 2002; Castaneda *et al.* 2008), and comorbidity of depression and anxiety disorders may have a non–additive effect on memory function (Kizilbash *et al.* 2002; Basso *et al.* 2007), between–study differences in comorbidity may have contributed to the inconsistency of findings.

The present null finding was predicted on the basis of several Study 1 EEG findings – namely, normative resting state spectral power in the alpha–2 and theta frequency

bands, and normative APF in PD. Taken together, psychophysiological and neuropsychological findings suggest that the neural systems underpinning LTM encoding, storage and retrieval are intact in the present PD sample.

8.6.1.3 Working Memory Capacity

The present null findings for Digit Span sub–tests (Forward Digit Span and Reverse Digit Span), which together constituted the factor Working Memory Capacity, replicates earlier findings (Lucas *et al.* 1991; Dractu & Bond, 1998; Castaneda *et al.* 2011; Deckersbach *et al.* 2011) and bolsters support for the null hypothesis. The prediction of normative performance on these sub–tests was based, in part, on the Study 1 null finding for APF, as previous research has found that resting state APF positively predicts performance on Digit Span sub–tests, particularly Reverse Digit Span (Angelakis *et al.* 2004; Clark *et al.* 2004). Although APF is proposed to correspond with the speed of access to encoded information (Klimesch, 1997), the specific mechanisms that mediate the relationship between APF and working memory function remain to be determined (Clark *et al.* 2004). Forward Digit Span measures the amount of verbal information that can be held in working memory at once (Lezak *et al.* 2004). The storage of verbal representations in working memory in the absence of external cues requires their active maintenance via sub–vocal rehearsal (Baddeley, 2010). In contrast, Reverse Digit Span requires both the storage and manipulation of working memory contents (Ramsay & Reynolds, 1995). The ability to hold and manipulate verbal information within working memory is of practical everyday significance and is crucial for tasks such as remembering telephone numbers and shopping lists (Groth–Marnat & Baker, 2003).

8.6.1.4 Sustained Attention

In comparison to healthy controls, individuals with PD showed impaired performance on measures that constituted the Sustained Attention domain. Compared to controls, patients missed more target stimuli and took longer to respond to targets during CPT. Increased errors of omission and RT prolongation during CPT performance are understood to signify lapses of attention (Riccio *et al.* 2002; Weissman *et al.* 2006). The present study administered a very simple CPT called a *1*–back test, which is the least cognitively taxing of a family of *n*–back paradigms that systematically vary in working memory load as a function of their integer prefix (*i.e. 1*–back, *2*–back…*n*–back) (Owen *et al.* 2005). In addition, the behavioural findings from Study 2 showed prolonged and more variable RT for target detection during performance of the oddball task, which is very simple CPT variant (Borgaro *et al.* 2003). Taken together, the present findings for the CPT and oddball tasks, although requiring replication, show impaired performance in PD on relatively undemanding tests of sustained attention.

Previous research reported prolonged RT during CPT performance in PD patients with comorbid MDD, but not PD without MDD (Kaplan *et al.* 2006). The present findings, by contrast, were not related to patients' comorbidity status. One possible explanation for these discrepant findings is that they relate to between–study methodological differences: whereas the earlier study contrasted PD patients with current MDD and healthy controls, the present study examined the between–group association of current comorbidity (including, but not limited to MDD) and CPT performance. However, examination of zero–order correlations of BDI score and CPT performance (results not shown) supports the conclusion that the present

findings could not be accounted for by patients' depressive comorbidity. Another possibility, given the relatively small number of subjects comprising each clinical sample in the earlier study (n = 11, as compared to n = 53 in the present study), is that the earlier study was inadequately powered and so the null finding represents Type II error.

Across decades of sustained attention research the most consistent finding is that performance on tasks of sustained attention declines over time, as indicated by a decline in signal detections and/or increased RT over time (Helton & Russell, 2011). This effect is known as vigilance decrement (Warm *et al.* 2008). Although the present study measured mean–level response accuracy and latency, as opposed to their change across time, the observed results suggest greater vigilance decrement in PD relative to controls. However future research might address whether vigilance performance in PD actually declines over time.

Although the present cross–sectional study cannot determine why the ability to sustain attention is compromised in PD, there are two current theories of vigilance decrement during sustained attention: mindlessness theory and resource depletion theory (Helton & Warm, 2008). Mindlessness theory proposes that vigilance decrement reflects the disengagement of awareness from the boring and repetitive vigilance task and performance automatization (Robertson *et al.* 1997; Manly *et al.* 1999). According to this account, performance decrement varies both as a function of task difficulty and the salience of one's current concerns. On simple vigilance tasks that do not exogenously support sustained attention, subjects become preoccupied with distracting, task–unrelated thoughts and their awareness disengages from the

task; the more salient one's current concerns, the greater the distraction (Smallwood *et al.* 2004). It is possible given the clinical phenomenology of PD, therefore, that perseverative disorder–related thoughts and imagery distract from the goal of sustaining attention to the task. According to the alternative, resource depletion theory, target detection failures during vigilance occur because vigilance tasks impose a continuous mental load which depletes limited attentional resources over time (Warm *et al.* 2008; Helton & Russell, 2011). Further research is needed to determine whether either of these two, competing theories can account for the observed deficit of sustained attention in PD.

Sustained attention is considered a basic attentional function that determines the efficacy of higher aspects of attention (*i.e.* selective attention, divided attention) and of cognition more generally (Cohen & O'Donnell, 1993; Sarter *et al.* 2001). For instance, the capacity to sustain attention is essential during the encoding and registration of new information and hence for learning and memory (Cowan, 1995). Although the present study found support for a relatively circumscribed neuropsychological deficit in PD, which did not predict disorder severity, there may be clinically and functionally significant ramifications of this deficit. This is because even relatively mild or circumscribed impairments on neuropsychological tests in the laboratory can translate into clinically significant problems outside of the laboratory, because real–world situations involve more complex processing and increased opportunities for distraction (Stein *et al.* 2002).

8.6.1.5 Sensorimotor Function

Patients and controls did not differ on measures derived from Tapping Test which

comprised the Sensorimotor Function domain. Measures of intra–individual psychomotor variability are relatively stable (Deary & Der, 2005) and may confer information that is obscured by mean–level performance measures (MacDonald *et al.* 2006). Evidence suggests that greater performance inconsistency is associated with poorer performance on a variety of cognitive tasks both cross–sectionally and longitudinally (Deary *et al.* 2001; MacDonald *et al.* 2003; Deary & Der, 2005). Performance inconsistency is also associated with normal ageing (Antsey *et al.* 2005; Williams *et al.* 2005) and with compromised CNS function, and may have multiple neurobiological origins (reviews MacDonald *et al.* 2006; Finkel & McGue, 2007). The present null finding for Tapping Test, in conjunction with the null findings for CRT and TMT Part A, suggests that psychomotor function is not impaired in PD. Moreover, as psychomotor slowing can affect scores on any neuropsychological measure that relies on speeded responses (White *et al.* 1997), these findings suggest that psychomotor slowing is an unlikely explanation for RT prolongation during CPT performance in PD.

8.6.1.6 Verbal Processing

Individuals with PD and healthy controls showed comparable performance on two tests of verbal fluency – a test of phonological fluency and a test of semantic fluency. Performance on tests of verbal fluency appears to depend upon word knowledge, episodic memory, working memory, and speed of information processing (Strauss *et al.* 2006). Moreover, as such tests tax executive abilities (e.g., self–monitoring output to prevent repetition and errors, inhibiting previous responses, and actively retrieving items from LTM) they are commonly used to assess the integrity of executive functions (Azuma *et al.* 2004; Henry & Crawford, 2004). The present findings

replicate earlier null findings for phonological fluency in PD (Airaksinen *et al.* 2005; Deckersbach *et al.* 2011) and extend these findings to semantic fluency.

8.6.1.7 Executive Function

Patients and controls did not differ in their performance of the two tests that constituted the Executive Function domain – Span of Visual Memory and Executive Maze. Span of Visual Memory is a visual span test adapted from the Corsi Block–tapping task (Kessels *et al.* 2000). Visual span tests are typically considered tests of non–verbal working memory capacity or attentional capacity (Howieson & Lezak, 2002), rather than tests of executive functions. Maze learning tests, by contrast, assess executive functions such as planning, strategising, and implementation in the context of learning and memorising visuospatial information (Bowden, 1989). Initially, when the maze is unfamiliar, visuospatial path information must be encoded in memory, whereas following repeated performance this information must be retrieved to aid performance. However, despite differences between the two tests, Span of Visual Memory and Executive Maze have the common property of assessing visuospatial memory. The ability to learn and remember visuospatial information is crucial in many areas of employment (e.g., art, graphic design, architecture) (Shum *et al.* 2000) and underpins many everyday activities, such as driving and navigating within an unfamiliar environment (Mapou, 1992).

Previous findings for visuospatial memory in PD have been inconsistent. Most (Asmundson *et al.* 1994; Kaplan *et al.* 2006; Castaneda *et al.* 2011; Deckersbach *et al.* 2011) but not all (Lucas *et al.* 1991; Deckersbach *et al.* 2011) studies reported null findings. Similarly, the findings for verbal memory have been inconsistent.

Given the discrepant findings, the question arises as to which clinical or other characteristics are associated with impaired LTM in PD, and which are associated with normative function, and whether memory function in PD shows trait– or state–dependent characteristics. Interestingly, the studies that reported impaired memory performance in either verbal (Asmundson *et al.* 1994; Dractu & Bond, 1998; Airaksinen *et al.* 2005) or non–verbal memory in PD (Lucas *et al.* 1991; Deckersbach *et al.* 2011) used non–computerized test delivery which may differentially affect performance of panic disordered subjects and unaffected controls. However, as performance on tests of declarative memory is influenced by multiple factors (Lezak *et al.* 2004) it is unlikely that a single between–study methodological difference may entirely account for the inconsistent findings.

8.6.2 Study Limitations

A limitation of Study 3 is that the neuropsychological test battery did not include a range of tests of sustained attention that vary in task load. In particular, the inclusion of more cognitively taxing *n*–back paradigm variants (e.g., *2*–back…*n*–back) (Owen *et al.* 2005) could test the effect of systematically varying task load on performance in PD. Previous work suggests that cognitive dysfunction may be more pronounced at higher attentional and executive loads in PD (Lautenbacher *et al.* 2002). However, the paradigms included in Study 3 were standard BRID paradigms that were selected to broadly tap core functions (Gordon *et al.* 2005), and thus were not specifically selected for the present research.

A further limitation of Study 3 is the possibility that the between–group finding for Sustained Attention – despite remaining borderline significant following Bonferroni–

correction for multiple comparisons (group main effect $p = .008$; corrected alpha for significance testing, $p < .05 / 7 = .007$) – represents Type I error. Replication of the finding within an independent sample is required to strengthen confidence in the finding.

8.6.3 Conclusions and Future Directions

The present findings support only a specific impairment of cognitive function within the domain of Sustained Attention in PD. By contrast, panic disordered subjects and unaffected controls did not differ in their performance on tests that constituted the following six cognitive domains: Information Processing Speed, Verbal Memory, Working Memory Capacity, Sensorimotor Function, Verbal Processing, and Executive Function. Across studies, however, neuropsychological findings for PD have been inconsistent, particularly within the cognitive domains of verbal and non–verbal LTM. As discussed, multiple between–study methodological differences and clinical sample selection factors likely account for at least some of the observed between–study variance.

Another possible cause of discrepant neuropsychological findings for PD is that neuropsychological heterogeneity may be an inherent feature of the disorder. Evidence suggests that PD is a highly heterogeneous disorder at multiple levels of function, from genotype (Klauke *et al.* 2010; Schumacher *et al.* 2011) to clinical phenotype (Cassano *et al.* 1999; Rucci *et al.* 2009; Kircanski *et al.* 2009; Batelaan *et al.* 2010b). Moreover, studies of PD treatment response, neurobiology and neuropsychology show that the disorder is not homogeneous (Coplan & Lydiard, 1998; Onur *et al.* 2006; Domschke & Dannlowski, 2010).

Additionally, longitudinal research may determine whether within–diagnosis neuropsychological variance in PD correlates with clinical outcomes (e.g., disorder course, treatment response). For instance, within–diagnosis neuropsychological variance in anxiety–related cognition has shown some utility in predicting response to treatment in PD (refs). Similarly, several affectively–neutral cognitive variables have shown utility in predicting response to treatment in MDD (refs). However, the utility of general (*i.e.* affectively–neutral) cognitive measures for supporting treatment decisions in PD has yet to be investigated.

Longitudinal research is also needed to determine whether deficits of sustained attention (and/or other neuropsychological deficits) temporally precede or develop subsequent to PD onset. If deficits of sustained attention were apparent prior to PD onset, and were established as risk factors for PD, this information could help identify individuals at risk for PD. In particular, any such causal risk factor could become the target of prevention intervention (Zvolensky *et al.* 2006c). To date, however, there are limited data relating to the onset of neuropsychological dysfunction in PD. Vasa *et al.* (2007) examined whether memory impairments in PD precede the onset of PD and may therefore serve as risk factors for its development, or whether they are a consequence of having the disorder. They investigated verbal and visual memory in children aged 9 – 20 years who were deemed at risk for anxiety disorders on account of a parental history of PD and/or MDD, and found that offspring memory performance was unrelated to parental psychopathology. Similarly, Micco *et al.* (2009) examined executive function in children aged 6 – 17 years with parental history of MDD and/or PD. They found that unaffected offspring of affected and unaffected parents had comparable performance across multiple tests,

including a CPT. Micco *et al.* concluded, as per Vasa *et al.*, that neuropsychological deficits in PD are state–dependent as they are only present in the current anxiety disorder. However, these two studies are limited by their cross–sectional design. Prospective studies contrasting neuropsychological performance of children who do and don't go on to develop PD are needed as such studies will have greater power to support or refute the null hypothesis.

Finally, longitudinal research is needed to clarify the relationship between HRV and sustained attention in PD. In healthy subjects, individual differences in HRV predicted cognitive performance on tests of sustained attention (*n*–back CPTs), such that that low HRV subjects performed worse than high HRV subjects (Hansen *et al.* 2003; 2004; 2009). Moreover, experimental manipulation of HRV via chronic exercise detraining altered cognitive function in the expected direction (Hansen *et al.* 2004). Although individual differences in resting HRV are relatively stable (Li *et al.* 2009), it is still possible to increase one's HRV through a range of behavioural strategies, such as diet, exercise, biofeedback and meditation (Thayer & Lane, 2009).

8.7 Summary of Chapter

The present study examined neuropsychological function in PD using a computerized test battery that indexed a broad range of cognitive functions, which spanned the cognitive domains of attention, memory, executive function, language, and sensory–motor function. The findings do not support a global cognitive deficit in PD. Rather, the findings support a relatively specific impairment of cognitive function on measures of sustained attention. Nevertheless, an impaired ability to sustain attention may have deleterious consequences for academic, employment and

social functioning (Castaneda *et al.* 2008) and may limit the efficacy of other aspects of attention and of cognition more generally (Cohen & O'Donnell, 1993; Sarter *et al.* 2001). The present findings raised a number of questions regarding the role of neuropsychological dysfunction in PD aetiology and maintenance, for instance, whether neuropsychological dysfunction is a risk factor for PD. Longitudinal research is needed in order to address these questions, so that the potential clinical benefits of neuropsychological assessment for PD may be realized.

Chapter 9

Overall Conclusions

9.1 Overview of Chapter

The present research was presented as three separate studies, each examining a different aspect of function in PD during the inter–panic interval. Study 1 (Chapter 6) examined resting state function in PD. In this study, multiple indices of central– and autonomic nervous system function were recorded 'at rest' in order to index a physiological baseline devoid of task–imposed information processing. Study 2 (Chapter 7) examined sensory information processing and the allocation of attention in PD using an auditory oddball task, which is a simple auditory discrimination task. Psychophysiological and behavioural measures were concomitantly–recorded during task performance to characterise brain, body and behavioural responses to two types of sensory stimuli, infrequent significant stimuli and frequent irrelevant stimuli. Study 3 (Chapter 8) examined cognitive function in PD using a neuropsychological test battery that encompassed multiple tests of attention, memory, executive functions, language, and sensory–motor function. In contrast to Studies 1 and 2, behavioural indices only were obtained for this study. This final chapter brings together the findings of these three studies and discusses their implications for PD research and clinical practice.

The chapter begins by recapitulating the findings of patient–control differences from Studies 1 – 3. Then, the discussion turns to the possible role that these patient–control

differences may play in PD aetiology and maintenance. The present research, being cross–sectional, may not, of course, determine whether or not a causal relationship exists between PD and each of the identified disorder markers, and if so, the direction of causality. However, given the theoretical and clinical importance of distinguishing different types of disorder markers (e.g., risk *vs.* maintenance factors, state *vs.* trait markers) (Kraemer *et al.* 2001; Zvolensky *et al.* 2006c), evidence for a possible role of these disorder markers in PD aetiology and maintenance, where available, is discussed. The next major chapter section brings together the findings from Studies 1 – 3 and considers possible interpretations of the overall pattern of results. This is followed by a discussion of the limitations of the present research. Finally, the chapter concludes with a discussion of several research strategies for future PD research which may yield useful information for PD theory and clinical practice.

9.2 Recapitulation of Findings

This section recapitulates the main between–group findings, both positive and negative, from Studies 1 – 3.

9.2.1 Study 1

Patients differed from controls on numerous CNS (QEEG) and ANS (cardiovascular, electrodermal) measures of resting state function. Positive QEEG findings included a global reduction in alpha–1 spectral power and alpha peak amplitude in PD compared to controls during the REC condition. Additionally, patients compared to controls showed reduced beta spectral power at frontal and temporal sites during REO (Group*Site interaction), and a scalp–wide reduction in beta spectral power during REC (trend). The final positive QEEG finding for this study was a frontal alpha–1

asymmetry (R<L alpha–1 power) that was evident in patients, but not controls, during REC. Patients also differed from controls on all measures of ANS function. In regards cardiovascular function, patients showed reduced RR interval, HRV and LF:HF ratio during both conditions, compared to controls. In regards EDA measures, patients showed slower SCL habituation than controls during REO, which was the only condition for which there was adequate data to compare. And, contrary to prediction, patients showed fewer non–specific SCRs than controls during both conditions.

There were few null findings for Study 1. The main null findings were for theta spectral power, alpha–2 spectral power, and alpha peak frequency.

9.2.2 Study 2

Patients and controls differed on many of the CNS (ERP) and behavioural measures of sensory information processing and attention recorded during performance of the auditory oddball task. Compared to controls, patients showed reduced P3 amplitude and latency for significant target stimuli, and increased N1 amplitude for non–significant standard tones. Patients and controls also differed in N1 amplitude topography (significant Group*Site interactions). In both conditions N1 amplitude was relatively centralized in PD compared to controls. Finally, patients showed longer and more variable reaction times in responding to targets tones, as compared to controls.

In addition to these positive findings, there were numerous null findings in Study 2. The null ERP findings were for N1 target amplitude, P2 amplitude and topography, and N2 amplitude and topography. Additionally, there was trend for fewer SCRs to significant target tones, in PD compared to controls.

9.2.3 Study 3

Neuropsychological performance data were aggregated into 7 empirically–defined cognitive domains (Rowe *et al.* 2007): Information Processing Speed, Verbal Memory, Working Memory Capacity, Sustained Attention, Sensorimotor Function, Verbal Processing, and Executive Function. In contrast to Studies 1 and 2, the majority of findings for this study were non–significant: patients and controls only differed on measures of Sustained Attention. Specifically, patients showed longer RT and made more errors of omission compared to controls during performance of CPT.

9.2.4 Summary: Recapitulation of Findings

The present research identified numerous PD–control differences spanning multiple levels of function (*i.e.* CNS physiology, ANS physiology, and behaviour) and different task conditions (*i.e.* task–free resting state, sensory information processing, and cognitive tests). Table 35 lists the positive between–group findings from the three studies and their effect sizes. From this table it is apparent that there were more significant findings and larger effect sizes for psychophysiological as compared to behavioural findings.

In some instances, these findings represent an important replication of earlier reports, within a relatively large sample. For instance, alpha–1 spectral power shows marked inter–individual variability (Chen *et al.* 2008), yet the single previous finding for resting state alpha–1 power in PD was obtained from a relatively small clinical sample (n = 7) (Newman *et al.* 1992). Reduced HRV, by contrast, is a relatively robust finding for PD (Friedman, 2007). Other findings, on the other hand, are apparently novel and thus require replication. For instance, previous studies do not appear to have examined

Table 35: Effect sizes for significant between–group differences [a]

Study/Variable [b]	Finding for PD (relative to controls)	Index	ES	Size
Study 1				
REC α–1 power	reduced	$\acute{\eta}_p^2$	.083	M–L
REO β power	altered topography	$\acute{\eta}_p^2$	.025	S
REC Alpha Peak Amplitude	reduced	$\acute{\eta}_p^2$	.096	L
REC FAA	asymmetry present	$\acute{\eta}_p^2$	.046	M
REC RR Interval [c]	reduced	*d*	.47	M
HRV [d]	reduced	*d*	.52	M
REC LF:HF [c]	increased	*d*	.39	S–M
REO NS.SCR [c]	fewer	*d*	.55	M
REO SCL–GRAD	reduced	*d*	.38	S–M
Study 2				
N1 Target Amp.	altered topography	$\acute{\eta}_p^2$	.049	M
N1 Standard Amp.	increased	$\acute{\eta}_p^2$	.026	S
N1 Standard Amp.	altered topography	$\acute{\eta}_p^2$	.096	L
P3 Amplitude	reduced	$\acute{\eta}_p^2$	.054	M
P3 Latencies	reduced	$\acute{\eta}_p^2$	.050	M
RT	longer	*d*	.61	M–L
RT–SD	greater	*d*	.61	M–L
Study 3				
CPT–RT	longer	*d*	.46	M
CPT Errors	greater	*d*	.49	M

[a] For ANOVAs, $\acute{\eta}_p^2$ = .01 denotes a small effect size (ES), medium = .06, and large = .16 (Cohen, 1988). For *t*–tests, *d* = 0.2 denotes a small ES, medium = 0.5, and large = 0.8 (Cohen, 1992). [b] Variables are defined in the appropriate Study chapter. [c] Between–group comparisons significant for both conditions. Largest ES only reported. [d] The two conditions have same ES.

sustained attention performance in PD, suggesting that the present finding is novel. Taken together, the present findings – notwithstanding the need for replication – indicate that panic disordered subjects differed from healthy control subjects on multiple measures of brain, body, and cognitive function.

9.3 Implications of Findings: Risk Factors, Maintenance Factors or Intermediate Phenotypes?

This section considers evidence for a possible role of several of the patient–control differences indentified by the present research in PD aetiology or maintenance. Patient–control differences indentified by cross–sectional research (*i.e.* disorder markers) include a broad typology of factors including, but not limited to, factors that contribute to the disorder's aetiology and maintenance (Kraemer *et al.* 1997; 2001) (see 3.4.1 Between–Subjects Design). Because different types of disorder markers (e.g., risk factors *vs.* maintenance factors) may differentially benefit clinical practice and research, the delineation of the different types is an important goal for clinical research (Zvolensky *et al.* 2006c). However, because it may not be possible to distinguish the different types with cross–sectional data, for instance, to establish causality (Kraemer *et al.* 2001), longitudinal data, where available in the extant literature, are presented. Of the numerous patient–control differences indentified by the present research (see Table 35), this section discusses the possible implications for PD research and clinical practice of only three psychophysiological disorder markers. These three – namely, spectral power, frontal alpha asymmetry (FAA) and heart rate variability (HRV) – were selected because the extant data support their classification as a particular type of disorder marker.

9.3.1 Spectral Power

9.3.1.1 Trait vs. State–Dependence

Among disorder markers, an important distinction exists between traits and state–dependent variables. Whereas the label 'trait' connotes temporal and cross–situational stability, state–dependent variables show systematic within–subject response variation over time (Kraemer *et al.* 1994). A number of longitudinal analyses have examined the temporal stability of EEG spectral power in order to disentangle its state and trait aspects. In non–clinical samples, resting state absolute spectral power shows high test–retest stability, with occasion–specific effects contributing minimally to the variance in EEG measures recorded under standardised conditions (review Thatcher, 2010: Kondacs & Szabo, 1999; Näpflin *et al.* 2007; Van Albada *et al.* 2007; Hagemann & Naumann, 2009), supporting the notion that spectral power reflects a trait characteristic of healthy individuals. By contrast, the test–retest stability of resting state spectral power has rarely been investigated in clinical populations, and does not appear to have been examined in PD. Recently however, Schmidt and colleagues (2012) in an uncontrolled study examined the test–retest stability of alpha spectral power and asymmetry in individuals with generalised SAD. These measures were obtained on two occasions one week apart, both during resting state and during anticipation of an emotional challenge (*i.e.* speech preparation). They found that alpha power was highly stable in both conditions (resting Pearson *r*s = 0.86 to 0.96; challenge *r*s = 0.85 to 0.91). Although these clinical and non–clinical findings support the view that resting state spectral power is a trait–like individual difference characteristic, future studies are needed in order to directly test the extent to which resting spectral power represents a state–related or enduring characteristic of PD.

9.3.1.2 Risk Factor or Consequence

Another question that has important implications for both research and clinical practice is whether resting spectral power temporally precedes and predicts PD onset, or whether it is a consequence of the disorder. For instance, physiologic traits that temporally precede PD onset may represent risk factors, the identification of which would help identify individuals at risk for the disorder. In particular, the identification of causal risk factors within the various organisational levels at which disorder risk is conferred (e.g., biological/genetic, psychological, social, and cultural/economic) is the essential first step in developing an integrative aetiological model for psychiatric disorders (Kendler, 2008). In contrast, traits that develop following PD onset may represent long–lasting consequences of having experienced the disorder (*i.e.* 'scars'). The identification of such disorder scars may aid understanding of the processes underlying a disorder's maintenance and course (Kraemer *et al.* 1994). Therefore, further research is needed in order to determine whether electrocortical abnormalities at rest predate and predict PD onset.

9.3.1.3 Malleability

Another important distinction among disorder markers exists between those that are malleable, and those that are not. Despite its reported high test–retest stability, resting state EEG spectral power is malleable, as is evident from several decades of research which shows that subjects can influence the amplitude and topography of EEG spectral components via neurofeedback training (Birbaumer *et al.* 2006). Malleable causal risk factors are candidate targets for prevention interventions (Zvolensky *et al.* 2006c). However, as it remains to be determined whether abnormal resting state electrocortical activity represents a causal risk factor for PD, it is unclear whether

neurofeedback would be effective as part of a PD prevention intervention. By contrast, malleable maintenance factors are the target of treatment interventions (Stice, 2002). Although there are limited data for PD specifically, across the anxiety disorders there is abundant evidence for the efficacy of neurofeedback treatment, typically as alpha and/or theta enhancement (reviews Moore, 2000; Hammond, 2005: Agnohotri *et al.* 2007; Walker, 2009), suggesting its potential utility for the treatment of PD. However, because QEEG profiles are typically not isomorphic with DSM diagnoses (Johnstone *et al.* 2005; Suffin *et al.* 2007; Hammond, 2010) individualised neurofeedback is likely to be more efficacious.

9.3.1.4 Treatment Response Prediction

Predictors of treatment response are a category of disorder marker that have received much attention of late. Treatment *predictors* are factors that influence the treatment outcome, whereas *differential predictors* or *moderators* differentially influence the response to one treatment agent versus another (Kraemer *et al.* 2006). Both treatment response and QEEG heterogeneity have been observed within many neuropsychiatric disorders (Coutin–Churchman *et al.* 2003; Johnstone *et al.* 2005; Coburn *et al.* 2006; Hammond, 2010), suggesting the potential utility of quantifiable neurophysiologic indices (*i.e.* QEEG profile) in treatment response prediction (Suffin *et al.* 2007). Indeed, a clear relationship between medication–free baseline resting QEEG profile, or recordings obtained within the first week of pharmacotherapy, and response to specific medications, has been reported in many disorders (Prichep, 2005), notably MDD (including refractory MDD) (review Hunter *et al.* 2007: Bares *et al.* 2007: Suffin *et al.* 2007; Bruder *et al.* 2008; Leuchter *et al.* 2009; Hunter *et al.* 2010), attention–deficit hyperactivity disorder (Arns *et al.* 2008), and obsessive compulsive disorder (Hansen

et al. 2003). As anti–depressant treatment response typically takes many weeks to gauge (Harmer *et al.* 2009; Leuchter *et al.* 2009; Hunter *et al.* 2010), the use of QEEG measures in either predicting the treatment response, or guiding treatment choice, of patients with major depression represents a vast improvement on the standard wait and see approach. Additionally, baseline alpha power predicted clinical improvement following a brief cognitive intervention in MDD, such that responders had less alpha activity at baseline (Deldin & Chiu, 2005).

In PD even first–line recommended psychotherapeutic interventions and pharmacologic agents are associated with substantial response heterogeneity, including treatment non–response and relapse (Ballenger, 1998; Slaap & den Boer, 2001; Bandelow & Rüfer, 2004; Busch & Milrod 2004; Landon & Barlow, 2004; Diemer *et al.* 2010). Therefore, predictors of treatment response are needed in order to identify which individual panic disordered patients are likely to benefit from a given treatment (Bandelow & Rüfer, 2004; Diemer *et al.* 2010). However, the investigation of within–diagnosis CNS function heterogeneity and, in turn, the identification of biological predictors of treatment response, is an under–developed research area in PD (Bandelow & Rüfer, 2004; Diemer *et al.* 2010). As resting state QEEG predictors of treatment response have been identified in many disorders (Prichep, 2005), this is a promising line of enquiry for PD that warrants further investigation.

9.3.1.5 Intermediate Phenotype

Several criteria for intermediate phenotypes have been proposed by Gottesman and colleagues. They are (1) association with the illness, (2) heritability, (3) stability (*i.e.* state–independence), (4) familial co–aggregation of the intermediate phenotype with

illness, and (5) presence of the intermediate phenotype in unaffected relatives of affected individuals at a higher rate than in the general population (Gottesman & Gould, 2003; Gould & Gottesman, 2006). Because resting state EEG spectral power meets several of these criteria it is recognised as a potential intermediate phenotype for psychiatric disorders (Begleiter & Porjesz, 2006; Zietsch *et al.* 2007). For instance, resting state spectral power shows high intra–individual stability over time (review Thatcher, 2010) and heritability (van Beijsterveldt & van Baal, 2002; Smit *et al.* 2005; Anokhin *et al.* 2006; Begleiter & Porjesz, 2006; Zietsch *et al.* 2007). Additionally, QEEG traits are less complex than clinical endpoints and, being relatively proximal to the genotype, provide greater power to identify genetic susceptibility loci (Begleiter & Porjesz, 2006). However, it is unclear whether two other proposed criteria for intermediate phenotypes are met in PD. These criteria (criteria 4 and 5, above) relate to the requirement that the phenotype and intermediate phenotype share a common genetic source (De Geus, 2002). Therefore, these questions and the test–retest stability of resting state spectral power in PD must be addressed before spectral power can be considered an intermediate phenotype for the disorder.

9.3.2 Frontal Asymmetry

9.3.2.1 Trait vs. State–Dependence

Because of the clinical importance of distinguishing trait–like markers for psychopathology, particularly risk factors, the test–retest stability of FAA has been investigated in clinical and non–clinical samples (Allen *et al.* 2004b). In healthy adults, resting FAA measures typically show moderate test–retest correlations across time intervals of several weeks or more (Tomarken *et al.* 1992; Debener *et al.* 2000; Hagemann *et al.* 2002; Allen *et al.* 2004b; Vuga *et al.* 2006). By contrast, high test–

retest correlation coefficients for alpha spectral power in non–clinical samples are typically reported (review Thatcher, 2010). Hagemann and colleagues (2002; replication study 2005) applied the latent trait–state theory in order to decompose resting FAA measures into trait, state and error components. In each study they obtained resting EEG from healthy subjects on multiple occasions, finding that scalp–wide approximately 60% of FAA variance was due to a temporally stable trait, and about 40% was due to state–like fluctuations. However, for frontal sites, including mid–frontal sites F3 and F4, the occasion–specific effects rose to 40–50%, suggesting that even under standardised laboratory conditions uncontrollable situational and subject–related factors account for substantial FAA variance.

In clinical studies, frontal EEG asymmetry and its stability has been investigated much more extensively in relation to depression than anxiety (Smit *et al.* 2007). Resting state studies have typically, but not always, reported reduced left frontal and/or increased right frontal activity in depression (review Thihbodeau *et al.* 2006). Several lines of evidence suggest that resting state FAA is relatively stable in depression. Firstly, there are findings that formerly depressed but currently euthymic individuals show left frontal hypo–activation, in comparison to never depressed controls (Henriques & Davidson, 1990; Gotlib *et al.* 1998; Allen & Cohen, 2010). Secondly, longitudinal findings that FAA is unrelated to changes in MDD symptom state suggest that FAA represents a stable diathesis (Allen *et al.* 2004b; McFarland *et al.* 2006; Vuga *et al.* 2006). Finally, findings that the test–retest stability for FAA in MDD is comparable to non–clinical samples (Allen *et al.* 2004b; Vuga *et al.* 2006) provide direct evidence for the temporal stability of resting FAA in MDD. Although the temporal stability of FAA in PD remains to be empirically tested, Schmidt *et al.*

(2012) recently reported that frontal asymmetry in SAD is moderately stable. Taken together, the extant findings suggest that resting state FAA is a relatively stable individual difference variable in both clinical and non–clinical samples, although state–related effects are significant.

9.3.2.2 Risk Factor or Consequence

Given the temporal stability of FAA, the question arises as to whether FAA precedes and predicts, or is a consequence of, anxiety and depressive psychopathology. Typically, FAA has been conceptualised as a stable trait that predisposes individuals to a particular pattern of approach/withdrawal emotional responding (Davidson, 1993; Coan & Allen, 2004). According to the prominent diathesis–stress model of frontal asymmetry, individual differences in frontal asymmetry represent a diathesis (*i.e.* risk factor) for anxiety and depression (Davidson, 1993; Coan & Allen, 2004).

According to Davidson:

> Individual differences in FAA "alter the probability that specific forms of emotional reactions will occur in response to the requisite environmental challenge. In the absence of such a challenge, the pattern of asymmetric activation will simply reflect a propensity, but will not necessarily culminate in differences in mood or symptoms" (Davidson, 2002, p. 193).

In accordance with the diathesis–stress model, resting FAA explains a significant degree of variance in affective dispositional characteristics across development: Whereas relatively greater left frontal activity at rest is associated with trait tendencies to approach or engage a stimulus, relatively greater right frontal activity at rest is

associated with trait tendencies for avoidance and withdrawal (Davidson, 1993; Coan & Allen, 2003). Individual differences in FAA emerge early in life and are associated both concurrently and prospectively with individual differences in approach– and withdrawal–related affective style and risk for depressive and anxiety psychopathology (Davidson, 1992; Fox *et al.* 1995; Kagan & Snidman, 1999; McManis *et al.* 2002; Buss *et al.* 2003; Henderson *et al.* 2004; Blackhart *et al.* 2006; Pössel *et al.* 2008; Hannesdóttir *et al.* 2010; Nusslock *et al.* 2011; McLaughlin *et al.* 2012), although the specific association between baseline FAA and subsequent panic symptomatology does not appear to have been investigated.

9.3.2.3 Malleability

There is some evidence that resting state FAA is malleable, and that the manipulation of inter–hemispheric balance via neurofeedback (review Hammond, 2005: Allen *et al.* 2001; Kerson *et al.* 2009) and repeated transcranial magnetic stimulation (rTMS) (review Zwanger *et al.* 2009) may exert beneficial effects in terms of affective responding. For instance, neurofeedback training was associated with long–lasting (1 – 5 year) changes in FAA and associated symptom reduction in depression (Baehr *et al.* 2001). In PD and PTSD several (mostly uncontrolled) studies have shown that stimulation of the dorsolateral PFC via rTMS exerts an anxiolytic effect, presumably due to a reduction in right PFC activity (Zwanger *et al.* 2009). These findings suggest the potential utility of neurofeedback and rTMS in the treatment of PD.

9.3.2.4 Intermediate Phenotype

Several attributes of resting state FAA suggest that it may be suitable as an intermediate phenotype for the depressive and anxiety disorders to which it has been

linked (Anokhin *et al.* 2006; Smit *et al.* 2007). Heritability and stability are central among those attributes which intermediate phenotypes ideally possess (De Geus, 2002; Gould & Gottesman, 2006). As reviewed, analyses of the test–retest stability of FAA indicate that it is moderately stable in both clinical and non–clinical samples. Anokhin *et al.* (2006) addressed the issue of FAA heritability in a twin study comprising a population–based sample of young adult female monozygotic and dizygotic twin pairs. They found that approximately 27% of the observed variance in broad band FAA at mid–frontal sites (F3 and F4) could be accounted for by genetic factors, representing low but significant heritability. Similar results were obtained in separate analyses for three alpha sub–bands. Smit *et al.* (2007) also addressed the question of resting FAA heritability, and because current criteria for an intermediate phenotype specify shared genetic liability for the phenotype and intermediate phenotype (De Geus, 2002; Gould & Gottesman, 2006), they also examined the pattern of shared risk for FAA and anxiety and depression. In this longitudinal design study comprising two age cohorts (young adult and middle–aged) of male and female twins and their non–twin siblings, a factor score summarising the risk for anxiety and depression was calculated from multiple scales on multiple measurement occasions. They found that FAA was only heritable in young adulthood, particularly so in females (females 37%, males 32%), and that the proportion of shared genetic liability for FAA and the risk for anxiety and depression was only significant in young females. The low heritability of FAA is consistent with the view that there is considerable developmental plasticity in the neural systems that mediate approach–withdrawal emotional behaviours (McLaughlin *et al.* 2012), and suggests limited utility of FAA as an intermediate phenotype for genetic studies of anxiety and mood disorders.

9.3.3 Heart Rate Variability

Reduced resting HRV is a common property of many pathological states, both physiological and psychological (reviews Thayer & Brosschot, 2005; Friedman, 2007; Thayer & Lane, 2009: Kemp *et al.* 2012), and is a powerful predictor of cardiac morbidity and mortality (reviews Brook & Julius, 2000; Thayer & Lane, 2007: Bigger *et al.* 1992; Dreifus *et al.* 1993; Dekker *et al.* 1997; 2000). In particular, individuals with PD are at increased risk for adverse cardiac outcomes such as ventricular arrhythmias, hypertension, stroke, myocardial infarction, heart failure and sudden cardiac death (Gorman & Sloan, 2000; Gomez–Caminero *et al.* 2005; Davies *et al.* 2008; Goodwin *et al.* 2009; Vogelzangs *et al.* 2010). Although the exact mechanisms linking PD to adverse cardiac outcomes are unknown (Jeejeebhoy *et al.* 2000; Miu *et al.* 2009), there is evidence that this relationship is mediated, at least in part, by autonomic imbalance, specifically decreased parasympathetic innervation of the heart, which exposes the heart to unopposed sympathetic stimulation (Friedman & Thayer, 1998b; Gorman & Sloan, 2000; Friedman, 2007).

9.3.3.1 Trait vs. State–Dependence

Reduced HRV indicative of low vagal tone and high SNS cardiac control is a robust finding in PD, notwithstanding some null findings (review Friedman, 2007). Moreover, reduced HRV in PD relative to unaffected controls is observed across a variety of laboratory conditions ranging from resting state to laboratory stressors and panicogenic challenge procedures (Yeragani *et al.* 1992; 1993; Middleton *et al.* 1994; Friedman & Thayer, 1998a; 1998b; Yeragani *et al.* 1998; Cohen *et al.* 2000; Yeragani *et al.* 2003; Sullivan *et al.* 2004; Garakani *et al.* 2009; Kang *et al.* 2010; Petrowski *et al.* 2010). These findings suggest that reduced HRV is a state–independent feature of

PD (Thayer & Lane, 2009). The present finding that HRV was not lower in unmedicated patients compared to matched controls runs counter to the majority of extant findings and was therefore contrary to prediction. However, the reason for this finding cannot be determined given the cross–sectional nature of the present research.

Several studies have directly tested the temporal stability of resting HRV in healthy subjects, and have reported good to excellent test–retest stability of resting HRV measures across periods ranging from one week to three years (Goedhart *et al.* 2007; Guijt *et al.* 2007; Li *et al.* 2009; Bertsch *et al.* 2012). Recently, Bertsch *et al.* (2012) applied the latent state–trait (LST) theory to decompose parasympathetic measures of resting HRV into their trait, situation–specific, and measurement error components. They obtained HRV measures from healthy subjects on three occasions, each separated by one week, in several conditions including resting state. LST analyses showed that about 30% – 40% of variance in a given HRV measure was due to occasion–specific effects, about 50% – 60% of variance was due to a latent trait, and measurement error contributed minimally. Taken together, these findings suggest that although situational and personal differences influence HRV measures at rest (Bertsch *et al.* 2012), resting HRV is a relatively stable individual difference variable (Thayer *et al.* 2009). The test–retest stability of resting HRV in PD does not appear to have been empirically tested to date though.

9.3.3.2 Risk Factor or Consequence

Various data suggest that individual differences in tonic HRV predate the development of PD (and other anxiety disorders) and may therefore represent a risk factor, as opposed to a consequence of the disorder. Firstly, the results of twin and family

studies suggest that up to 65% of variance in resting HRV may be attributed to genetic factors (Snieder *et al.* 1997; Kupper *et al.* 2004; Snieder *et al.* 2007; Wang *et al.* 2009). Additionally, individual differences in vagal tone emerge early in infancy (Huffman *et al.* 1998) and are associated throughout development with trait–like differences in temperament and emotion regulation (reviews Beauchaine, 2001; Porges, 1992: Friedman & Thayer, 1998a; Santucci *et al.* 2008). Further, low HRV is associated with a range of risk factors for PD and other anxiety disorders. For instance, high trait anxiety, which is a non–specific risk factor for PD and other chronic anxiety disorders (Brandes & Bienvenu, 2006), is associated with reduced HF spectral power in non–clinical samples (Bleil *et al.* 2008; Miu *et al.* 2009). Similarly, individuals who report non–clinical panic attacks and are thus deemed at risk for PD and a range of psychopathologic conditions (Goodwin *et al.* 2004; Baillie & Rapee, 2005; Wittchen *et al.* 2008; Kinley *et al.* 2011), showed reduced HRV across several conditions (Friedman *et al.* 1993; Friedman & Thayer, 1998a; Yeragani *et al.* 1995). Recently, a longitudinal, population–based study examined whether measures of HRV in adolescents (10 – 12 years old) predicted self–reported anxiety symptoms two years later (Greaves–Lord *et al.* 2010). Although baseline measures of resting state HRV did not predict future anxiety, a measure of HRV reactivity to orthostatic challenge predicted anxiety symptoms in girls, but not boys.

Although the above findings, taken together, suggest that low HRV may predate PD onset, these findings are limited either by being cross–sectional, or, in the case of the Greaves–Lord *et al.* study, relate to anxiety as opposed to panic–spectrum symptoms. To date, however, direct evidence for the predictive utility of low HRV in the development of PD or panic symptoms appears to be lacking.

9.3.3.3 Malleability

Although resting HRV levels are a relatively stable individual difference variable, they are also malleable, and may be altered through a range of measures (De Meersman & Stein, 2007; Thayer *et al.* 2009). Low HRV is associated with a range of deleterious outcomes in terms of cognitive function, emotion regulation, attention regulation, morbidity and mortality (reviews Beauchaine, 2001; Thayer & Brosschot, 2005; Friedman, 2007; Thayer & Lane, 2007; Thayer *et al.* 2009; 2010), suggesting that HRV represents a "malleable substrate for a wide range of processes associated with self–regulation, adaptation, and health" (Thayer *et al.* 2009, p. 147). For instance, low HRV is associated with a range of lifestyle–related factors that are modifiable (reviews De Meersman & Stein, 2007; Thayer & Lane, 2007; Thayer *et al.* 2010). These include diet (Mozzafarian *et al.* 2008; Park *et al.* 2009), smoking (Hayano *et al.* 1990; Tsuji *et al.* 1996; Stolarz *et al.* 2003), physical inactivity (Gutin *et al.* 1997; Rennie *et al.* 2003; Hansen *et al.* 2004; Tuomainen *et al.* 2005; Sandercock *et al.* 2005), alcohol and drug consumption (Reed *et al.* 1999), and obesity (Karason *et al.* 1999; Li *et al.* 2010).

Interestingly, many of these lifestyle factors are associated with PD and may therefore be the target of HRV–increasing strategies. Smoking, for instance, is associated both concurrently and prospectively with panic–spectrum symptoms (Zvolensky *et al.* 2003; 2005a; Zvolensky & Bernstein, 2005) and is a putative risk and maintenance factor for PD (Zvolensky *et al.* 2006c; Feldner *et al.* 2008). However, the HRV–suppressing effects of smoking are reversible and almost immediate upon smoking cessation (Minami *et al.* 1999). Exercise avoidance is another HRV–lowering behaviour that is a common complication of PD (Broocks *et al.* 1997; White *et al.*

2006). Individuals with PD may fear and avoid exercise–induced bodily sensations, as these sensations are similar to or have become conditioned to autonomic arousal sensations (Clark, 1986; Barlow, 2002; White *et al.* 2006), and acute exercise may induce panic attacks and anxiety in PD (Broocks *et al.* 1998). However, across diagnostic groups, exercise has an anxiolytic effect comparable to CBT, according to a recent meta–analysis (Wipfli *et al.* 2008). Moreover, exercise interventions have been trialled in a range of psychological disorders (reviews Ströhle, 2009; Wollf *et al.* 2011), and in PD as either an adjunct or an alternative to pharmacotherapy (Broocks *et al.* 1998; Wedekind *et al.* 2010). Although the anxiolytic effect of exercise in PD is believed to relate to interoceptive exposure (Wolff *et al.* 2011), the inverse association of resting HRV and habitual exercise (Rennie *et al.* 2003) suggests increased HRV as another possible mechanism. Finally, given the high rates of substance use, abuse and dependence in PD (Kessler *et al.* 2006; Sareen *et al.* 2006; Zvolensky *et al.* 2006a; b; 2008; Robinson *et al.* 2008), alcohol and drug use may contribute to low HRV in PD.

Chronic stress is another modifiable factor that has been associated with lower HRV (reviews Thayer & Lane, 2007; Thayer *et al.* 2010: Vrijkotte *et al.* 2000; Kang *et al.* 2004). By contrast, various relaxation techniques such as meditation (Murata *et al.* 2004), autogenic training (Miu *et al.* 2009), and HRV biofeedback (Wheat & Larkin, 2010) have demonstrated effectiveness in increasing HRV. Wheat and Larkin (2010) recently reviewed evidence for the effectiveness of HRV biofeedback. The 14 reviewed studies encompassed non–clinical and medical samples (e.g., asthma), but only two psychiatric samples (MDD and PTSD). Overall, all studies reported increased HRV during biofeedback practice, although 5 of 7 studies that examined the long–term effects reported that the benefits were not maintained.

Some therapeutic interventions may also increase HRV in PD. Garakani *et al.* (2009) compared the effect of 12 weeks of CBT treatment with CBT plus sertraline (a SSRI) on HRV. They found that CBT treatment statistically increased resting HRV and decreased HR, whereas the combined treatment did not alter either. However, clinical findings in regards the effect of SSRI pharmacotherapy on HRV in PD, as previously discussed, have been mixed; previous studies have reported that SSRI treatment either increased (Tucker *et al.* 1997; Yeragani *et al.* 2000; Sullivan *et al.* 2004) or decreased (Licht *et al.* 2010) HRV in PD. From the extant findings, therefore, it is unclear whether the most commonly prescribed anti–depressant treatments for PD confer a protective, adverse, or non–significant effect on cardiovascular function, in terms of HRV.

In sum, the above evidence suggests that a range of behavioural strategies may be adopted to increase HRV in patients with PD, including diet, exercise, weight loss, meditation, biofeedback and CBT. However, the available evidence does not provide clear support for the HRV improving, cardio–protective benefits of SSRI treatment.

9.3.3.4 Intermediate Phenotype

Because low HRV meets each of the previously–enumerated criteria for intermediate phenotypes, it has been proposed as a candidate intermediate phenotype for PD (Melzig *et al.* 2009; Thayer & Lane, 2009). As reviewed, the extant literature indicates that HRV is reliably associated with PD (Friedman, 2007), is heritable (e.g., Wang *et al.* 2009), and is relatively stable, as indicated by its cross–situational stability in PD (Thayer & Lane, 2009) and its test–retest stability in healthy subjects (e.g., Bertsch *et al.* 2012). Additionally, there is evidence that low HRV and PD co–aggregate within

families (Friedman & Thayer, 1998a; Friedman, 2007), and that HRV is lower in unaffected children of panic disordered parents compared to children of healthy controls (Srinivasan *et al.* 2002), suggesting that PD and low HRV share a common genetic source. Although it appears that no study has examined the genetic correlation of PD and HRV, a recent twin study comprising middle–aged male twins found that shared genetic influences accounted for over 80% of the covariance of depressive symptoms and HRV measures (Su *et al.* 2010). Taken together, therefore, the evidence in support of HRV as an intermediate phenotype for PD is relatively strong.

9.3.4 Summary: Implications of Findings

The reviewed findings provide preliminary support for the classification of three types of psychophysiological markers for PD – that is, resting state EEG spectral power, FAA and HRV. Taken together, the extant literatures suggest that resting spectral power, HRV and, to a lesser extent FAA, are relatively stable individual difference characteristics. Moreover, extant findings indicate that individual differences in these parameters emerge early in life and, particularly in the cases of FAA and HRV, are associated across development with trait–like differences in emotional responding. Nevertheless, it remains to be empirically tested in appropriate longitudinal studies whether these CNS and ANS parameters represent risk factors for PD.

The extant findings also indicate that resting state spectral power, FAA and HRV are malleable. Malleable causal risk factors are ideal targets of prevention interventions, whereas malleable maintenance factors are the focus of treatment interventions (Zvolensky *et al.* 2006c), suggesting their potential clinical utility. For instance, each of these psychophysiological parameters may be altered through biofeedback

techniques, pointing to the potential utility of this underutilised treatment option for PD. By contrast, HRV may be altered through a diverse range of lifestyle–related and treatment interventions. However, the finding by Licht *et al.* (2010) that anti–depressant use was longitudinally associated with a lowering of HRV in anxiety and depressive disorders, in conjunction with the present (albeit, cross–sectional) finding that medication use was associated with lower HRV in clinical participants, is a concern, and warrants further investigation.

In regards treatment response prediction, the extant clinical literature provides abundant examples within other psychiatric populations of the clinical utility of QEEG spectral parameters in guiding treatment decisions, suggesting the potential utility of this approach for PD. However, it may be that a range of markers of treatment response from different levels of function (e.g., CNS, ANS, behaviour, cognition, affect, clinical measures) may more accurately predict treatment response than single measures (e.g., Kemp *et al.* 2008; Leuchter *et al.* 2009). Finally, the reviewed evidence suggests that low HRV may be suitable as a non–specific intermediate phenotype for PD.

The foregoing review only discussed three disorder markers for PD (*i.e.* spectral power, FAA and HRV). Nevertheless, it is conceivable that the other markers identified by the present research, and that were not included in the above review because the extant literature to date does not support their classification as a particular type of disorder marker, will have utility for PD research and clinical practice. For instance, ERPs directly reflect the effect of neurotransmitters on cortical neuronal activity and therefore have the potential to predict or monitor an individual's response

to central–acting pharmacologic agents (Polich & Herbst, 2000; Pogarell *et al.* 2006). Notably, P3, which is a highly–researched ERP component typically elicited within an oddball paradigm (Key *et al.* 2005), has supported a range of clinical applications within other neuropsychiatric populations (Polich, 1998). Reduced oddball P3, which is considered a clinically useful index of cognitive dysfunction (Polich & Herbst, 2000), has been a replicated finding within numerous neuropsychiatric disorders (review Hansenne, 2006), and is considered a clinically useful index of cognitive dysfunction (Polich & Herbst, 2000). In Alzheimer's dementia, for instance, P3 amplitude has shown utility in aiding differential diagnosis, prediction of treatment response, and evaluating treatment response (review Pogarell *et al.* 2006). Studies show that although a range of biological and environmental factors contribute to P3 variance (Polich & Kok, 1995), oddball P3 shows good test–retest stability when recorded in healthy subjects under standardised conditions (review Polich & Herbst, 2000). By contrast, reduced P3 amplitude is considered a state marker of depression, a trait marker of schizophrenia, and a risk factor for alcoholism (Hansenne, 2006). Therefore, although P3 amplitude has demonstrated clinical utility (Polich, 1998), research is needed in order to determine the nature of P3 amplitude reduction in PD. In particular, research is needed to disentangle its state/trait and aspects in PD.

In sum, the present research identified numerous disorder markers spanning multiple levels of function (e.g. CNS, ANS, behaviour, and cognition). Considered together, these markers could conceivably support a range of clinical applications in PD. However, an essential first step in translating disorder markers into clinically useful applications is to accurately classify each marker (Zvolensky *et al.* 2006c). For instance, it would be pointless and a waste of resources to implement a panic

prevention program that aimed to alter a marker unless that marker was actually a causal risk factor for PD (Craske & Zucker, 2002). Moreover, as PD and other anxiety disorders are assumed to be the product of multiple risk factors, and complex interactions thereof, a failure to account for the complexity of risk processes would also stymie prevention efforts (Feldner *et al.* 2004; De Meersman & Stein, 2007).

Additionally, the identified multi–level disorder markers have potential applications for PD research. For instance, the identification of multi–level disorder markers may spur risk factor research and thereby aid understanding of the disorder's aetiology. Additionally, as intermediate phenotypes must, in the first instance, be associated with an illness (Gottesman & Gould, 2003), the identification of disorder markers is the first of many steps in the identification of intermediate phenotypes.

9.4 Integrating the Findings

9.4.1 Attention

Upon examination of the findings of Studies 1 – 3 a pattern emerges, in that a substantial proportion of the findings indicate either impaired attentional processing or diminished capacity for attentional processing in PD. Findings from the present research that relate to attention include the Study 1 findings for resting state alpha–1 and HRV, which suggest a reflect reduced capacity in PD for performance on tasks of attention/alertness (α–1, Klimesch, 1999) and sustained attention (HRV, Thayer *et al.* 2009). Whereas these Study 1 findings *predict* a reduced ability to modulate and sustain attention in a goal–directed manner in PD, several findings from Studies 2 and 3 provide evidence to that effect. These Study 2 findings were reduced P3 amplitude, longer and more variable RT, and fewer SCRs (trend) during the auditory oddball task.

In the context of the oddball task, each of these findings indicates reduced attention to task–relevant stimuli (P3 amplitude, Polich, 2007; RT, Riccio *et al.* 2002; SCRs, Öhman *et al.* 2000). Study 3 findings were increased errors of omission and longer RT during CPT. In the context of CPT performance errors of omission and RT prolongation signify lapses of attention (Riccio *et al.* 2002; Weissman *et al.* 2006). Taken together, these findings show a pervasive disturbance of attention in PD that is evident at multiple levels of function (CNS, ANS, behaviour, cognition), on multiple indices, and even in the absence of task–imposed information processing.

Empirically, there is a well–established association between attentional disturbances and PD (and other anxiety disorders). However, the research literature on attention in PD, which encompasses a variety of experimental paradigms that differentially tap attentional function (Cisler & Koster, 2010), has typically investigated attentional processes in relation to threat–related as opposed to neutral stimuli (Dupont *et al.* 2000). A recent meta–analysis of 172 studies sought to quantify the attentional bias towards threat stimuli in clinically anxious and high trait anxiety non–clinical subjects (Bar–Haim *et al.* 2007). In each study included in the meta–analysis verbal or pictorial threat–related stimuli that were congruent with the anxiety group were selected. For instance, studies of attentional bias in PD typically use verbal stimuli relating to concerns of physical (e.g., suffocate, palpitations), social (e.g., humiliation, faint) or mental catastrophe (e.g., insane) (Craske *et al.* 2009). The meta–analytic findings showed that a threat–related bias in attention was a robust phenomenon in anxious subjects, irrespective of clinical status or experimental paradigm, whereas by contrast non–anxious controls did not show a differential attentional allocation towards threatening relative to neutral stimuli. Notably, a positive bias for threat–related

compared to neutral stimuli was evident in PD (k = 7, N = 170, Cohen's d = 0.50) (Bar–Haim *et al.* 2007).

The present findings complement the research literature on attentional biases in PD by demonstrating attentional disturbances to threat–neutral stimuli and attention–related disturbances in the absence of task–imposed processing. The present findings also extend this literature, in which the outcome measures are typically behavioural, not psychophysiological. Attention serves the vital adaptive function of orienting the organism to important sources of information in the environment (Öhman *et al.* 2000). Measures of attention therefore index what is important to the individual. Considered together, these findings document a breakdown in the adaptive modulation of attention according to a spectrum of significance (Williams, 2006); in the anxiety disorders there is an excessive bias towards danger cues and a concomitant reduction in attention towards goal–relevant, but disorder–unrelated cues (Gordon *et al.* 2007).

According to cognitive accounts, attentional biases (and information processing biases more generally) play a central role in the aetiology and maintenance of PD and other anxiety disorders (e.g., Clark, 1986; Mathews, 1990; Beck & Clark, 1997; Mathews & MacLeod, 2002; McNally, 2002). The above meta–analytic finding that high trait anxiety individuals preferentially attend to threat stimuli (Bar–Haim *et al.* 2007) is consistent with attentional bias being a risk factor for developing an anxiety disorder, because high trait anxiety is itself a risk factor for developing an anxiety disorder (Barlow, 2002). However, controlled longitudinal studies in which attentional biases for threat were manipulated in individuals deemed at risk for the development of an

anxiety disorder are needed to determine if such biases constitute causal risk factors for the anxiety disorders.

Recently, a number of treatment interventions that explicitly aim to manipulate attention have been trialled in several anxiety disorders, including PD. In line with evidence of individual differences in the use of attentional strategies to cope with anxiety–provoking situations (Watts, 1989; Aver *et al.* 2003), different types of attentional manipulations have been implemented. Some attentional manipulations, for instance, aim to divert attention away from potentially anxiety–provoking cues, and towards neutral cues (e.g., Bar–Haim, 2010). Other strategies involve focussed attention to either enhance the processing of safety cues (e.g., Wells *et al.* 1997) or to enhance extinction in the context of exposure (e.g., Bitran *et al.* 2008). Although each of these strategies has shown promise, the effectiveness of these different strategies is often idiosyncratic (Mobini & Grant, 2007).

The are a number of ways in which psychophysiological indices of attention or attention capacity may be utilised to improve PD clinical outcomes, both in the context of attention modification interventions specifically, and in clinical settings more generally. Psychophysiological indices may probe covert aspects of attention that are not amenable to behavioural assessment (Thayer *et al.* 2000). For instance, ERP indices may precisely map the time course of attention–related processes and identify which information processing stages are disrupted (Reinvang, 1999). This information could aid in treatment response prediction. For instance, exposure–based treatments as opposed to verbally–mediated therapy are likely to be more efficacious for an individual who showed an automatic (*i.e.* pre–attentive) but not strategic (*i.e.* post–

attentive, conscious) bias for threat stimuli, and vice versa (Mobini & Grant, 2007). Alternatively, an individual who showed 'hypervigilant–avoidant' pattern of attention to threat, that is an automatic orienting to followed by subsequent disengagement (Mogg & Bradley, 1998), might benefit from an attention modification strategy that facilitates extinction.

Event–related potential indices that reflect aspects of attention could also be used to gauge treatment response. For instance, high trait anxiety students showed altered ERP responses to threat cues (angry faces) following an attention modification intervention (Eldar & Bar–Haim, 2010). Additionally, P3 amplitude to neutral stimuli such as oddball target stimuli, as previously discussed, has demonstrated utility in a range of clinical applications, including gauging treatment response (Polich, 1998; Pogarell *et al.* 2006). Finally, the multi–level findings of attentional disturbance in PD highlight the integrative nature of processes that support attention, and the fact that interventions aimed at any one or more of these levels of function may be efficacious in ameliorating attentional disturbances. For instance, manipulation of resting HRV has been demonstrated longitudinally to influence performance on cognitively demanding tasks of sustained attention and executive functions (review Thayer *et al.* 2009).

Attention is a complex construct (Riccio *et al.* 2002) and impairments in attentional processes are present in the majority of neuropsychiatric disorders (Maruff & Pantelis, 1999). Therefore it is imperative to accurately determine the nature of attentional disturbances in PD, or more accurately, a given individual with PD. For the above–stated reasons, the accurate assessment of attentional processes and their change over time in PD may best be accomplished with psychophysiological measures such as

ERPs. In addition to an attention–based explanation of the present findings, another useful heuristic that helps to link findings from different levels of function (*i.e.* CNS, ANS, behaviour, cognition, and affect) is diminished physiology flexibility.

9.4.2 Diminished Physiological Flexibility

The present psychophysiological findings, in common with many of the previously reported findings for PD, fit a theoretical model of diminished physiological flexibility (DPF). The observation that healthy physiology is typically expressed in high levels of adaptive variability has led to the notion of DPF as a marker of pathology (Thayer & Lane, 2000; Friedman, 2007): whereas early accounts of healthy physiology emphasised steady–state function (*i.e.* homeostasis), current views of self–regulation, including those founded on dynamic systems theory, emphasise the importance of adaptive responsiveness to changing environments (Friedman & Thayer, 1998a; Friedman, 2007).

In healthy individuals, the body responds rapidly to meet environmental stress, followed by a rapid return of physiological activity to baseline levels upon removal of the stressor (Hoehn–Saric, 2007; Mataix–Cols & Phillips, 2007). By contrast, in individuals with chronic as opposed to episodic anxiety disorders (e.g., PD, PTSD, GAD), there is less physiological differentiation of baseline activity and stress–related reactivity. In comparison to healthy subjects, individuals with chronic anxiety show reduced autonomic reactivity to minor everyday and laboratory stressors (Hoehn–Saric, 2007). By contrast, disorder–specific stressors may elicit exaggerated responses. Empirically, DPF in PD is observed as heightened ANS activity during baseline

conditions, reduced responses to minor stressors, and delayed habituation (Hoehn–Saric, 2007; Lang & McTeague, 2009).

Specific empirical findings for PD that are consistent with DPF include, importantly, reduced HRV (Friedman, 2007). Indices of HRV reflect parasympathetic modulation of the heart via the vagus nerve (Friedman & Thayer, 1998a; Friedman *et al.* 2002), which is able to rapidly effect phasic, directional changes in the HR in support of current metabolic, attentional or cognitive demands (Thayer & Lane, 2000). Phasic modulation of the HR, within the LF to HF spectral range occurs in the order of seconds, even at rest (Malik *et al.* 1996). As discussed, reduced HRV across development is found in a range of psychological and medical conditions associated with reduced self–regulatory capacity (reviews Porges, 1992; Beauchaine, 2001; Thayer & Brosschot, 2005; Friedman, 2007; Thayer *et al.* 2010). Delayed habituation is another common finding in PD that is consistent with DPF (Hoehn–Saric, 2007). Parente *et al.* (2005) examined ANS change in PD associated with anticipatory anxiety and fear using a public speaking challenge. They found that in symptomatic PD patients SCL was consistently high across the entire experimental session and prolonged recovery period, and was little affected by the challenge task, whereas in non–symptomatic patients treated with SSRIs and in healthy controls SCL increased in response to the challenge. By contrast, HR responses to public speaking challenge were normal in PD, but cortisol responses were absent (Petrowski *et al.* 2010), suggesting that attenuated physiologic reactivity does not necessarily occur uniformly across response systems. Interestingly, McTeague *et al.* (2009) found that individuals with more generalised social phobia showed startle response and ANS activity consistent with DPF, in comparison to patients with circumscribed social phobia and

healthy controls. During exposure to imagery of general (*i.e.* disorder–unrelated) threat, individuals with more generalised social phobia showed less startle response potentiation, and had higher resting state HR in comparison to the two other groups. Therefore, DPF may distinguish between anxiety disorder subtypes.

Many of the psychophysiological findings from Studies 1 and 2 are consistent with a DPF explanation. Study 1 resting state findings that are consistent with DPF include increased HR, reduced HRV (reduced HRV and increased LF:HF ratio), delayed SCL habituation, and fewer NS.SCRs in PD. Taken together these findings show increased tonic activity, in conjunction with reduced phasic modulation, within the cardiovascular and electrodermal systems. (Although, as previously discussed, an alternative explanation for the NS.SCR finding, relating to skin hydration, could not be ruled out.) Additionally, reduced alpha–1 spectral power and FAA, to the extent that they reflect increased baseline arousal, are consistent with DPF. Also, the Study 2 findings of increased N1 amplitude to task–irrelevant stimuli and decreased P3 amplitude to task–relevant stimuli in PD are broadly consistent with DPF in that they reflect poor discrimination of significant and irrelevant stimuli (Hoehn–Saric, 2007).

A number of different mechanisms for DPF have been proposed. The most prominent and comprehensive of these explains the phenomenon in neurophysiologic terms. According to Friedman, Thayer, and Lane (Friedman & Thayer, 1998a; b; Thayer & Lane, 2000; Friedman, 2007), who draw on Porges' work on vagal tone as an index of emotion and attention regulation (e.g., Porges, 1992), reduced autonomic flexibility in chronic anxiety is a consequence of reduced top–down vagally–mediated inhibition which, in turn, stems from hypoactivity within prefrontal CAN structures. With a

deficit in the parasympathetic branch of the ANS, autonomic balance is chronically weighted in the sympathetic direction, resulting in sustained arousal but impaired reactivity. This failure of inhibition, moreover, is proposed to account for inflexibility at multiple levels of function in PD, not just the ANS. Thus, reduced vagal inhibition is proposed to account for a diminished response range across the autonomic, perceptual, behavioural, cognitive and affective levels in PD (Friedman & Thayer, 1998a; Friedman, 2007).

Additionally, a psychological explanation of DPF has been proposed by Hoehn–Saric and colleagues, such that individuals with chronic anxiety are so preoccupied with their internal bodily and mental state that they pay little attention to stressors that are unrelated to their pathology (Hoehn–Saric & McLeod, 2000). According to Hoehn–Saric (2007), a psychological explanation for DPF represents an alternative to the aforementioned vagal explanation. However, the two explanations are not mutually exclusive, they simply represent different levels of explanation; evidence suggests that reduced vagal inhibition is associated with a failure to inhibit prepotent but inappropriate responses in attention (Thayer & Friedman, 2002). Similarly, a second putatively alternative explanation, in which DPF arises due to a CNS failure to discriminate threat and safety signals (Hoehn–Saric, 2007), may also be explained in terms of reduced prefrontal inhibition of CAN structures (Thayer *et al.* 2012).

9.5 Research Limitations

Several limitations of the research methodology may be identified. Firstly, it is unclear to what extent the present clinical sample is representative of the wider panic disordered population. Clinical participants were recruited from a range of clinical and

community settings, with view to enhancing the representativeness of the sample. In a similar vein, patients with comorbid anxiety disorders and/or unipolar mood disorders, if secondary to PD, were included in the study because extensive comorbidity is the norm in both clinical and community panic disordered populations (APA, 2000). Certainly, inspection of patients' clinical and demographic data did not reveal any obvious sample selection bias in terms of, for instance, gender ratio, age range or clinical measures. Nevertheless, the clinical sample was a sample of convenience that may differ from the wider panic disordered population in some important respects. In particular, given that individuals with severe agoraphobic avoidance typically avoid travelling to unfamiliar places (Perugi *et al.* 2007), it is conceivable that only a truncated range of the agoraphobic spectrum was represented in the present research; anecdotally, several potential research participants declined participation upon being informed that participation necessitated venturing outside of their homes.

A second possible limitation is that due to the strong covariance between measures of depression symptoms and PD severity (BDI and PDSS, respectively) it was not possible to investigate the effect of each, independent of the other, on psychophysiological and neuropsychological outcome measures. Panic disorder and depression overlap substantially, both at the diagnostically sub–threshold (*i.e.* symptom) and threshold (*i.e.* comorbidity) levels (Ball *et al.* 1995; Mineka *et al.* 1998; Kaufman & Charney, 2000; Krueger & Finger, 2001; Preisig *et al.* 2001; Kessler *et al.* 2005b). Studies in both clinical and community samples have found that comorbidity of panic and depression is the most prevalent form of anxiety–depression comorbidity, and lifetime and current MDD comorbidity in PD is considered a marker for more severe, persistent and disabling illness (Roy–Byrne *et al.* 2000). Additionally, research

in twins suggests that common genetic factors can account for the majority of PD and depression comorbidity (Mosing *et al.* 2009). Given this phenomenological and aetiological overlap, which suggests the presence of non–distinct clinical entities (Watson, 2005; Goldberg *et al.* 2009), it may be argued that it is neither feasible nor desirable to investigate the independent effect of PD and depression severity on psychophysiological or neuropsychological measures.

Another study limitation that must be noted is that patients were not specifically asked whether they experienced panic during the assessment. Although number of clinical participants indicated that they had found the psychophysiological assessment uncomfortable or somewhat anxiety–provoking, none indicated that they had experienced a panic attack. Whilst none of the patients appeared visibly distressed on the visual monitor, this does not rule out the occurrence of panic. Additionally, self–reported state anxiety (STAI) ratings were not obtained until end of the assessment. This delay occurred in order to minimize the differences between the assessment protocols of clinical and control subjects, as the STAI questionnaire was not part of the control subjects' assessment. Although there is typically a low concordance of self–reported clinical measures, such as state anxiety and psychophysiological indices (Wilhelm & Roth, 2001; Mauss *et al.* 2005), the delay in obtaining state anxiety ratings would have lessened the ability to detect a relationship between self–reported anxiety and psychophysiological measures.

Another potential limitation of the present research is that the assessment start time was not the same for all participants. Therefore, circadian effects could conceivably have affected the findings as there are significant circadian effects on many

psychophysiological and behavioural measures. For instance, psychophysiological measures for on which there are significant circadian influences include resting state EEG (Klimesch, 1999), ERPs (Polich & Kok, 1995), and HRV (Bonnemeier *et al.* 2003). However, as the assessment time varied non–systematically in patients versus controls, it is unlikely that the assessment time contributed significantly to the results. Moreover, published findings indicate that BRID data collected at different sites at pseudo–random times of day did not differ on any neuropsychological performance or electrophysiological measure according to site (Paul *et al.* 2007).

Additionally, the limitations of cross–sectional research must be noted. The mere association of a psychophysiological or other marker with a diagnostic group does not signify causation (Kraemer *et al.* 2001). Yet, even within cross–sectional research, multi–level multivariate analyses permit the identification and evaluation of patterns across different levels of function, which may reveal important information that would not be discernable in univariate analyses (Cacioppo *et al.* 2000b; Berntson *et al.* 2007). However, the identification of multi–level disorder markers is but one step in a sequence of steps that are needed to delineate multi–level risk and maintenance factors and their interplay (Stice *et al.* 2002; Zvolensky *et al.* 2006c).

Finally, the inherent problem of multiple comparisons in multivariate research must be noted. Several strategies were adopted in the present research in order to reduce the number of statistical analyses such as, for example, by aggregating variables and conducting repeated–measures design where possible and, moreover, effect sizes for inferential tests were reported. Nevertheless, the possibility of Type I error cannot be ruled out, increasing the need for independent replication of the findings.

9.6 Future Directions

This section identifies several research strategies which, if implemented in future PD research, are likely to yield useful information for PD theory and clinical practice.

Firstly, an important step for future PD research, beyond documenting the co–occurrence of multi–level disorder markers, will be to determine the ways in which different disorder markers interact. Theoretically, a number of specific types of interactions between different disorder markers – some of which have a role in the disorder's aetiology and/or maintenance, and others that do not – are possible (Kraemer *et al.* 2001). Determining the nature of these interactions through evaluation of mediating and moderating processes (Baron & Kenny, 1986) has both theoretical and practical relevance. For instance, determining the type of interactions between multi–level disorder markers, especially risk factors, is an important step in developing multi–level aetiological models (Kendler, 2008). Determining the nature of these interactions also aids in the classification of disorders markers. As previously discussed, this is an important goal for clinical research because different types of disorder markers (e.g., risk *vs.* maintenance factors, state *vs.* trait markers), may differentially benefit clinical practice.

A second type of research that warrants investigation in PD is the within–subject association of CNS and ANS measures. Multi–level integrative studies have a capacity for such within–subject analyses that is lacking less–integrative studies. On theoretical grounds it is expected that in healthy subject the anatomically distributed network of CNS and ANS structures that support emotion and attention are optimally loosely coupled in order to support flexible and responsive engagement with the environment

(Friedman, 2007). By contrast, it is expected that in generalised anxiety disorders such as PD, which are characterised by inappropriate threat responses and deficient inhibition, the CNS and ANS elements of this network are rigidly coupled (Friedman, 2007). However, in psychophysiological research CNS and ANS measures are rarely recorded together, and even when they are, statistical tests to directly test and quantify the correspondence of CNS and ANS measures are infrequently performed (Hagemann *et al.* 2003). Therefore, empirical evaluation of the relative strength of CNS and ANS coherence in panic disordered compared to unaffected controls is warranted.

Another important line of enquiry for future PD research is the identification of multi–level markers that cut across diagnostic boundaries. This is an important area for investigation because it is often claimed that the current categorical diagnostic system in general, and PD diagnostic boundaries in particular, is inherently imprecise (Smoller & Tsuang, 1998; Charney, 2003; Bearden & Freimer, 2006; Begleiter & Porjesz, 2006; Andrews *et al.* 2008; Brandão *et al.* 2008; Linden & Fallgatter, 2009; Domschke & Dannlowski, 2010). The current diagnostic system has been criticised, especially in the lead–up to the publication of DSM, because its diagnostic boundaries are based on the apparent as opposed to actual similarity of different clinical entities (e.g., Gottesman & Gould, 2003; Watson, 2005; Hyman, 2007; Linden, 2008; Malhi & Lagopolous, 2008; Goldberg *et al.* 2009; Kendler *et al.* 2011). Within–diagnosis heterogeneity and comorbidity, which are the norm across all DSM diagnoses (Widiger & Samuel, 2005), and particularly the mood and anxiety disorders (Mineka *et al.* 1998; Krueger & Finger, 2001; Wittchen *et al.* 2003; Craske *et al.* 2009; Andrews *et al.* 2008), are often cited as evidence that the current diagnostic system

lacks precision (e.g., Widiger & Clark, 2000; Watson, 2003; Maj, 2005; Watson, 2005; Widiger & Samuel, 2005; Hyman, 2007; Linden & Fallgatter, 2009). Within–diagnosis heterogeneity in PD is apparent at many levels of analysis, including at the levels of clinical expression, disorder course, response to treatment and to laboratory challenge procedures, neurobiology, neuropsychology, and so on (Coplan & Lydiard, 1998; Charney, 2003; Meuret *et al.* 2006; Onur *et al.* 2006; Rucci *et al.* 2009; Batelaan *et al.* 2010b; Domschke & Dannlowski, 2010).

Additionally, various data demonstrate phenomenological and aetiological continuity across the anxiety and mood disorders, and highlight the imprecision of current criteria–based diagnoses. At the phenomenological level, for instance, many of the symptoms of fear, anxiety and negative affect, including worry, rumination, avoidance, autonomic arousal and panic attacks are common to different anxiety disorders and depression (Brown *et al.* 1998; Mineka *et al.* 1998; Watson, 2005; Craske *et al.* 2009; Goldberg *et al.* 2009). And at the aetiological level, results of multivariate genetic analyses suggest a substantial degree of shared aetiology between different anxiety disorders and MDD (e.g., Scherrer *et al.* 2000; Kendler *et al.* 2003; Hettema *et al.* 2005; Hettema *et al.* 2006; Mosing *et al.* 2009; Tambs *et al.* 2009; Kendler *et al.* 2011). Commonalities (and differences) are also observed across the anxiety disorders in terms of behavioural, psychophysiological, and cognitive responses to threat–stimuli (reviews Lissek *et al.* 2005; Craske *et al.* 2009). For instance, an attentional bias for disorder–relevant threat stimuli is a robust finding across the anxiety disorders (review Bar–Haim *et al.* 2007). This converging evidence of common aetiological mechanisms across the anxiety and mood disorders, suggest that future PD research using multivariate data–driven approaches may delineate the

underlying mechanisms that are common to, and those that are unique to, PD and its common comorbidities. Additionally, such an approach may help resolve some of the inconsistencies in the PD research literature finding, which may be accounted for, in part, because of the disorder's substantial heterogeneity (Charney, 2003).

In conclusion, a range of research strategies have been identified that have the potential to yield information of benefit for PD research and clinical practice. However, there is at present a 'translational gap' that applies to PD research and neuropsychiatric research more generally, and there is a need for increased translation of knowledge gained from PD research into clinically beneficial applications (Gordon *et al.* 2007; Clarke *et al.* 2010). Knowledge derived from PD research has the potential to support a range of clinical applications and thereby improve clinical outcomes for individuals with PD – notably in the areas of treatment response prediction, treatment response monitoring, the development of novel treatment interventions, the identification of risk factors for prevention interventions, and the clarification of treatment mechanisms of action (Zvolensky *et al.* 2006c). Additionally, there is a need for greater uptake of knowledge derived from PD research into extant theoretical models of PD which, in turn, may foster more refined theoretically–driven research.

Appendix A: Inclusion and Exclusion Criteria for Clinical Participants

INCLUSION CRITERIA

Male or female from 18 to 75 years.

Must meet criteria for a primary and current diagnosis of Panic Disorder with or without agoraphobia according to DSM–IV. Duration of Panic Disorder minimum 1 year. Diagnosis confirmed by MINI.

Co–morbid Axis 1 anxiety disorder or depression allowed only if secondary to Panic Disorder.

English as first language. Or, if English is a second language participant must have lived in an English speaking country for longer than 20 years and used English on a daily basis.

Normal vision (glasses ok), hearing and dexterity (hand movement).

EXCLUSION CRITERIA

Current use of psychotropic medication other than SSRI or SNRI anti–depressant. Use of benzodiazepine class drugs within previous 2 weeks.

A personal history, or a first–degree relative, diagnosed with Attention Deficit Hyper–activity Disorder, Schizophrenia or Bipolar Disorder.

A personal history of physical brain injury resulting in loss of consciousness lasting more than 10 minutes.

Personal history of stroke or neurological disorder such as Parkinson's Disease, Epilepsy, Alzheimer's or Multiple Sclerosis.

A serious medical condition related to the thyroid or heart, or a history of cancer.

A blood borne illness such as HIV, Hepatitis B or Hepatitis C.

A history of addiction to drugs such as Heroin, Cocaine or Amphetamines.

A history of heavy consumption of Marijuana or Alcohol. Current use of $\geq$8 standard drinks/day (males) and $\geq$4 standard drinks/day (females). Current use of Marijuana or other illicit drugs.

Appendix B: Information Flyer for Patients

THE UNIVERSITY OF ADELAIDE AUSTRALIA

Department of Psychiatry
Faculty of Health Sciences

PANIC DISORDER INTERNATIONAL BRAIN DATABASE
INFORMATION FOR PARTICIPANTS

Volunteers (18 – 75 years) with Panic Disorder are sought to participate in the world's first standardised international database of Panic Disorder.

Participants would be required to satisfy the study's inclusion and exclusion criteria before being permitted to participate in the study.

This study has the potential to greatly advance scientific knowledge about Panic Disorder and its treatment. One hypothesis to be tested using this database concerns the linkage between the physical manifestations of anxiety in Panic Disorder and the brain's processing of sensory information. A difficulty in screening or processing sensory information in highly complex sensory environments, such as supermarkets, may be involved in the perpetuation of the symptoms of Panic Disorder. Participation in this study will involve approximately 6 hours of commitment.

An honorarium payment of **$100** would be paid to participants who undergo the screening process and subsequently participate in this study.

Details regarding the assessment procedures are outlined below:

Initial Screening

Participant suitability will be determined by administration of a brief structured interview via telephone.

Web–based questionnaire

This questionnaire is designed to measure your general health and wellbeing. It would be done prior to your scheduled appointment.

Tests carried out at your scheduled appointment

1) Psychophysiological testing: This assessment is non–invasive and involves the placing of recording devices on the surface of the scalp. Measures of reaction time, respiration, heart rate, muscular activity and skin conductance will also be taken. Recordings are taken while you complete a series of tasks that are administered via a computer screen.

2) The NEO FFI test: This is a short personality test that will be administered during preparation for the psychophysiological assessment referred to above.

3) Psychometric testing: These tests are designed to assess motor, language, attention, memory and planning skills. They involve you answering a number of questions either via a microphone or via a computer touch–screen. All instructions are administered via headphones.

4) Cheek swab: You will be asked for a cheek swab to measure DNA. Your consent to provide a DNA sample is entirely voluntary and is independent of your decision to participate in the study's other tests.

Panic and anxiety questionnaires and panic frequency diary

These instruments would measure frequency and severity of your panic attacks, type of panic symptoms and degree of impairment. You would complete some of them during, and others following your scheduled appointment at the laboratory.

Diagnostic structured interview

The CIDI–Auto test is a computerised diagnostic interview that will be administered at a scheduled time following the above tests.

Ethics Approval

This study has been approved by the Central Northern Adelaide Health Service Ethics of Human Research Committee of the Queen Elizabeth Hospital and the Flinders Clinical Research Ethics Committee of Flinders Medical Centre.

If you are interested in participating in this study or have any queries, please do not hesitate to contact either; Vikki Wise on 0405 313473 (mobile), 8201 3088 (work), or via email vikki.wise@adelaide.edu.au ; or Prof. Alexander McFarlane on 8303 5200, email alexander.mcfarlane@adelaide.edu.au .

Appendix C: Inclusion and Exclusion Criteria for Control Participants

INCLUSION CRITERIA

Male or female, minimum age 6 years.*

English as first language. Or, if English is a second language participant must have lived in an English speaking country for longer than 20 years and used English on a daily basis.

Normal vision (glasses ok), hearing and dexterity (hand movement).

EXCLUSION CRITERIA

A personal history, or a first-degree relative, diagnosed with Attention Deficit Hyper-activity Disorder, Schizophrenia or Bipolar Disorder.

A personal history of physical brain injury resulting in loss of consciousness lasting more than 10 minutes.

Personal history of stroke or neurological disorder such as Parkinson's Disease, Epilepsy, Alzheimer's or Multiple Sclerosis.

A serious medical condition related to the thyroid or heart, or a history of cancer.

A blood borne illness such as HIV, Hepatitis B or Hepatitis C.

A history of addiction to drugs such as Heroin, Cocaine or Amphetamines.

A history of heavy consumption of Marijuana or Alcohol. Current use of $\geq$8 standard drinks/day (males) and $\geq$4 standard drinks/day (females). Current use of Marijuana or other illicit drugs.

* *Note.* Control participants in the present study were aged 18 years or older

Appendix D: Patient Information Sheet

FLINDERS UNIVERSITY
ADELAIDE • AUSTRALIA

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PATIENT INFORMATION SHEET:

PANIC DISORDER INTERNATIONAL BRAIN DATABASE

BACKGROUND

You are invited to participate in a research project investigating factors associated with panic disorder. However, before you decide whether or not you wish to participate, we need to be sure that you understand

why we are doing it, and
what it would involve if you agree.

Please read the following information carefully and be sure to ask any questions you have.

The person conducting the research will be happy to discuss it with you and answer any questions that you may have.

You are also free to discuss it with outsiders if you wish (i.e. family, friends and/or your doctor).

You do not have to make an immediate decision and your participation is purely voluntary. If you agree to participate, you may change your mind and withdraw at any stage without affecting your present or future management and care from your doctor.

PURPOSE OF THE STUDY

This research is part of a collaboration between researchers at Flinders University, the University of Adelaide and the Brain Resource Company Ltd. (BRC), which is a biotechnology company. BRC comprises a global consortium of scientists and clinicians whose aim is to bring advances in human brain science from the laboratory into the clinic. All research carried out by BRC is approved by a Scientific Advisory Committee composed of scientists of the highest calibre and the results are published in high quality international journals.

The aim of the research is to develop a standardized international database of information about brain function for scientific and medical purposes. This involves collection of standard information from people who do not have brain function disorders and comparing it with similar information obtained from those who do, in order to assist the diagnosis and treatment of these conditions. The particular condition that will be investigated in this study is panic disorder. It is anticipated that data from up to 100 participants will be collected in Adelaide. The research will form part of the PhD project of Ms Vikki Wise, who is a postgraduate student working under the supervision of Professor Alexander McFarlane at the University of Adelaide and Associate Professor Richard Clark at Flinders University.

PROCEDURES

Participation in this study will involve approximately 6 hours of your time. The tests listed below will be performed at either one of the two testing facilities of the Cognitive Neuroscience Laboratory – one at Flinders University, and the other at Belair Road, Kingswood Adelaide. The follow-up appointment for the administration of the CIDI-Auto structured interview would occur in a room at the University of Adelaide's Department of Psychiatry at Royal Adelaide Hospital.

Before deciding whether or not to participate in this study, it is important that you understand conditions associated with the tests to be performed.

On the day of the laboratory tests, your hair must be clean and completely dry. You will not be able to use **hair conditioner, gel, hair cream, hair spray, or foam mousse. These substances can make brainwave recordings difficult.**

You will not be able to use any **makeup** and will need to wear **comfortable clothing**, especially a top with a loose fitting neck.

No alcohol, marijuana or recreational drugs can be consumed within 6 hours before brainwave recording. Regular smokers should try to **reduce consumption of tobacco and caffeine (including cola and chocolate)** and not smoke or consume caffeine within 2 hours before brainwave recording. **Tobacco smoking is not allowed during the tests**.

Co-operation on these matters is vital, so if you feel you cannot comply, you should not agree to participate.

The tests to be undertaken include:

Psychophysiological testing: This assessment is completely non-invasive and entails measuring and recording brainwaves (or electroencephalographs - EEG). A recording cap will be placed on your head and small electrical currents from the surface of your scalp will be measured while you perform a series of simple tasks that are administered via a computer screen. Measures of your reaction time, breathing and heart rates, muscular activity and skin conductance will also be taken.

The NEO FFI test: This is a short personality questionnaire that will be administered while you are preparing for the psychophysiological assessment referred to above.

Psychometric testing: These tests are designed to assess motor, language, attention, memory and planning skills. You will be asked to answer a number of questions either via a microphone or via a computer touch-screen. All instructions are administered via headphones.

Cheek swab: You will be asked for a cheek swab to collect saliva to obtain a DNA sample. DNA will be collected because there is increasing evidence that panic disorder is related to a person's genetic makeup. These results will be entered into the database and used to see whether panic disorder is related to particular genetic patterns.

The cheek swab will be obtained by rubbing a sterile cotton bud for 20 seconds inside your mouth between the cheek and gum.

All details that personally identify you will be removed from the sample, replaced by code number and stored under secure conditions, so that only the researchers directly involved with the study will have access to them. Genetic information about members of your family is not required for the research and results of your genetic analysis will not be available to your family members. The research therefore does not have the potential to detect non-paternity or non-maternity.

Because work on the genetic basis of panic disorder is still preliminary, results of your genetic analysis will not diagnose any specific condition or reveal conclusive connections with your panic disorder in the foreseeable future. For this reason you will not be given the results of your genetic testing.

Your DNA sample, identified only by a code, will be stored securely for 7 years, in accordance with standard research requirements. After that time it will be destroyed. It will NOT be made available for any other research without first obtaining your specific consent.

The genetic testing is entirely voluntary and you are free to not provide the check swab without giving reasons, while still participating in other aspects of the study.

Panic and anxiety questionnaires and panic frequency diary: These will record the frequency and severity of your panic attacks, the types of panic symptoms you experience and the degree to which they impair your life. You would complete them after the tests described above.

CIDI-Auto diagnostic structured interview: This is a computerised interview that will be administered approximately two weeks after you have completed the above tests.

WHAT ARE THE DISCOMFORTS, RISKS AND SIDE EFFECTS?

All procedures used in this study are completely non-invasive. However, should you experience any distress or discomfort during the testing procedure you may wish to discontinue your assessment. You would then be advised to discuss the matter with your referring clinician.

WHAT ARE THE PERSONAL BENEFITS OF PARTICIPATING?

No direct benefits to participants are anticipated, although the use of this database may ultimately yield more effective treatments for Panic Disorder.

CONFIDENTIALITY

The information obtained from involvement in this study will be treated in the strictest confidence and you will not be individually identifiable in any resulting publications or reports. You are entirely free to discontinue participation at any time or to decline to answer particular questions. All your data will be transmitted to the central analysis facility of the Brain Resource Company Ltd. for inclusion in an international database, which will be made available for scientific and clinical purposes. All details that personally identify you will be removed from the data and replaced by a unique ID code before being used for any purpose and before inclusion in the database.

Any details identifying you will be treated confidentially and stored separately and independently of the database. As stated above, your DNA results will not diagnose any condition. Your sample will not be made available for testing for any purpose at any time in the future without your specific consent, and no identifiable genetic information will be available to any 3rd party (including family members).

WITHDRAWAL OF CONSENT / INVOLVEMENT IN STUDY

You may withdraw your consent at any stage, without affecting your rights or the responsibilities of the investigator in any respect. You have the right to withdraw from participating in the study at any time. If you give your consent to the collection and use of your DNA and then later change your mind, the sample and any information derived from it will be destroyed.

IS THERE ANY PAYMENT FOR PARTICIPATING?

To compensate you for the amount of time you will spend taking the tests, as well as any travel expenses you incur, you will be reimbursed **$100**. A voucher enabling you to park free of charge will be provided if you undertake the tests at Flinders University. Parking at the Belair Road facility is free. Funding is not available to provide further payment for other transport costs.

FUNDING OF STUDY

The researchers are being paid by The Brain Resource Company Ltd to cover the salary costs of staff employed for this study. Any surplus funds contribute to research in the Researcher's Unit.

WHAT ARE MY RIGHTS?

If you suffer injury by participating in this research you are not automatically entitled to compensation and may have to take legal action in order to receive payment or compensation for such injury. By participating in this study, your normal legal rights under common law will not be affected.

IF YOU REQUIRE FURTHER INFORMATION ABOUT THE STUDY

Should you require further details about the project, either before, during or after the study, you may contact Professor Alexander McFarlane, at the University of Adelaide on 8303 5200, or Associate Professor Richard Clark at Flinders University on 8201 2425.

WHAT IF I HAVE A QUESTION ABOUT THE STUDY?

This study has been reviewed by the Flinders Clinical Research Ethics Committee. Should you wish to discuss the project with someone not directly involved, in particular in relation to matters concerning policies, your rights as a participant, or if you wish to make a confidential complaint, you may contact the Administrative Officer - Research, Ms. Carol Hakof, on 8204 4507.

Appendix E: Participant Information Sheet: Controls

FLINDERS UNIVERSITY
ADELAIDE • AUSTRALIA

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PARTICIPANT INFORMATION SHEET:

INTERNATIONAL BRAIN DATABASE

BACKGROUND

You are invited to participate in a research project investigating factors associated with brain function. However, before you decide whether or not you wish to participate, we need to be sure that you understand

why we are doing it, and
what it would involve if you agree.

Please read the following information carefully and be sure to ask any questions you have. Professor Richard Clark, Chief Investigator, will be happy to discuss it with you and answer any questions that you may have. You are also free to discuss it with family, friends and/or your doctor.

You do not have to make an immediate decision and your participation is purely voluntary. If you agree to participate, you may change your mind and withdraw at any stage without affecting your present or future management or care from your doctor.

PURPOSE OF THE STUDY

This research is part of a collaboration between Professor Richard Clark at Flinders University and the Brain Resource Company Ltd. (BRC), which is a biotechnology company.

The BRC is a commercial enterprise which undertakes research. It is comprised of a global consortium of scientists and clinicians whose aim is to bring advances in human brain science from the laboratory into the clinic. Data collected from such scientists and clinicians in the USA, Europe and Australia, such as in this study, are collected in an identical fashion from individual volunteers and stored in the BRC's Database. All data stored in the database is de-linked from the identity of individuals from whom it is collected. The database is also made available on a commercial basis ie rights to access the information stored in the database are sold to interested users, including pharmaceutical companies. The identity of

contributors to the database does not form part of the database. The BRC's standardised methodology brings together 33 dimensions of brain function. The Database contains data from healthy males and females ranging in age from 5 to 86, and individuals clinically diagnosed with a particular disorder before treatment and after treatment. This data, plus our analysis tools, identifies what is a common response, and how a patient in a Pharmaceutical trial or a Clinical Patient differs from the signature characteristics.

The aim of our research is to increase the number of datasets in the BRC's Database of information so that this can be used for scientific and medical purposes. This involves collection of standard information from people who do not have brain function disorders and comparing it with similar information obtained from those who do, in order to assist the diagnosis and treatment of these conditions.

PROCEDURES

Participation in this study will involve approximately 3-4 hours of your time. The tests listed below will be performed at either the Cognitive Neuroscience Laboratory, Flinders University or the rooms of the Rehabilitation and Performance Health Clinic located at 63 Belair Rd., Kingswood. Before deciding whether or not to participate in this study, it is important that you understand the conditions associated with the tests to be performed.

RECORDING OF DEMOGRAPHIC DETAILS

A web-based questionnaire will be used to obtain your demographic details, a detailed medical history, psychological functioning and previous life experiences. This questionnaire will need to be completed during your appointment. You will need to access the internet and register on-line with an identification code that we will supply to you at your appointment. We will provide access to the internet via one of the laboratory computers or alternatively a hard copy of the questionnaire and a quiet room can be provided if you would prefer to complete a paper and pencil version of the questionnaire. This information is then entered into The Brain Resource Company's (BRC) database. Information contained in this database is confidential.

RECORDING OF BRAINWAVES

Psychophysiological testing: This assessment is completely non-invasive and entails measuring and recording brainwaves (or electroencephalographs –EEG). A recording cap will be placed on your head and small electrical currents from the surface of your scalp will be measured while you perform a series of simple tasks that are administered via a computer screen. Measures of your reaction time, breathing and heart rates, muscular activity and skin conductance will also be taken.

The NEO FFI test: This is a short personality test that will be administered during preparation for the psychophysiological testing referred to above.

Psychometric testing: These tests are designed to assess motor, language, attention, memory and planning skills. They involve you answering a number of

questions either via a microphone or via a touchscreen computer. All instructions are administered via headphones.

Cheek swab: You will be asked for a cheek swab to evaluate DNA. DNA will be collected because there is increasing evidence that some brain disorders are related to a person's genetic makeup. This DNA will be tested to look at what genes are present in the sample and how they function. It is possible to use these tests to identify inherited diseases. However, this will not be done as part of this research. These results will be entered into the database and used to see whether brain function is related to particular genetic patterns.

The cheek swab will be obtained by rubbing several sterile cotton buds for 20 seconds inside your mouth between the cheek and gum. All details that personally identify you will be removed from the cheek swab sample, replaced by a code number and stored under secure conditions, so that only the researchers directly involved with the study will have access to them. Genetic information about members of you family is not required for the research and results of the genetic analysis will not be available to your family members. The research therefore does not have the potential to detect non-paternity or non-maternity. Because work on the genetic basis of many of these disorders is still preliminary, results of your genetic analysis will not diagnose any specific condition or reveal conclusive connections with disorders in the foreseeable future. For this reason you will not be given the results of your genetic testing. Your DNA sample, identified only by code, will be stored securely for 7 years, in accordance with standard research requirements. After that time the sample will be destroyed, though the information extracted from the DNA sample will be retained in the database for the purposes of scientific research. Your sample will NOT be made available for any other research without first obtaining your specific consent.

The genetic testing is entirely voluntary and you are free to not provide the cheek swab without giving reasons, while still participating in other aspects of the study.

RECORDING OF MAGNETIC RESONANCE IMAGING (MRI)

If you choose to do so, brain function will also be measured through the use of MRI. This is a non-invasive procedure carried out on a separate day under the supervision of a staff radiologist. It involves lying still inside a magnet to allow images of brain tissue to be obtained. Whilst in the magnet, you will be offered either earplugs or headphones since the machine is very noisy for much of the time during the procedure. This noise is a normal part of the MRI scan and there is no need for you to worry or be concerned by it. You do not have to undertake an MRI if you do not wish to do so. This procedure is not advised for people who suffer discomfort in small, confined spaces. An honorarium payment of $50 will be made for completion of this aspect of the study

This assessment is conducted at Perrett Medical Imaging, Wakefield Hospital, 270 Wakefield St Adelaide.

If you have any queries about recording of EEG or MRI, please contact Associate Professor Richard Clark at the Cognitive Neuroscience Laboratory on 8201 2425.

PREPARATIONS

On the day of laboratory tests, your hair must be clean and completely dry. You

will not be able to use **hair conditioner, gel, hair cream, hair spray, or foam mousse. These substances can make brainwave recordings difficult**. You will not be able to use any **makeup** and will need to wear **comfortable clothing**, especially a top with a loose fitting neck. **No alcohol, marijuana or recreational drugs can be consumed** within 6 hours before brainwave recording. Regular smokers should try to **reduce consumption of tobacco and caffeine (including cola and chocolate)** and not smoke or consume caffeine within 2 hours before brainwave recording. **Tobacco smoking is not allowed during the tests.**

Co-operation on these matters is vital, so if you feel you cannot comply, you should not agree to participate.

WHAT ARE THE DISCOMFORTS, RISKS AND SIDE EFFECTS?

All procedures used in this study are completely non-invasive. However, should you experience any distress or discomfort during the testing procedures, you may wish to discontinue your assessment. As stated above, participating in the MRI scan involves lying still inside a magnet to allow images of brain tissue to be obtained. Some people may find this to be an uncomfortable experience and it is not suggested for people who find small, confined spaces uncomfortable.

WHAT ARE THE PERSONAL BENEFITS OF PARTICIPATING?

There is no direct benefit to you from taking part in the project. We hope that the use of this database may ultimately yield more effective treatments for various brain disorders.

CONFIDENTIALITY

The information obtained from involvement in this study will be treated in the strictest confidence and none of the participants in this study will be individually identifiable in any resulting publications or reports. You are entirely free to discontinue participation at any time or to decline to answer particular questions. All your data will be transmitted to the central analysis facility of the Brain Resource Company Ltd. for inclusion in an international database, which will be made available for scientific and clinical purposes. All details that personally identify you will be removed from the data and replaced by a unique ID code before being used for any purpose and before inclusion in the database. Your personal details remain with the local researchers and are not transferred to the Brain Database Company.

Any details identifying you will be treated with confidentiality and stored only at Flinders University, separately and independently of the database. The Brain Resource Company will not have access to your identifying details. As stated above, your DNA results will not diagnose any condition. Your sample will not be made available for testing for any other purpose at any time in the future without your specific consent, and no identifiable genetic information will be available to any 3rd party (including family members).

WITHDRAWAL OF CONSENT/INVOLVEMENT IN STUDY
You have the right to withdraw from participation in the study at any time. If you give your consent to the collection and use of your DNA and then later change your mind, the sample and any information derived from it will be destroyed.

IS THERE ANY PAYMENT FOR PARTICIPATING?
To compensate you for the amount of time you will spend taking he tests, as well as any travel expenses you incur, you will be reimbursed $100. Funding is not available to provide further payment for other transport costs.

FUNDING OF STUDY
The researchers are being paid by The Brain Resource Company Ltd. To cover the salary costs of staff employed for this study. Any surplus funds contribute to research in the Researcher's Unit.

WHAT ARE MY RIGHTS?
If you suffer injury by participating in this research you are not automatically entitled to compensation and may have to take legal action in order to receive payment or compensation for an alleged injury. By participating in this study, your normal legal rights will not be affected.

IF YOU REQUIRE FURTHER INFORMATON ABOUT THE STUDY
Should you require further details about the project, either before, during or after the study, you may contact

The Cognitive Neuroscience Laboratory, Flinders University on 8201 3088.
or
Professor Richard Clark at Flinders University on 8201 2425.

ETHICS APPROVAL & CONTACT PERSONS
This study has been reviewed by the Flinders Clinical Research Ethics Committee. Should you wish to discuss the project with someone not directly involved, in particular in relation to matters concerning policies, your rights as a participant, or if you wish to make a confidential complaint, you may contact the Administrative Officer – Research, Ms Carol Hakof, on 8204 4507

Appendix F: Informed Consent Declaration: Clinical Participants

FLINDERS UNIVERSITY
ADELAIDE • AUSTRALIA

School of Psychology
Faculty of Social Sciences
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Adelaide 5001 Australia
Telephone: (+61 8) 8201 3088
Facsimile: (+61 8) 8201 3877

PANIC DISORDER INTERNATIONAL BRAIN DATABASE

INFORMED CONSENT DECLARATION

I,.....hereby consent to my involvement in the research project explained above.

- I have read the information sheet, and I understand the reasons for this study.
- The research worker has explained to me how it will affect me.
- My questions have been answered to my satisfaction.
- My consent is given voluntarily.
- I understand that the purpose of this research project is to improve the quality of medical care, but my involvement may not be of benefit to me.
- I have been given the opportunity to have a member of family or a friend present while the project was explained to me.
- I authorise Prof. Alexander McFarlane, Associate Prof. Richard Clark, and/or authorised staff and students to carry out the following:
    - collect psychophysiological measures*
    - conduct psychological testing*
    - administer CIDI-Auto structured interview*
    - collect a cheek swab for DNA analysis*

  * delete where inapplicable or authorisation is not given
- I understand that data acquired from me will belong to the Brain Resource Company Ltd. and will form part of an international database for scientific and clinical purposes. I understand that scientists and clinicians may have access to this data and that the data may be utilised for clinical or commercial purposes. I further understand that any information that identifies me personally will not form part of the database and would be held in confidence on a separate secure server of the Brain Resource Company Ltd.
- I hereby permit BRC to use my data and confer ownership of this data to BRC. I also agree to the incorporation of my data in the international database and its use for any scientific or commercial purpose at any time.

Please sign here to indicate your informed consent for non-DNA procedures:

Signature.....Date.....

Please sign here to indicate your informed consent for the collection of DNA:

Signature.....Date.....

Should you require further details about this project so that your consent to participate is fully informed you may contact either: Vikki Wise on 8201 3088; Professor Alexander McFarlane, Head of the University of Adelaide Node of CMVH on 8303 5200**;** or Professor Richard Clark at the School of Psychology, Flinders University on 8201 2425.

Signature of witness.....Date.....

Printed name of witness.....

I have explained this study to the participant and am satisfied the participant fully understands the procedures involved.

Signature of information provider.....Date.....

Printed name of information provider……..

Appendix G: Informed Consent Declaration: Control Participants

FLINDERS UNIVERSITY OF SOUTH AUSTRALIA

CONSENT TO PARTICIPATION IN RESEARCH

I, _____ request and give consent to my

first or given names surname

involvement in the research project: International Brain Database Project

I acknowledge that the nature, purpose and contemplated effects of the research project, especially as far as they affect me and have been fully explained to my satisfaction by

_____ and my consent is given voluntarily

first or given names surname

I acknowledge that details of the following procedures have been explained to me, including indications of risks; any discomfort involved; anticipation of length of time and the frequency with which the procedure(s) will be performed:

☐ collect psychophysiological measures
☐ carry out magnetic resonance imaging
☐ to conduct psychological testing
☐ to collect a cheek swab for DNA analysis for the purposes set out in the participant information sheet

(tick the procedures which you agree to)

I understand that data acquired from me will belong to the Brain Resource Company Ltd. (BRC) and will form part of an international database for scientific and clinical purposes. I understand that scientists and clinicians may have access to this data and that the data may be utilised for clinical and commercial purposes. I further understand that any information that identifies me personally will not form part of the database.

I hereby permit BRC to use my data. I also agree to the incorporation of my data in the international database and its use for any scientific or commercial purpose at any time.

I have understood and am satisfied with the explanations that I have been given.

I have been provided with a written information sheet.

I understand that my involvement in this research project and/or the procedure(s) may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.

I acknowledge that I have been informed that should I receive an injury as a result of taking part in this study, I may need to start legal action to determine whether I should be paid.

I declare that I am over the age of 18 years.

Signature of research participant: _____ Date: _____

Signature of Witness: _____

Printed Name of Witness: _____

I, _____ have described to _____

the research project and the nature and effects of the procedure(s) involved. In my opinion he/she understands the explanation and has freely given his/her consent.

Signature: _____ Date: .....

Status in project:

LIST OF WEB–BASED QUESTIONNAIRES

Personal Details

Includes questions regarding date of birth, gender, country of birth, marital status, weight, height, occupation, highest level of education, number of years of education, and ethnicity.

Vision*

Asks whether subject has any vision impairment, or if they wear glasses or contact lenses.

Hearing*

Asks whether subject has difficulties with their hearing.

Mobility*

Asks whether subject has restricted movement or reduced manual dexterity.

Handedness

Subject is asked which hand they predominantly use for various tasks, as well as the handedness of their biological mother and father. Based on Annet (1970).

Mobile Phone Use*

Subject is asked whether they regularly use a mobile telephone, and if so, asks further questions concerning the frequency and duration of their mobile telephone calls.

Learning Difficulties / Dyslexia*

Asks whether subject has ever experienced learning difficulties or dyslexia.

Psychiatric History*

Subject is asked whether they have ever been diagnosed with a psychiatric disorder, or if there is a history of psychiatric disorders in their family.

Neurologic History*

Subject is asked whether they have ever been diagnosed with a neurological disorder, or if there is a history of neurological disorders in their family.

Sleep History*

Subject is asked whether they have ever experienced any of a given list of sleep symptoms in the previous month. Questions are based on Maislin *et al.* (1995).

Eating Habits*

Subject is asked whether they can't control what or how much they eat, or if they spend a great deal of time restricting what they eat.

Smoking History

Fagerström Test for Nicotine Dependence (Heatherton *et al.* 1991). This is the most frequently used instrument designed to assess nicotine tolerance and dependence.

Alcohol History*

Subject is asked whether they regularly consume alcohol.

Marijuana Use*

Subject is asked whether they regularly smoke marijuana.

Recreational Drugs*

Subject is asked whether they regularly take nonprescription/ recreational drugs (other than marijuana).

Relevant Surgery*

Subject is asked whether they have ever undergone surgery for a condition related to their brain, head, or spine.

Physical Trauma*

Subject is asked whether they have ever experienced physical trauma (physical injury) to their head and lost consciousness.

Somatic and Psychological Health Report (SHERE)

The SPHERE (Hickie *et al.* 2001) is used to screen for undiagnosed common psychiatric disorders. Used for post–

	recruitment screening of control subjects.
Depression Anxiety Stress Scales (DASS)	The shortened version of DASS (Lovibond & Lovibond, 1995a; b) consists of 21 questions which measure the core symptoms of depression, anxiety and stress (7 questions each).
Emotional Intelligence (EQ)	EQ comprises 33 questions, which are divided into the domains of self esteem, empathy and social relationships (Kemp *et al.* 2005).
Prescription Drugs*	Subject is asked whether they are currently taking any prescription medications.
Early Life Stress	Comprises 19 questions relating to childhood stress.
Traumatic Experience*	Comprises 11 questions relating to traumatic experiences. Questions are derived from Composite International Diagnostic Interview (CIDI, World Health Organization, 1997) PTSD section.

*Subjects who answer affirmatively to these questions go on to answer further questions in the Optional Section of Web–based Questionnaire.

Appendix I: Recent Medication Questionnaire

Participant 8-digit identification number: ___/___/___/___/___/___/___/___

Date: ___/___/___

The purpose of this questionnaire is to determine which medication/s you have taken recently to reduce your symptoms of anxiety or depression, or to help you sleep. As these drugs may affect the measures of brain electrical activity that we are recording, this information is important.

Please indicate if you have taken any such prescription medication within the past **two weeks**.

- Medication type 1

Name of medication:_____

Dates taken:_____

Dosage:_____

- Medication type 2

Name of medication:_____

Dates taken:_____

Dosage:_____

Please indicate if you have taken any such prescription medication in the period between **six months** and **two weeks** ago.

- Medication type 1

Name of medication:_____

Approximate dates taken: _____

Dosage: _____

- Medication type 2

Name of medication:_____

Approximate dates taken: _____

Dosage: _____

Appendix J: Panic Attack Diary

For the next **two weeks**, starting today _____/_____ please record the details of each panic attack or limited symptom attack you experience in the space provided below, as soon as practical following its occurrence. A **panic attack** is defined as a discrete period of intense fear or discomfort that has a sudden onset, and rapidly (usually within 10 minutes) builds to a peak. A panic attack is accompanied by at least 4 of the following 13 somatic or cognitive symptoms, whereas a **limited-symptom attack** (LSA) is defined by the presence of 1-3 of these symptoms*.

- ❑ Palpitations, racing or pounding heart
- ❑ Sweating
- ❑ Trembling or shaking
- ❑ Sensations of shortness of breath or smothering
- ❑ Feeling of choking
- ❑ Chest pain or discomfort
- ❑ Nausea or abdominal distress
- ❑ Feeling dizzy, unsteady, light-headed or faint
- ❑ Derealization (feelings of unreality) or depersonalization (being detached from self)
- ❑ Fear of losing control or going crazy
- ❑ Fear of dying
- ❑ Parasthesias (numbness or tingling sensations)
- ❑ Chills or hot flushes

Unexpected panic attacks (including LSA) occur in the absence of any identifiable situational trigger (i.e., they occur "out of the blue") whereas **expected** attacks occur either upon exposure to, or in anticipation of exposure to a particular situational trigger. **Situational triggers** may be external (eg entering a shopping centre) or internal (eg catastrophic cognitions about the significance of heart palpitations).

*These definitions are from DSM-IV, American Psychiatric Association (1994).

To be completed by researcher:

Participant's 8-digit personal ID number: _ _ _ _ _ _ _ _ _ _

PA in two-week period:
Unexpected _____
Expected _____
Total _____

LSA in two-week period:
Unexpected _____
Expected _____
Total _____

Today's date: ___/___/___

Time of attack: ________ ❑ AM ❑ PM Duration (min):__________

Type of attack: ❑ Expected ❑ Unexpected

Panic symptoms - check all that apply:

❑ Racing/pounding heart
❑ Sweating
❑ Trembling or shaking
❑ Shortness of breath
❑ Feeling of choking
❑ Chest pain/discomfort
❑ Nausea
❑ Dizziness/faintness
❑ Derealization or depersonalization
❑ Fear of losing control
❑ Fear of dying
❑ Parasthesias
❑ Chills or hot flushes

❑ Full panic attack ❑ Limited-symptom attack

Today's date: ___/___/___

Time of attack: ________ ❑ AM ❑ PM Duration (min):__________

Type of attack: ❑ Expected ❑ Unexpected

Panic symptoms - check all that apply:

❑ Racing/pounding heart
❑ Sweating
❑ Trembling or shaking
❑ Shortness of breath
❑ Feeling of choking
❑ Chest pain/discomfort
❑ Nausea
❑ Dizziness/faintness
❑ Derealization or depersonalization
❑ Fear of losing control
❑ Fear of dying
❑ Parasthesias
❑ Chills or hot flushes

❑ Full panic attack ❑ Limited-symptom attack

Today's date: ___/___/___

Time of attack: ________ ❑ AM ❑ PM Duration (min):__________

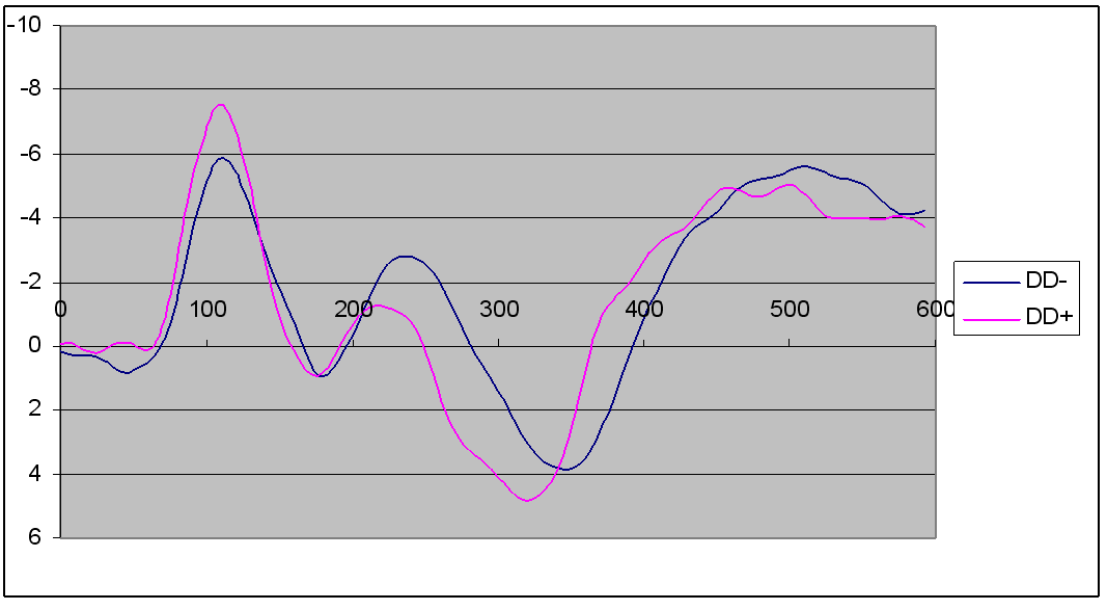
Type of attack: ❑ Expected ❑ Unexpected

Panic symptoms - check all that apply:

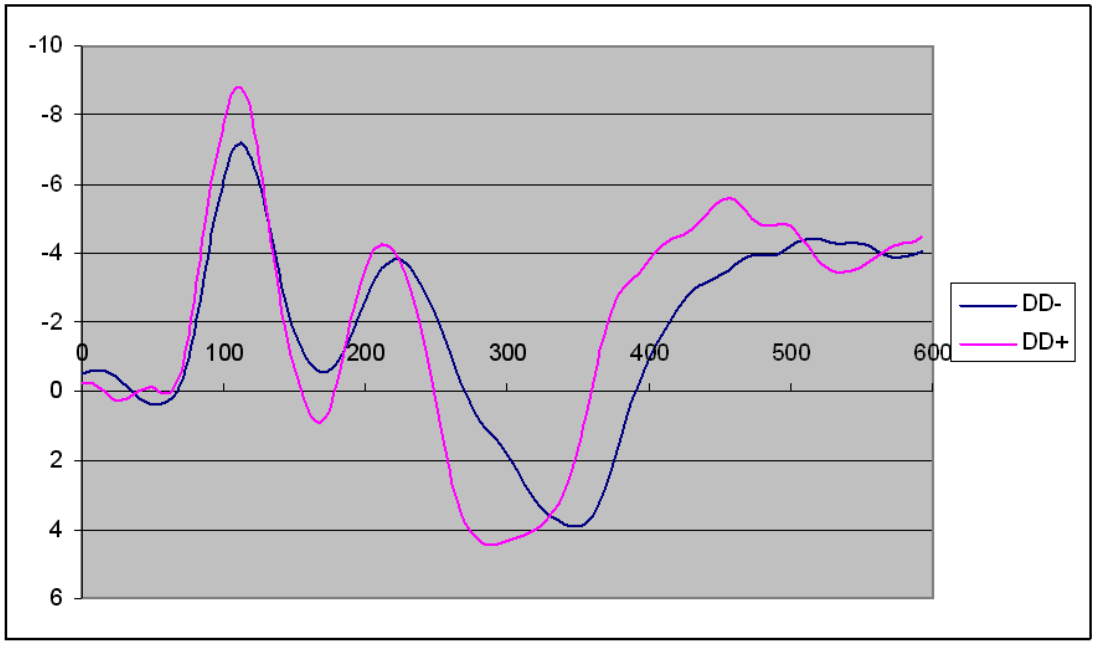
❑ Racing/pounding heart
❑ Sweating
❑ Trembling or shaking
❑ Shortness of breath
❑ Feeling of choking
❑ Chest pain/discomfort
❑ Nausea
❑ Dizziness/faintness
❑ Derealization or depersonalization
❑ Fear of losing control
❑ Fear of dying
❑ Parasthesias
❑ Chills or hot flushes

❑ Full panic attack ❑ Limited-symptom attack

Fz

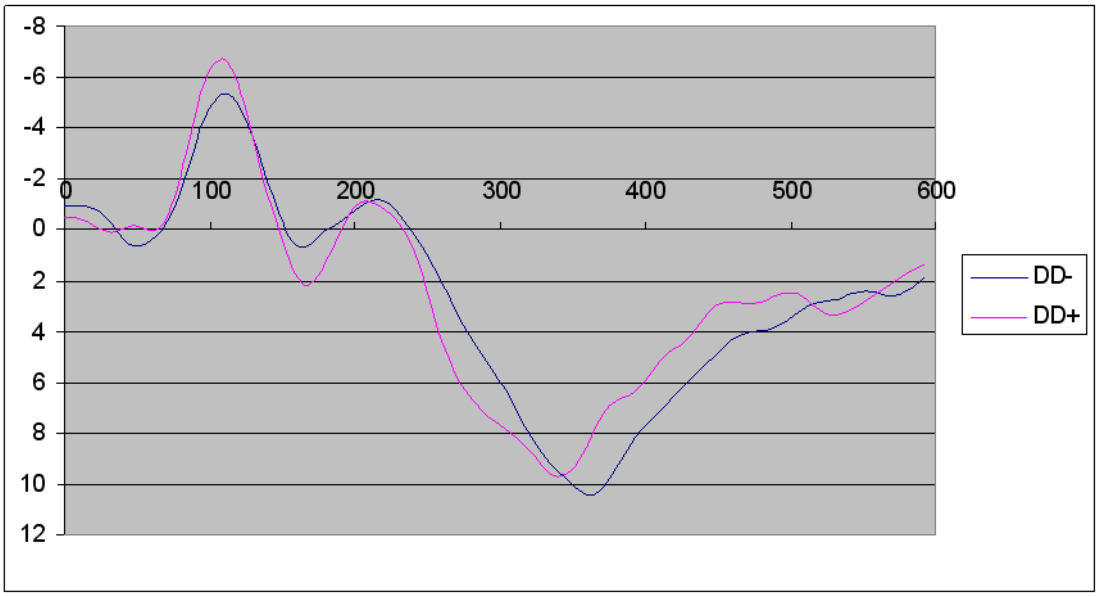


Cz



Grand averaged ERP waveforms to target tones for PD without depersonalisation (DD–; *n* = 18) and with frequent depersonalisation (DD+; *n* = 13) at sites Fz (top panel) and Cz (bottom panel). Amplitude values (μV) are on ordinate axes, latency post–stimulus (ms) is shown on abscissae. Figures show raw data without missing value replacement.

Pz



Grand averaged ERP waveforms to target tones for PD patients without depersonalisation (DD–; *n* = 18) and with frequent depersonalisation (DD+; *n* = 13) at site Pz. Amplitude values (µV) are on the ordinate axis, latency post–stimulus (ms) is shown on abscissa. Figure shows raw data without missing value replacement.

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