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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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.