Is Goal Conflict Specific Rhythmicity a Biomarker for a Type of Clinical Anxiety?

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A thesis submitted in fulfilment of the degree of Masters of Science, at the University of Otago, Dunedin, New Zealand.

October 2017
I would firstly like to say a HUGE thank you to my supervisor, Professor Neil McNaughton. I am immensely grateful for all your encouragement, wisdom and advice over the past four years. I could not have asked for a better supervisor and would not have been able to complete this masters without your help and guidance. Thank you especially for your wise words and support during the recovery from my head injury - it made all the difference. Your humility and quirky sense of humour has made this journey a great one.

I would also like to thank Shabah Shadli for kindly collecting the patient data included in this thesis. I am also deeply grateful for your constant availability and willingness to answer my questions and help sort data problems. I have really appreciated your contribution to this piece of work.

Thank you also to Professor Paul Glue for being available for consultation and kindly teaching me and Lisa how to administer the DSM-5 MINI. Thank you to Lisa Labuschagne for administering the MINI interview to patient participants. Thank you also to Dr Richard Linscott for developing an online recruitment programme for patient participants during this study, and being willing to consult and discuss aspects of this research project over the past few years.

To my wonderful friends and family who have stood by me with unwavering support over the past few years – thank you. This thesis would not have been completed without you all in my life. Thank you for keeping me grounded when the pressures of balancing clinical training, research and life seemed slightly ridiculous. Thank you for laughing with me, eating my baking, and allowing me to be my crazy self. Thank you for seeing the best in me and constantly reminding me of this. I have learnt so much from all of you and love you heaps.

And lastly, but certainly not least, thank you to my God. No words can express my gratefulness for all you have given me during this adventure. This thesis is a testament to your faithfulness and kindness in my life. Thank you for writing with me and teaching me invaluable truth along the way.

_But he said to me, “My grace is sufficient for you; for my power is made perfect in weakness.”_
Abstract
Mental disorder diagnoses are currently based on arbitrary symptom checklists and lack the identification of underlying neurological dysfunction. As a result, clinicians assign diagnostic labels with low accuracy, leading to poor treatment selection and delivery and reduced quality of life for many individuals. Goal Conflict Specific Rhythmicity (GCSR), measured using a Stop Signal Task (SST), appears to be the first neural biomarker for diagnosing one process underlying clinical anxiety. While previous research has shown that GCSR is an ‘anxiolytic-sensitive’ biomarker, the present study aimed to take the first steps toward validating GCSR as a ‘clinical anxiety’ biomarker within a patient sample. According to McNaughton and Corr (2004)’s theory, it was predicted that patients diagnosed with Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) ‘anxiety disorders’ would on average show higher GCSR than control participants. In this study, the Electroencephalogram (EEG) of 86 participants recruited from Student Job Search (SJS) and 21 patients diagnosed with DSM-5 anxiety disorders was recorded while participants underwent a SST. GCSR values of SJS participants who obtained Spielberger’s Trait Anxiety (STAI-T) scores in both the clinically high and normal ranges were compared to GCSR obtained by anxiety disorder patients. Consistent with predictions, GCSR tended to be higher in individuals diagnosed with DSM-5 anxiety disorders compared to SJS controls with low STAI-T scores. GCSR also tended to increase in the positive direction as STAI-T scores increased, with anxious patients producing similar, if not higher, GCSR than SJS participants with STAI-T scores in the clinical range. Overall, these results provide preliminary support for GCSR as the first biological biomarker for one clinical anxiety process. Further research, including a larger sample of anxiety disorder patients and an appropriately matched healthy control group, is required to strengthen conclusions and progress the translation of this biomarker into clinical settings.
List of Figures

Figure 1.1. The 2D defence system proposed by Gray and McNaughton (2000), and updated by McNaughton and Corr (2004) ........................................................................................................................................9

Figure 1.2. Symptomatic comorbid anxiety with panic as a syndrome .................................................................12

Figure 1.3. Anxiety as a syndrome with symptomatic comorbid panic .................................................................14

Figure 2.1. A summary of the Stop Signal Task ................................................................................................29

Figure 2.2. General outline of the experimental procedure .................................................................................33

Figure 3.1. Goal Conflict Specific Rhythmicity (GCSR, log micro V²) calculated from F8 EEG of SJS participants as a function of increasing frequency (Hz) in Blocks 1, 2, and 3 of the SST ......................42

Figure 3.2. GCSR (log μV²) obtained from F8 as a function of increasing frequency (Hz) for high, medium, and low STAI-T scorers ...........................................................................................................45

Figure 3.3. Goal Conflict Specific Rhythmicity (GCSR; log μV²) obtained from F8 as a function of increasing frequency (Hz) for the above cut-off STAI-T group and the matched below cut-off STAI-T group ...........................................................................................................................................50

Figure 3.4. GCSR (log μV²) obtained from F8 as a function of increasing frequency (Hz) for Patient and Below Cut-off SJS participants ...............................................................................................................53

Figure 3.5. GCSR (log μV²) obtained from F8 as a function of increasing frequency (Hz) for Patient and Above Cut-off SJS participants ...............................................................................................................56

Figure 4.1. Behavioural measures calculated for ‘Below Cut-off’, ‘Above Cut-off’, and Patient participants in block 1,2 and 3 of the SST .................................................................................................................68

Figure 4.2. A diagrammatic prediction of the pattern of Stop Specific Power values obtained based on one hypothesised theoretical explanation for anomalous block 1 results ........................................................................70
List of Tables

Table 1.1. Relative effectiveness of drugs used to treat anxiety and depressive disorders ..................17

Table 3.1. Demographic information for groups of SJS participants separated based on STAI-T score ........................................................................................................................................43

Table 3.2. Demographic information for ‘Above Cut-off’ SJS, ‘Below Cut-off’ SJS and Patient participants ........................................................................................................................................46

Table 3.3. Behavioural information for the three groups of participants for all blocks of the SST ........47
List of Abbreviations

2D Two-dimensional
ANOVA Analysis of Variance
BIS Behavioural Inhibition System
BIS/BAS Behavioural Activation System/Behavioural Inhibition System
CRT Choice Reaction Time
DSM-5 Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG Electrocardiogram
EEG Electroencephalogram
EPQ-R Eysenck Personality Questionnaire-Revised
FFFS Fight, Flight, Freeze System
GAD Generalized Anxiety Disorder
GCSR Goal Conflict Specific Rhythmicity
GoRT Go Reaction Time
ICD-10 World Health Organisation International Classification of Diseases, 10th edition
MAOI Monoamine oxidase inhibitors
MINI DSM-5 Mini International Neuropsychiatric Interview
MRT Mean Reaction Time
OCD Obsessive Compulsive Disorder
PD Panic Disorder
PID-5 Personality Inventory for DSM-5
RDoC Research Domain Criteria
RSA Rhythmical Slow Activity
SAD Social Anxiety Disorder
SP Specific Phobia
SSD Stop Signal Delay
SSRI Selective serotonin Reuptake inhibitors
SSRT Stop Signal Reaction Time
SST Stop Signal Task
STAI-T Spielberger State-Trait Anxiety Inventory Y-form trait anxiety
Chapter 1: Introduction

Anxiety: a problem for the individual and society

Mental disorders are prevalent and extremely disabling. About half the people in New Zealand will meet diagnostic criteria for a mental disorder in their lifetime (Oakley-Browne, Wells, Scott, Kessler, & Üstün, 2008). Anxiety disorders are the most common type of mental disorder in New Zealand, and are experienced by 15% of the general population in a given 12-month period. Alarmingly, one in four New Zealanders will suffer from an anxiety disorder at least once in their lifetime (Oakley-Browne et al., 2008). Clearly, these often silent and hidden disorders are severely affecting the lives of many in our society.

Anxiety disorders create a large economic burden on the population as a consequence of psychiatric and psychological treatment costs, unemployment/sickness benefits, lost work days and poor physical health (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014; Marciniak, Lage, Landbloom, Dunayevich, & Bowman, 2004; Smit et al., 2006). Furthermore, they impose a heavy burden on the afflicted individuals and their families through lowered employment opportunities, impaired psychosocial functioning and compromised quality of life (Andrews, Henderson, & Hall, 2001; Mendlowicz & Stein, 2000). In a systematic review of data in 2010, 7% of all suicides globally were attributed to anxiety (Baxter et al., 2014). Epidemiological surveys administered by the World Health Organisation World Mental Health Survey Initiative have found that the disability in social and personal role functioning attributed to anxiety disorders is greater than the disability attributed to a range of physical disorders including arthritis, asthma, back/neck pain, cancer, chronic pain, diabetes, headaches, heart disease, high blood pressure, and stomach ulcers (Ormel et al., 2008). It is important we address this concerning problem facing the general population.
Current diagnoses and treatment of anxiety

Medical professionals and clinicians have significant difficulty accurately diagnosing anxiety disorders. In primary care settings, only one third of individuals suffering from anxiety are correctly identified (Lecrubier, 2000), and furthermore, only an estimated one to two thirds of patients receive the correct specific anxiety disorder diagnosis (Olariu et al., 2015). In particular, Generalized Anxiety Disorder (GAD) is the most difficult anxiety disorder to diagnose and has a recognition rate in primary care of only 33% (Brown, Di Nardo, Lehman, & Campbell, 2001; Weiller, Bisserbe, Maier, & Lecrubier, 1997). Krueger (1999) conducted a factor analysis of anxiety disorder symptom patterns and found significant overlap between anxiety syndromes. He concluded that focusing on the symptom manifestations of separate anxiety disorders may give rise to diagnostic problems, and advocated identification of ‘core psychopathological problems’ to diagnose anxiety subtypes instead.

Poor diagnostic accuracy has significant negative implications for treatment success and long-term patient prognosis. Patients must first be correctly identified before they can be successfully treated. Understanding the organic cause of a client’s presenting problems is fundamental to appropriately selecting and implementing individualised and effective treatments. Failure to do so can limit the success of treatments and long-term recovery. Currently, less than one third of primary care patients with anxiety disorders receive adequate psychotherapy or pharmacotherapy treatments that meet the criterion for quality care (Mendlowicz & Stein, 2014). While multiple factors may account for this finding, we cannot overlook the contribution of current diagnostic limitations. An improved system of diagnosis is thus required. This, in turn, will guide more accurate prediction of treatment response and the selection and delivery of effective interventions and quality care.
Limitations of current diagnostic systems

Currently, mental disorders in general and anxiety disorders in particular have no biological means of diagnosis (Insel et al., 2010). Instead, they are diagnosed using clinician-defined, symptom-based, criteria. One commonly used diagnostic system is the Diagnostic and Statistical Manual of Mental Disorders, currently in its 5th edition (DSM-5, American Psychiatric Association, 2013). According to the DSM-5, ‘Anxiety Disorders’ is a broad label that includes Generalised Anxiety Disorder (GAD), Specific Phobia (SP), Panic Disorder (PD), Social Anxiety Disorder (SAD), Agoraphobia, Selective Mutism, Separation Anxiety Disorder, Anxiety Disorder due to Another Medical Condition, Substance/Medication-induced Anxiety Disorder, and Other Specified, or Unspecified Anxiety Disorder. Thus, DSM-5 ‘Anxiety Disorders’ include features of both excessive fear and excessive anxiety, where ‘fear’ is defined as the emotional reaction to immediate/imminent threat or danger that is either real or perceived, and ‘anxiety’ is defined as the emotional reaction that accompanies the anticipation of future threat/danger (American Psychiatric Association, 2013). Obsessive Compulsive Disorder (OCD) was previously placed within the ‘Anxiety Disorder’ category in the third and fourth editions of the DSM, however is classified separately in the DSM-5 under ‘Obsessive-Compulsive and Related Disorders’. In comparison, another diagnostic system known as The World Health Organisation International Classification of Diseases, now in its 10th edition (ICD-10, World Health Organization) does distinguish phobias from anxieties, but groups anxieties with depression within “neurotic, stress-related, and somatoform” disorders. Across DSM-5 and ICD-10, there is currently no clear distinction between anxiety and fear. Although clinicians rely heavily on these diagnostic schemes, some major limitations have been raised with their use in both clinical and research areas (Insel, 2013; Insel et al., 2010; Van Praag, 1995)
General medicine repeatedly emphasises the need to understand (and treat) the root cause of pathology rather than merely observe and ‘place a Band-Aid’ on the superficial symptoms. Unfortunately, psychiatry fails to match the use of biological diagnostic tests and objective biomarkers that is widely observed in general medicine. Instead, the DSM-5 and ICD-10 assign diagnoses depending on the type of superficial symptoms a patient presents with (e.g. chest tightness, breathlessness) and the specific situations where these arise (e.g. social situations, enclosed spaces). Although these presenting symptoms may provide an indication of the underlying pathology, biological diagnostic tools are essential if we are to arrive at confident and accurate conclusions.

The medical phenomenon of ‘chest pain’ provides one clear illustrative example of the importance of identifying the organic cause of pathology. Even if we exclude psychiatric causes, symptoms of chest pain can reflect a variety of underlying dysfunctions including a cardiac arrest or a type of gastro-oesophageal disease (Fruergaard et al., 1996). If the symptom ‘chest pain’ was considered alone and used to develop a treatment protocol, identical treatments would be delivered to patients with potentially very distinct sources of pathology and often result in death. Physiological tests instead are used to confirm the exact underlying pathology and determine the type of treatment required. The diagnosis of a cardiac arrest is contingent upon observing an abnormal electrocardiogram and high levels of cardiac enzymes in a blood test. Conversely, the diagnosis of a gastro-oesophageal disease is contingent upon obtaining positive results on an oesophago-gastro duodenoscopy, pH monitoring in the oesophagus, and oesophageal manometry (Fruergaard et al., 1996). Once these unique underlying pathologies are identified, distinct treatments can be implemented.

In a similar way to general medicine, the diagnosis of psychological disorders should be based on underlying dysfunction rather than symptom presentations (Krueger, 1999). This is because, like chest pain, similar clinical anxiety symptoms may arise from a variety of
distinct pathologies and therefore require distinct treatments. Conversely, diverse symptom profiles may in fact be a consequence of the same underlying dysfunction and therefore require similar treatment approaches. An improved method of recognising the unique dysfunction underlying specific types of anxiety is critical to improving the current status of patient care and prognosis.

Further limitations associated with the clinical utility of the DSM-5 and ICD-10 have also been identified. Specifically, the boundaries distinguishing different DSM-5 and ICD-10 anxiety disorders do not accurately predict treatment response (Insel et al., 2010). For example, 45% of patients diagnosed with Panic Disorder (PD) do not respond to recommended first line treatments for PD (i.e. Selective Serotonin Reuptake Inhibitors, Marchesi, 2008; Otto, Tuby, Gould, McLean, & Pollack, 2001). Furthermore, the DSM-5 and the ICD-10 generally allow only a single primary diagnosis for each patient (i.e., they allow no co-morbid or secondary diagnosis). Although this simplifies the conceptualisation of a patient’s psychological difficulties, mental disorders are rarely pure in real life. More than 90% of patients with Generalised Anxiety Disorder (GAD) also present with at least one further co-morbid psychiatric condition (Kessler, Keller, & Wittchen, 2001). Among those diagnosed with GAD, 80% meet the diagnostic criteria for multiple axis 1 disorder diagnoses, which includes all psychological diagnoses except intellectual disabilities and personality disorders. Furthermore, 60% meet diagnostic criteria for multiple anxiety disorders (Reinhold, Mandos, Rickels, & Lohoff, 2011). Failure to account for co-morbidity and/or the presence of secondary disorders may result in limited treatment success leading to prolonged psychological disturbance.

There is thus a clear need to address these current limitations in mental disorder diagnosis. Fortunately, research has revealed potential for improvement. Analysis of epidemiological data has shown that 50% and 70% of the population burden caused by any anxiety disorder, and GAD respectively, could be avoided with better care (Andrews, Issakidis,
Furthermore, there is evidence that appropriately selected and implemented treatments can improve the quality of life and long-term outcomes of patients diagnosed with anxiety disorders (Mendlowicz & Stein, 2014).

A solution to the problem of current psychiatric diagnosis would be to have available neurally-grounded biomarkers for distinct mental disorders. In efforts to enhance diagnosis and subsequent treatment of mental disorders, the US National Institute of Mental Health has established the Research Domain Criteria (RDoC) project. In a recent report, they stated “Our expectation…is that identifying syndromes based on pathophysiology will eventually be able to improve outcomes” (Insel et al., 2010). Such an approach will require a unified and collaborative effort between clinicians and researchers. Nonetheless, it holds significant promise to alleviate at least some of the distress and burden currently caused by anxiety disorders.

**Preclinical Neuropsychology: A Potential Solution**

Preclinical neuropsychology research has the potential to address the limitations associated with the current diagnostic systems (i.e. DSM-5 and ICD-10) that assign a ‘loose’ anxiety label to a diverse array of superficial symptom presentations. Although confusion exists among clinicians surrounding the separation of ‘anxiety’ from ‘fear’, the pharmacological evidence appears clear cut. There are currently two types of drugs prescribed to treat DSM-5 Anxiety Disorders: anxiolytics and panicolytics. Anxiolytic drugs, as a class, reduce some instances of anxiety (e.g. GAD), however they have no common effect on phobia, panic, depression or obsession (McNaughton, 2002). In contrast, panicolytic drugs generally alleviate panic, depression and obsession, as well as anxiety (Seddon & Nutt, 2007). Thus, there is a division in the therapeutic actions of anxiolytics and panicolytics. This suggests that there is a separation in the neural systems underlying the syndromes classified by the general DSM-5 ‘Anxiety Disorder’ label. It appears that the neural systems underlying processes of
anxiety are pharmacologically distinct from those systems underlying panic, phobia, depression and obsession. The identification of neural activity specific to these separate underlying systems will aid in the development of distinct biological biomarkers for anxiety processes and fear processes, and give rise to a new biologically grounded definition of ‘anxiety’. As a result, the current clinician-defined diagnostic systems will be transformed into more rational and biologically grounded systems.

A Neuropsychological Theory of Anxiety and Fear Disorders

This pharmacological separation between anxiolytic and panicolytic drugs provided the framework for Gray and McNaughton (2000)'s initial two dimensional (2D) neuropsychological theory of defensive reactions and their disorders, later updated by McNaughton and Corr (2004). The fundamental axiom of this theory lies in the definition that anxiolytics exert their effects on a Behavioural Inhibition System (BIS; the ‘anxiety’ system) but not on a Fight, Flight, Freeze System (FFFS; the ‘fear’ system). Instead, the FFFS is sensitive to the therapeutic action of panicolytics.

There are two dimensions described by this neuropsychological theory; defensive direction and defensive distance. Defensive direction categorises ‘fear’ processes and ‘anxiety’ processes as dimensional opposites; defensive avoidance and defensive approach, respectively. This dimension is a categorical measure where anxiety describes reactions that function to enhance defensive approach. In contrast, fear describes reactions that function to enhance defensive avoidance. Defensive approach is regulated by the BIS, which is activated under situations of goal conflict (i.e. approach-avoidance, approach-approach, and avoidance-avoidance conflict). Usually, if one goal is activated, a signal is sent to the motor systems, which produce an appropriate motor response, and to the hippocampus, which ignores the signal. However, if two incompatible goals are activated simultaneously the hippocampus detects the goal conflict and activates the BIS. The BIS initially inhibits on-going behaviour
and replaces it with risk assessment behaviour. The outputs of the BIS aim to reduce goal conflict by increasing arousal and creating an attentional and negative emotional emphasis to identify the least aversive goal. In contrast, defensive avoidance and fear-related behaviours are regulated and controlled by the FFFS.

The other dimension of this theory, defensive distance, relates to the perceived immediacy of the threat (i.e. how much time is available to respond to the threat). Specific behaviours are hierarchically organised along this dimension, corresponding to the hierarchical organisation of underlying neural modules responsible for their control. For example, at the smallest defensive distance, activity occurs in the lowest neural level (the periaqueductal grey). When defensive distance is at its greatest, activity occurs in the highest neural level (the prefrontal cortex). Thus, defensive direction and defensive distance combine to determine the nature of behaviour produced at a specific point in time and space. Figure 1.1 presented below provides a visual summary of this 2D defence system.

Health, Morbidity, and Co-morbidity

An important prediction of this 2D neuropsychological theory is that hyper-activity arising within distinct modules will produce distinct symptoms, and hyper-reactivity will produce distinct syndromes. Any one of the modules or neural control areas can become active under a variety of different conditions. When modules become active, specific behaviours and autonomic changes are produced to enhance defensive avoidance or approach. Critically, these behavioural and autonomic outputs become maladaptive when the particular context does not involve a real threat, or the symptoms are produced in excessive proportion to the magnitude of the threat. For example, when a real threat is present (e.g. a grizzly bear), neural activity arising in the periaqueductal grey will produce normal adaptive behavioural and autonomic changes (i.e. increased cardiac output, increased breathing rate, normal panic). Conversely, in the presence of a weak threat hyper-reactivity of the periaqueductal grey will result in the same
Figure 1.1. The 2D defence system proposed by Gray and McNaughton (2000), and updated by McNaughton and Corr (2004). Brain areas are in capitals, normal function of an area is in lower case, closest current disorder is in italics. The dimension of defensive direction describes the parallel systems of defensive avoidance (i.e. FFFS) presented on the left, and defensive approach (i.e. BIS) presented on the right. The BIS is sensitive to all types of anxiolytics, whereas the FFFS is not sensitive to anxiolytics but sensitive to panicolytics. The BIS is suggested to control anxiety-related behaviours and the FFFS, fear-related behaviours. The BIS relies on brain activity in the theta range to carry out its operations. Theta reduction predicts anxiolytic action with no false positives or negatives recorded. The second dimension of defensive distance describes the hierarchical organisation of neural areas and their corresponding functional output in relation to the perceived immediacy of threat. Neural activity at each level of the hierarchy will produce specific behavioural and autonomic output. Hyper-activity of a module will lead to the production of symptoms, and hyper-reactivity will lead to the production of a syndrome. Extensive reciprocal connections between different modules within the parallel systems may account for the co-morbidity of two or more distinct disorders, secondary disorders, or the complex presentation of symptoms associated with a primary disorder. Neurotransmitters Noradrenaline (NA) and 5-hydroxytryptamine/Serotonin (5HT) regulate both the BIS and FFFS. Neurotransmitter receptor distribution and density differs between the two systems, thus accounting for different sensitivities of each system to therapeutic drugs. BDZ = benzodiazepine receptors; OCD = obsessive compulsive disorder; PAG = periaqueductal grey; PFC = Prefrontal cortex; RSA = Rhythmical Slow Activity. Figure taken from McNaughton (2014); Legend taken from McIntosh (2015).
behavioural and autonomic output - but now these are inappropriate and maladaptive for the particular context (clinical panic). Additionally, epileptiform discharge in the periaqueductal grey and other neural areas can result in the production of spontaneous panic when no danger or perception of threat is present at all (Dantendorfer, Amering, et al., 1995; Dantendorfer, Windhaber, & Maierhofer, 1995; Deakin, 1998).

An important prediction arises from the assumption that hyper-reactivity of distinct modules leads to distinct syndromes. This prediction is that characteristics of each distinct syndrome will be determined by the neural level that is hyper-reactive (i.e. dependent on defensive distance) and the defensive system of which the module is a part of (i.e. dependent on defensive direction). For example, in the presence of a weak threat (e.g. being introduced to an unfamiliar person), hyper-reactivity in the highest level of the defensive approach system (i.e. the dorsal stream of prefrontal cortex) may lead to the production of Social Anxiety Disorder (SAD). Alternatively, not in the presence of a weak threat but in anticipation of any threat (e.g. anticipation of germs), hyper-reactivity in the highest level of the defensive avoidance system may produce excessive hand washing consistent with Obsessive Compulsive Disorder (OCD). In sum, hyper-reactivity of the FFFS modules such as the ventro-lateral periaqueductal grey, medial hypothalamus, amygdala and frontal cortices may correspond, respectively, to a pure panic disorder, simple through complex phobic disorders (i.e. primary avoidance), and obsessive compulsive disorders. Similarly, hyper-reactivity of the BIS modules such as the medial hypothalamus, amygdala, hippocampus, frontal cortices and prefrontal cortices may represent, respectively, focused anxiety, generalized anxiety, agoraphobia and social anxiety. The differential distributions of serotonin 1A (5-HT$_{1A}$) receptors relative to serotonin (5HT) terminals in the parallel systems and at different module levels may explain differential therapeutic drug effects. For example, therapeutic effects of certain 5HT$_{1A}$ drugs (e.g. buspirone) are more restricted, alleviating cases of GAD but not panic
Seddon & Nutt, 2007). Alternatively, 5HT reuptake inhibitor drugs produce more effects on a very wide range of 5HT receptors, alleviating both anxiety and panic.

McNaughton and Corr (2004)'s 2D theory additionally provides an explanation for the occurrence of co-morbid disorders and the production of secondary disorders. Hyper-reactivity may separately arise in different modules and therefore produce distinct co-morbid syndromes with unique underlying aetiologies. In contrast, neural activity arising in one specific module can directly, or indirectly, influence the neural activity in a different module through the presence of bidirectional reciprocal connections between modules of the parallel systems. Consequently, secondary symptoms and syndromes may arise in a normal module due to abnormal inputs from a hyper-reactive syndromal module. Over time, processes of learning and environmental feedback can reinforce and strengthen connections between modules accounting for the development of a secondary disorder. For example, Agoraphobia (i.e. anxiety) may develop in people who suffer from panic, via conditioning of the BIS, particularly if they are neurotic (Andrews, Stewart, Morris-Yates, Holt, & Henderson, 1990).

This development from primary morbidity in the FFFS to additional BIS-activation symptoms is outlined in Figure 1.2 (McNaughton & Corr, 2016). Pure physiological/neurological panic first arises from pathological activity or reactivity in the PAG. This may cause neural activation in other modules of the FFFS, such as the amygdala, resulting in increased arousal. An individual may then come to associate the initial panic attack with the situation it originally occurred in (e.g. a crowded space, social situation). This conditioned anxiety develops as a result of activation of the BIS via reciprocal connections with the FFFS. Conditioned anxiety further increases the individual’s arousal and, consequently, may trigger subsequent panic attacks in mildly threatening situations, thus creating a vicious negative cycle. To cope with conditioned anxiety, the individual may develop a pattern of maladaptive avoidance behaviour to situations where panic attacks have occurred and as a result, present in
Figure 1.2. Symptomatic comorbid anxiety with panic as a syndrome. Spontaneous activity (or hyper-reactivity) of the periaqueductal grey arises in lower levels of the fight-flight-freeze system (FFFS; bottom left). This generates pathological panic attacks. Active avoidance and arousal are increased through ascending neural connections of the FFFS (solid outline filled gray arrows, width indicates degree of activation, simple black double headed arrows show available connections). The occurrence of a panic attack in a distinctive and threatening environmental situation may occur, and result in the learning of anticipatory anxiety, particularly in neurotic individuals (dashed outline filled gray arrow). This conditioning is mediated by the hippocampus and amygdala, and the normal spread of neural activity through the behavioural inhibition system (BIS). The overall result is abnormal panic producing normal levels of fear and anxiety given the level of perceived threat generated by the panic. This implies that a treatment such as Cognitive Behavioural Therapy may improve anxiety, and some panic, while leaving a primary, neurological, incidence of panic intact. Figure taken and legend adapted from McNaughton and Corr (2016).

the clinic with a diagnosis of Agoraphobia with panic. Cognitive Behavioural Therapy (CBT) targeting avoidance behaviour and catastrophic misinterpretations of panic symptoms will likely break the negative cycle that has developed, and consequently improve functioning.
However, the primary morbidity (i.e. hyper-reactivity of the PAG) will remain and continue to give rise to a low level of residual panic attacks (McNaughton & Corr, 2016).

This symptomatic development can also occur in the opposite direction, with primary morbidity in the BIS generating associated FFFS-activation symptoms (McNaughton & Corr, 2016). As outlined in Figure 1.3, hyper-reactivity within modules of the BIS will cause high levels of general arousal presenting as Generalised Anxiety Disorder. Increased general arousal, in turn, may precipitate the occurrence of panic attacks, especially in individuals who have a lower stimulus input threshold for PAG activation. Consequently these panic attacks, precipitated by high general arousal, may further increase original BIS anxiety through processes of learning and conditioning. In turn, this will further increase general arousal and lead to higher frequency of panic attacks. Critically, treatments targeting general anxiety will likely reduce general arousal, and the consequent occurrence of panic attacks.

Separating ‘Anxiety Disorders’ from ‘Fear Disorders’

Based on defensive direction, McNaughton and Corr (2004) proposed a separation between disorders of ‘fear’ from disorders of ‘anxiety’. Fear related behaviours correspond to defensive avoidance, and anxiety related behaviours to defensive approach. Accordingly, McNaughton and Corr (2004) describe DSM-5 Specific Phobia (SP), Panic Disorder (with/without Agoraphobia), and OCD as disorders of defensive avoidance (i.e. ‘fear’ disorders). All three disorders are sensitive to panicolytics but not anxiolytics and therefore are predicted to be associated with dysfunction of the FFFS. In contrast, Agoraphobia, SAD, and GAD are described as disorders of defensive approach (i.e. ‘anxiety’ disorders). These disorders are at least partially sensitive to the therapeutic actions of anxiolytics and therefore are by definition associated with dysfunction of the BIS. Despite some variation in the sensitivity to anxiolytics of the ‘anxiety’ disorders, they are all commonly affected by anxiolytics as a class (McNaughton, 2002).
Figure 1.3. Anxiety as a syndrome with symptomatic comorbid panic. Spontaneous activity (or hyper-reactivity) of the hippocampus, amygdala, or both, occurs in upper levels of the behavioural inhibition system (BIS; top right) and generates pathological generalised anxiety. Other types of anxiety increase through descending neural connections (solid outline filled grey arrows) and also ascending connections (not shown) of the BIS. As a result, general peripheral arousal increases (e.g. adrenaline levels) resulting in the activation of the periaqueductal grey (dashed outline filled grey arrow) leading to the occurrence of panic attacks. This occurs particularly in individuals who display a predisposition to panic. Additionally, neural activity also spreads throughout the fight-flight-freeze system (FFFS) via descending and ascending connections. The overall result is that abnormal anxiety generates symptoms of panic and fear that are normal given the level of perceived anticipatory threat generated by the pathological anxiety. Figure taken and legend adapted from McNaughton and Corr (2016).

The link between hyper-reactivity of modules - or of their regulatory systems – to specific syndromes may provide the key to developing the first neurologically grounded biomarker for any mental disorder (McNaughton & Corr, 2016). Identifying hyper-reactivity in particular neural modules or systems controlling the BIS and/or the FFFS will detect specific
patients who share a common underlying neural dysfunction for their symptoms. These patients may consequently respond to the same treatment protocols. Even in the absence of symptoms, individuals who have hyper-reactive modules will elicit greater than expected levels of output in response to a particular stimulus input. In other words, these individuals will produce a normal level of output following a sub-normal input stimulus, or an excessive level of output in response to a normal input stimulus. Critically, measuring the level of output from a module in response to a set stimulus input will detect those patients with hyper-reactive modules. Developing a method of assessing hyper-reactivity of the regulatory systems controlling the BIS and the FFFS will provide objective neural biomarkers for disorders of defensive approach (i.e. ‘anxiety’ disorders) and disorders of defensive avoidance (i.e. ‘fear’ disorders), respectively. Additionally, individuals with distinct co-morbid disorders will be more easily identified by detecting hyper-reactivity in more than one distinct module (McNaughton & Corr, 2016).

**Development of an Anxiety-Specific Biomarker**

Investigating the therapeutic action of anxiolytics on neural activity, relative to panicolytics and other drug classes, may provide one method of identifying an anxiety-specific biomarker (McNaughton, 2014). Critically, there are no ‘magic bullet’ drugs that produce a limited specific therapeutic effect. Instead, every drug produces a main effect and multiple side effects. When looking at the effects of a single drug, there is no way of disentangling its main therapeutic effect from the range of side effects it also produces. However, when comparing the actions of drugs against each other, any effects that are shared across a class of drugs must be a main effect and those not shared are non-specific side effects. For example, anxiolytic drugs acting at 5HT1A receptors, GABA_A receptors, or voltage gated calcium channels, individually produce a range of effects on panic, muscle relaxation, depression, addiction, insomnia and epilepsy. However, as their name suggests, their only common shared action as
a class is alleviation of generalised anxiety (Baldwin, Ajel, Masdrakis, Nowak, & Rafiq, 2013; McNaughton, Kocsis, & Hajos, 2007). As seen in Table 1.1, both classical (i.e. benzodiazepines) and novel (i.e. buspirone, pregabalin) anxiolytics share an overlapping anxiety reducing effect; therefore this is their main effect. Any alteration of neural activity, cognitions, or behaviour that anxiolytics as a class produce, consequently, must be related to anxiety. Such shared changes cannot be related to panic because buspirone has no therapeutic effect on panic. Likewise, pregabalin is not antidepressant. Critically, neural activity that is changed by all anxiolytics may provide a biological biomarker for BIS regulation and a means of detecting potential hyper-reactivity underlying one distinct anxiety syndrome (Corr & McNaughton, 2016; McNaughton, 2014).

Using this logic, we have recently developed a neural biomarker for BIS reactivity. In rat hippocampi, the frequency of Rhythmical Slow Activity (RSA, 4-12Hz) is reliably reduced by all known anxiolytics – e.g. barbiturates, benzodiazepines, 5HT$_{1A}$ receptor agonists, calcium channel blockers, and Selective Serotonin Reuptake Inhibitors (McNaughton et al., 2007; Siok, Taylor, & Hajós, 2009). Importantly, antipsychotic or sedative drugs (e.g. haloperidol, chlorpromazine), that do not reduce anxiety, do not reduce the frequency of RSA (McNaughton et al., 2007). A reduction in RSA frequency has predicted clinical anxiolytic action with 100% success over many decades of testing. According to these findings, as summarised by McNaughton and Corr (2004), anxiolytics produce their anxiety alleviating effects by acting on the BIS, which carries out its functional operations through theta activity (4-12Hz). Thus, rodent RSA elicited by reticular stimulation may be the first ever neurologically grounded biomarker for one anxiety specific process. This is supported by the finding that when blocked RSA is replaced with artificial brain rhythms, behavioural dysfunction is restored (McNaughton, Ruan, & Woodnorth, 2006).
Table 1.1. Relative effectiveness of drugs used to treat anxiety and depressive disorders. No drug has a single therapeutic effect on one disorder. BDZ₁ (Classical benzodiazepines), BDZ₂ (Novel benzodiazepines), BUS (Buspirone and related 5HT-1A agonists), and PGB (Pregabalin, calcium channel blockers) share only a common anxiolytic effect on Generalised Anxiety and Social Anxiety. As a class, they produce no shared effect on panic, phobia, obsession, or depression. These ‘anxiolytic’ drugs all reduce the frequency of elicited theta. The observed variation in therapeutic action of drugs between different disorders can be attributed to variation in receptor density location within different brain areas. This variation in relative drug effectiveness suggests separation in the neural control of these disorders. IMI (Imipramine and other tricyclic antidepressants excluding clomipramine); CMI (Clomipramine); MAOI (Monoamine oxidase inhibitors); SSRI (Selective Serotonin Reuptake Inhibitors). Table and text constructed based on information taken from McNaughton (2002), McNaughton (2014) and Corr and McNaughton (2016).

<table>
<thead>
<tr>
<th></th>
<th>Panic</th>
<th>Generalised Anxiety</th>
<th>Obsessions/ Compulsions</th>
<th>Unipolar Depression</th>
<th>Atypical Depression</th>
<th>Simple Phobia</th>
<th>Social Anxiety</th>
<th>Elicited theta frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BDZ₁</strong></td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>BDZ₂</strong></td>
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<td>-</td>
<td>0</td>
<td>-</td>
<td>?</td>
<td>( )</td>
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</tr>
<tr>
<td><strong>BUS</strong></td>
<td>0</td>
<td>-</td>
<td>( )</td>
<td>-</td>
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<tr>
<td><strong>IMI</strong></td>
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<td>-</td>
<td>( )</td>
<td>-</td>
<td>( )</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>CMI</strong></td>
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<td>-</td>
<td>--</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>( )</td>
<td>(?)</td>
</tr>
<tr>
<td><strong>MAOI</strong></td>
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<td>( )</td>
<td>-</td>
<td>-</td>
<td>(-)</td>
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<td>(-)</td>
</tr>
<tr>
<td><strong>SSRI</strong></td>
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<td>-</td>
<td>--</td>
<td>-</td>
<td>?</td>
<td>(-)</td>
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<tr>
<td><strong>PGB</strong></td>
<td>0</td>
<td>-</td>
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</tr>
</tbody>
</table>
Based on this rat finding, a human anxiety specific biomarker was further developed - providing the very first human biomarker for an anxiolytic-specific process. As goal conflict activates the BIS (McNaughton & Corr, 2004), we attempted to elicit neural activity related to BIS activation during a task that involves situations of goal conflict, the Stop Signal Task (SST). Due to ethical considerations, hippocampal depth recording of neural activity, as used in rodent experiments, was not feasible for measuring neural activity in humans. Instead, an Electroencephalogram (EEG) method was used to record superficial frontal brain activity predicted to be entrained by hippocampal activity arising from deep within the brain (Young & McNaughton, 2009). It was predicted that the detection of neural activity arising from the hippocampus during situations of goal conflict would represent the functional output of the BIS when activated.

In this SST task, participants were exposed to situations of approach, avoidance, and approach-avoidance conflict. Neural activity representing BIS activation (i.e. Goal Conflict Specific Rhythmicity, GCSR) was measured by subtracting the average EEG power recorded during periods of approach and avoidance from periods of approach-avoidance conflict. Interestingly, situations of approach-avoidance goal conflict were found to elicit right frontal (F8) brain activity in the 5-12 Hz frequency range (i.e. GCSR, Neo, Thurlow, & McNaughton, 2011). This GCSR was positively linked to measures of Spielberger’s Trait Anxiety (Spielberger & Gorsuch, 1983) and Eysenck’s Neuroticism (Eysenck & Eysenck, 1991). Critically, it was reduced by a range of anxiolytics (pregabalin, benzodiazepines, and 5HT1A drugs) that share only a common anxiety alleviating effect but no intersecting effect on depression or panic (McNaughton, Swart, Neo, Bates, & Glue, 2013; Shadli, Glue, McIntosh, & McNaughton, 2015). These findings suggest GCSR, detected during the SST, represents neural activity associated with BIS activation.
Although administration of anxiolytics immediately reduces RSA in rats (McNaughton et al., 2007) and GCSR in humans (Neo et al., 2011), it takes several weeks for full anxiety-alleviating therapeutic benefits of anxiolytics to be obtained. This observation suggests the BIS may support an anxiety-specific process contributing to the onset and maintenance of an anxiety syndrome. Critically, chronic hyper-reactivity of the BIS may result in dysfunctional regulation of this anxiety-specific process resulting in clinical anxiety. Thus, high GCSR may act as a biomarker indicating dysfunctional hyper-reactivity of the BIS, predictive of one type of clinical anxiety syndrome.

GCSR would be the very first way of identifying a sub-group of neurally distinct ‘anxiety disorder’ patients whose psychological symptoms arise from BIS hyper-reactivity, as opposed to other underlying dysfunctions. McNaughton (2014) predicted that individuals with hyper-reactive BISs would yield high GCSR scores relative to those with normally functioning BISs. Thus, high GCSR will reflect one type of neural dysfunction underlying one specific anxiety syndrome. Identifying this organic cause for symptom manifestations will allow better prediction of treatment response. Reductions in GCSR predict anxiolytic action therefore it is expected that individuals with a hyper-reactive BIS – and who, therefore, produce strong GCSR – may benefit from anxiolytic drug treatment. Critically, clinical validation and translation of this biomarker for BIS hyper-reactivity is the first step in the long process of transforming and enhancing the current systems of mental disorder diagnosis.

**The present study: towards clinical validation of an anxiety process biomarker**

Research to date has focused on the investigation of GCSR within a ‘healthy’ population of individuals recruited through the Student Job Search Organisation (McIntosh, 2015; McNaughton et al., 2013; Neo et al., 2011; Shadli et al., 2015). Based on these findings, GCSR correlates with personality measures such as Neuroticism and Trait Anxiety (Neo et al.,
2011; Shadli et al., 2015), is sensitive to the action of anxiolytic drugs (McNaughton et al., 2013; Shadli et al., 2015), and holds promise as the first ever biological biomarker for one anxiety specific process. Importantly, GCSR has not yet been validated within a patient sample of individuals diagnosed with anxiety disorders. Such validation is required to further develop GCSR as a biologically grounded biomarker for one type of anxiety. We aimed to take the first steps in the clinical validation of GCSR within a sample of ‘anxiety disorder’ patients.

According to this aim, we recruited a sample of patients who presented with a DSM-5 Anxiety Disorder, and reported not currently receiving pharmacological treatment. A sample of control participants, who did not explicitly report experiencing anxiety, were also recruited via Student Job Search (SJS) to allow comparison. The patient sample underwent a diagnostic assessment to determine their appropriate DSM-5 diagnosis. All participants then completed a combination of personality questionnaires using a computer delivery system and had their EEG recorded in the Stop Signal Task (SST) that we previously developed. GCSR was measured for all participants and statistical analyses performed to determine if GCSR was higher within the sample of patients with DSM-5 anxiety disorders compared to the SJS control sample. It was predicted that DSM-5 ‘anxiety disorder’ patients on average would show higher GCSR than control participants.

Early in this study, it was discovered that the rate of patient recruitment was lower than anticipated. Preliminary analyses were therefore conducted on the large group of participants recruited from Student Job Search (SJS). Using a high STAI-T score as a proxy for anxiety disorder, we compared GCSR obtained from nominally ‘anxious’ SJS participants with high STAI-T scores against matched nominally ‘non-anxious’ SJS participants with low STAI-T scores. We then assessed whether GCSR differences generalised across recruitment methods to the small sample of patient participants with a DSM-5 anxiety disorder diagnosis who explicitly reported experiencing symptoms of panic, fear, and anxiety. This study design
attempts to compensate both for the small number of patients and for the lack of an appropriately matched ‘healthy’ control group for the anxiety disorder patient sample. The logic involves two steps. First, a comparison of matched high and low STAI-T groups, where any differences can be attributed to STAI-T. Second, a comparison of the high and low STAI-T groups, separately, with a patient group who report particularly high STAI-T scores. If the patients have similar, or more extreme, GCSR to the high STAI group, their difference can be assumed to be STAI-related and to be larger than normal, rather than due to sampling bias.
Chapter 2: General Methods

All data presented in this thesis were collected by two experimenters (me and Shabah Shadli) as part of an ongoing larger project investigating the clinical translation of a biomarker for one type of anxiety specific process. Shabah Shadli collected the EEG data obtained from the patient sample, and I collected the majority of the EEG data obtained from the Student Job Search (SJS) participant sample. The present study specifically investigated the relationship between DSM-5 anxiety disorders, as a whole, and GCSR – our proposed anxiety biomarker. The following details relating to the Stop Signal Task (SST), EEG recording, ECG recording (data not reported), questionnaire administration, and data analysis were identical for both patient and SJS participants tested by the two experimenters, except where specified. The diagnostic DSM-5 Mini International Neuropsychiatric Interview (MINI) was administered only to participants in the patient group by two clinical psychology trainees (me and Lisa Labuschagne), who had received instruction from a psychiatrist (Professor Paul Glue).

Participants

Two groups of participants were recruited for this study: participants recruited through Student Job Search and patients. The SJS participant group consisted of 26 males and 60 females aged 18 to 37 years (mean = 21.9 years). The patient participant group consisted of 7 males and 14 females aged 18 to 48 years (mean = 30.2 years).

The large sample of participants were recruited from the University of Otago through the Student Job Search organisation and reported no major illness in the previous 30 days, no regular use of psychotropic medication in the past six months and no alcohol consumption in the 24 hours prior to the experiment. Additionally, none had received any medical or psychological treatment for depression, anxiety or other emotional disorder within the previous
12 months. No information was collected specifically about their current or previous experience of clinical anxiety.

The patient participants were recruited in a variety of ways including newspaper advertisements (See Appendix A), supermarket advertisements (See Appendix B), online internet advertisements (See Appendix C), and in response to newspaper and magazine articles reporting on the larger research project (these articles included an invitation to people with symptoms of anxiety, panic and fear to participate; see Appendix D). All patient participants reported suffering from ongoing symptoms of anxiety, fear, or panic but were not currently receiving medication treatment for their anxiety disorder. The patient sample consisted of individuals whose primary disorder(s) met the diagnostic criteria for pure Social Anxiety Disorder (n = 4), pure Generalised Anxiety Disorder (n = 5), pure Panic Disorder (n = 1), co-morbid Social Anxiety Disorder and Agoraphobia (n = 1), co-morbid Social Anxiety Disorder, Panic Disorder and Generalised Anxiety Disorder (n = 2), co-morbid Panic Disorder and Agoraphobia (n = 1), co-morbid Panic Disorder and Generalised Anxiety Disorder (n = 1), co-morbid Social Anxiety Disorder and Generalised Anxiety Disorder (n = 2), co-morbid Generalised Anxiety Disorder and Alcohol Dependence (n = 1), co-morbid Generalised Anxiety Disorder, Panic Disorder and Posttraumatic Stress Disorder (n = 1), and co-morbid Panic Disorder and Posttraumatic Stress Disorder (n = 2). It was important to test patients in the absence of anxiolytic treatment as we have found that anxiolytic drugs affect the strength of the GCSR signal obtained (Shadli et al., 2015). Initiation of psychological treatment was not an exclusion criterion. Otherwise, patients were healthy and did not report any major illness in the previous 30 days. Patients reported no regular use of psychotropic medication in the previous six months, or alcohol consumption in the previous 24 hours before participating in this experiment.
All SJS participants received monetary compensation ($15 per hour) for the time and effort spent in undertaking the experiment. All patient participants received petrol vouchers as reimbursement for the time and effort spent in undertaking the experiment ($20 per hour). No monetary reward or punishment was received in the experimental tasks. Only right-handed SJS participants were recruited for this study as the sample of potential participants through SJS was large enough to exclude left-handed participants. This was important because previous experiments revealed that the GCSR effect was lateralized to right frontal areas of the human brain. Both left and right-handed patient participants were recruited (left n = 3, right n = 17).

Ethical approval for this study was obtained from the University of Otago Ethics Committee (approval number: H15/005). All participants provided informed consent prior to undergoing testing (See Appendix E for information and consent forms).

**Apparatus/Materials**

*Mini International Neuropsychiatric Interview*

The Mini International Neuropsychiatric Interview (MINI) English version 6.0.0 (American Psychiatric Association, 1994) was administered to all participants in the patient group by a clinical psychology trainee. The interviewer never acted as the experimenter for the same participant. The MINI is a brief structured interview used to aid in the diagnosis of major Axis I psychiatric disorders outlined by the DSM-IV and ICD-10. It comprises a series of precise closed questions that require the patient to respond with a yes or no answer. Questions in the MINI are relevant to the following 15 diagnostic categories: Major Depressive Episode, Suicidality, Manic and Hypomaniac Episodes, Panic Disorder, Agoraphobia, Social Phobia (Social Anxiety Disorder), Obsessive-Compulsive Disorder, Posttraumatic Stress Disorder, Alcohol Dependence/Abuse, Substance Dependence/Abuse (Non-Alcohol), Psychotic Disorders and Mood Disorder with Psychotic Features, Anorexia Nervosa, Bulimia Nervosa, Generalized Anxiety Disorder, and Antisocial Personality Disorder. Patients in this study were
asked questions relevant to all diagnostic domains. The MINI was conducted in a quiet private room with the patient seated in a chair.

**Task Presentation and Recording of Participant Responses**

The SST and a questionnaire delivery program were presented on PC computers with a monitor size of 360mm x 375mm. Participants were seated in an office chair in front of the computer screen, which was located at eye level, approximately 135cm away from their face. In the experimental task, participants responded to stimuli using a standard computer mouse. Right-handed participants used their right index finger and right second finger to make appropriate left and right mouse clicks, respectively. Left-handed participants used their left index finger and left second finger to make appropriate right and left mouse clicks respectively. The presentations of stimuli, recording of responses and other aspects of the SST task, and also questionnaire delivery programs, were performed using purpose-built programmes written in Visual Basic 6.

**Questionnaires/Demographic data**

Participant responses to a variety of personality questionnaire items were recorded for the purpose of the main study investigating the relationship of current personality measures with GCSR. These are not reported in this thesis except for aggregate scores on the Spielberger State-Trait Anxiety Inventory (Spielberger & Gorsuch, 1983), Eysenck’s Neuroticism scale score (Eysenck & Eysenck, 1991), and Anxiousness and Depressiveness scores from the Personality Inventory of the DSM-5 (American Psychiatric Association, 2013).

All participants were presented with a computer-delivered questionnaire program identical to that developed and used by McIntosh (2015). This questionnaire program was delivered to each participant in two sections: Part 1 prior to the SST and Part 2 following the SST (See Appendix F for Part 1 of the questionnaire, and Appendix G for Part 2 of the
questionnaire). Part 1 of the questionnaire program presented the Spielberger State-Trait Anxiety Inventory Y-form (Spielberger & Gorsuch, 1983) Trait Anxiety scale items (i.e. excluding the State scale), the Eysenck Personality Questionnaire-Revised (EPQ-R, Eysenck & Eysenck, 1991) Extroversion and Neuroticism scale items (i.e. excluding Psychoticism and Lie scales), and the Behavioural Activation System/Behavioural Inhibition System (BIS/BAS, Carver & White, 1994) BIS scale items (i.e. excluding the BAS scale). Participants responded to the EPQ items using a 4-point response scale (No-almost never; No-sometimes; Yes-often; Yes-almost always) rather than the conventional 0-1 (No-Yes) scale. This allowed the main study to more precisely investigate the relation of individual EPQ items with GCSR. Part 2 of the questionnaire presented Depressiveness, Anxiousness, Emotional Lability, Perseveration, Separation Insecurity, Withdrawal, Anhedonia, Risk-taking, Intimacy Avoidance and Restricted Affectivity scale items from the Personality Inventory of the DSM-5 (PID-5, American Psychiatric Association, 2013). Additionally, Part 2 also included questions about sleep and depression history. The standard Statistics New Zealand format was used to collect information about each participant’s gender, age, ethnicity, and handedness. Standard weight and height scales were used to measure each participant’s weight and height.

EEG Recording

EEG data were collected from each participant by fitting a Waveguard EEG cap (ANT Neurotechnology) to their head. There were three sizes of EEG caps: Large (head circumference 57-64cm), Medium (53-57cm) and Small (47-53cm). Each participant was fitted with the appropriately sized EEG cap according to their head circumference. EEG recordings were made from the scalp surface using Ag/Agcl electrodes within the EEG cap. The electrodes were located on the EEG cap in the arrangement of the International 10:20 electrode placement system with recordings from 16 channels: F7, F3, Fz, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, and T6. The Fp1 electrode was used to detect artefact activity, requiring removal, which was
caused by eye-blinks. All electrodes were independent and re-referenced following data collection to the average of separate A1 (electrical reference) and A2 mastoid electrodes (also located in the cap). A 3ml syringe and Precision Glide 16 gauge blunt needle (Becton, Dickenson & Co, New Jersey, USA) was used to insert Electro-gel (Electro Cap International, USA) into each electrode recorded from. The EEG cap was connected to the ASA Neurotechnology EEG machine, which provided measurements of impedance as well as recording EEG. Electrical activity was sampled from the brain at a rate of 256Hz throughout recording before being down-sampled to 128 Hz for analysis. Band pass filters were set to 1-36Hz. All participants underwent EEG recording in a small cubicle (certified body protected area for electrical recording) located in the Department of Psychology and the University of Otago.

**ECG Recording**
ECG data were collected from each participant by fitting four stick-on electrodes onto both arms and legs of each participant. Electrodes used were Ambu White Sensor 0415M ECG electrodes (Ambu A/S Baltorpbakken 13 DK-2750 Ballerup, India). These electrodes were then connected to an Edan SE-1010 PC-based ECG Machine (Model: SE-1010, Edan USA, 4204 Jutland Drive, Suite B, San Diego, CA 92117). ECG data are not reported in this thesis.

**Storage of Confidential Participant Data**
Patient participant data were collected and stored in a confidential manner to allow 3- and 6-month follow-up as part of the main project. Patient EEG data, ECG data, personal details and personality questionnaire response data were stored on the computer in a password-protected folder. This password-protected folder was only visible on the desktop when a researcher was logged on to the computer under the password-protected username. Hard copies of each patient’s information consent form, scored MINI form, and participant details were also stored
within a folder contained in a locked filing cabinet. Personal identifying details for SJS participants were not retained and all of their data was coded only by participant number.

**Stop Signal Task (SST)**

In the present experiment, the SST was derived from an original task used by Aron and Poldrack (2006). The ‘C’ code for this original SST was kindly provided by Dr Aron, and converted to Visual Basic by Neil McNaughton and used by Neo et al. (2011) in their initial study. Four modifications were made to the original task for its use in Shadli et al. (2015) and the current study: (1) Using a similar method to Carter et al. (2003), short and long Stop Signal Delays (SSDs) were generated as a proportion of the ongoing average Go reaction time of each participant. However, intermediate SSDs were derived by tracking to 50% of participant responding, as in the original task. This modification was made to promote optimal statistical analysis following data collection by allowing SSD types to be easily separated into equal-sized non-overlapping short, intermediate, and long groups. (2) Following a response on each trial, participants received feedback (i.e. presentation of smiley face for successful trial responses, and frowney face for unsuccessful trial responses). (3) Colour was added to the Go stimulus to increase its discrimination. (4) To prevent strategic slowing of Go responses, feedback was provided if a participant’s Go response was substantially slower than their Go reaction time obtained during the initial phase of Go testing (i.e. 1.5 times average pure Go reaction time). Components of the current SST are summarised in Figure 2.1 and described below.

**Go Trials**

At the beginning of each Go trial, a white fixation circle was presented at the centre of the monitor screen against a black background. After 500ms, the white Go stimulus appeared within the fixation circle. The Go stimulus was an arrow symbol that pointed towards the left (<) or the right (>). Participants were required to respond to the Go stimulus by performing a
right mouse click if the Go stimulus pointed towards the right, or a left mouse click if the stimulus pointed toward the left. If the participant made a response click, or following 1000ms if no click was performed, the white fixation circle and Go stimulus disappeared from the screen. If the participant’s response was correct (e.g. left click response to left pointing arrow or right click response to right pointing arrow), a smiley face appeared on screen 500ms following their correct response. In contrast, if an incorrect response was made (e.g. opposite click response to direction of arrow, or no click response made), a frowney face appeared on screen 500ms after a participant’s incorrect response. Each trial was presented 1000ms following the presentation of the previous trial. All participants were instructed to respond as fast and accurately as possible. Furthermore, they were encouraged to remain still and try their hardest not to make head or neck movements throughout the task, except for during the rest periods.

Stop Trials

The Stop trials in this SST were identical to the Go trials, with the exception that a 1000Hz auditory tone (Stop signal) was presented following a delay of variable length (Stop Signal Delay, SSD) since the Go stimulus appeared. The auditory tone sounded until a click response was made, or for 500ms if no click response was made. The Stop tone signalled the participant to withhold their click response.

Participants were informed that both going and stopping were equally important and that the program was designed so it was not possible for them to successfully withhold their click response on every Stop trial, but they should try their best. If the participant successfully inhibited their response after hearing the auditory tone, a smiley face was presented for 500ms. In contrast, if the participant did not successfully inhibit their response, a frowney face was presented for 500ms.
Figure 2.1. A summary of the Stop Signal Task. On both Go and Stop trials, a white fixation circle is first presented against a black background on the screen. Then, in the centre of the circle, a Go stimulus (arrow-like symbol pointing to the left or right) is presented. Participants are instructed to respond as fast and accurately as possible to the Go stimulus by performing a left/right mouse click according to the direction of the Go symbol. A smiley face is presented for correct responses, and a frowney face for incorrect responses. On Stop trials, an auditory Stop signal is presented after a variable delay since the Go stimulus and signals the participant to inhibit their response. Following successful response inhibitions, a smiley face is presented. Following unsuccessful inhibitions, a frowney face is presented. The pre-trial black screen reappears 1500ms following the presentation of the Go stimulus in the previous trial. Figure modified by Neil McNaughton from Shadli et al. (2015).
Phases of Testing

Initial Block of Go Trials

In this initial block of testing, 30 Go trials were presented without Stop trials. This was a primary Choice Reaction Time (CRT) task similar to that used by Carter et al. (2003), but differing in the number of trials presented. No feedback pertaining to the participant’s Go reaction time was given during this phase. Otherwise, all components of the Go trials presented in this phase were identical to Go trials presented later in the SST. The major purpose of this initial phase of testing was to record participant response measurements required to generate the Go Mean Reaction Time (MRT). The Go MRT, in turn, was used to calculate initial lengths of SSDs and the maximum Go reaction time (which determined whether feedback was presented to the participant to speed up their responding).

The Stop Task

The Stop task was similar to the primary CRT but included both Go trials and Stop trials. In the current SST, there were a total of 396 trials. Participants completed three blocks of 132 trials and experienced a rest break (minimum 1 minute - maximum 2 minutes) in between each block of trials. Each block of 132 trials contained 33 Stop trials and 99 Go trials. The Stop trials in this task were grouped into three types based on the length of the SSD (i.e. short, intermediate, and long). Each one of these SSD trial types was presented in a counterbalanced order within each block of three Stop trials. Each Stop trial was presented pseudo-randomly every four trials in the same sequence for all participants. There were no differences between blocks of the SST other than the time elapsed since the start of the SST.

In the SST phase, participant instructions and other important task details were similar to Neo et al. (2011). Participants were re-presented with the instructions three times throughout the SST (at the start of each block). Participants who strategically slowed their Go response to increase the likelihood of successfully inhibiting their response received feedback instructing
them to speed up their response in the future. If a participant made their response before the Go stimulus was presented (on both Go and Stop trials), the trial was removed prior to data analysis.

Control of Stop Signal Delay Length

The only difference between Stop and Go trials was the presentation of an auditory Stop signal after a delay period of variable length since the Go stimulus in Stop trials. To promote optimal statistical analysis, the control of SSDs differed in the present SST to Neo et al. (2011) but was identical to that used by Shadli et al. (2015).

In the current SST, three distinct nominal staircases generated short, medium and long SSDs. Short SSDs were set to 20% of the average Go reaction time recorded from the previous 16 Go trials presented. Similarly, long SSDs were set to 70% of the average Go reaction time recorded from the previous 16 Go trials. Medium SSDs, however, were set initially to 45% of the average Go reaction time recorded from the previous 16 Go trials, but then tracked participant responding by decreasing one step following unsuccessful participant inhibitions, and increasing one step following successful inhibitions. This tracking of intermediate SSDs was similar to Aron and Poldrack (2006) and Neo et al. (2011) but the present SST used 30ms tracking steps instead of the original 50ms steps.

The average Go reaction time calculated from the initial CRT phase was used in block 1 to generate the SSDs. However, in blocks 2 and 3, initial SSD values were set to the appropriate proportion of the average Go reaction time obtained from the last 16 trials of the previous block. There was a restriction placed on medium SSDs from taking on a value within 50ms of the values of either long or short SSDs. We expected that the stair-casing system used to generate intermediate SSDs would track to 50% successful participant inhibitions. This was
desired because the BIS theory predicts that when approach-avoidance is balanced (i.e. 50% successful inhibition), maximal goal conflict will be produced which activates the BIS.

Procedure

The outline of the general procedure is presented in Figure 2.2. Information sheets outlining the details and procedure of the experiment were provided to all participants before they attended the experimental session. Participants were given the opportunity to ask questions about the experiment before their session (i.e. through email) or after they arrived for their session. Informed consent was obtained from each participant at the start of the experiment, before testing began.

![Figure 2.2. General outline of the experimental procedure.](image)

Patient participants were first administered the MINI diagnostic interview whereas SJS participants were not. The experimenter then measured the circumference of each participant’s head and marked Fp1 and Fp2 according to the International 10:20 system on their forehead using a blue marker. The weight and height of each participant was obtained before they were taken to the computer to complete Part 1 of the computer-delivered questionnaire program.
(EPQ-R; Extroversion and Neuroticism: BIS/BAS; BIS: and STAI-Trait; Trait Anxiety). Participants were encouraged to continuously work through each question and not remain on any one item for too long. The time taken to complete Part 1 of the questionnaire program was around 10 minutes.

After completing Part 1 of the questionnaire, participants were guided to the certified body protected area for electrical recording room. While the participant sat in the seat, the experimenter selected and fitted the appropriately sized EEG cap to their head. The experimenter then attempted to reduce the impedance between the electrode and the participant’s scalp. This was achieved by injecting electrode gel into each electrode, and using the tip of the blunt needle to gently abrade the scalp and increase the conductance of the electrode to optimise electrical recordings. After the impedance of each electrode was reduced sufficiently (to below 5KΩ), the EEG cap was connected to the ASA Neurotechnology EEG machine. The time taken to fit the EEG cap and sufficiently reduce the impedance was about 20-40 minutes.

Before EEG recording started, the experimenter performed two tests on the participants to determine whether the EEG recording system was recording clear brain activity. The first test was of alpha rhythm and was conducted by instructing each participant to close their eyes and relax for ten seconds. The second test was of eye-blink artefact and was conducted by instructing each participant to blink once per second for a ten-second period. The noise level of the EEG electrical recording on the monitoring screen during these two tests was assessed by the experimenter. If the experimenter judged the EEG quality to be insufficient, further attempts were made to reduce electrode impedance. If the EEG quality was judged sufficient, behavioural testing began.
The experimenter verbally provided task instructions before the SST commenced (these were the same as the visual instructions presented below). The experimenter informed each participant that it was impossible to successfully withhold their response on every Stop trial. Before the SST began, participants were presented with the following instructions on the monitor screen.

“*Remember to respond as FAST as you can once you see the arrow. Press the left mouse button if you see the left arrow " < ". Press the right button if you see the right arrow " > ". However, if you hear a beep, your task is to stop yourself from pressing a button. Stopping and Going are equally important*”.

Then, the experimenter left the room and the participant began the SST when they were ready. The experimenter was present in the next-door room and available if the participant required help at any time. The time taken to complete the SST was about 30 minutes.

Following completion of the SST, the experimenter applied one ECG electrode to each participant’s arms and legs (i.e. 4 electrodes in total). Then, an alpha asymmetry test was conducted. Participants were instructed to relax, while opening and closing their eyes for one minute intervals over a ten minute period. During this period, the resting electrical brain activity and heart rate was recorded for each participant. (Data obtained from this test are not reported in this thesis.) The time taken to complete the alpha asymmetry test and ECG recording was 10 minutes.

Following the alpha asymmetry test, the experimenter disconnected the EEG cap from the machine and removed it from the participant’s head. Skin cleansing wipes (Briemarpak, Australia) were used to remove all pen markings from the participants’ face and scalp. Towels were used to remove electrode gel from the participant’s hair and face. ECG electrodes were also removed from each participant’s arms and legs. Participants were then asked to complete Part 2 of the computer-delivered questionnaire program (i.e. sleep questions, depression
history, and PID-5 items). The time taken to complete Part 2 of the questionnaire was about 10 minutes. At the end of the experimental session, SJS participants signed for their monetary reimbursement of $15 per hour and patient participants signed for their petrol vouchers ($20 per hour).

**Data Processing and Analysis**

*Behavioural Data*

The following measures were recorded from each trial of the SST: trial and block number, trial type (Go or Stop), SSD value, reaction time, staircase index (1-3), staircase moves for each staircase and left/right/null responses. Three summary behavioural measures were calculated: (1) average Go Reaction Time (Go RT) across all Go trials (ms); (2) average SSD for the middle staircase (ms); and (3) Stop-Signal Reaction Time (SSRT, ms). The Stop Signal Reaction Time was calculated by subtracting the mean SSD on the intermediate staircase from the median go reaction time, according to the Horse Race Model outlined by Logan and Cowan (1984).

*EEG Artefact Removal*

All EEG data was processed using a purpose built program made in Visual Basic 6 by Neil McNaughton. Artefact contained in the EEG recordings was removed in three separate stages. First, to eliminate residual high frequency noise (including electrical signals at 50Hz) from the EEG traces, a simple three point running mean (providing a cut-off at 43 Hz) acted as a low pass filter. Secondly, artefact caused by eye-blinks was removed from the raw EEG traces according to a method outlined by Zhang et al. (2017). Thirdly, the experimenter visually scanned the remaining EEG traces to identify any residual artefact caused by movement or eye-blinks that were not appropriately removed by the program. The original recording from Fp1 was used as a comparison to ensure eye-blinks had properly been removed. Missing value
markers were used to replace remaining eye-blink or movement related artefact across all channels.

*Spectral Power Post-Processing – Stop trials and Go trials*

EEG data were first converted to calibrated microvolt values. Then, power analyses were conducted by applying a nominal overlapping Hanning window to a 1-second period during each trial. Application of the Hanning window on Stop trials began at 0.25 seconds prior to presentation of the Stop (auditory) signal and ended at 0.25 seconds following the termination of the Stop signal. On Go trials, the Hanning window was applied at the same position as the Stop signal in the immediately adjacent Stop trial. The cosine waveform of the Hanning window allowed maximum power to be extracted from the central 0.5 seconds (section of interest) and minimum power from the 0.25 seconds at each end of the 1 second period. Using the Hanning window resulted in improved quality and doubled frequency resolution of the Fourier transform that followed than would have been obtained using a 0.5s square window. All data then underwent Fast Fourier Transformation and log transformation to normalize error variance, before the averages of Stop and Go trials for each participant and SSD type were calculated.

**Statistical Analyses**

*Obtaining GCSR*

For each participant, Goal Conflict Specific Rhythmicity (GCSR) values were calculated from each block of trials and frequency step extracted by the Fourier transform. Firstly, for each participant and SSD type, the average, matching trial, ‘Go’ power was subtracted from the average ‘Stop’ power to obtain the power specific to the Stop signal. Secondly, the Stop-Go differences averaged over both the long and the short SSD trials were subtracted from the average Stop-Go differences of the intermediate SSD trials. This provided a calculation for the
individual GCSR values, which were equivalent to the interaction effect of trial type with the quadratic component of SSD in a conventional ANOVA of simple power values.

These GCSR values were then subjected to 3 point smoothing to reduce error variance that is produced as a result of applying the Fourier Transform in the previous steps. The Fourier Transform, with a 1s window, has to allocate the power of the signal to a specific integer frequency (i.e. 4 Hz or 5 Hz) even if the power falls in between specific frequencies (e.g. 4.5 Hz). Slight differences in the frequency can then mean that the Fourier Transform at sometimes allocates the power to the lower frequency (i.e. 4 Hz), and at other times to the higher frequency (i.e. 5 Hz), therefore generating large error variance across trials for the power value at each frequency. Applying a 3-point smoothing transformation averages across frequencies to reduce this error variance (e.g. reducing differences between 4 and 5 Hz) and also provides a visually clearer signal, reducing power spikes at particular frequency values.

Analysis of Variance (ANOVA)

We performed four ANOVA analyses using the IBM SPSS Statistics Package (See Chapter 3) on GCSR values that had undergone 3 point smoothing. The specific purposes and details of each ANOVA are outlined below.

Analysis 1: Comparison of High, Medium and Low STAI-T SJS Scorers
Nominally healthy participants recruited from SJS were separated into distinct nearly equal sized groups of high, medium and low STAI-T scorers and subjected to ANOVA to investigate group differences in GCSR. The number of participants differed slightly in each of the three groups as participants with the same STAI-T score were kept in the same groups. The high STAI-T scoring group contained 21 SJS participants (mean score = 46.7), the medium group contained 18 SJS participants (mean score = 36.7), and the low group contained 22 SJS participants (mean score = 29.3).
Analysis 2: Comparison of Clinically High STAI-T SJS Scorers and Matched SJS Controls

Participants recruited from SJS were separated into a group of high STAI-T scorers and a demographically matched group of low STAI-T scorers and subjected to ANOVA to investigate group differences in GCSR. Cut-off STAI-T scores used in the present study to separate SJS participants into these distinct groups were taken from a review of the existing literature. In the research literature, Fisher and Durham (1999) found that the mean STAI-trait values obtained from clinical GAD groups within six treatment outcome studies ranged from 47 to 61. Based on the review, Fisher and Durham (1999) established a clinically significant STAI-T cut-off point at 46. This meant individuals who produced STAI-T scores below 46 were classified within the functional range and those that scored above 46 or above were classified in the functionally impaired range. In the present study, we accordingly selected our clinical-level STAI-T cut-off point at 45. The mean STAI-T score obtained by SJS participants who fell above this cut-off was 51.6. This mean score fell within the range of means obtained from other clinically anxious treatment groups therefore we concluded that our ‘Above Cut-off’ (i.e. nominally ‘anxious’) SJS group had similar STAI-Trait characteristics to previous diagnosed clinically anxious groups. However, it should be noted that this group had been recruited through SJS and had not self-identified as clinically anxious. They had therefore not received the MINI and could not be assigned a DSM diagnosis. The control comparison group of ‘Below Cut-off’ (i.e. nominally ‘non-anxious’) SJS participants was constructed by selecting SJS participants with STAI-scores below the clinical cut-off in such a way as to closely as possible match the age, gender and ethnicity of the ‘Above Cut-off’ STAI-T scorers. There were 12 SJS participants included in each of the ‘Above Cut-off’ and ‘Below Cut-off’ STAI-T groups.
Analyses 3 and 4: Comparison of Patients, Clinically High STAI-T SJS Scorers and Matched SJS Controls

Participants recruited from SJS and separated into ‘Above Cut-off’ and matched ‘Below Cut-off’ STAI-T groups (see analysis 2), along with patient participants, were subjected to separate pair-wise ANOVAs to investigate differences in GCSR between the groups. Patient participants were recruited on the basis that they reported suffering from ongoing symptoms of anxiety, fear, or panic. There were 12 SJS participants each of the ‘Above Cut-off’ and ‘Below Cut-off’ STAI-T groups, as before, and 19 patient participants.
Chapter 3: Results
As described in Chapter 1, the primary aim of the current study was to investigate GCSR strength within a sample of anxiety disorder patients compared to healthy controls. Due to the low number of patients recruited during the study period, a preliminary analysis was conducted on the much larger number of participants recruited from Student Job Search (n=86). We expected that within the large sample of SJS participants, there would be individuals who were experiencing symptoms of anxiety, fear and panic, which could be quantitatively similar to patient samples but not explicitly reported as disorder since this was not mentioned during recruitment. On this basis, we aimed to separate these ‘anxious’ SJS participants from ‘non-anxious’ SJS participants, post hoc, using their responses on personality questionnaires, specifically their STAI-T scores. Our initial analysis simply split the available participants into three groups based on STAI-T score (high, medium, and low STAI-T score) with no attempt to match on demographics. We next assessed potential differences in GCSR strength between ‘Above Cut-off’ SJS participants (defined as having STAI-T scores in the clinical range) and matched ‘Below Cut-off’ SJS participants (defined as having STAI-T scores below the clinical range). Importantly, this procedure ensured that recruitment of the two groups was the same. Finally, we compared the strength of GCSR produced by ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants to the GCSR produced by a small sample of participants recruited as patients and diagnosed with a range of DSM-5 anxiety disorders. Here, our interest was to test for generalisation of our ‘Above Cut-off’ (i.e. nominally ‘clinically anxious’) results across recruitment methods to a sample that met DSM criteria. This chapter presents the results from these analyses.
Analyses of large SJS Sample

Overall Demographic Data and Goal Conflict Specific Rhythmicity - see also subgroup demographics and GCSR data below.

There were 26 male and 60 female participants recruited from SJS in this study. Participants were aged between 18 to 37 years old (mean age = 22). STAI-T scores obtained by participants ranged from 23 to 58 (mean STAI-T score = 38.4). Neuroticism scores ranged from 0 to 22 (mean Neuroticism score = 6.4).

Goal Conflict Specific Rhythmicity (GCSR) values were extracted, as previously (McIntosh, 2015; Shadli et al., 2015) from the right frontal site (F8), and calculated as the difference in stop signal power (i.e. stop minus matching go) for intermediate SSDs relative to the stop-go power difference averaged over short and long SSDs (see also Chapter 2). As shown in Figure 3.1, significant positive GCSR was obtained on average across all blocks of the SST (Intercept, F(1, 63) = 3.949, p = 0.05). This pattern of positive GCSR obtained across blocks and frequencies was consistent with greater power being detected during intermediate SSD trials compared to short and long SSD trials. On average across all blocks, GCSR decreased with increasing frequency (Frequency[Linear], F(1, 63) = 7.756, p = 0.007), however the form of this variation in GCSR across frequencies differed between blocks (Blocks x Frequency[Quadratic], F(1, 63) = 7.481, p = 0.008). In block 1, GCSR was weakly positive from 5 to 10 Hz and became weakly negative at 10 to 11 Hz. In block 2, GCSR was positive across frequencies ranging from 5 to 10 Hz, with a peak at 8 Hz. GCSR became weakly negative at 10 to 11 Hz. In block 3, positive GCSR values were observed across 5 to 8 Hz and 10 to 11 Hz, with a peak at 6 Hz.
Figure 3.1. Goal Conflict Specific Rhythmicity (GCSR, log micro V²) calculated from F8 EEG of SJS participants as a function of increasing frequency (Hz) in Blocks 1, 2, and 3 of the SST. GCSR was generally positive across frequencies and blocks. GCSR became weakly negative at 10 to 11 Hz in blocks 1 and 2, but was positive across other frequencies. GCSR peaked at 5 Hz in block 1, at 8 Hz in block 2, and at 6 Hz in block 3.

Analysis One: Comparison of GCSR Obtained by High, Medium and Low STAI-T Scorers
An ANOVA was performed on the large sample of SJS EEG data to explore differences in GCSR between SJS participants separated into three approximately equal groups. The groups were separated based on STAI score: (1) participants who obtained a ‘low’ STAI-T score (STAI-T < 34); (2) participants who obtained a ‘medium’ STAI-T score (STAI-T = 34-39); and (3) participants who obtained a ‘high’ STAI-T score (STAI-T > 39). The ANOVA was performed separately for block 1, 2, and 3, but contained the same within-subjects factor (frequency, Hz), between-subjects factor (group, 3 levels of STAI-T scores: high, medium and low) and measure variable (GCSR, log µV²) for all blocks.

Analysis One: Demographic Data and GCSR Results
As shown in Table 3.1, the ratio of male to female participants was smallest in the ‘High’ STAI-T group and largest in the ‘Low’ STAI-T group. The mean age of participants in all three
groups was similar around 21 to 23 years old. The mean Neuroticism, PID-5 Anxiety and PID-5 Depressivity scores were all highest in the ‘High’ STAI-T group and lowest in the ‘Low’ STAI-T group. The difference in these scores was larger between the ‘High’ and ‘Medium’ STAI-T groups compared to the ‘Medium’ and ‘Low’ STAI-T groups.

Table 3.1. Demographic information for groups of SJS participants separated based on STAI-T score. M:F = number of male/female participants, percentage male given in brackets; Age = age range of participants in years, mean age given in brackets; Neur = mean Neuroticism; STAI-T = mean Spielberger Trait Anxiety; PID-5 Anxiety = DSM-5 Personality Inventory mean anxiety score; and PID-5 Depressivity = DSM-5 Personality Inventory mean depressivity score.

<table>
<thead>
<tr>
<th></th>
<th>M:F (%M)</th>
<th>Age in years (average)</th>
<th>STAI-T</th>
<th>Neur</th>
<th>PID-5 Anxiety</th>
<th>PID-5 Depressivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>6:23 (21%)</td>
<td>18-30 (20.8)</td>
<td>48.2</td>
<td>10.9</td>
<td>27.3</td>
<td>27.1</td>
</tr>
<tr>
<td>Medium</td>
<td>8:18 (31%)</td>
<td>18-37 (23.3)</td>
<td>37.1</td>
<td>5.3</td>
<td>18.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Low</td>
<td>12:19 (39%)</td>
<td>18-32 (21.9)</td>
<td>30.0</td>
<td>3.0</td>
<td>14.4</td>
<td>16.5</td>
</tr>
</tbody>
</table>

As seen in Figure 3.2, GCSR strength in block 1 appeared to be greatest at lower frequencies for both the low and high STAI-T groups and not for the medium STAI-T group, however there was no reliable difference between groups in GCSR variation across frequencies (Group x Frequency[all trends], all F(2, 75) < 1.536, all p > 0.222). There was also no significant difference in strength of GCSR averaged across frequency between groups in block 1 (Group, F(2, 75) = 1.091, p = 0.341). In block 2 (Figure 3.2), GCSR appeared to be more strongly positive between 7-8 Hz in the high STAI-T group compared to both the medium and low STAI-T groups. However the variation across frequencies was not significantly different between groups (Group x Frequency[all trends], all F(2, 70) < 2.374, all p > 0.101) and the overall difference between groups was not significant (Group, F(2, 70) = 0.196, p = 0.823). In block 3 (Figure 3.2), GCSR appeared to be slightly more positive between 5 to 8 Hz on average across high and medium STAI-T groups compared to the low STAI-T group, but this apparent difference did not approach statistical significance (Group, F(2, 67) = 0.326, p = 0.723).
The bottom graph displayed in Figure 3.2 presents GCSR averaged across all blocks of the SST for the three STAI-T groups. On average across blocks, GCSR displayed a tendency to decrease with increasing frequency for high, medium, and low STAI-T groups (Frequency [linear], F(1, 63) = 7.756, p = 0.007). GCSR appeared to be most strongly positive in the high STAI-T group compared to the medium and low STAI-T groups, although this did not approach significance (Group x Frequency[all trends], all F(2, 63) < 0.723, all p > 0.489).

Overall, despite superficial appearance, this first analysis provided no reliable indication that GCSR strength differed between SJS participants who obtained a high STAI-T score compared to a medium or low STAI-T score. While SJS participants with high STAI-T scores may have shown stronger positive GCSR, particularly in block 2, compared to medium and low STAI-T scorers, this was not a reliable difference. Importantly, this analysis was conducted on a larger sample of SJS participants than previously, however it was limited by its lack of control for demographic differences between the groups separated according to STAI-T score. Confounding factors such as gender (which was clearly unbalanced), age, ethnicity, and other demographic variables may have introduced a sampling bias into this analysis and masked potential differences between groups. We, therefore, conducted a second analysis to investigate potential differences in GCSR between high and low STAI-T scorers controlling for age, gender and ethnicity.
Figure 3.2. GCSR (log $\mu$V²) obtained from F8 as a function of increasing frequency (Hz) for high, medium, and low STAI-T scorers. Block 1, 2 and 3 are presented in relative order starting at the top of the figure. The average of GCSR produced across all blocks for the three groups is presented at the bottom of the figure. Overall, there was a tendency for GCSR to be stronger in the high STAI-T group compared to the medium and low STAI-T groups, particularly in block 2, however this tendency was not significant.
As shown in Table 3.2, the ratio of male to female participants and mean age of participants was identical in both ‘Above Cut-off’ and ‘Below Cut-off’ SJS participant groups. Mean Neuroticism, PID-5 Anxiety and PID-5 depressivity scores were all higher in the ‘Above Cut-off’ group compared to the ‘Below Cut-off’ group (Group, all F(1, 34) > 52.4, all p < 0.001). The ratio of male to female participants was higher in the sample of Patients compared to the ‘Above Cut-off’ and ‘Below Cut-off’ SJS groups. The mean age of Patients (30 years) was also higher than the mean age of participants in both the ‘Above’ and ‘Below’ Cut-off groups (20 years). The mean Neuroticism, STAI-T, PID-5 Anxiety, and PID-5 Depressivity scores were all significantly higher in the Patient sample compared to the ‘Below Cut-off’ SJS sample (Group, all F(1, 37) > 112.3, all p < 0.001). There were no significant differences in the mean STAI-T and PID-5 Depressivity scores obtained by the ‘Above Cut-off’ group compared to the Patient group (Group, both F(1, 37) < 2.2, both p > 0.15). However, the mean Neuroticism (Group, F(1, 37) = 4.970, p = 0.032) and PID-5 Anxiety (Group, F(1, 37) = 5.867, p = 0.02) scores were significantly higher in the Patient sample than the ‘Above Cut-off’ group.

Table 3.2. Demographic information for ‘Above Cut-off’ SJS, ‘Below Cut-off’ SJS and Patient participants. M:F = number of male/female participants, percentage male given in brackets; Age = age range of participants in years, average given in brackets; STAI-T = mean Spielberger Trait Anxiety; Neur = mean Neuroticism; PID-5 Anxiety = DSM-5 Personality Inventory mean anxiety score; and PID-5 Depressivity = DSM-5 Personality Inventory mean depressivity score. Standard deviation for STAI-T, Neur, PID-5 Anxiety, and PID-5 Depressivity given in brackets.

<table>
<thead>
<tr>
<th></th>
<th>M:F</th>
<th>Age, years (average)</th>
<th>STAI-T</th>
<th>Neur</th>
<th>PID-5 Anxiety</th>
<th>PID-5 Depressivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below</td>
<td>4:14 (22%)</td>
<td>18-27 (20)</td>
<td>33.9 (4.2)</td>
<td>3.2 (3.1)</td>
<td>15.4 (3.8)</td>
<td>17.9 (6.1)</td>
</tr>
<tr>
<td>Above</td>
<td>4:14 (22%)</td>
<td>18-28 (20)</td>
<td>51.5 (4.1)</td>
<td>12.6 (4.3)</td>
<td>24.3 (6.6)</td>
<td>29.8 (9.1)</td>
</tr>
<tr>
<td>Patient</td>
<td>7:14 (33%)</td>
<td>18-48 (30)</td>
<td>54.7 (7.8)</td>
<td>15.5 (3.9)</td>
<td>28.9 (3.9)</td>
<td>32.5 (9.4)</td>
</tr>
</tbody>
</table>
Table 3.3. Behavioural information for the three groups of participants for all blocks of the SST. GoRT = median reaction time in Go trials (ms); SSRT = Stop signal reaction time (ms) estimated using the horse race model; $P_{inhibit}$ = probability of inhibiting response on Stop trials, for trials with short, medium and long SSDs respectively.

<table>
<thead>
<tr>
<th>Block</th>
<th>Group</th>
<th>Go RT</th>
<th>SSRT</th>
<th>$P_{inhibit}$ Short</th>
<th>$P_{inhibit}$ Medium</th>
<th>$P_{inhibit}$ Long</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Below</td>
<td>420.4</td>
<td>224.9</td>
<td>73.6%</td>
<td>45.6%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>Above</td>
<td>407.5</td>
<td>223.9</td>
<td>70.7%</td>
<td>44.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>438.1</td>
<td>239.7</td>
<td>75.2%</td>
<td>51.8%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>Below</td>
<td>411</td>
<td>212.3</td>
<td>80.7%</td>
<td>44.9%</td>
<td>15.2%</td>
</tr>
<tr>
<td></td>
<td>Above</td>
<td>415.1</td>
<td>212.4</td>
<td>70.4%</td>
<td>43.7%</td>
<td>15.7%</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>451.5</td>
<td>230.5</td>
<td>80.4%</td>
<td>43.4%</td>
<td>10.3%</td>
</tr>
<tr>
<td></td>
<td>Below</td>
<td>406.3</td>
<td>213.7</td>
<td>78.1%</td>
<td>42.2%</td>
<td>8.9%</td>
</tr>
<tr>
<td></td>
<td>Above</td>
<td>399.5</td>
<td>197.3</td>
<td>70.3%</td>
<td>45.2%</td>
<td>12.6%</td>
</tr>
<tr>
<td></td>
<td>Patients</td>
<td>438.0</td>
<td>215.5</td>
<td>80.6%</td>
<td>48.8%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

As shown in Table 3.3, the median recorded reaction time obtained from Go trials (Go RT) across all three blocks tended to be slower for Patient participants than ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants, although no reliable differences were found (Group, all $F(1, 37) < 3.7$, all $p > 0.063$). Similarly, the Stop Signal Reaction Time (SSRT) obtained by Patients also appeared slower compared to ‘Above’ and ‘Below’ Cut-off SJS participants across all three blocks of the SST, however this difference was not significant (Group, all $F(1, 37) < 2.982$, all $p > 0.093$). SSD trials were divided into short, medium and long trials and the percentage correct inhibition of responses was calculated. There were no consistent differences in $P_{inhibit}$ short, medium and long
values between Patient, ‘Above Cut-off’, and ‘Below Cut-off’ participants across blocks (Group, all $F(1, 37) < 3.3$, all $p > 0.075$).

**Analysis Two: Comparison of GCSR Obtained by ‘Above Cut-off’ STAI-T Scorers and ‘Below Cut-off’ Matched Controls**

To address the limitation of potential sampling bias in the first analysis, a second analysis was conducted between a group of SJS participants with STAI-T scores in the clinically high range (‘Above Cut-off’, STAI-T > 45) and a control group with STAI-T scores not in the clinically high range (‘Below Cut-off’, STAI-T < 46) but matched to the above cut-off group on gender and age. Note that the ‘Below Cut-off’ group in this analysis was different from the ‘low’ group in the first analysis as it contained participants that were included in both the ‘low’ and ‘medium’ groups of the first analysis. As before, ANOVAs were performed separately for blocks 1, 2, and 3 to investigate differences in GCSR across frequencies. Each ANOVA had one within-subjects factor (frequency, Hz), one between-subjects factor (group, 2 different levels of STAI-T scores; Above Cut-off and Below Cut-off) and a single measure variable (GCSR, log µV²).

As shown in Figure 3.3, block 1 GCSR appeared to decrease somewhat with increasing frequency for both ‘Above Cut-off’ and ‘Below Cut-off’ SJS groups, although this tendency was not significant (Frequency [linear], $F(1, 30) = 1.821$, $p = 0.187$). GCSR produced by SJS participants in the ‘Below Cut-off’ group, contrary to prediction, was positive across all frequencies and appeared stronger than the GCSR produced by SJS participants in the ‘Above Cut-off’ group in block 1. However, this qualitative observation was not reliable as there was no significant difference in GCSR strength averaged across frequencies between the two groups (Group, $F(1, 30) = 2.215$, $p = 0.147$).

In block 2 (Figure 3.3), significant positive GCSR was present across both groups, with the greatest effects observed at intermediate frequencies (Frequency [quadratic], $F(1, 32) = 5.486$, $p = 0.026$; Frequency [order 4], $F(1, 32) = 10.671$, $p = 0.003$). In the ‘Above Cut-off’
group, GCSR was weakly positive at lower frequencies, increasing to a peak at 7 Hz, before
decreasing again and becoming negative at 9 to 11 Hz. In the ‘Below Cut-off’ group, GCSR
was positive across all frequencies, with a peak at 8 Hz. The GCSR peak at 7 Hz produced by
the ‘Above Cut-off’ group was stronger than the GCSR peak at 8 Hz produced by the ‘Below
Cut-off’ group. The variation in curve shape was reliable (Group x Frequency [cubic], F(1, 32)
= 4.262, p = 0.047; Group x Frequency [order 5], F(1, 32) = 7.563, p = 0.010). Although peak
GCSR was stronger in the ‘Above Cut-off’ group compared to the ‘Below Cut-off’ group, there
was no reliable difference in overall GCSR strength averaged across frequencies between
groups (Group, F(1, 32) = 0.256, p = 0.616) in block 2.

In block 3 (Figure 3.3), GCSR produced by the ‘Above Cut-off’ group was positive
across all frequencies, whereas GCSR produced by the ‘Below Cut-off’ was weakly positive
at 4 to 5 Hz, becoming negative between 6 to 11 Hz. GCSR in the ‘Above Cut-off’ group
appeared stronger than the GCSR in the matched ‘Below Cut-off’ group across frequencies,
but this difference did not reach significance (Group, F(1, 30) = 1.662, p = 0.207; Group x
Frequency [Linear], F(1, 30) = 2.078, p = 0.160; Group x Frequency [Quadratic], F(1, 30) =
1.053, p = 0.313).

The graph displayed at the bottom of Figure 3.3 presents the average GCSR across all
blocks of the SST for the ‘Above Cut-off’ and ‘Below Cut-off’ SJS groups. On average across
blocks, GCSR decreased with increasing frequency across both groups (Frequency [linear],
F(1, 28) = 11.896, p = 0.002). In the ‘Above Cut-off’ group, GCSR was positive between 5 to
9 Hz, peaking at 7 Hz, before becoming negative at 10 to 11 Hz. In the ‘Below Cut-off’ group,
GCSR was positive between 5 to 7 Hz, and became weakly negative between 8 to 11 Hz. There
was a tendency for GCSR to be more strongly positive in the ‘Above Cut-off’ group compared
to the ‘Below Cut-off’ group across frequencies and blocks of the SST, although this tendency
did not approach significance (Group x Frequency[all trends], all F(1, 28) < 1.7, all p > 0.2).
Figure 3.3. Goal Conflict Specific Rhythmicity (GCSR; log \( \mu V^2 \)) obtained from F8 as a function of increasing frequency (Hz) for the above cut-off STAI-T group and the matched below cut-off STAI-T group. Block 1, 2 and 3 are presented in relative order starting at the top of the figure. The average of GCSR produced across all blocks for the two groups is presented at the bottom of the figure. In block 1, GCSR appeared stronger in the Below Cut-off group compared to the Above Cut-off group. In blocks 2 and 3, the reverse pattern was observed, with GCSR tending to be stronger in the Above Cut-off group compared to the Below Cut-off group.
After controlling for specific demographic variables (i.e. age, gender and ethnicity), small differences in GCSR were observed between SJS participants with STAI-T scores in the ‘clinically high’ range (i.e. ‘Above Cut-off’) and SJS participants with STAI-T scores below the ‘clinically high range’ (i.e. ‘Below Cut-off’). Given the small sample size, and low level of statistical significance, these apparent group differences must be interpreted cautiously. Nonetheless, the results of the second analysis indicated that GCSR was slightly higher in the ‘Below Cut-off’ group compared to the ‘Above Cut-off’ group in block 1. In blocks 2 and 3, the reverse pattern was found with slightly higher GCSR observed in the ‘Above Cut-off’ group compared to the ‘Below Cut-off’ group. These apparent group differences appeared stronger than the subtle group differences observed in the first analysis where demographic variables were not controlled for. This suggests that sampling biases may have masked the presence of stronger group differences in the larger sample of SJS participants analysed in the first analysis.

**Comparison of SJS and Patient Participants**

In the analysis conducted on a sample of SJS participants, subtle group differences were found in the strength of GCSR obtained from ‘Above Cut-off’ SJS participants compared to matched ‘Below Cut-off’ SJS participants. Particularly in blocks 2 and 3, GCSR appeared to be more strongly positive in the ‘Above Cut-off’ SJS group compared to the ‘Below Cut-off’ SJS group, although these qualitative differences were not generally reliable and so must be interpreted cautiously. Nonetheless, our findings are consistent with the presence of small differences in GCSR between nominally ‘anxious’ and ‘non-anxious’ SJS participants when recruitment methods are matched. We conducted further analyses to test the generalisation of these small SJS group differences to a sample of patient participants diagnosed with a variety of DSM-5 anxiety disorders, who were recruited via a different method. We first investigated the presence of differences in GCSR strength between Patients and ‘Below Cut-off’ SJS participants predicting similar effects to those between ‘Above Cut-off’ and ‘Below Cut-off’. We then
investigated the presence of GCSR differences between Patients and the ‘Above Cut-off’ SJS participants predicting that there would be no difference.

Analysis Three: Comparison of GCSR Obtained by Clinical Patients and ‘Below Cut-off’ SJS Participants

An ANOVA was performed on the sample of ‘Below Cut-off’ SJS participants (used in analysis two) and a sample of Patient participants to explore differences in GCSR between these nominally ‘healthy’ SJS control participants and patient participants diagnosed with DSM-5 anxiety disorders. The ANOVA was performed separately for block 1, 2, and 3, but contained the same within-subjects factor (frequency, Hz), between-subjects factor (group, 2 levels: ‘Below Cut-off’ SJS and patients) and measure variable (GCSR, log µV²) for all blocks.

As shown in Figure 3.4 block 1, positive GCSR was obtained on average across both the Patient group and the ‘Below Cut-off’ group (Intercept, F(1, 33) = 7.395, p = 0.010). GCSR appeared to be more strongly positive in the ‘Below Cut-off’ SJS group compared to the Patient group, particularly between 8 to 10 Hz. However no reliable difference in GCSR variation across frequencies or strength of GCSR on average across frequencies was found between groups (Group x Frequency[all trends], all F(1, 33) < 0.718, all p > 0.403; Group, F(1, 33) = 0.675, p = 0.417).

In block 2 (Figure 3.4), positive GCSR tended to be observed at all frequencies on average across both groups; however this tendency approached, but did not reach significance (Intercept, F(1, 34) = 3.877, p = 0.057). GCSR tended to be more strongly positive in the Patient group than in the ‘Below Cut-off’ group between frequencies 5 to 7 Hz. Between 8 to 9 Hz, GCSR was slightly more positive in the ‘Below Cut-off’ group compared to the Patient group. Although GCSR showed qualitative differences between the Patient and ‘Below Cut-off’ groups, there were no reliable differences in overall GCSR strength or GCSR variation across
Figure 3.4. GCSR (log μV²) obtained from F8 as a function of increasing frequency (Hz) for Patient and Below Cut-off SJS participants. Block 1, 2 and 3 are presented in relative order starting at the top of the figure. The average of GCSR produced across all blocks for the three groups is presented at the bottom of the figure. In block 1, GCSR obtained by the Below Cut-off group tended to be greater than GCSR obtained by the Patient group. Alternatively, in blocks 2 and 3, GCSR tended to be lower in the Below Cut-off group compared to the Patient group. This effect was particularly strong in block 3, with GCSR being significantly greater in the Patient group than the Below Cut-off group.
frequencies between groups (Group, F(1, 34) = 0.076, p = 0.784; Group x Frequency[all trends], all F(1, 34) < 3.1, all p > 0.09).

In block 3 (Figure 3.4), Patient participants produced stronger positive GCSR compared to ‘Below Cut-off’ SJS participants, who produced negative GCSR. Strong positive GCSR was observed across all frequencies in the Patient group, whereas in the ‘Below Cut-off’ group, negative GCSR was observed between 7 to 11 Hz. This difference in GCSR strength on average across frequencies between ‘Below Cut-off’ and Patient groups was reliable (Group, F(1, 33) = 4.922, p = 0.034).

The bottom graph of Figure 3.4 shows the average GCSR across all blocks of the SST for both groups. On average across blocks, frequencies, and groups, significant positive GCSR was obtained (Intercept, F(1, 32) = 7.742, p = 0.009). GCSR displayed a tendency to decrease with increasing frequency when averaging across blocks, and this tendency reached significance (Frequency [linear], F(1, 32) = 8.772, p = 0.006). GCSR was positive across all frequencies in the Patient group, but was weakly negative in the ‘Below Cut-off’ group between 8 to 11 Hz. Across all frequencies, GCSR appeared more strongly positive in the Patient group than in the ‘Below Cut-off’ group, although this difference was not reliable Group x Frequency[all trends], all F(1, 32) < 1.3, all p > 0.25).

Analysis Four: Comparison of GCSR Obtained by Clinical Patients and ‘Above Cut-off’ SJS Participants
An ANOVA was performed on the sample of ‘Above Cut-off’ SJS participants (used in analysis two) and a sample of patient participants to explore differences in GCSR between these nominally ‘anxious’ SJS control participants and patient participants diagnosed with DSM-5 anxiety disorders. The ANOVA was performed separately for block 1, 2, and 3, but contained the same within-subjects factor (frequency, Hz), between-subjects factor (group, 2 levels: ‘Above Cut-off’ SJS and Patients) and measure variable (GCSR, log µV²) for all blocks.
As shown in Figure 3.5 block 1, positive GCSR was obtained across frequencies for Patient participants, whereas ‘Above Cut-off’ participants tended to show weak positive GCSR between 5 to 7 Hz, but negative GCSR between 8 to 11 Hz. There was no significant difference in GCSR variation across frequencies between ‘Above Cut-off’ and Patient groups (Group x Frequency[all trends], all F(1, 33) < 2.0, all p > 0.15). There was also no reliable difference in strength of GCSR on average across frequency between groups (Group, F(1, 33) = 0.747, p = 0.394).

In block 2 (Figure 3.5), positive GCSR was observed on average across both Patient and ‘Above Cut-off’ participants, although this did not reach significance (Intercept, F(1, 34) = 3.171, p = 0.084). There was a difference in GCSR variation across frequency between Patients and the ‘Above Cut-off’ SJS group that just achieved significance in the absence of Bonferroni correction (Group x Frequency[order4], F(1, 34) = 4.168, p = 0.049). On average across Patient participants, GCSR was strongest at lower frequencies and steadily decreased with increasing frequency, becoming weakly positive at higher frequencies. On average across SJS participants in the ‘Above Cut-off’ group, GCSR was weakly negative at 5 Hz, increased to a strong positive peak at 7 Hz, before decreasing again and becoming negative at 9 Hz. Overall, there was no significant difference in GCSR strength between the two groups (Group, F(1, 34) = 1.008, p = 0.323).

In block 3 (Figure 3.5), significant positive GCSR was obtained across frequencies on average for ‘Above Cut-off’ SJS and Patient participants (Intercept, F(1, 33) = 5.222, p = 0.029). GCSR obtained by Patient participants appeared to be more strongly positive on average across frequencies than GCSR obtained by ‘Above Cut-off’ participants, although this difference between groups was not reliable (Group, F(1, 33) = 1.088, p = 0.304).
Figure 3.5. GCSR (log µV²) obtained from F8 as a function of increasing frequency (Hz) for Patient and Above Cut-off SJS participants. Block 1, 2 and 3 are presented in relative order starting at the top of the figure. The average of GCSR produced across all blocks for the three groups is presented at the bottom of the figure. Across all blocks, patient participants obtained similar, if not stronger, GCSR to Above Cut-off SJS participants. No reliable differences in average GCSR strength across frequencies were found between patient and Above Cut-off SJS participants in blocks 1, 2 or 3.
The bottom graph of Figure 3.5 shows the average GCSR across all blocks of the SST for the ‘Above Cut-off’ and Patient groups. On average across blocks, frequencies, and groups, significant positive GCSR was obtained (Intercept, F(1, 32) = 10.096, p = 0.003). GCSR decreased with increasing frequency when averaging across blocks (Frequency [linear], F(1, 32) = 8.523, p = 0.006). There was no reliable difference in GCSR strength or variation across frequencies between ‘Above Cut-off’ and Patient participants when averaging across blocks (Group, F(1, 32) = 2.108, p = 0.156; Frequency x Group[all trends], F(1, 32) < 2.503, p > 0.123).

Summary of analyses 3-4
Overall, the third and fourth analyses showed that the subtle group differences in GCSR strength detected in analysis two were qualitatively generalised to a small patient sample. In block 1, ‘Below Cut-off’ SJS participants produced higher GCSR values than Patient participants. In blocks 2 and 3, there was a tendency for GCSR to be stronger in the Patient group compared to the ‘Below Cut-off’ SJS group. These differences were most evident in block 3, where a significant difference in GCSR strength between Patients and ‘Below Cut-off’ SJS participants was found. When averaging across patients and ‘Above Cut-off’ SJS participants, strong positive GCSR was detected. Although there was a reliable difference in variation of GCSR across frequencies between Patients and ‘Above Cut-off’ groups in block 2, there were no reliable differences in GCSR strength between these two groups across blocks.

In sum, small differences in GCSR strength detected in analysis two were even stronger when comparing patient participants against ‘Below Cut-off’ SJS participants. There was no reliable difference in overall GCSR strength between patients and ‘Above Cut-off’ SJS participants. This allows the results of analysis two to generalise to patient samples despite the difference in recruitment methods.
Overall Summary of Results
This chapter first reported the results from a preliminary analysis on a large SJS sample investigating GCSR differences between nominally ‘anxious’ (i.e. ‘Above Cut-off’) and ‘non-anxious’ (i.e. ‘Below Cut-off’) participants. When controlling for demographic factors, subtle GCSR differences were found between ‘Above’ and ‘Below’ Cut-off SJS participants. Specifically, in block 1 GCSR appeared higher in the ‘Below Cut-off’ group, whereas in blocks 2 and 3 GCSR appeared higher in the ‘Above Cut-off’ group. Caution must be taken when interpreting these results as these qualitative differences in GCSR were not reliable. The results of the primary analysis investigating GCSR differences between a small sample of anxiety disorder patients and healthy ‘Below Cut-off’ SJS controls were then reported. In this analysis, subtle GCSR differences observed between ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants generalised to, and became even more pronounced, within a DSM-5 anxiety disorder patient sample. Again, GCSR appeared stronger in the ‘Below Cut-off’ group compared to the Patient sample in block 1, although this apparent difference was unreliable. Alternatively, Patients produced stronger GCSR in blocks 2 and 3 than ‘Below Cut-off’ participants. This difference was most clearly seen in block 3 where GCSR differences between groups were reliable. Overall, the results reported in this chapter provide tentative support for higher GCSR in patients diagnosed with DSM-5 Anxiety Disorders compared to ‘Below Cut-off’ controls in blocks 2 and 3 of the SST.
Chapter 4: Discussion

Aims and Results of the Study
This study aimed to take important first steps in validating an anxiolytic-sensitive biomarker - GCSR - within a clinical ‘anxiety’ patient sample. In chapter one, it was predicted that DSM-5 ‘anxiety disorder’ patients on average would produce higher GCSR than control participants. The results of the present study were broadly consistent with this hypothesis. Patient participants, who displayed clinically high STAI-T scores, produced stronger positive GCSR compared to SJS control participants with non-clinical STAI-T scores. These preliminary findings are important first steps in the validation and translation of GCSR to clinical settings. Nonetheless, there are some limitations of this study that reduce the strength of the conclusions that can be drawn. These include the recruitment of only a small number of patient participants during the study period, and the lack of an appropriately matched control sample. Further research addressing these limitations will allow more confident conclusions. In the long-term, clinical validation and translation of this anxiolytic-sensitive biomarker will contribute to the transformation of mental disorder diagnostic systems to more rational and biological systems, enhancing treatment selection and effectiveness.

Due to the low number of patients recruited during the time period of this study, preliminary analyses were first conducted on a large sample of SJS participants who did not explicitly report symptoms of anxiety, fear, or panic. We expected that, within the sample of SJS participants, there would be individuals who were experiencing similar symptoms of anxiety, fear, and panic, to the patients with DSM-5 anxiety diagnoses. Although the presence of anxiety symptoms within the sample of SJS participants was not specifically assessed via clinical interview, we aimed to separate ‘anxious’ participants from ‘non-anxious’ participants using STAI-T scores as a proxy measure for anxiety. The STAI is designed to have high scores in clinical populations and to some extent represents an aggregate measure of reported clinical
anxiety symptomatology. Potential differences in GCSR strength between predicted ‘anxious’ and ‘non-anxious’ SJS participants were explored.

The first preliminary analysis specifically investigated differences in the strength of GCSR between SJS participants who obtained ‘High’, ‘Medium’, and ‘Low’ STAI-T scores. Results showed a tendency for ‘High’ STAI-T scorers to produce stronger positive GCSR than ‘Medium’ and ‘Low’ STAI-T scorers, although these differences were variable, small and unreliable. Importantly, there were multiple confounding factors not controlled for between groups in this analysis that may have accounted for the large variation and low statistical significance observed. These three groups not only differed on the basis of their STAI-T scores, but also on other demographic factors such as gender. It is possible that demographic differences between groups distorted results, masking true differences in GCSR between groups.

A second preliminary analysis on SJS participants was therefore conducted to investigate GCSR differences between high and low STAI-T scorers, while controlling for demographic variables (i.e. gender, age). In this analysis, a clinical cut-off STAI-T score was selected based on relevant literature and SJS participants with a score above this cut-off were classified as ‘Above Cut-off’. In contrast, participants who scored below this cut-off were classified as ‘Below Cut-off’ and then selected as pair-wise matches for ‘Above Cut-off’ participants on the basis of demographic factors. After controlling for demographic factors, somewhat stronger group differences between ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants were found than between the groups of the first analysis. This was consistent with potential sampling biases masking the observation of true group differences in the first analysis. Contrary to predictions, ‘Below Cut-off’ participants tended to produce stronger GCSR than ‘Above Cut-off’ participants in block 1, however this effect was not significant. In contrast, GCSR tended to be more strongly positive in the ‘Above Cut-off’ participants compared to the
‘Below Cut-off’ participants in blocks 2 and 3, although again this was not reliable. This latter finding was in the direction consistent with predictions. Importantly, caution must be taken when interpreting these results due to the small sample size and low level of statistical significance. Nonetheless, GCSR appeared stronger in individuals with high STAI-T scores compared to matched low STAI-T scorers who were selected via the same recruitment method, particularly in blocks 2 and 3 of the SST.

Further analyses were then conducted to investigate whether observed GCSR differences between ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants in analysis two generalised across recruitment methods and could be observed in a small sample of patients diagnosed with DSM-5 ‘anxiety disorders’. Importantly, this investigation addressed the primary aim of this study – to explore whether GCSR is stronger in individuals diagnosed with DSM-5 anxiety disorders compared to non-anxious control participants. Overall, the results showed that differences in GCSR between ‘Above Cut-off’ and ‘Below Cut-off’ SJS-recruited participants generalised to, and became more pronounced in, the sample of ‘anxiety disorder’ advertisement-recruited patients. STAI-T scores were also highest in the patient sample, compared to both ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants; suggesting that high STAI-T in analyses one and two was a reasonable proxy for a conventional anxiety diagnosis.

In block 1, again contrary to prediction, ‘Below Cut-off’ SJS participants tended to produce higher GCSR values than patient participants. In blocks 2 and 3, stronger positive GCSR was obtained in patients compared to ‘Below Cut-off’ SJS participants. This effect was most evident in block 3, where significant differences in GCSR were observed between ‘Below Cut-off’ SJS participants and patients. Importantly, while the GCSR of patients differed from ‘Below Cut-off’ SJS participants across blocks, patients and ‘Above Cut-off’ SJS participants generally produced similar patterns of GCSR across blocks.
In sum, patients (who had the highest STAI-T scores) and who explicitly reported symptoms of anxiety, tended to produce stronger positive GCSR in blocks 2 and 3 of the SST compared to SJS participants with low STAI-T scores, who did not explicitly report symptoms of anxiety. Patients produced similar, if not higher, GCSR values than ‘Above Cut-off’ SJS participants (with lower average STAI-T scores). Critically, the observed GCSR differences between matched ‘Above Cut-off’ and ‘Below Cut-off’ SJS participants in analyses one and two were even stronger in the patient sample. This suggests that the GCSR differences between clinically anxious patients and control ‘healthy’ SJS participants were not due to a lack of appropriate matching, but more likely to higher STAI-T scores in the patient sample. Overall, this study yielded two important preliminary conclusions: (1) GCSR tends to be higher in individuals diagnosed with DSM-5 anxiety disorders compared to non-anxious SJS controls; and (2) GCSR tends to increase in the positive direction as STAI-T increases.

**Progression toward Clinical Validation and Translation of GCSR**

The primary conclusion drawn from this study is that on average, GCSR tends to be higher in individuals diagnosed with anxiety disorders compared to control participants. This preliminary conclusion is consistent with predictions based on previous findings. Prior research has shown that GCSR correlates with personality measures of traits related to clinical anxiety (e.g. Neuroticism, STAI-T) and is reliably reduced by the action of therapeutic anxiolytic drugs (McNaughton et al., 2013; Neo et al., 2011; Shadli et al., 2015). Thus, GCSR has been previously established as an ‘anxiolytic-sensitive’ biomarker. Importantly, conclusions from the present study provide tentative support that GCSR is not only an ‘anxiolytic sensitive’ biomarker but also a biomarker for ‘clinical anxiety’, with the potential for clinical translation and application.

The findings of the present study also support theoretical predictions made by McNaughton and Corr (2004)'s neuropsychological model of defensive reactions and their
disorders. According to McNaughton (2014), high GCSR is predicted to be a biomarker for hyper-reactivity of the BIS. Critically, it is the chronic hyper-reactivity of the BIS that is proposed to contribute to the dysfunctional regulation of one anxiety-specific process, and over time the emergence of at least one clinical anxiety syndrome. Therefore, McNaughton hypothesised that GCSR may be predictive of one type of clinical anxiety syndrome. The results of this study indicate that compared to controls, a heterogeneous group of anxiety disorder patients on average displayed higher levels of BIS activation in situations of goal conflict during blocks 2 and 3 of the SST. In other words, patients produced higher levels of BIS output compared to controls in response to the same level of stimulus input. This provides further support for BIS hyper-reactivity underlying one clinical anxiety specific process, despite our sample also including people reporting clinical anxiety for other reasons.

Importantly, GCSR representing BIS activation is predicted to be associated with the system regulating defensive approach (i.e. the ‘Anxiety’ system) and not defensive avoidance (i.e. the ‘Fear’ system). Thus, McNaughton and Corr (2004) predict that true disorders of defensive approach and true disorders of defensive avoidance may be distinguished by BIS reactivity/GCSR strength. For example, high GCSR would be expected in individuals suffering from disorders of defensive approach. This would be consistent with BIS hyper-reactivity underlying symptom manifestations. In contrast, high GCSR would not be expected in individuals suffering from disorders of defensive avoidance. This is because their underlying pathology is not necessarily related to regulation of the BIS, but rather the FFFS. In the present study, the small patient sample was composed of individuals diagnosed with a range of DSM-5 ‘Anxiety Disorders’. This sample included not only individuals suffering from disorders of ‘defensive approach’ (i.e. anxiety), but also disorders of ‘defensive avoidance’ (i.e. fear), as defined by McNaughton and Corr (2004). Although all patients reported experiencing symptoms of anxiety, fear, and panic, the specific neural dysfunction underlying symptom
manifestations was likely diverse within this sample. Despite this, it still appears that the sample included a substantial number of patients who shared one common underlying neural dysfunction: BIS hyper-reactivity (i.e. high GCSR). This likely lead to the observation of higher GCSR on average cutting across the DSM-5 anxiety disorder diagnostic labels in patients compared to controls. However, heterogeneity may have clouded these results – a possibility that could be tested once the patient sample is considerably larger.

The Relationship of GCSR to STAI-T and other Personality Measures
The second conclusion of the present study is that GCSR tends to increase positively as STAI-T increases. This finding is consistent with previous research showing a positive correlation between GCSR and STAI-T (Neo et al., 2011; Shadli et al., 2015). The State-Trait Anxiety Inventory is a frequently used measure of clinical anxiety and demonstrates good discriminant and convergent validity with other measures of anxiety and psychopathology (Bieling, Antony, & Swinson, 1998; Spielberger & Gorsuch, 1983). The observed relationship between GCSR and STAI-T, both previously and in this study, supports the theoretical prediction that GCSR represents one specific process predictive of clinical anxiety.

Although a positive relationship between STAI-T and GCSR was identified in the present study, there was variability in GCSR patterns observed across blocks when participants were separated into groups based on STAI-T. Additionally, group differences in GCSR were small and unreliable. This is also consistent with previous research concluding that STAI-T does not predict GCSR with high accuracy. In fact, the shared variance of STAI-T and Neuroticism predicts GCSR better than either STAI-T or Neuroticism alone (McIntosh, 2015; Neo et al., 2011). Furthermore, it has been suggested that STAI-T is not a ‘pure’ measure of anxiety. In an investigation of the underlying structure of the State Trait Anxiety Inventory trait scale, Bieling et al. (1998) found that STAI-T also assesses components of depression and negative affect (Bieling et al., 1998). Thus, while the present results and previous research
findings suggest STAI-T assesses components of the trait underlying GCSR, it does not seem to be a complete measure. GCSR appears to represent a trait that is only partially captured by STAI-T (McIntosh, 2015).

Critically, it is predicted that GCSR is associated with one specific type of anxiety and will only be observed strongly in some anxious patients. This prediction is based on McNaughton and Corr (2004)’s theory that the dysfunctional regulation of the BIS gives rise to some cases of clinical anxiety, but not all. Current measures of clinical anxiety, such as the STAI-T, aim to widely assess aspects of clinical anxiety (including components of fear as well). Therefore, STAI-T is likely predictive of a range of DSM-5 anxiety disorders, whereas GCSR is expected to only predict a few. GCSR may represent only one part of current measures of clinical anxiety, which would further explain the observed partial relationship between GCSR and STAI-T.

In the present study, high GCSR tended to not only be associated with increased STAI-T scores, but also with increased Neuroticism, PID-5 Anxiety and PID-5 Depressivity scores. This finding is not surprising given previous research reporting a positive correlation between Neuroticism and GCSR (Neo et al., 2011; Shadli et al., 2015) and Bieling et al. (1998)’s finding that STAI-T provides a measure of not only trait anxiety but also aspects of depression and negative affect. However, it does raise the question as to whether GCSR is specific to clinical anxiety, or instead, specific to a trait that underlies both anxiety and depression or psychopathology in general. The high co-morbidity between anxiety and depression makes it difficult to assess the specificity of GCSR to clinical anxiety within a patient population. Consistent with this, our patient group had not only the highest STAI-T and PID-5 anxiety scores but also the highest PID-5 depressivity scores. Nonetheless, robust research indicating that GCSR is an anxiolytic sensitive biomarker suggests that GCSR is more likely predictive of clinical anxiety than depression. The significant overlap in the symptomology and traits
assessed by these current personality questionnaires makes it difficult to obtain a clear understanding of the relationship GCSR has with clinical anxiety when using these existing personality measures as a proxy for anxiety. Critically, direct assessment of GCSR within a ‘pure’ clinical anxiety patient sample (i.e. without co-morbid depression) and comparison with mixed and/or pure depression samples is the most robust method, and is required, to establish GCSR as an anxiety-specific biomarker.

The ‘Trait-like’ Nature of GCSR

In this study, a smooth distribution of GCSR values was obtained across patients and SJS participants who produced a range of STAI-T scores. This finding is consistent with GCSR representing a personality-like factor that is associated with the regulation of the BIS, rather than a discrete pathological process. This means that it is not necessarily the presence of high GCSR that causes clinical anxiety, but high GCSR may reflect dysfunctional regulation of the BIS that predisposes some individuals to developing clinical anxiety. Diagnosing individuals with clinical anxiety based on the detection of high individual GCSR may be inappropriate and lead to high rates of false positives. While there is, as yet, no evidence for the presence of high GCSR in the absence of clinical anxiety, there is also no evidence that high GCSR confirms symptoms of clinical anxiety. Instead, identifying high GCSR in patients presenting with significant levels of clinical anxiety may allow more precise understanding of the underlying pathology associated with their anxiety, and will predict subsequent treatment response.

Exploration of Unexpected Results

While the present results yielded predicted differences in GCSR between clinically anxious patients and ‘Below Cut-off’ SJS controls in blocks 2 and 3 of the SST, unpredicted differences were observed in block 1. Specifically, GCSR appeared to be higher in ‘Below Cut-off’ SJS participants with low STAI-T scores compared to patient participants with high STAI-T scores. This inconsistent block 1 pattern generalised across analyses involving different recruitment
methods, and importantly, is inconsistent with hyper-reactive BISs underlying one type of clinical anxiety. Further exploration of its cause is required.

One potential explanation for the inconsistent block one result is that the observed trend was a product of random variation or error. This explanation is supported by the lack of statistical significance associated with these block 1 GCSR differences across both analyses. To explore this explanation further, analysis of a larger sample of SJS participants with ‘Below Cut-off’ STAI-T scores and anxious patients is required to investigate the reliability of the observed trend. If this trend is replicated and reaches statistical significance in a larger analysis, we can conclude that it is in fact a true effect warranting theoretical or practical explanation. However, if this trend is not replicated in a larger analysis, we can conclude it was merely a product of random variation.

Provided the inconsistent block 1 trend is replicated in a larger analysis in the future, there are some practical and theoretical explanations that may account for it. One practical explanation for the discrepant block 1 results is that SJS participants with ‘Below Cut-off’ STAI-T scores performed differently during the SST compared to patients and participants with ‘Above Cut-off’ STAI-T scores. To further explore this hypothesis, a comparison of SST behavioural measures, which provide an indirect representation of the response style and strategy used by participants when completing the SST, was conducted. The behavioural measures obtained from ‘Below Cut-off’ SJS participants were specifically compared to those obtained from ‘Above Cut-off’ SJS and patient participants across all three blocks of the SST. If differences in response style and behaviour during the SST could account for the observed discrepant block one results, we would expect to observe similar behavioural measures in ‘Above Cut-off’ and patient participants, but quantitatively different behavioural measures in
Figure 4.1. Behavioural measures calculated for ‘Below Cut-off’, ‘Above Cut-off’, and Patient participants in block 1, 2 and 3 of the SST (information also reported in Chapter 3, Table 3.7). GoRT = median reaction time in Go trials (ms); SSRT = Stop signal reaction time (ms) estimated using the horse race model; $P_{\text{inhibit}}$ = probability of inhibiting response on Stop trials, for trials with short, medium and long SSDs respectively.

‘Below Cut-off’ participants in block 1. As reported in Chapter 3 and repeated diagrammatically in Figure 4.1, there were no reliable differences in the percentage of correctly inhibited responses on short, medium, and long Stop trials in blocks 1, 2, or 3 in ‘Below Cut-off’ SJS participants compared to patient and ‘Above Cut-off’ SJS participants. Furthermore, there were no reliable differences in Go Reaction Time (GoRT) or Stop Signal Reaction Time (SSRT) in ‘Below Cut-off’ SJS participants compared to patients and ‘Above Cut-off’ SJS
participants. In fact, qualitative differences in SSRT and GoRT tended to be found more between ‘Above Cut-off’ and patient participants. Therefore, differences in behavioural measures, representing participant behaviour and strategy during the SST, do not account for the anomalous block 1 results.

Although there are no clear practical explanations for the anomalous block 1 results, possible theoretical hypotheses must be considered. One hypothesised theoretical explanation is presented diagrammatically in Figure 4.2 below. According to this explanation, anxious patients and participants with high STAI-T scores take longer to adapt to the SST testing situation than participants with low STAI-T scores. This may result in anxious patients and ‘Above Cut-off’ participants displaying higher levels of anticipatory goal conflict in both Go and Stop trials of short, medium and long SSD trials during block 1. As outlined in Chapter 2, individual GCSR is calculated by first subtracting the average Go power from the average Stop power to produce a Stop Signal Specific power value. Stop-Go differences averaged across both long and short SSD trials are then subtracted from the average Stop-Go differences in intermediate SSD trials to produce GCSR values. Critically, if patients and ‘Above Cut-off’ participants produce high levels of anticipatory conflict in both Go and Stop trials in block 1, there will be little power difference between Stop and Go trials resulting in only small Stop Signal Specific power values being obtained. This, in turn, will lead to the observation of weaker GCSR in block 1. In contrast, this theoretical explanation presumes that ‘Below Cut-off’ participants adjust quickly to the SST situation and do not display anticipatory conflict in Go trials of block 1. Instead, goal conflict is only produced in Stop trials resulting in clearer Stop-Go power differences and the observation of stronger Stop Specific Power values. This may have led to the observation of stronger detected GCSR in ‘Below Cut-off’ participants in block 1 compared to anxious patients and ‘Above Cut-off’ SJS participants.
Figure 4.2. A diagrammatic prediction of the pattern of Stop Specific Power values obtained based on one hypothesised theoretical explanation for anomalous block 1 results. Predicted Stop Specific Power values from ‘Above Cut-off’ SJS and patient participants during short, intermediate and long Stop Signal Delay (SSD) trials in blocks 1, 2 and 3 of the Stop Signal Task (SST) are presented at the top. Predicted Stop Specific Power obtained from ‘Below Cut-off’ SJS participants during short, intermediate and long Stop Signal Delay (SSD) trials in blocks 1, 2 and 3 of the Stop Signal Task (SST) are presented below. According to this hypothetical explanation, ‘Above Cut-off’ participants and patients display slow adaptation to the SST resulting in generalised anticipatory goal conflict in both Go and Stop trials producing low levels of Stop Specific Power in block 1. This could explain the observation of low GCSR values in anxious participants detected in block 1. As ‘Above Cut-off’ participants and patients adjust to the SST in blocks 2 and 3, anticipatory conflict decreases in Go trials, resulting in an increase in Stop Specific Power values. This would lead to an increase in the strength of GCSR values during blocks 2 and 3. In contrast, it is predicted that ‘Below Cut-off’ participants adjust quickly to the testing situation and do not produce anticipatory conflict in Go trials during block 1. This would result in higher Stop Specific Power values being obtained during block 1, and in turn, higher GCSR values. As the SST progresses, ‘Below Cut-off’ participants might habituate to the situations of goal conflict therefore Stop Specific Power reduces in the intermediate SSD trials. If this was the case, GCSR values obtained from ‘Below Cut-off’ SJS participants in blocks 2 and 3 would reduce.
According to this theoretical explanation, it is further predicted that as the patients and ‘Above Cut-off’ participants adjust to the SST testing situation, their anticipatory goal conflict decreases in Go trials resulting in the production of stronger positive GCSR values in blocks 2 and 3. Whereas GCSR values obtained by ‘Below Cut-off’ SJS participants decrease during blocks 2 and 3 of the SST due to participants experiencing habituation to goal conflict. Importantly, this theoretical explanation is only a hypothesis and requires further research to investigate its accuracy. Restrictions of time prevented this study from investigating this hypothesis, however in the future, an analysis of the power produced during Stop and Go trials and the resulting stop-specific rhythmicity in short, intermediate, and long SSD trial across all three blocks of the SST is required. Importantly, this will allow our theoretical hypothesis to be tested and the predicted differences in Stop Specific power between patients and participants with high and low STAI-T scores to be directly explored.

Limitations Warranting Further Research

This study contained some limitations that reduce the strength of conclusions made, and require modification in future research. Firstly, we did not assess for the presence of anxiety, fear, or panic symptoms in SJS participants via clinical interviews. SJS participants were not assessed for an anxiety disorder using the DSM-5 MINI for two main reasons: (1) Insufficient time and resources to administer the MINI to all participants during the study period; and (2) the MINI is effective at clarifying the type of mental disorder an individual is suffering from, however is not frequently used to identify an individual suffering from a mental disorder. Despite our justification for excluding the MINI, there was resulting uncertainty whether there were SJS participants who met criteria for diagnosis of an anxiety disorder within the SJS sample. It is quite possible there were SJS participants who were experiencing similar anxiety symptoms to patient participants. Separating SJS participants on the basis of STAI-T scores was an attempt to distinguish ‘anxious’ SJS participants from ‘non-anxious’ SJS participants,
however high STAI-T does not directly translate to an anxiety disorder diagnosis. Caution must be taken when using the STAI-T scale as a diagnostic marker for anxiety as it is designed as a self-report personality measure rather than an anxiety disorder diagnostic marker and consequently may give rise to high rates of false positives. In the future, an anxiety screen for SJS participants should be incorporated into the methodology. This would allow detection of participants with symptoms that meet the diagnostic criteria for a DSM-5 anxiety disorder. The MINI would then be administered to participants who obtained a positive result on the anxiety screen to identify the appropriate diagnosis. Participants who screened positively would comprise a ‘patient’ sample and be could be compared to control SJS participants who did not meet diagnostic criteria for an anxiety disorder.

A second limitation of this study was the analysis of only a small patient sample (patient N = 22). This was a direct result of difficulty recruiting patients during the study period due to a low response rate to newspaper and supermarket advertisements and a delay in the development of an online advertisement and recruitment program. Critically, recruitment of only a small patient sample restricted the type of analyses that could be conducted and the hypotheses that could be investigated. In this small patient sample, individuals with a range of DSM-5 anxiety disorder subtypes were combined into one group, incorporating both disorders of ‘defensive avoidance’ and disorders of ‘defensive approach’. Based on theoretical predictions that only individuals with disorders of defensive approach will have hyper-reactive BISs, it is likely that the average GCSR signal obtained from this patient sample was attenuated by combining disorders of defensive avoidance and approach. In the future, recruitment of a larger sample of patients diagnosed with DSM-5 anxiety disorders will allow exclusion of individuals predicted to suffer from disorders of ‘defensive avoidance’ from the ‘clinical anxiety’ group. Based on the assumption that DSM-5 diagnoses such as GAD are more likely to contain people suffering from disorders of ‘defensive approach’ and panic disorder more likely to contain people
suffering from disorders of ‘defensive avoidance’, we would predict that analysing a ‘pure’ group of individuals with disorders of ‘defensive approach’ will result in an even stronger GCSR signal being detected. Future analyses of a larger group of patients will also increase the power of statistical analyses, increase the likelihood of detecting true differences, and will allow more precise investigation of the relationship between GCSR and specific types of DSM-5 anxiety disorder diagnosis and/or specific symptomatology.

A third limitation of this study was the lack of an appropriate ‘healthy’ control group for comparison with the anxiety patient sample. In the present study, a sample of nominally ‘healthy’ SJS participants was used as a control group for the sample of anxiety disorder patients. There were limitations associated with the use of this control group as it was not matched to the patient sample for gender, age, ethnicity, socioeconomic status or other demographic characteristics. It is possible that differences in these demographic factors contributed to the group differences in GCSR observed. Furthermore, the patient sample was recruited via a different method from the SJS sample, thus introducing a potential sampling bias.

The design of this study attempted to compensate for the lack of an appropriately matched non-anxious ‘healthy’ control group. The first step of this study comparing matched ‘Above Cut-off’ and ‘Below Cut-off’ STAI-T groups, controlled for important demographic and recruitment variables. Critically, in this matched analysis, any differences in GCSR between high and low STAI-T groups were attributed to STAI-T. The second step of this study compared ‘Above’ and ‘Below’ Cut-off groups, with a patient group who reported particularly high STAI-T scores. In this comparison, we predicted that if the patients had similar, or more extreme, GCSR to the ‘Above Cut-off’ SJS group, GCSR differences between patients and ‘Below Cut-off’ SJS participants could be attributed to STAI-T and clinical anxiety, rather than sampling biases. This two-step study design provided some control for potential sampling
biases and confounding factors that could have distorted or masked true GCSR differences between groups. As a result, we cautiously conclude that GCSR appears to be higher in individuals experiencing clinical anxiety. Nonetheless, proper control groups are required in future studies to address this limited study design and allow reliable validation of GCSR as a biomarker for clinical anxiety, and not merely an anxiolytic sensitive biomarker.

The selection of appropriate control groups is difficult but fundamental to allowing the drawing of conclusions around whether GCSR differences are most likely attributable to clinical anxiety, or to other factors such as demographic variables, differing recruitment methods, other mental disorders or psychopathology in general. In future studies, a healthy control group, representative of individuals in the general population who do not experience symptoms of anxiety, should be included. A variety of recruitment methods may be used to obtain a population representative sample (e.g. selecting from electoral role and then screening and separating individuals who have an anxiety disorder diagnosis from those who do not). Control individuals would then need to be matched to patient participants on important demographic factors such as gender, age, ethnicity and SES. Additionally, inclusion of psychiatric control groups in future studies will allow precise investigation of the specificity of GCSR to clinical anxiety rather than other mental disorders or psychopathology in general. For example, identical recruitment methods could be used to select a sample of patients with DSM-5 anxiety disorders and little or no Major Depression and a sample of individuals with DSM-5 Major Depression but little or no anxiety. These samples could then be matched to each other based on demographic factors. A comparison of GCSR strength between the two groups would assess whether GCSR is a biological biomarker for anxiety, depression, or a trait that underlies psychopathology in general. A similar approach could be taken on other mental disorders to investigate the specificity of GCSR to clinical anxiety. Additionally, a separate analysis of
GCSR within males and females is required as thus far all analyses have been performed on samples of males and females together.

**The Exciting Road Ahead**

Validation of our EEG biomarker within a large DSM-5 ‘Anxiety disorder’ patient sample is the first step in transforming current symptom based diagnostic systems to more rational and biologically grounded systems. Once GCSR is reliably validated as a biomarker for ‘clinical anxiety’ within a large patient sample, the focus of future research should turn to disentangling the precise organic structure of DSM-5 anxiety disorder diagnoses and developing additional biomarkers for other dysfunctional processes underlying specific mental disorders.

Given the pharmacological and preclinical neuropsychological findings outlined in Chapter 1, it appears there is a distinction between the underlying processes of ‘fear’ and the underlying processes of ‘anxiety’. This distinction is neither recognised nor clear in current symptom based diagnostic systems for mental disorders (American Psychiatric Association, 2013; World Health Organization, 2010). The differential therapeutic effects of anxiolytics and panicoanalytic drugs on distinct DSM-5 anxiety subtypes (Corr & McNaughton, 2016; McNaughton, 2014) suggests the structure of DSM-5 has at least some neural grounding. Drugs, which change the frequency of GCSR, are more effective in treating some DSM-5 anxiety diagnoses than others (i.e. anxiolytics treat some cases of GAD, but generally not panic). This suggests that high GCSR scorers may be more likely to fall within certain subtypes of DSM-5 anxiety disorders (e.g. GAD). The next step is to investigate the precise relationship of GCSR to specific sub-types of DSM-5 ‘anxiety’.

Based on McNaughton and Corr (2004)’s theory, it is predicted that there will be a group difference in GCSR strength between disorders of defensive approach (GAD, SAD, and Agoraphobia) and disorders of defensive avoidance (Panic disorder, Specific phobia, OCD). This group difference will be particularly strong when comparing GAD against Primary panic,
and when potential cases of co-morbidity are excluded from the participant sample. However, despite expecting some group differences, it is also predicted that negative GCSR cases in the ‘defensive approach’ (i.e. anxiety) groups and positive GCSR cases in the ‘defensive avoidance’ (i.e. fear) groups will be observed. For example, some cases of GAD will be caused by high GCSR whereas other cases not (anxiolytics are only effective in some cases of GAD). Similarly, some cases of panic disorder may have developed secondary to anxiety/ hyper-reactivity of the BIS. Thus, individuals with both anxiety and panic could have a mix of high GCSR and normal with the latter being associated with more primary panic dysfunction.

While exploration of the organic structure underlying DSM-5 anxiety disorder diagnostic labels is an important next step, attempts to move away from reliance on DSM-5 criteria to classify patient groups is also required in future research. Current and previous studies investigating GCSR rely on DSM-5 diagnostic criteria to create patient groups. However, as outlined in Chapter 1, there are major limitations associated with the DSM-5, and diagnostic criteria focused on symptom presentations appears to be arbitrary. It is predicted that within a specific DSM-5 anxiety disorder diagnostic category, there will be individuals with different dysfunctional processes underlying their symptom presentation. In the future, separating groups based on GCSR strength and exploring the associated group outcomes will likely give rise to a clearer understanding of the superficial symptom profile and observable outcomes of individuals who commonly share hyper-reactive BISs.

Biological biomarkers for other types of anxiety and mental disorders are urgently required to address the serious limitations inherent in current diagnostic systems. A clear direction for future exploration is the identification and development of biomarkers for processes of defensive avoidance. An obvious place to start would be with Klein (1994)'s theory predicting that individuals with panic disorder display a lower ‘suffocation alarm threshold’ and are therefore more likely to produce spontaneous panic when exposed to a
suffocation provocation test (i.e. CO\textsubscript{2} inhalation) than patients without panic or healthy controls. This theory has been supported by research showing that individuals with panic disorder have a lower panic threshold to carbon dioxide (CO\textsubscript{2}) inhalation and are more likely to experience CO\textsubscript{2} induced panic attacks compared to a range of clinical populations including depressed patients (Kent et al., 2001). Developing a clearer understanding of the underlying biological dysfunction of specific DSM-5 anxiety sub-types and other mental disorders will shift the focus of current diagnostic systems away from an over-reliance on superficial symptom profiles. Importantly, identification and validation of distinct biological biomarkers for unique pathological processes will greatly enhance treatment selection and delivery. This is one valuable piece of the puzzle required to combat the concerning poor delivery of adequate ‘quality care’ treatments for anxiety (Mendlowicz & Stein, 2014).

**Conclusion**

The present results hold significant promise for improving current mental disorder diagnostic systems. In chapter 1, I argued that DSM-5 diagnoses do not reflect underlying neural dysfunction but instead focus on the patient’s superficial symptoms. This means that patients with distinct neural pathologies may present with similar symptom profiles. Conversely, patients with the same underlying dysfunction may present with a diverse array of symptom profiles. Using the current symptom-based diagnostic systems, there is no way of assessing what the true neural pathology underlying symptom presentation is and, as a result, the selection of effective treatments is seriously compromised.

The results of the present study provide preliminary evidence that GCSR is the first ever biomarker for clinical anxiety. While further research is required to strengthen conclusions, this finding is ground-breaking and holds strong potential to alleviate a significant amount of the personal and economic burden of mental disorders currently weighing on individuals, families and communities. The ongoing development of distinct biomarkers for
unique processes underlying psychopathology in the future will allow more accurate diagnosis of mental disorders. Furthermore, biomarkers may be used to predict treatment response, and therefore will enhance the selection and implementation of effective treatments to individuals suffering from mental disorders. The results of the present study appear to signal the dawning of a new era, where the prognosis and long-term outcomes for these individuals will be radically improved.
References


McIntosh, J. (2015). *Goal Conflict Specific Rhythmicity, Trait Anxiety and Neuroticism: Towards Clinical Translation of an Anxiety Biomarker*. (Bachelor of Science (Honours) Honours Dissertation), University of Otago, University of Otago library.


Appendix A: Newspaper advertisement used to recruit patient participants

**Symptoms of anxiety, fear or panic?**

We are seeking volunteers for research on patterns of electrical activity in the brain associated with anxiety: male or female, aged 18-40, otherwise healthy, and considering seeking, or have not yet started, treatment. Study time is 2 hours, including psychological assessment, with 3 and 6 month follow-up phone calls. Some other criteria apply that our staff can discuss with you upon enquiry. Volunteers will be reimbursed for transport costs.

**For more information:**
Shabah Shadli
03-479 5835
anxiety@otago.ac.nz

This study has been approved by the University of Otago Human Ethics Committee (Health) H15/005
Appendix B: Supermarket advertisement used to recruit patient participants

Anxiety and the Brain
Do you have symptoms of anxiety, fear or panic?

The Psychology Department is looking for volunteers for a research study into patterns of electrical activity in the brain associated with anxiety. If you are male or female, aged 18-40, otherwise healthy, and considering seeking, or have not yet started, treatment for your symptoms then please contact Shabah by phone (03-479 5835) or e-mail (shabah.shadli@otago.ac.nz) for an information sheet. Volunteers will be reimbursed for transport costs and time.

This study has been approved by the University of Otago Human Ethics Committee (Health) H15/005.
Appendix C: Online internet advertisements used to recruit patient participants.

Does anxiety, fear or panic get the better of you?

Free help is available through the Department of Psychology

CLICK HERE TO FIND OUT MORE

(Terms and conditions apply)
Appendix D: Newspaper and magazine article used to recruit patient participants


New tool could help diagnose anxiety and improve treatment

By Jamie Morton

10:40 AM Thursday Jul 14, 2016

Arachnophobia is a common form of anxiety. Photo / Getty Images

A Kiwi researcher aiming to create the world's first biomarker for a psychiatric disorder is appealing for help from those who suffer from anxiety.

Professor Neil McNaughton, of Otago University's Department of Psychology, is trying to transform nearly 50 years of theoretical research into a novel tool that could help clinicians quickly and easily diagnose sufferers of anxiety -- and prescribe the right medication.

Such a leap would be "game-changing" for tackling what remained one of the most common mental disorders in New Zealand: more than 200,000 Kiwis have been diagnosed with an anxiety disorder at some point in their lives.

Over recent decades, McNaughton and his colleagues have developed a detailed theory of how, in certain brain structures, hyperactivity generates abnormal symptoms and "hyper-reactivity" leads to specific clinical syndromes.

Their work has also sought non-invasive ways to measure how so-called "threat-approach" and "behavioural inhibitions" systems were activated in anxiety sufferers.
In a three-year study supported by a million-dollar Health Research Council grant, McNaughton wants to test whether a specially developed biological marker could measure brain reactions of untreated anxiety sufferers that would show that they could be placed into distinct groups and treated accordingly.

"The most important thing I'm interested in asking is, are some patients different from others in a way that doesn't match the standard symptomatic diagnosis that we get these days?"

A biological marker, he said, should be able to predict treatment efficacy better than current symptom-based diagnoses, while boosting treatment results and cost-effectiveness.

The marker would measure an electrical rhythm generated by a particular part of the brain in response to "goal conflict" in a task.

"A doctor could, in principle, use this by fitting an electrode cap on the patient and running them through the test," McNaughton said.

"Unfortunately, at the moment, it is not sensitive enough for diagnosis of a single person and cannot be used for repeat testing."

But it could be used to test effects of drugs in groups of people, and McNaughton and his colleagues hoped to use it as an anchor to develop clinically useful diagnostic tests.

"I'd like to think that, if this works, we'll have the first genuine biomarker for any psychiatric disorder," he said.

"While some people might argue around the edges as to whether there are some already, certainly, for anxiety, this would be pretty much a game changer."

This was because it would provide a "solid biological basis" for giving sufferers a diagnosis that allowed clinicians to determine the best the treatment for them, he said.

"At the moment, a patient will walk in with a whole mass of symptoms. It's always a mess, and if you try one drug, then 30 per cent of the time you may be lucky.

"If we could change that to just checking out the patient with a simple test that tells you what to treat them with, then that would be a major improvement."

It didn't necessarily have to be drugs that the marker indicated as the best treatment option, he said.

"In fact, there are a lot of reasons for supposing anti-anxiety drugs are not particularly good at treating anxiety, but just for holding the symptoms down, kind of like aspirin rather than an antibiotic."

McNaughton is extending the study from Dunedin to other regions, including Auckland, and is keen to hear from people willing to take part.

"We need not only people who have some kind of anxiety disorder, but also those who don't, so we can draw comparisons between them."
ANXIETY IN NEW ZEALAND

• Anxiety disorders are very common among Kiwis. The 2011/2012 New Zealand Health Survey indicated that 6.1 per cent of Kiwis -- or more than 200,000 people -- had been diagnosed with an anxiety disorder at some point. These included generalised anxiety disorder, phobias, post-traumatic stress disorder and obsessive compulsive disorder.

• Rates were highest among women -- 7.7 per cent, compared with 4.4 per cent of men -- and anxiety disorder was particularly high among women aged between 25 and 54.

&bull: According to the Health Loss in New Zealand study, anxiety, along with depressive disorders, were the second leading cause of health loss for New Zealanders, accounting for 5.3 per cent of all health loss, behind only coronary heart disease. For women, they were the leading cause.

- NZ Herald

Read more by Jamie Morton Email Jamie Morton
Stop Signal EEG and Personality

(Principal Investigator: Professor Neil McNaughton, Department of Psychology, 03-479 7634)

INFORMATION SHEET FOR PARTICIPANTS

Introduction

Thank you for showing an interest in this project. Please read this information sheet carefully. Take time to consider and, if you wish, talk with relatives or friends, before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

What is the aim of this research project?

This project investigates how the electrical activity of your brain varies when you are trying to stop a response once you have started making one. We are particularly interested in how one specific brain rhythm (which appears when stopping and going are in conflict with each other) relates to current questionnaires that measure anxiety-related traits. The results should show how the various personality trait measures relate to trait variation in the conflict response and should also provide a basis for developing a new conflict response scale, extreme responses on which could potentially be used to diagnose a specific kind of anxiety disorder. The brain rhythm data will also provide a reference population against which clinical groups can be compared in future.

Who is funding this project?

This project is part of the work funded by a grant to Professor Neil McNaughton and collaborators at the University of Otago and the University of Auckland from the Health Research Council of New Zealand.

Who are we seeking to participate in this project?

We are seeking participants who are 18-40 years old, healthy (with no major illness in the previous 30 days), with no regular use of psychotropic medication in the last 6 months and no use of alcohol in the 24 hours before testing. You should be willing to receive medical and psychiatric screening interviews and undergo a urine test for psychotropic compounds.

You will NOT be able to participate in the project because it may involve an unacceptable risk to you if have:

1. Susceptibility to photosensitivity.
2. A history of seizure.
3. A history of allergic skin reactions to chemical agents including detergents.

If you participate, what will you be asked to do?

For the main part of the test, we will record the electrical activity from your scalp, heart and a finger during a ten minute rest period and in a “stop signal” task with stimuli delivered on a computer screen and through earphones and to which you will make responses using a computer mouse. You will be interviewed about your physical and mental health and also be asked to complete several questionnaires that measure aspects of your mood and personality. The whole experiment will take about three hours. In recognition of the time, inconvenience, and travel costs in attending for testing, you will be compensated at a rate of $15 for each hour of attendance.

Preparation for the experiment

Hair products and natural oils on our scalp make it difficult to record your brain activities. It is important to us that you come with a clean scalp. Please avoid using any hair products on the day of the experiment. We recommend that you wash your hair on the day or the day before and avoid using a hair conditioner. For participants with glasses, we also recommend that you wear contact lenses if possible for your own comfort.

Electrical recording procedure

You will put on an electro-cap as shown in the picture. We will fill the electrodes (small metal discs) attached to the cap with a gel that conducts brain signals from your scalp to our recording system. To achieve good recordings, we will abrade your skin gently before applying the gel. The electrodes are then connected to an amplifier that allows us to record your brain rhythms (EEG). We will also attach stick-on electrodes to your body to record your heart activity (ECG) and a clip on electrode to an index finger to measures your skin resistance/perspiration (GSR). The whole system is regularly tested and passes the current standards for connecting electrical equipment to people.

Is there any risk of discomfort or harm from participation?

There is a risk of allergic skin reaction to the electrode gel and of minor discomfort from the abrasion of the skin surface during gel application. Exposure to stimuli on a computer screen has a rare risk of inducing seizures in those with or without a history of seizure. If you have a history either of photosensitivity or of any form of seizure you should not take part. The person running your electrical testing is required to be trained in the procedures for connecting you to the equipment and to have a current First Aid Certificate (with training renewed every two years by the New Zealand Red Cross) so that they can respond appropriately to any unexpected adverse events that occur during testing.

What data will be collected, and how will they be used?

Your physical and mental health status, questionnaire scores, and electrical recordings will be stored in secure computer databases and will be identified only with your participant number. Any paper records will be stored securely in locked filing cabinets. Health status will be assessed only to exclude participants who do not meant the entry criteria. Questionnaire and electrical data will be subjected to group statistical analysis to determine general group-wide personality trait relationships and reference data. Urine samples, identified only by participant number, will be disposed of by the analysing laboratory using their usual procedures and only the qualitative,
present/absent, result returned by the laboratory will be used for inclusion/exclusion. Data will be stored for 10 years and then deleted.

**What about anonymity and confidentiality?**

No identifying data will be recorded. All collected data will be linked only to your participant number. All data will be stored securely and accessed only by study personnel. Reporting of the completed research will be of aggregated data over all participants and no data will be reported linked to an individual participant number.

**Can Participants Change their Mind and Withdraw from the Project?**

You may withdraw from participation in the project at any time and without any disadvantage to yourself of any kind.

**What if Participants have any Questions?**

If you have any questions about our project, either now or in the future, please feel free to contact either:-

Shabah Shadli (Telephone: 03 479 5835) or Professor Neil McNaughton (Telephone: 03 479 7634)
shabah.shadli@otago.ac.nz nmcn@psy.otago.ac.nz

*This project has been reviewed and approved by the University of Otago Human Ethics Committee (Health: H 15/005). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479-8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.*
Stop Signal EEG and Personality

(Principal Investigator: Professor Neil McNaughton, Department of Psychology, 03-479 7634)

CONSENT FORM FOR PARTICIPANTS

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time without disadvantage.
6. I am aware that undergraduate students will be present and will carry out some parts of the experiment.
7. I know that as a participant I will undergo electrical (EEG/ECG/GSR) testing, physical and mental health screening, and a qualitative urine test for psychotropic drugs and complete questionnaires assessing emotion, as listed in the information sheet. I understand that I may decline to answer any interview or questionnaire question without disadvantage of any kind.
8. I know that no personal identifying information will be included in the paper records and electronic files which represent the data from the project, and that these will be placed in secure storage and kept for at least ten years.
9. I understand the nature and size of the risks of discomfort or harm that are explained in the Information Sheet, including the rare risk of computer screen-induced seizures.
10. I understand that the results of the project may be published but my anonymity will be preserved and only group data reported.

I agree to take part in this project.

...............................................................................

(Full name)

...............................................................................

(Signature of participant) .................................................. (Date)
This project has been reviewed and approved by the University of Otago Human Ethics Committee (Health: H 15/005). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479-8256 or email gary.witte@otago.ac.n). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
EEG Testing for an Anxiety Process

(Principal Investigator: Professor Neil McNaughton, Department of Psychology, 03-479 7634)

INFORMATION SHEET FOR PATIENTS

Introduction
Thank you for showing an interest in this project. Please read this information sheet carefully. Take time to consider and, if you wish, talk with relatives, friends, or your doctor, before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

What is the aim of this research project?
This project investigates how the electrical activity of your brain varies when you are trying to stop a response once you have started making one. We are particularly interested in how one specific brain rhythm (which appears when stopping and going are in conflict with each other) relates to current questionnaires that measure anxiety-related traits. The results should show how the various personality trait measures relate to trait variation in the conflict response and should also provide a basis for developing a new conflict response scale, extreme responses on which could potentially be used to diagnose a specific kind of anxiety disorder. We predict that some people with any of a range of anxiety symptoms will have a stronger conflict brain rhythm compared both to other people with much the same anxiety symptoms and to a non-clinical population. We expect this stronger rhythm will be linked to a greater treatment response. It is important for us that we measure this rhythm before you receive any treatment as we already know that a variety of anti-anxiety drugs strongly affect it.

Who is funding this project?
This project is part of the work funded by a grant to Professor Neil McNaughton and collaborators at the University of Otago and the University of Auckland from the Health Research Council of New Zealand.

Who are we seeking to participate in this project?
We are seeking participants who are 18-40 years old, who are suffering from ongoing symptoms of anxiety, fear, or panic and who are intending to seek treatment for this. You should otherwise be healthy (with no major illness in the previous 30 days), with no regular use of psychotropic medication in the last 6 months and no use of alcohol in the 24 hours before testing. You should be willing to receive medical and psychiatric screening interviews; be willing for us to contact your GP prior to the commencement of the study, if necessary, about your medical history; and be willing to undergo a urine test for psychotropic compounds immediately prior to EEG testing.
You will NOT be able to participate in the project, because it may involve an unacceptable risk to you, if you have:

1. Susceptibility to photosensitivity.
2. A history of seizure.
3. A history of allergic skin reactions to chemical agents including detergents.

If you participate, what will you be asked to do?

For the main part of the test, we will record the electrical activity from your scalp, heart and a finger during a ten minute rest period and in a “stop signal” task with stimuli delivered on a computer screen and through earphones and to which you will make responses using a computer mouse. You will be interviewed about your physical and mental health and also be asked to complete several questionnaires that measure aspects of your mood and personality. The whole experiment will take about three hours. You will also be asked to return to the laboratory at 3 months and 6 months after your initial testing session at which time we will give you a brief interview to determine any changes in your anxiety-related symptoms, ask you to report on any treatment you have received since the initial testing session, and fill out some of the original questionnaires for a second time. These follow up tests are likely to take about one hour. In recognition of the time, inconvenience, and travel costs in attending for testing, you will be compensated at a rate of $15 for each hour of attendance at the end of each test period.

Preparation for the experiment

Hair products and natural oils on our scalp make it difficult to record your brain activities. It is important to us that you come with a clean scalp. Please avoid using any hair products on the day of the experiment. We recommend that you wash your hair on the day or the day before and avoid using a hair conditioner. For participants with glasses, we also recommend that you wear contact lenses if possible for your own comfort.

Electrical recording procedure

You will put on an electro-cap as shown in the picture. We will fill the electrodes (small metal discs) attached to the cap with a gel that conducts brain signals from your scalp to our recording system. To achieve good recordings, we will abrade your skin gently before applying the gel. The electrodes are then connected to an amplifier that allows us to record your brain rhythms (EEG). We will also attach stick-on electrodes to your body to record your heart activity (ECG) and a clip on electrode to an index finger to measures your skin resistance/perspiration (GSR). The whole system is regularly tested and passes the current standards for connecting electrical equipment to people.

Is there any risk of discomfort or harm from participation?

There is a risk of allergic skin reaction to the electrode gel and of minor discomfort from the abrasion of the skin surface during gel application. Exposure to stimuli on a computer screen has a rare risk of inducing seizures in those with or without a history of seizure. If you have a history either of photosensitivity or of any form of seizure you should not take part. The person running your electrical testing is required to be trained in the procedures for connecting you to the equipment and to have a current First Aid Certificate (with training renewed every two years by the New Zealand Red Cross) so that they can respond appropriately to any unexpected adverse events that occur during testing.
What data will be collected, and how will they be used?

Your physical and mental health status, questionnaire scores, and electrical recordings will be stored in secure computer databases and will be identified only with your participant number. Identifying data, including the identity of your GP, will be stored separately from the study data and will be used only for contact purposes. Any paper records will be stored securely in locked filing cabinets. Physical health status will be assessed only to exclude participants who do not meet the entry criteria. Mental health status will be assessed to allow exclusion of some conditions but, in particular, will be used to assess the classification of your anxiety disorder within the DSM diagnostic system. Your questionnaire, diagnostic and electrical data will be subjected to group statistical analysis to determine general group-wide personality trait relationships and differences from reference data. Urine samples, identified only by participant number, will be disposed of by the analysing laboratory using their usual procedures and only the qualitative, present/absent, result returned by the laboratory will be used for inclusion/exclusion. Data will be stored for 10 years and then deleted.

What about anonymity and confidentiality?

All information generated in this study will be considered highly confidential and must not be disclosed to any persons not directly concerned with the study. However, authorized regulatory officials and sponsor personnel will be allowed full access to the records. Only participant initials and unique participant study numbers will identify participants on data documents or in the database and identity data will be stored separately. However, participants' full names may be made known to a regulatory agency or other authorized official (e.g. GP) if necessary. All data will be stored securely and accessed only by study personnel. Reporting of the completed research will be of aggregated data over all participants and no data will be reported linked to an individual participant number.

Can Participants Change their Mind and Withdraw from the Project?

You may withdraw from participation in the project at any time and without any disadvantage to yourself of any kind.

What if Participants have any Questions?

If you have any questions about our project, either now or in the future, please feel free to contact either:-

Shabah Shadli (Telephone: 03 479 5835) or Professor Neil McNaughton (Telephone: 03 479 7634)
shabah.shadli@otago.ac.nz nmcn@psy.otago.ac.nz

This project has been reviewed and approved by the University of Otago Human Ethics Committee (Health: H 15/005). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479-8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
Stop Signal EEG and Personality

(Principal Investigator: Professor Neil McNaughton, Department of Psychology, 03-479 7634)

CONSENT FORM FOR PATIENTS

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time without disadvantage.
6. I am aware that undergraduate students will be present and will carry out some parts of the experiment.
7. I know that as a participant I will undergo electrical (EEG/ECG/GSR) testing, physical and mental health screening, and a qualitative urine test for psychotropic drugs and complete questionnaires assessing emotion, as listed in the information sheet. I understand that I may decline to answer any interview or questionnaire question without disadvantage of any kind.
8. I know that no personal identifying information will be included in the paper records and electronic files which represent the data from the project, and that these will be placed in secure storage and kept for at least ten years.
9. I understand the nature and size of the risks of discomfort or harm that are explained in the Information Sheet, including the rare risk of computer screen-induced seizures.
10. I understand that the results of the project may be published but my anonymity will be preserved and only group data reported.

I agree to take part in this project.
I agree that my GP can be contacted for information about my health and to receive health related information about me from this project

...............................................................................................................................  ..............................................................................................................................
(Full name)                                               (GP name, location)
This project has been reviewed and approved by the University of Otago Human Ethics Committee (Health: H 15/005). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479-8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
Appendix F: Questionnaire Part 1

State Trait Anxiety Inventory

A number of statements which people have used to describe themselves will be given below. Read each statement and then click on the appropriate box below the statement to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

*Response format for every STAI item is:

ALMOST NEVER
SOMETIMES
OFTEN
ALMOST ALWAYS
-----

I feel pleasant
I feel nervous and restless
I feel satisfied with myself
I wish I could be as happy as others seem to be
I feel like a failure
I feel rested
I am “calm, cool, and collected”
I feel that difficulties are piling up so that I cannot overcome them
I worry too much over something that really doesn’t matter
I am happy
I have disturbing thoughts
I lack self-confidence
I feel secure
I make decisions easily
I feel inadequate
I am content
Some unimportant thought runs through my mind and bothers me
I take disappointments so keenly that I can’t put them out of my mind
I am a steady person
I get in a state of tension or turmoil as I think over my recent concerns and interests
Eysenck Personality Questionnaire

Please answer each question by selecting the most appropriate box under each question. There are no right or wrong answers, and no trick questions. Work quickly and do not think too long about the exact meaning of the questions.

Please remember to answer each question

-----

Do you have many different hobbies?

No- none
No- not many
Yes- a few
Yes- lots

*Response formats for remaining EPQ items are:

No- Almost never
No- Sometimes
Yes- Often
Yes- Almost Always

-----

Does your mood often go up and down?

Are you a talkative person?

Do you ever feel ‘just miserable’ for no reason?

Are you rather lively?

Do you often worry about things you should not have done or said?

Can you usually let yourself go and enjoy yourself at a lively party?

Are you an irritable person?

Do you enjoy meeting new people?

Are your feelings easily hurt?

Do you tend to keep in the background on social occasions?

Do you often feel ‘fed-up’?

Do you like going out a lot?

Are you often troubled about feelings of guilt?

Do you prefer reading to meeting new people?

Would you call yourself a nervous person?

Do you have many friends?

Are you a worrier?
Would you call yourself happy-go-lucky?
Do you worry about awful things that might happen?
Do you usually take the initiative in making new friends?
Would you call yourself tense or ‘highly strung’?
Are you mostly quiet when you are with other people?
Can you easily get some life into a rather dull party?
Do you worry about your health?
Do you like telling jokes and funny stories to your friends?
Do you like mixing with people?
Do you suffer from sleeplessness?
Have people said that you sometimes act too rashly?
Do you nearly always have a ‘ready’ answer when people talk to you?
Have you often felt listless and tired for no reason?
Do you like doing things in which you have to act quickly?
Do you often make decisions on the spur of the moment?
Do you often feel life is very dull?
Do you often take on more activities than you have time for?
Do you worry a lot about your looks?
Have you ever wished that you were dead?
Can you get a party going?
Do you worry too long after an embarrassing experience?
Do you suffer from ‘nerves’?
Do you often feel lonely?
Are you easily hurt when people find fault with you or the work you do?
Do you like plenty of bustle and excitement around you?
Are you sometimes bubbling over with energy and sometimes very sluggish?
Do other people think of you as being very lively?
Are you touchy about some things?
When your temper rises, do you find it difficult to control?
Behavioural Inhibition Scale/Behavioural Activation Scale

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says by selecting the appropriate box below. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses.

*Response format for every BIS scale item is:

very true for me
somewhat true for me
somewhat false for me
very false for me
-----

Even if something bad is about to happen to me, I rarely experience fear or nervousness.

Criticism or scolding hurts me quite a bit.

I feel pretty worried or upset when I think or know somebody is angry at me.

If I think something unpleasant is going to happen I usually get pretty "worked up."

I feel worried when I think I have done poorly at something important.

I have very few fears compared to my friends.

I worry about making mistakes.
Appendix G: Questionnaire Part 2
Sleep Questions

We want to ask you some questions about your sleep

Please select an answer to the question from the drop down list

-----

In general, what time do you go to sleep each night?

6pm-8pm
8pm-10pm
10pm-midnight
midnight-2am
2am-4am
4am-6am
-----

In general, what time do you wake up each morning?

2am-4am
4am-6am
6am-8am
8am-10am
10am-midday
midday or later
-----

In general, how variable is your sleep start time between different nights?

0-30 minutes
30 minutes - 1 hour
1 hour - 1.5 hours
1.5 hours - 2 hours
2 hours or more
-----

In general, how long does it usually take you to get to sleep each night?

0-30 minutes
30 minutes - 1 hour
1 hour - 1.5 hours
1.5 hours - 2 hours
2 hours or more
-----

I use an alarm to wake me up...

Never
Only for early events
Often
Always
-----
How often do you wake up during the night?

0
1-2
3-4
5+

-----

If you wake up in the night, how long does it generally take you to fall back asleep?

0-10 minutes
10-20 minutes
20-30 minutes
30 minutes or more

-----

On average, how many total hours do you sleep per night?

0-2
2-4
4-6
6-8
8-10
10+

-----

Depression Question
We want to ask you a question about your past experience with depression.

Please select an answer to the question from the drop down list

-----

Which statement about past substantial (more than a few days) periods of depression is most true for you?

I have never been depressed for more than a few days at a time.
I have experienced a period of substantial depression.
I have experienced multiple periods of substantial depression.
I have experienced a period of clinically diagnosed depression.
I have experienced multiple periods of clinically diagnosed depression.
I have experienced a period of clinically diagnosed major depressive disorder.
I have experienced multiple periods of clinically diagnosed major depressive disorder.

-----
The Personality Inventory for DSM-5

This is a list of things different people might say about themselves. We are interested in how you would describe yourself. There are no right or wrong answers. So you can describe yourself as honestly as possible, we will keep your responses confidential. We'd like you to take your time and read each statement carefully, selecting the response that best describes you.

*The response format for all PID-5 items is:

Very False or Often False
Sometimes or Somewhat False
Sometimes or Somewhat True
Very True or Often True

-----

I don't get as much pleasure out of things as others seem to.

People would describe me as reckless.

I avoid risky situations.

When it comes to my emotions, people tell me I'm a "cold fish".

I prefer not to get too close to people.

I dread being without someone to love me.

My emotions sometimes change for no good reason.

I keep to myself.

Nothing seems to interest me very much.

I almost never enjoy life.

I often feel like nothing I do really matters.

I'm an energetic person.

I avoid risky sports and activities.

I have no limits when it comes to doing dangerous things.

I don't have very long-lasting emotional reactions to things.

It is hard for me to stop an activity, even when it’s time to do so.

I do a lot of things that others consider risky.

I worry a lot about being alone.

I've missed out on things because I was busy trying to get something I was doing exactly right.

I’d rather be in a bad relationship than be alone.

I keep approaching things the same way, even when it isn’t working.

I'm very dissatisfied with myself.
I have much stronger emotional reactions than almost everyone else.
I can't stand being left alone, even for a few hours.
The future looks really hopeless to me.
I like to take risks.
When I want to do something, I don't let the possibility that it might be risky stop me.
I go out of my way to avoid any kind of group activity.
It is hard for me to shift from one activity to another.
I worry a lot about terrible things that might happen.
I have trouble changing how I'm doing something even if what I'm doing isn't going well.
The world would be better off if I were dead.
I keep my distance from people.
I don't get emotional.
I'm so ashamed by how I've let people down in lots of little ways.
I avoid anything that might be even a little bit dangerous.
I prefer to keep romance out of my life.
I don't show emotions strongly.
I often worry that something bad will happen due to mistakes I made in the past.
I get very nervous when I think about the future.
I rarely worry about things.
I enjoy being in love.
I prefer to play it safe rather than take unnecessary chances.
I get fixated on certain things and can't stop.
People tell me it's difficult to know what I'm feeling.
I am a highly emotional person.
I often feel like a failure.
I break off relationships if they start to get close.
I'm always worrying about something.
I worry about almost everything.
I don't mind a little risk now and then.
I talk about suicide a lot.
I'm just not very interested in having sexual relationships.
I get stuck on things a lot.
I get emotional easily, often for very little reason.
I almost never feel happy about my day-to-day activities.
I fear being alone in life more than anything else.
I get stuck on one way of doing things, even when it's clear it won't work.
I am a very anxious person.
I don’t like spending time with others.
I feel compelled to go on with things even when it makes little sense to do so.
I never know where my emotions will go from moment to moment.
I always expect the worst to happen.
I steer clear of romantic relationships.
I'm not interested in making friends.
I say as little as possible when dealing with people.
I'm useless as a person.
I'll do just about anything to keep someone from abandoning me.
Life looks pretty bleak to me.
I really live life to the fullest.
Nothing seems to make me feel good.
I do what I want regardless of how unsafe it might be.
I don’t like to get too close to people.
Everything seems pointless to me.
I never take risks.
I get emotional over every little thing.
I never show emotions to others.
I often feel just miserable.
I have no worth as a person.
I'm always fearful or on edge about bad things that might happen.
I never want to be alone.
I know I'll commit suicide sooner or later.
My emotions are unpredictable.
I don't deal with people unless I have to.
I don't react much to things that seem to make others emotional.
I avoid social events.
I rarely get enthusiastic about anything.
I don't think about getting hurt when I'm doing things that might be dangerous.
I prefer being alone to having a close romantic partner.
I feel guilty much of the time.
I hate to take chances.