

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.

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## DECLARATION

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

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List of Abbreviations

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

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

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