Topographic distribution of human brain activity associated with cognitive processing in anxiety disorders

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Abstract

Increased attention towards threatening stimuli in both the external and internal environments is thought to be a factor in the causation and maintenance of pathological anxiety. Attentional biases for threatening information have been demonstrated in anxiety disorders, however the cortical mechanisms involved remain unclear. In this investigation, an Emotional Stroop task consisting of neutral, positive, depression-related and anxiety-related words, was used to investigate attentional biases in 14 Panic Disorder patients and 32 psychiatrically healthy controls. The standard colour-word Stroop was also performed to determine whether any general cognitive deficits exist in Panic Disorder. Steady-state probe topography (SSPT), a brain electrical activity imaging methodology, was used to investigate participants’ brain activity during performance of the tasks. It was hypothesised that Panic Disorder is associated with specific biases for disorder-specific information and thus patients would exhibit increased interference for anxiety-related words only, compared to neutral words. Mean reaction times for the Standard Stroop was similar for the two groups. For the Emotional Stroop task, neither group showed an interference effect for any emotional category. However, Panic Disorder patients performed the Emotional Stroop significantly more slowly than the Controls. The SSPT data suggest that the Standard and Emotional Stroop tasks are associated with different patterns of brain activity in the Control and Panic Disorder groups despite the similarities in the reaction time data. Specifically, the Standard Stroop was marked by strong temporo-parietal excitation in the Panic Disorder group only. In addition, anterior SSVEP patterns further differentiated between the Control and Panic Disorder groups. The most striking finding for the Emotional Stroop was strong sustained bilateral temporo-parieto-occipital excitation in the Panic Disorder group. In addition, a subgroup of the Controls exhibited increased interference for anxiety-related words and therefore the brain activity for this group and the remainder of Controls who did not show interference was analysed separately. It was found that the presence of interference for anxiety-related words was associated with right prefrontal inhibition prior to response. Other time-varying changes in the SSVEP further distinguished between the subgroup of Controls who showed an interference effect and those who did not.
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Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in the text of the thesis. To the best of my knowledge, this thesis contains no material previously published or written by another person except where due reference is made in the text of the thesis.

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Abbreviations

5-HT ........ 5-Hydroxytryptamine
(serotonin)

BA .......... Brodmann’s Area

BOLD ....... Blood-oxygen level-dependent

BZD .......... Benzodiazepine

CBF ........ Cerebral blood flow

CIDI ...... Composite International
Diagnostic Interview

CPT ........ Continuous performance task

CR .......... Conditioned response

CS .......... Conditioned stimulus

EEG ......... Electroencephalogram

eg ........... exempli gratia; for example

EP .......... Evoked potential

ERP ........ Event related potential

fMRI ....... Functional magnetic resonance
imaging

GABA .... Gamma-aminobutyric acid

GAD ....... Generalised Anxiety Disorder

ie .......... id est; that is

IQ .......... intelligence quotient

LC .......... Locus coeruleus

MHPG .... 3-methoxy-4-hydroxy-
phenylethylene-glucol

MRI....... Magnetic resonance imaging

MRS....... Magnetic resonance
spectroscopy

msec ...... Millisecond

NAd ...... Noradrenalin

OCD...... Obsessive-compulsive disorder

PET ....... Photon emission tomography

PTSD ..... Post traumatic stress disorder

rCBF ..... Regional cerebral blood flow

sd.......... Standard deviation

SHPQ..... Simplified hand preference
questionnaire

SPECT ... Single photon emission
computed tomography

SPM ...... Statistical parametric mapping

SSPT ...... Steady state probe topography

SSRI....... Selective serotonin re-uptake
inhibitor

SSVEP ... Steady state visual evoked
potential

STAI ...... Spielberger State/Trait Anxiety
Inventory

US ........ Unconditioned stimulus
CHAPTER 1   Introduction

This study investigates the brain activity associated with specific cognitive and emotional tasks in relation to anxiety disorders. Anxiety normally serves a purpose in the day to day functioning of an individual, and functions to warn of imminent danger and prepare the body for appropriate action. When anxiety is excessively strong, is inflated compared to the perceived danger, or is triggered by situations known to be harmless, it is considered abnormal. Abnormal anxiety may be short-lived or it may become chronic. Chronically abnormal anxiety may be manifested as one of the anxiety disorders, such as Panic Disorder, Generalised Anxiety Disorder or Social Phobia.

The present study focuses on Panic Disorder, which is characterised by panic attacks in which anxiety symptoms escalate in a short period of time to a severity that renders the sufferers fearing for their health and safety. In addition, fear of future panic attacks often results in individuals altering their daily habits to avoid certain situations in which panic attacks may occur. To understand the underlying mechanisms that contribute to the causes and maintenance of anxiety, Panic Disorder has been investigated with both biological and cognitive approaches. Biological approaches have investigated the neural circuitry and neurochemical contributions to anxiety and anxiety-related behaviour, particularly in animals (LeDoux, 1995a). The brain structures shown to be essential in specific aspects of animal models of fear include the amygdala, hippocampus and prefrontal cortex, and the breakdown in the regulation of these structures may lead to an exaggerated fear response similar to that seen in Panic Disorder (Armony and LeDoux, 1997).

In humans, the expression and experience of negative emotions, such as fear and disgust, appears to be mediated by anterior cortical structures (Davidson, 1992; Davidson, 1993). Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have shown that, in addition to anterior cortical structures, subcortical structures are often activated for negative emotions (eg Lane et al, 1997; Teasdale et al, 1999). Anxiety in particular may involve the right parieto-temporal region, which appears to important in emotional arousal (Heller, 1993), in addition to anterior brain structures.
Investigations of the neurophysiology of Panic Disorder itself have utilised both electrophysiological and neuroimaging techniques to reveal the underlying neural mechanisms that contribute to anxiety. In particular, abnormalities of the right hemisphere and the hippocampal region have been identified in individuals with Panic Disorder (eg Fontaine et al, 1990; Reiman, 1987). In addition, abnormalities of the left parietal cortex have been observed, which may reflect neurochemical dysfunction (Meyer et al, 2000; Nordahl et al, 1998). Dysregulation of the serotonergic, noradrenergic systems and benzodiazepine mediated gamma-aminobutyric acid (GABA) system have also been implicated in Panic Disorder (Krystal et al, 1996; Salzman et al, 1993).

Other approaches to understanding anxiety disorders, including Panic Disorder, have focussed on cognitive aspects. In particular, anxiety disorders have been consistently associated with attention towards threatening stimuli (Mathews and MacLeod, 1994), and such attentional biases may play a part in the causation and maintenance of pathological anxiety (Beck et al, 1985; Clark, 1988). The Emotional Stroop task has commonly been used to study attentional biases for threatening stimuli in anxiety. It is based on the original Stroop task (Stroop, 1935) which requires participants to identify the ink colour of colour-names and coloured shapes or symbols as fast as possible. It has been found that ability to name the ink colour is consistently disrupted by a contrasting colour name and produces a reliable measure of interference (MacLeod, 1991). In the Emotional Stroop task, colour names are replaced with words of various emotional valence and significance. The difference in the time to name the ink colour of threatening words as compared to neutral words is termed Emotional Stroop interference. Emotional Stroop interference has been shown to be elevated in anxiety disorders (Williams et al, 1996; Williams et al, 1997), and particularly for Panic Disorder (McNally, 1994).

Investigations of the neurophysiology of the Emotional Stroop have been limited to psychiatrically healthy participants, and have noted a particular role for the left frontal regions and the anterior cingulate, in processing threat stimuli (Compton et al, 2003; George et al, 1994; Whalen et al, 1998a). Activation of other cortical and subcortical structures has also been observed (Compton et al, 2003; Isenberg et al, 1999), although no consistent results have emerged. While the association between elevated Emotional Stroop interference and clinical anxiety has been well documented (Mathews and MacLeod, 1994;
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Williams et al, 1997), there have to date been no studies investigating the underlying neural mechanisms of Emotional Stroop performance in anxiety disorders. The present study aims to address this issue by examining the differences in brain activity between healthy controls and Panic Disorder participants during performance of an Emotional Stroop and standard Stroop task.

The present study uses steady-state probe topography (SSPT) methodology to compare brain activity at multiple sites in Panic Disorder and Control participants during performance of both the Standard Stroop and Emotional Stroop tasks. The SSPT technique utilises a steady-state visually evoked potential (SSVEP) as the irrelevant probe stimulus, which is altered in regions of the brain engaged in the cognitive processes being investigated. One of the main advantages of the SSPT technique over traditional ERP techniques is its ability to provide a continuous measure of time-varying processes, and to index both tonic (Silberstein et al, 1990) and transient alterations in regional brain activation (Silberstein et al, 1995). Another advantage of the SSPT technique is that it is relatively unaffected by noise and common artifacts such as eye movement, muscle tension and eye blinks. In addition, the sixty-four recording electrodes utilised in the present study permits good spatial resolution. The SSPT technique is also relatively non-invasive and is inexpensive compared to PET and fMRI techniques.

In the present study, the neurophysiology of the Standard and Emotional Stroop tasks in women with Panic Disorder and a psychiatrically healthy Control group was investigated using the SSPT technique. The Standard Stroop task comprised the incongruent Stroop which was compared to the congruent Stroop. The Standard Stroop task was included in the present study was to determine whether general cognitive deficits existed in the Panic Disorder group, and also to determine the specificity of observed neurophysiological effects within the Emotional Stroop.

The Emotional Stroop consisted of four different categories of words, namely, anxiety-related, depression-related, positive and neutral words. The comparison task consisted of categorised neutral words. In addition, ratings of emotionality confirmed the intended emotional impact of the Emotional Stroop words. In both tasks, participants were required to respond verbally to the ink colour of the words presented.
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This thesis is divided into seven chapters. Chapter 2 reviews the biological approaches to understanding anxiety, with a focus on Panic Disorder. In this chapter, animal models which have provided information regarding the underlying neurophysiology of anxiety, and evidence of anxiety-related neurotransmitter dysfunction in humans are discussed. Other approaches which have utilised neuroimaging techniques to further elucidate the neural mechanisms of anxiety will also be explored. In this chapter, the reader is given an overview of the brain regions previously associated with abnormal function in anxiety, and Panic Disorder in particular.

Cognitive approaches to investigating attentional biases in anxiety disorders are introduced in Chapter 3, with an emphasis on Panic Disorder. Following an overview of the original Stroop task, this chapter introduces the Emotional Stroop, which has been used extensively as a tool to investigate attentional biases in both clinical and subclinical anxiety. The use of the Emotional Stroop task, particularly in Panic Disorder, and the factors contributing to the production of interference are discussed. In addition, the limited number of neurophysiological investigations of the Emotional Stroop in non-psychiatric populations is reviewed.

Chapter 4 introduces the steady state probe topography (SSPT) technique which utilises the steady state visual evoked potential (SSVEP), and was used in the present study to investigate regional brain activity associated with the Standard and Emotional Stroop tasks. Chapter 4 also presents the aims and hypotheses of the present study.

Details of the task construction and methods employed in the present study for recording and analysing the SSPT data is presented in Chapter 5. The following chapter, Chapter 6, presents the results of the present study. Both behavioural and electrophysiological experimental results are presented.

In Chapter 7, both the behavioural and SSPT findings for the Control and Panic Disorder groups are discussed. In addition, the finding of a subgroup of Controls who exhibited Emotional Stroop interference is examined. This is followed by conclusions drawn from the present study and a discussion of future directions in the neurophysiology of the Emotional Stroop in anxiety disorders.
CHAPTER 2 Neurophysiology Of Anxiety

This section will review literature relevant to understanding the neurophysiology of anxiety, with a focus on Panic Disorder. In particular, the classification and diagnosis of Panic Disorder within the framework of anxiety disorders will be stated in section 2.1. In section 2.2, the aetiology of Panic Disorder will be explored, and will focus on the biological correlates of anxiety. Investigations of fear in animals have contributed to the understanding of fear and anxiety in humans and will be explored in section 2.2.1. Following this, the neurochemistry of anxiety including evidence for neurotransmitter dysfunction and receptor abnormalities in Panic Disorder will be examined in section 2.2.2. Advances in neuroimaging and electroencephalographic (EEG) techniques have also contributed to the understanding of the neurophysiological basis of anxiety and anxiety disorders and will be explored in section 2.2.3.

2.1 Panic Disorder diagnosis

Panic Disorder first appeared as a discrete diagnosis in the third edition of Diagnostic and Statistical Manual of Diseases (DSM-III: American Psychiatric Association, (APA), 1980) and was continued and refined in a subsequent revision (DSM-III-R: APA, 1987). In DSM-III (APA, 1981), Panic Disorder was differentiated from Generalised Anxiety Disorder (GAD); prior to this time, both diagnoses were encompassed within ‘anxiety neurosis’. In addition, agoraphobia, simple phobia and social phobia were recognised as distinct diagnoses. In the revised edition of DSM-III (DSM-III-R: APA, 1987) it was recognised that Panic Disorder could occur with or without agoraphobia. It also included the first psychological criterion for Panic Disorder in which fear of subsequent attacks became an important aspect of diagnosis.

Further revision brought about DSM-IV (APA, 1994) which further defines and clarifies Panic Disorder. The essential feature of Panic Disorder in DSM-IV is:

“the presence of recurrent, unexpected Panic Attacks, followed by at least 1 month of persistent concern about having another Panic Attack, worry about
the possible implications or consequences of the Panic Attack, or a significant behaviour change related to the attacks”

(p397, DSM-IV; APA, 1994)

To qualify for Panic Disorder, the panic attacks should not be due to substance ingestion such as caffeine, carbon dioxide or other stimulants. Panic attacks should also not be due to a general medical condition, and should not be associated with other factors such as separation anxiety, post traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), or specific or social phobias.

A panic attack is defined as an acute exacerbation of anxiety made up of a discreet period of intense fear or discomfort, in which four or more of the following somatic or cognitive symptoms develop abruptly and reach a peak within 10 minutes:

1. palpitations, pounding heart or accelerated heart rate
2. sweating
3. trembling or shaking
4. sensations of shortness of breath or smothering
5. feeling of choking
6. chest pain or discomfort
7. nausea or abdominal distress
8. feeling dizzy, unsteady, light-headed or faint
9. derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. fear of losing control or going crazy
11. fear of dying
12. paraesthesia (numbness or tingling sensations)
13. chills or hot flushes

(p395, DSM-IV; APA, 1994)
Thus the criteria for Panic Disorder (with or without agoraphobia) require both of the following criteria to be met:

1. recurrent unexpected panic attacks

and

2. at least one of the attacks has been followed by one month (or more) of one (or more) of the following:
   i persistent concern about having additional attacks
   ii worry about the implications of the attack and its consequences
   iii a significant change in behaviour relate to the attacks.

For a diagnosis of Panic Disorder to occur, at least two unexpected panic attacks are required, although most individuals experience considerably more (APA, 1994). Unexpected or spontaneous panic attacks are defined as those not associated with a known trigger, that is, they occur ‘out of the blue’. Situationally predisposed attacks, which are more likely to occur on, but not always associated with, exposure to a situational trigger, also occur frequently in Panic Disorder. Less common in Panic Disorder are situationally bound attacks, which are those that occur immediately and invariably on exposure to a trigger.

DSM-IV notes that the frequency and severity of panic attacks can vary widely. In addition to the symptoms listed above, individuals often display characteristic concerns about the implications of panic attacks, such as the fear of losing control or going crazy. Others may fear the panic attacks are an indication of an undiagnosed life-threatening illness (eg heart disease) often despite medical testing and reassurance to the contrary. Individuals with recurrent panic attacks may significantly change their behaviour in response to the attacks, while denying the fear of another attack or its consequences. In its extreme, this can lead to avoidant behaviour that meets criteria for agoraphobia, resulting in the diagnosis of Panic Disorder with agoraphobia (APA, 1994).
2.1.1 **Associated features of Panic Disorder**

DSM-IV (APA, 1994) indicates that lifetime prevalence of Panic Disorder (with or without agoraphobia) is between 1.5% and 3.5%. In addition, lifetime prevalence has been for women appears to be three times higher than in men (Joyce et al, 1989). DSM-IV (APA, 1994) also states that agoraphobia occurs in less than half of people with Panic Disorder. The age at onset varies but is typically between late adolescence and the mid-30s. Although agoraphobia can occur at any stage of the illness, it is most often seen within the first year of recurrent panic attacks. Major Depression occurs in 50%-60% of people with Panic Disorder, and comorbidity with other anxiety disorders is common. There is also evidence for a genetic contribution to the development of Panic Disorder (McNally, 1994).

2.2 **The aetiology of Panic Disorder**

Panic Disorder has been studied in a variety of ways depending on the view behind the research. Two main streams of research into the development and maintenance of Panic Disorder include those centred on biological contributions and those utilising cognitive approaches. The cognitive view is based on theoretical models of emotional disturbance (e.g. Beck et al, 1985; Bower, 1981; Clark, 1988) which suggest attentional biases for emotionally relevant material may be responsible for the development and maintenance of emotional disorders, particularly in anxiety. Researchers have used a number of methods to demonstrate attentional biases in anxiety, and Panic Disorder in particular. One method involves a variation of the Stroop paradigm (Stroop, 1935) which has been used extensively to demonstrate attentional biases in anxiety disorders. The use of the emotional version of the Stroop task forms the basis of the present thesis and this will be explored in depth in Chapter 3.

The biological view of clinical forms of anxiety, such as Panic Disorder, holds that emotional disturbance results from misfiring of regular circuits in the brain responsible for ‘normal’ fear and anxiety. The proposed contributions to anxiety include the dysregulation of neural circuits involving both cortical and subcortical structures of the brain, including the amygdala. Dysfunction of particular neurotransmitters and their specific receptors have also been implicated in Panic Disorder. Animal correlates of negative emotion which using fear conditioning paradigms, have contributed to the understanding of fear in humans, and
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has implications for pathological anxiety. Neuroimaging methods such as PET and fMRI, as well as electroencephalographic techniques, have shed light on neural mechanisms related to normal and pathological emotion. The biological contributions to the understanding of anxiety and Panic Disorder in particular, are explored further in section 2.2.1.

2.2.1 Animal correlates of anxiety

Fear serves a purpose in the day to day functioning of an individual, including warning of imminent danger and preparing the body for appropriate action (for example, the fight or flight response). While the fight-or-flight mechanism has an evolutionary purpose in enabling both animals and humans to escape from harm, when the fear becomes greater than warranted by the situation, disorders of anxiety such as Panic Disorder may be present. In Panic Disorder, the regulation of normal ‘fear’ circuits within the brain may break down (Armony and LeDoux, 1997) leading to an exaggerated response such as a panic attack.

Fear can be readily elicited in animals, and there exist a number of quantative measures that can be made regarding fear, particularly in animals (LeDoux, 1995a). While investigations of animal fear may only approximate human fear, animal experimentation can go much further into the underlying neurocircuitry than can be achieved with humans. Comparisons of the effect of specific subcortical lesions in monkeys and humans shows great similarities (Aggleton and Mishkin, 1986) suggesting that investigations of animal emotion is useful in understanding fear in humans. Specifically, many behavioural similarities between humans and primates following damage to the amygdala, have been observed (Aggleton, 1992). In addition, researchers within the field have considered it reasonable to extrapolate primitive emotional responses, such as fear, from animal to human emotion (LeDoux, 1992).

While the application of animal fear to human emotion has its limitations (McKinney, 1988), fear is an important concept in Panic Disorder. Indeed, fear of panic is necessary for a diagnosis of Panic Disorder, and fear of losing control, going crazy or dying are some of the symptoms experienced during a panic attack (DSM-IV: APA, 1994). This section briefly reviews research on the neural basis of fear as learned from animal experimentation. In particular, the neural basis of conditioned fear in animals and its relevance to anxiety in humans is briefly explored.
Neurophysiology of anxiety

Conditioned fear, also known as aversive conditioning, is a technique commonly used to study fear reactions in laboratory animals. In a typical experimental paradigm, a neutral stimulus such as an auditory tone (or a flash of light) is presented to an animal several times, in conjunction with an aversive event such as a mild foot shock. Subsequently, when the tone is presented in the absence of the foot shock, the animal shows the characteristic signs of fear that it exhibited following the actual foot shock: freezing behaviour, increased blood pressure, increased heart rate and startle reaction (Gallagher and Chiba, 1996; LeDoux, 1995a).

In the typical fear conditioning paradigm, the neutral stimulus (eg tone, light) is named the Conditioned Stimulus (CS), the aversive event (eg shock) is the Unconditioned Stimulus (US), and the fear behaviour and expressions of the animal is labelled the Conditioned Response (CR). Fear conditioning is a powerful tool for studying the neural basis of emotion for three main reasons. Firstly, the conditioned fear is quickly learned, secondly, once learned the fear is difficult to extinguish, and thirdly, the CS (ie light, tone) is neutral and is unlikely to hold any emotional significance for the animal outside of the experiment (LeDoux, 1995a). Because it elicits a repeatable response with minimal training, the fear conditioning paradigm has been a successful tool in studying emotional learning in animals (LeDoux, 1995b).

Regardless of different experimental preparations and CR measures used in previous investigations of fear conditioning in animals, the common finding is of the essential role of the amygdala (LeDoux, 1995a). The main role of the amygdala is in determining whether a stimulus is dangerous or not (LeDoux, 1995b) and it is crucial in the learning, consolidation, retention and expression of conditioned fear (Davis et al, 1994).

Early experiments investigating the effects of removal of the temporal lobe, which also removed the amygdala, from non-human primates showed bizarre behavioural changes (Kling and Brothers, 1992). Subsequent studies showed that, in animals, removal of only the amygdala produces emotional unresponsiveness to all types of sensory stimuli (Aggleton and Mishkin, 1986). Each sense (sight, smell, taste, hearing, touch) has inputs into the amygdala (Ono et al, 1995), and may serve as a basis for learning the association between the Conditioned Stimulus and Unconditioned Stimulus in the fear conditioning
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paradigm. Sensory information converges at the lateral nucleus of the amygdala via the thalamus directly, or from thalamo-cortical projections (LeDoux, 1993). The expression of fear appears to be modulated by the central nucleus of the amygdala and projections from this site have been associated with physical responses to stress such as bradycardia, increases in blood pressure, freezing behaviour, startle reflex and release of stress hormones (LeDoux, 1995a).

Rats also develop fear reactions to the chamber the fear conditioning took place in, which is known as contextual conditioning. Lesions of the hippocampus and its projections to the amygdala appear to interfere with contextual conditioning (LeDoux, 1995a). The most obvious similarity is between the contextual conditioning of an animal, who responds fearfully when placed in the cage fear conditioning previously occurred in, and anxiety disorders is the phobic avoidance of Panic Disorder patients for situations in which a panic attack occurred (Gorman et al, 2000). For example, an individual may avoid certain places or situations because of the association with previous panic attacks (Hoehn-Saric and McLeod, 1988). Considering that emotional memories mediated by the amygdala system are indelible, even after behavioural aspects are extinguished (LeDoux, 1995b), it is reasonable to draw the analogy to Panic Disorder patients who may no longer panic, but maintain a degree of phobic avoidance (Gorman et al, 2000). While fear conditioning in animals aids in understanding the human experience of fear, it does not address the subjective emotional experience, which depends on the conscious appraisal of a threatening stimulus or situation (LeDoux, 1995a).

The prefrontal cortex may also be involved in maintaining anxiety. Following an animal's exposure to the fear conditioning paradigm, if the CS (eg light or tone) is presented repeatedly in the absence of the US (eg shock), the fear reactions gradually become weakened, a process known as extinction (Armony and LeDoux, 1997). While the amygdala appears to be important in the learning of conditioned fear, erasing such behaviour appears to involve the frontal lobe. In particular, the medial prefrontal cortex has been shown to mediate the extinction process, with lesions of the area significantly inhibiting the process (Morgan et al, 1993).
Thus the amygdala appears to be a key site for fear processing and learning in animals, which has implications for studying anxiety disorders, and in particular, Panic Disorder. Brain structures such as the hippocampus, appears to play a role in contextual conditioning, and the medial prefrontal has been associated with extinction of the fear response. A breakdown of the balance between the amygdala, hippocampus and the prefrontal cortex may result in powerful, indelible fear responses that are independent of strict contextual constraints (Armony and LeDoux, 1997). These structures may play a part in the genesis and maintenance of pathological anxiety, including Panic Disorder. While the study of fear in animals is convenient and allows far more in vivo analysis than is available in humans, it may only be considered an approximate model of fear in humans. The advent of neuroimaging methodologies such as PET and fMRI have allowed fear conditioning paradigms, similar to those used in animal research, to be studied in humans. These studies have shown that a number of structures, including the amygdala, are also important in human fear.

Using PET to record regional cerebral blood flow (rCBF), Morris et al (1998) demonstrated activation of the amygdala in ten healthy male participants, responding to a classical fear-conditioning paradigm. Participants were presented with two pictures of angry faces; one of which was associated with a loud burst of noise, the other was not. In half the trials, a neutral face masked the angry face after 30 msec, preventing conscious awareness of the stimulus. A significant increase in rCBF was noted in the right, but not the left amygdala during presentation of the conditioned angry face. For unmasked presentations, the opposite effect was produced, with increased blood flow in the left, but not the right amygdala. In an earlier study using a similar paradigm with unmasked presentation of stimuli, activity in the right amygdala was shown to covary with the activity in the pulvinar nucleus of the thalamus (Morris et al, 1997). That study also highlighted the role of other right hemispheric structures including the orbitofrontal cortex and superior frontal gyrus during presentation of the unpaired conditioned stimulus.

The use of neuroimaging techniques that require successive repetition of stimuli may mask effects in structures that habituate to repetition. This is particularly relevant for the amygdala, which has been shown to rapidly habituate to presentation of fearful faces (Whalen et al, 1998b). Habituation of the amygdala has also been shown to occur in an
aversive conditioning paradigm (Büchel et al, 1998). Büchel et al (1998) presented four neutral faces, half of which were paired with a loud tone and half which were not. Comparison of the two conditions revealed that the CS previously paired with the aversive tone produced activation of the anterior cingulate and insula, areas which are thought to be involved in emotional processing. The activation of the amygdala was revealed only through a time by condition interaction, suggesting rapid habituation to the CS previously paired with the aversive tone.

While the evidence is limited, aversive conditioning in humans appears to activate similar structures known to be involved in aversive conditioning in animals (LeDoux, 1998), such as the amygdala, as well as structures the amygdala has connections with including the thalamus and the prefrontal cortex. The amygdala appears to be activated even when conscious awareness is absent (Morris et al, 1998), suggesting an automatic component to the perception of emotional facial expressions. It is this automaticity that may be one of the hallmarks of anxiety disorders (McNally, 1995).

2.2.2 Neurotransmitter dysfunction in anxiety

In this section, the roles of the neurotransmitter systems implicated in Panic Disorder, including the serotonin system, the noradrenergic system and the GABA-mediated benzodiazepine (BZD) receptor complex, will be briefly reviewed. Medications that relieve anxiety have an effect on these neurotransmitter systems and receptor complexes, thus promoting further investigations. In addition, both the serotonin and noradrenergic systems have projections to and from structures identified in animal models of fear, while altered BZD receptor function has also been observed in fear-related structures (LeDoux, 1995a). Specific neurotransmitter and receptor abnormalities have been explored with the expectation that a further understanding of altered cerebral function in pathological anxiety will be gained.

2.2.2.1 Serotonergic dysfunction in Panic Disorder

The efficacy of selective serotonin re-uptake inhibitors (SSRIs) has been demonstrated in Panic Disorder (Bell and Nutt, 1998), which indicates a role for serotonin (5-HT) in the disorder. SSRIs were originally developed as antidepressants, however, they are also
effective in relieving anxiety symptoms in Panic Disorder (Bell and Nutt, 1998) and Generalised Anxiety Disorder (GAD: Deakin, 1998). The effectiveness of SSRIs, which specifically inhibit serotonin re-uptake within the central nervous system, has been considered to be the most compelling evidence for 5-HT dysfunction in anxiety disorders (Coplan and Lydiard, 1998).

The main source of serotonergic nuclei is the raphe nucleus, located in the medulla, which projects widely through the entire brain. The rostral serotonergic nuclei project to cortical and subcortical regions and can be divided into two groups based on distinct projections and characteristics (Grove et al, 1997). The Dorsal Raphe Nucleus (DRN) and Medial Raphe Nucleus (MRN) have projections to and from various structures such as the hypothalamus, thalamus, periaqueductal grey (PAG), locus coeruleus (LC), amygdala, hippocampus and cortical areas with have been directly or indirectly implicated in animal studies of fear (Graeff et al, 1993; LeDoux, 1995a; Tanaka, 1999). Each pathway is thought to have a distinct role in anticipatory fear and autonomic responses associated with panic as well as the cognitive and motor behaviour responses to anxiety.

As well as the efficacy of SSRIs, evidence for serotonin dysfunction in Panic Disorder have come from a variety of sources including peripheral biological markers of serotonergic function including metabolites and platelets (Sheehan et al, 1993) and the anxiogenic and abnormal neuroendocrine responses to 5-HT agonists (Bell and Nutt, 1998). However, the results of such studies have not yielded consistent results (Grove et al, 1997). Further evidence for 5-HT dysfunction in anxiety has come from other medications that have been successfully used in Panic Disorder, such as tricyclic antidepressants and monoamine oxidase inhibitors, which act on the serotonergic system in indirect ways (Sheehan et al, 1993).

Clinical and experimental findings of 5-HT dysfunction in Panic Disorder have led to two theories being developed: 5-HT excess and 5-HT deficit. Each theory is able to explain some, but not all experimental findings (Nutt, 1998). Grove et al (1997) propose an alternate theory that does not rely on abnormally high or low levels of 5-HT, but instead is a model of dysfunction of 5-HT that results from the homeostatic failure of the serotonin system via connections with other related structures.
2.2.2.2 Noradrenalin dysfunction in Panic Disorder

Located in the posterior pons, the locus coeruleus (LC) is the main site of noradrenalin neurons (NAd) in the brain. Ascending neurons from the LC project to areas implicated in anxiety such as the amygdala, hypothalamus, hippocampus, entorhinal cortex and PAG as well as projections to most other cortical regions (Coplan and Lydiard, 1998). The connections of the LC with other areas of the brain put it in a position to integrate external sensory and internal visceral data and influence other fear-related neural structures (Sullivan et al, 1999).

Studies of uncontrollable stress in animals have shown altered NAd function (Charney et al, 1990). In anxious and fearful situations, healthy human subjects have shown an increase in circulating NAd and its metabolite, 3-methoxy-4-hydroxy-phenlethylene-glucol (MHPG) suggesting a relation between NAd and anxiety (Bremner et al, 1996). In Panic Disorder, increases in plasma NAd, urinary MHPG and cerebrospinal fluid MHPG have been observed at baseline, but no consistent pattern has emerged (Bremner et al, 1996).

Administration of drugs that increase synaptic availability of NAd, such as yohimbine, provokes panic in Panic Disorder patients, while drugs that reduce available NAd, such as clonidine, ameliorate anxiety (Sullivan et al, 1999). In addition, yohimbine and clonidine produce respective changes in levels of circulating MHPG (Krystal et al, 1996).

Further evidence for NAd dysfunction in anxiety comes from anti-anxiety drugs including benzodiazepines, morphine and tricyclic antidepressants, which depress the activity of the LC neurons, thus implicating it in anxiety and panic (Charney et al, 1990). Reciprocal serotonergic projections to and from the LC exist (Grove et al, 1997) suggesting SSRIs may also have an indirect effect on the LC.

Thus the LC-NAd system is implicated in anxiety through its connections to fear-related neural structures as well as excessive levels of NAd and its metabolites in stressful conditions and in anxiety disorders, particularly during pharmacological challenge with yohimbine or clonidine. The efficacy of anti-anxiety drugs that act on the LC-NAd system is also evidence for its role. Given its connections, particularly with the amygdala and prefrontal cortex, the LC may be critical for the establishment of the appropriate emotional response to a given situation (Sullivan et al, 1999).
2.2.2.3 Benzodiazepine function in Panic Disorder

The anxiolytic properties of benzodiazepines (BZDs) are considered evidence for the role of BZD receptors in anxiety disorders (Lydiard et al, 1996). It is thought that BZDs act to increase the inhibitory effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the site of the GABA<sub>A</sub> receptor (Woods and Charney, 1988). Inverse BZD agonists, which bind to BZD receptors with a high affinity, provoke physiological and behavioural responses opposite to those of BZDs (Krystal et al, 1996). Neuroimaging methods such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) have utilised radiolabelled receptor ligands to investigate the regional distribution of BZD receptor sites in anxiety disorders.

Using radiolabelled [11C]iomazenil in PET, which has a high affinity for BZD receptors, Malizia et al (1998) found a global reduction in BZD receptors in Panic Disorder patients compared to controls. This reduction was highest in the right prefrontal and temporal sites. The patients were taking antidepressants at the time of the study, but had never taken BZDs. These results accord with reduced sensitivity of BZD receptors seen by Roy-Byrne et al (1990) which may be attributable to reduced receptor numbers. Using <sup>1</sup>H-Magnetic Resonance Spectroscopy, a novel technique, Goddard et al (2001) found reductions in occipital levels of GABA in Panic Disorder patients compared to controls. However the data is preliminary and limited by technical issues within the occipital cortex, and the results do not preclude GABA/BZD abnormalities from being located at other sites.

Not all studies have found evidence of reduced BZD function. Using radiolabelled Flumazenil in SPECT, Kuikka et al (1995) found the mean right to left ratio of BZD uptake was higher in Panic Disorder patients compared to controls. Eleven of the seventeen patients also showed an increased right to left BZD uptake ratio for the prefrontal area in particular. While the authors state that the patients were medication free at the time of the study, they do indicate for how long and whether BZDs had been previously used. Taking this into account, Brandt et al (1998) conducted a similar SPECT study with BZD naïve Panic Disorder patients and found an increased number of BZD receptors in the right prefrontal area and a trend for increased receptor density in the right temporal area.
Kaschka et al (1995) also used [123-I]iomazenil in SPECT and found that the Panic Disorder patients showed a significant decrease in BZD receptors in the left temporal area, compared to dysthymic controls. The Panic Disorder patients were BZD naïve and had been maintained on tricyclic antidepressants for a number of weeks. Dysthymic controls, who were also taking tricyclic antidepressants, were used to control for medication status and the mild levels of depression found in patients with Panic Disorder. Decreases in BZD receptor density in the left hemisphere have also been observed in another SPECT study (Bremner et al, 2000), however the decreases were located in parietal and hippocampal areas.

Thus most PET and SPECT studies have found abnormalities in the right or left prefrontal and temporal areas, with either an increase or a decrease in receptor density observed. While PET and SPECT may theoretically provide comparable results in quantitation of benzodiazepine receptor binding (Bremner et al, 1999), the discrepancies may be due to a number of methodological issues (Malizia, 1999), the most important of which is that in SPECT, short intervals between injection of the ligand and scanning are likely to reflect delivery effects rather than BZD binding effects (Onishi et al, 1996). In fact, Kaschka et al (1995) found that decreases in binding in the inferior temporal lobes and inferior frontal lobes were detectable at 10 minutes as well as at 2 hours post-injection, suggesting that these changes reflect delivery effects related to altered blood flow.

Three different, but inter-related neurotransmitter systems have been implicated in Panic Disorder. The 5-HT, NAd and BZD-GABaergic systems have been shown to be dysfunctional in anxiety, and in particular, Panic Disorder. The evidence for dysfunction comes from several sources, including medications used to treat panic as well as from peripheral markers of altered neurotransmitter function and studies utilising neuroimaging methodologies investigating receptor characteristics. In addition, projections of the serotonin and noradrenalin systems and the BZD receptor locations involve structures known to be essential in animal fear (LeDoux, 1995a), and may represent regions of abnormalities in pathological anxiety.
2.2.3 Neurophysiology of Panic Disorder

This section will describe neurophysiological investigations into anxiety, focusing on Panic Disorder in particular. Contributions to understanding the neurophysiology of anxiety disorders have come from sources using a variety of techniques, such as electroencephalographic (EEG), event-related potential (ERP), Positron Emission Tomography (PET) and functional MRI (fMRI). These methodologies have been used to study ‘normal’ emotions and emotional processing in non-patient groups. Non-patient neurophysiological investigations are assumed to reveal non-pathological brain processes associated with the experience, expression or perception of emotional stimuli. Identifying the locus of the ‘normal’ experience of emotion may infer regions of aberrant brain activity in disorders of emotion, such as Panic Disorder. The neurophysiology of non-pathological emotion will be explored in section 2.2.3.1, thus identifying regions where brain activity may be altered in Panic Disorder. Section 2.2.3.2 reviews the literature investigating the neurophysiology of Panic Disorder patients, which has indicated the importance of a number of brain regions including regions observed to be active during ‘normal’ emotion as well as those implicated in animal fear. Section 2.2.3.3 will introduce the concept of emotional processing in Panic Disorder.

2.2.3.1 Neurophysiology of non-pathological emotion

Recent research into the neurophysiology of non-pathological emotions has suggested that the experience and the expression of positive and negative emotions are lateralised, particularly in anterior regions. Davidson (1992) proposes that approach-related emotions, such as happiness, are associated with greater relative activation of the left anterior region while withdrawal-related emotions such as fear and disgust are associated with greater relative activation of the right anterior region. A number of studies investigating the relationship between anterior brain asymmetries and affective style have supported Davidson’s proposal. Tomarken et al (1992) recorded resting EEG asymmetry from female undergraduate students, on two separate occasions, three weeks apart. Subjects also completed questionnaires designed to determine positive and negative constructs and level of emotional intensity. Subjects with stable activation of the left anterior region, which was defined as reduced mean alpha power, reported more positive affect and less negative
affect. In addition, subjects with relative left frontal activation reported experiencing more intense positive affect in response to viewing positive films than females with stable right frontal activation who reported more intense negative affect to negative films (Wheeler et al, 1993). The presence general positive and negative affect in individuals may affect situational approach and withdrawal behaviour and may be reflected in anterior EEG asymmetries. Sutton and Davidson (1997) administered questionnaires assessing positive affect and situational approach and negative affect and behavioural inhibition in response to threat to undergraduate volunteers. Resting EEG asymmetry, which was recorded on two separate occasions, showed great stability. As predicted, greater left frontal alpha activation was associated with higher reported approach behaviour while greater right frontal alpha activation was associated with more inhibitory behaviour.

Anterior alpha asymmetries have also distinguished between reward and punishment trials for a task in which subjects could win or lose money (Sobotka et al, 1992). In that study, greater left frontal activation was associated with reward whereas greater right frontal activation was observed during the punishment trials. It is important to note that EEG was carefully selected for the portion of the task where participants learned whether they could win or lose money. The importance of selecting the appropriate EEG epochs has been highlighted in a study by Davidson et al (1990). In that study, EEG was recorded from subjects while they viewed films chosen to elicit positive and negative emotions. Analysis of EEG corresponding to the spontaneous display of facial signs of emotional revealed that compared to happiness, disgust was associated with greater right anterior activation. In contrast, happiness was associated with greater left anterior temporal activation. When EEG during each film was summed, no reliable differences in anterior asymmetries were observed. Davidson (1992; 1993) has emphasised that frontal asymmetries occur particularly for the expression and experience of emotion rather than for the perception of emotional information.

Other studies have also observed frontal lateralisation of EEG during emotional tasks. Using formulated questions shown previously to elicit various emotions (happiness, excitement, sadness, and fear), Ahern and Schwartz (1985) showed relative left hemispheric activation for happy stimuli, and relative right hemispheric activation for fear stimuli in a group of female undergraduates. This relative lateralisation occurred in frontal
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sites for the alpha band. However, EEG was recorded from four anterior sites only, which may have masked effects occurring in posterior cortical regions. Activation of the right hemisphere has been found for viewing of negative stimuli, using event-related potentials (ERPs). Roschmann and Wittling (1992) found significant changes in ERP magnitude in the right frontal and right parietal areas for negative stimuli compared to neutral stimuli. The negative stimuli consisted of faces deformed by dermatological disease, and the recovered faces served as the neutral stimuli. Using similar stimuli, Kayser et al (1997) also found right hemispheric activation for negative compared to neutral stimuli, however, changes in the amplitude of the components of interest (N225 and P285) were maximal over the parietal region.

The studies of Roschmann and Wittling (1992) and Kayser et al (1997) were not exploring the experience or expression of emotion, rather they were investigating the perception of emotional information, which appears to preferentially involve the parietal region. Mini et al (1996) demonstrated significant mid-parietal alterations in the amplitude of P300 and N400 ERP components during viewing of emotional pictures compared to neutral pictures. These alterations occurred for both positively and negatively valenced stimuli, and although laterality effects could not be determined because only midline electrodes were used, the study implicates the parietal region in emotional processing. One model of emotional function proposes that the right parieto-temporal region in particular is specialized for the processing of emotional information, and is activated during states of high emotional arousal (Heller, 1993). Thus the experience/expression of emotion is modulated by frontal regions, with greater left hemisphere activation for positive emotions while greater activation of the right hemisphere is noted for negative emotions. The perception of emotional information can also produce frontal asymmetries, but is delineated by posterior activation, particularly of the right parietal region. These studies emphasize the need to distinguish the experience and perception of emotion as they are likely to be mediated by different neural mechanisms (Davidson, 1993).

In vivo neuroimaging techniques such as PET and fMRI have revealed activation of subcortical structures for the experience and expression of emotion, suggesting that the issue of laterality raised by electrophysiological investigations is a complex one. Using fMRI, Canli et al (1998) explicitly investigated hemispheric asymmetry in females and
found relatively more right hemisphere activation in response to negative pictures, while positive pictures produced relatively more activation of the left hemisphere. Closer inspection of the data revealed that activation in both left and right frontal and temporal regions occurred for positive pictures, however more left than right hemispheric activation occurred. In contrast, viewing negative pictures activated right frontal structures, with no significant activation in the left hemisphere, except for the anterior cingulate. Participants rated the pictures on valence and arousal, to ensure that the pictures elicited the target emotion.

In contrast, neuroimaging studies of the experience of emotion, where participants are required to recall events in their life in order to elicit target emotions, have not observed laterality effects, instead consistent activation of subcortical regions has been found, particularly for negative emotions. George et al (1995) found that recall of life events eliciting sadness was associated with increased rCBF in right frontal regions, as well as in the left cingulate and subcortical structures including the putamen, caudate and thalamus. Recall of life events engendering happiness, however, did not significantly activate any region. The paucity of activation for positive emotions was also observed by Schneider et al (1995), who found that increased rCBF in the caudate and the left amygdala occurred for sadness only. In addition, no significant activation of frontal or temporal regions occurred. Unlike other studies of a similar nature that identified participant-relevant life events in order to produce the target emotion (eg Lane et al, 1997; George et al, 1995), participants were asked to try to feel the same emotion (happy or sad) as depicted by a series faces of increasing emotional intensity, which may be a source of discrepancy in the results. Using recall of life events to induce happiness, sadness, disgust and neutral moods, Lane et al, (1997) found that all emotions, compared to neutral task, increased rCBF in the prefrontal cortex as well as the thalamus. In addition, both sadness and happiness were associated with activation of the right prefrontal region, while disgust produced activation in the left prefrontal region. Similar to George et al (1995) and Schneider et al (1995), activation of the caudate was observed for sadness. Although explicit analysis was conducted, no activation asymmetries were revealed.

Using fMRI, Teasdale et al (1999) presented pictures with specific captions to evoke negative and positive emotions, and also found a common activation in the medial
prefrontal region as well as the right anterior cingulate. In addition, the negative pictures and captions activated the right thalamus while positive stimuli produced activation in the left parietal region and bilateral insula. Lane et al (1999) also showed increased rCBF in the medial prefrontal region, but for viewing pleasant stimuli only. Other regions showing increased blood flow included the right anterior temporal and left occipital regions and the putamen. However, unpleasant stimuli produced activation in the right occipital region only, highlighting the role of more posterior regions in processing emotional stimuli. Lang et al (1998) specifically investigated the role of posterior regions in response to presentations of neutral, pleasant and unpleasant pictures. Unpleasant pictures only activated right occipital and parietal structures while pleasant pictures activated right and left occipital structures. Although activation of anterior regions was not explored in that study, the findings emphasize the role of posterior regions in emotional processing of visual stimuli.

Activation of subcortical structures during presentation of negatively valenced emotion appears to be a common feature of neuroimaging studies. Common areas of activation are the amygdala (Schafer et al, 2002; Schneider et al, 1995; Taylor et al, 1998), the thalamus (George et al, 1995; Lane et al, 1997; Teasdale et al, 1999) and the basal ganglia (George et al, 1995; Lane et al, 1997; Schneider et al, 1995). The experience and expression of emotion in particular, appears to show consistent alpha EEG changes in anterior regions (Davidson et al, 1990; Sutton and Davidson, 1997; Tomarken et al, 1992; Wheeler et al, 1993). Other imaging techniques such as fMRI and PET have shown that frontal regions are commonly activated for both negative and positive emotions and emotional stimuli (Canli et al, 1998; George et al, 1995; Lane et al, 1997; Lane et al, 1999; Teasdale et al, 1999) although no consistent laterality effects have been observed for either emotion. The inconsistencies are likely to relate to a number of factors including differing stimuli and methods for inducing emotion, as well as the different imaging techniques themselves. Another factor possibly contributing to inconsistent results is the issue of temporal resolution, which is poor particularly in PET, and may mask time-varying responses to emotional stimuli such as those observed in ERP studies (eg Kayser et al, 1997; Roschmann and Wittling, 1992). Posterior regions such as the parietal and occipital cortices have also been shown to be activated for processing visually presented emotional
stimuli (Lane et al, 1997; Lane et al, 1999; Lang et al, 1998; Taylor et al, 1998; Teasdale et al, 1999). The parietal region in particular has shown consistent emotion-related EEG and ERP effects (Kayser et al, 1997; Mini et al, 1996; Roschmann and Wittling, 1992) that may indicate a role in emotional perception unrelated to valence (Davidson, 1993).

2.2.3.2 Neurophysiology of pathological emotion

Heller (1993) provides a framework in which activation of certain brain regions are associated with different emotional states. In her model, Heller (1993) extends the notion of frontal lobe asymmetries related to emotional valence to include the right parietotemporal region for both the experience of emotion and the processing of emotional information. In particular, it is suggested in the model that the right parieto-temporal region is suited for modulating autonomic arousal, behavioural arousal and direction of attention in relation to emotional states, and interacts with frontal systems to contribute to individual emotional characteristics. The model suggests that anxiety is characterised by an unpleasant (negative) valence and high emotional arousal and therefore would be likely to elicit greater right-than-left frontal activation and increased activity in the right parietotemporal region. Further empirical research using this model has identified two distinct types of anxiety, within non-psychiatric groups, based on EEG alpha patterns. Participants with self-reported ‘anxious arousal’, which is characterised by acute anxiety and panic, have demonstrated greater right hemispheric activity as measured by reduced resting EEG alpha power (Nitschke et al, 1999). Emotional arousal has also been found to activate the right parietal region in anxious individuals (Heller et al, 1997). In that study, subjects were selected on the basis of self-reported anxious apprehension, which is characterised by generalised worry and rumination about future misfortune. During a task designed to elicit anxious emotional arousal, a selective increase in right parietal activation was observed. The studies described above highlight the need to distinguish different types of anxiety. In particular, they functionally separate anxiety characterised by anxious arousal, such as that seen in Panic Disorder, from anxiety characterised by generalised worry, such as that in GAD.

While electrophysiological investigations of Panic Disorder have seldom focussed on the question of laterality as suggested in Heller’s model (Heller, 1993), they still offer insight
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into regions of brain abnormalities in the disorder, and point to the origin of cognitive or emotional processing deficits which may be present. Studies of ‘resting’ EEG, where the patients are instructed to do nothing in particular, have found a percentage of Panic Disorder patients exhibit EEG abnormalities (Bystritsky et al, 1999; Datendorfer et al, 1996; Lepola et al, 1990; Stein and Udhe, 1989). However, differences between the resting EEG of Panic Disorder patients and controls have not always been observed (Knott, 1990). Focal EEG changes, limited to the right anterior and temporal region, have also been observed in a limited number of patients with atypical panic attacks (Weilberg et al, 1995). Right temporal lobe EEG abnormalities in Panic Disorder were also observed by Bystritsky et al (1999) and in the exploratory data of Abraham and Duffy (1991).

Structural changes in the brain may account for altered EEG patterns. Using MRI, Fontaine et al (1990) found a higher percentage of abnormalities in Panic Disorder patients (12/30) compared to age-matched controls. Eleven of the 12 patients exhibited temporal lobe abnormalities, and in 7 patients these were lateralised to the right hemisphere. Wurthmann et al (1997) found Panic Disorder to be associated with bilateral enlargement of cortical CSF spaces, predominately located in the prefrontal regions, in 7 of the 21 Panic Disorder patients studied. Several case studies have reported patients with panic attacks brought on by lesions to temporal lobe structures, most often located in the right hemisphere (Kellner et al, 1996/1997). In contrast, there have also been reports of panic attacks controlled with anticonvulsive therapy following discovery of left hemispheric temporal lobe EEG abnormalities (McNamara and Fogel, 1990). In addition, lesions of the right parietal lobe have also been associated with panic attacks (Alemayehu et al, 1995). These studies provide evidence of resting EEG abnormalities and alterations in structural components of the brain may relate to the symptoms of Panic Disorder, and implicate the right hemisphere in particular. However, there remains the question of whether these abnormalities are an indication of underlying pathology that gives rise to Panic Disorder, or whether it is a result of long term effects of panic attacks on the brain. The answer is not clear, however it is worth noting that Wurthmann et al (1997) found no correlation between structural abnormalities and duration of Panic Disorder.

Pure ‘resting state’ studies, where patients are instructed to do nothing or no pharmacological challenge is given, is difficult in Panic Disorder. The abnormal responses
of psychiatric patients to physiological and psychological stresses such as those endured during neuroimaging techniques, such as PET scanning, may inhibit the ability to produce a ‘resting state’ (Jones et al, 1991), and as such may bias the outcome. However, PET studies of the ‘resting state’ provided the first investigations into Panic Disorder, following its inclusion as a distinct disorder in DSM-III (APA, 1980), and in contrast to electrophysiological investigations, indicated the involvement of subcortical structures.

Sodium lactate has been shown to be a reliable panicogenic agent in Panic Disorder patients, but have a minimal effect in normal control subjects (Reiman, 1987). In a preliminary study, cerebral blood flow (CBF) was measured in 7 patients who were known to panic following lactate infusion, 3 Panic Disorder patients who were not sensitive to lactate, and 6 psychiatrically healthy controls while in a resting, non-panic state (Reiman et al, 1984). Seven regions thought to be important in panic and anxiety were defined and investigated, however only one region revealed significant differences. The results showed an abnormal right-greater-than-left asymmetry of blood flow in the parahippocampal gyrus in the lactate-sensitive Panic Disorder patients only. Reiman et al (1986) also showed that lactate sensitivity was associated with abnormal CBF, blood volume and oxygen metabolism asymmetries in the parahippocampal gyrus in Panic Disorder patients. No asymmetries were noted for the non-psychiatric controls or for the lactate-insensitive Panic Disorder patients. It was revealed in a further study that the asymmetry of may have been due to increases in right parahippocampal blood flow and oxygen metabolism measurements (Reiman, 1987). Further analysis revealed that the group differences were not attributable to other variables such as medications, number of anxiety symptoms or number of severe symptoms during the PET scans.

Hippocampal structures have been implicated in other studies of Panic Disorder. Single photon emission tomography (SPECT) was used to measure CBF in lactate-sensitive Panic Disorder patients and lactate-insensitive control patients at rest in a study by De Cristofaro and colleagues (1993). A group of 7 panic disorder patients, who had been medication free for at least 2 weeks (most of whom had never been medicated), showed a significant decrease bilaterally in the hippocampal region, incorporating the hippocampus, parahippocampus and the amygdala. Significant increases in left occipital blood flow and an asymmetry in the inferior frontal cortex were also seen in the Panic Disorder patients.
Increases in glucose metabolism in the left hippocampus and parahippocampal area have also been observed in Panic Disorder patients compared to controls. Bisaga et al (1998) investigated cerebral metabolic activity in Panic Disorder patients, who were sensitive to lactate and had been free of medication for at least one month. While the alterations in glucose metabolism occurred in the same region described by Reiman and colleagues (1984, 1986), it is in the opposite direction. This discrepancy may be due to some methodological differences including handedness, gender and medication status, which differed between the studies.

Metabolic asymmetry in the hippocampal region has also been observed by Nordahl and colleagues (1990). Twelve Panic Disorder patients, who had been free of medication for at least 11 days, and 30 controls underwent PET glucose metabolism measurements while performing an auditory continuous performance task (CPT). A simple task was employed to engage the subjects’ attention, rather than requiring a ‘resting’ baseline from participants, which has inherent issues in anxiety disorders. Hippocampal metabolic ratio (left/right) was calculated and found to be significantly lower in patients compared to controls. This result is similar to Reiman et al (1984, 1987) however, in contrast, no differences in global metabolism were observed. Anxiety levels as measured by the STAI-state were not found to correlate with metabolism in any of the regions postulated to be associated with anxiety. It is not known whether the Panic Disorder patients were lactate sensitive, however 9 of the 12 patients had known sensitivity to caffeine.

Nordahl et al (1998) also revealed decreased left/right hippocampal ratios in Panic Disorder patients. Nine Panic Disorder patients who had responded to a trial of imipramine therapy with a cessation of panic attacks and no fear of an impending attack for at least one week prior to scanning were compared to 43 psychiatrically healthy controls. Twelve non-medicated Panic Disorder patients from the previous study (Nordahl et al, 1990) were also used as a comparison group. All subjects performed a simple continuous performance task (CPT) to engage their attention during PET scanning. Compared to the controls, the treated patients retained the abnormally low left/right glucose metabolic ratio within the hippocampal region as well as the prefrontal region that the untreated Panic Disorder patients displayed. These results suggest a trait abnormality of Panic Disorder, which appears to be independent of treatment.
More recently, Dager et al (1999) have used a new imaging technique, magnetic resonance spectroscopy (MRS) to investigate the distribution and magnitude of brain lactate responses to infusion of lactate in Panic Disorder patients and control subjects. Twelve of the 15 Panic Disorder patients and none of the controls were found to be sensitive to lactate infusion. Comparisons between the lactate-sensitive Panic Disorder patients and the controls revealed greater global brain lactate increases in response to lactate infusion in Panic Disorder, which was not lateralised nor localised to any region. In addition, whole brain lactate was not correlated with either panic or anxiety symptoms. Panic Disorder patients who did not panic in response to lactate infusion and the healthy controls showed no differences in brain lactate responses.

Thus it appears that sensitivity to chemically-induced panic attacks in Panic Disorder is associated with changes in blood flow and metabolism, often involving the parahippocampal and hippocampal regions. While the direction of change observed has been inconsistent, the hippocampal and parahippocampal areas represent the same regions that have been implicated in contextual fear in animals (LeDoux, 1995a), and may hold a similar role in the development and maintenance of Panic Disorder.

Effective treatment of Panic Disorder has also been associated with changes in blood flow, indicating regions of possible neurochemical dysfunction. Nordahl et al (1998) compared glucose metabolism in imipramine-treated and unmedicated Panic Disorder patients, treatment was found to be associated with increased glucose metabolism within the left parietal area. Comparisons between the controls and treated group showed no significant differences in this area. Imipramine is a tricyclic antidepressant that affects NAd and serotonin reuptake, and thus the results of Nordahl et al (1998) implicate a dysfunction of these neurotransmitters within the parietal region. Dysregulation of serotonin within the left parietal region has also been implicated in an additional study. Meyer et al (2000) compared administration of D-Fenfluramine, which increases neuronal levels of serotonin, in healthy and Panic Disorder participants using PET measurements of rCBF. Prior to administration of D-Fenfluramine, the Panic Disorder patients, compared to controls, exhibited decreased rCBF in the left posterior parietal-temporal cortex. Administration of the drug was associated with an increase in rCBF in this region for Panic Disorder patients, indicating an area of dysfunction related to the disorder. Thus in addition to abnormalities
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of blood flow and metabolism in the hippocampal and parahippocampal region, there is evidence of a trait abnormality in Panic Disorder, within the left parietal region, that appears to be related directly to neurochemical dysregulation, and may reflect the role of serotonin in anxiety, as previously discussed in section 2.2.2.1.

2.2.3.3 Emotional processing in Panic Disorder

Following Davidson’s proposal (Davidson, 1992), Panic Disorder, which is characterised by negative emotions and avoidance behaviour, should also be associated with relative right frontal activation, particularly if patients are confronted with stimuli that motivate greater levels of avoidance. To investigate this proposal, Wiedemann et al (1999) showed 23 Panic Disorder patients and 25 controls emotional and neutral pictures while EEG was recorded from 19 sites, and referenced to the vertex. The pictures consisted of panic-relevant stimulus (emergency situation), neutral stimulus (mushroom picture), anxiety-relevant/panic-irrelevant stimulus (spider picture) and emotionally relevant/anxiety irrelevant stimulus (erotic picture). Arousal, valence and dominance dimensions were assessed for each phase of the experiment. As predicted, the Panic Disorder patients exhibited greater right-than-left frontal activation during the ‘resting’ phase, which was not observed in the controls. Viewing of the panic-relevant picture also resulted in increased right frontal activation compared to the left in Panic Disorder patients but not the controls, nor for the neutral picture. In addition, the panic-relevant picture was judged as more negatively valenced by the Panic Disorder patients compared to the controls.

Thus there is limited evidence that the frontal laterality hypothesis of Davidson (1992) is true in Panic Disorder, which is characterised by negative emotions as well as avoidance behaviour. Panic Disorder is also consistent with Heller’s anxious arousal state (Heller, 1993). While anxious arousal may predominate in Panic Disorder (Heller et al, 1998), to date, there has been no empirical research to specifically explore whether the predicted greater right-than-left hemispheric activity pattern of brain activity in anxious arousal (Nitschke et al, 1999) exists in Panic Disorder patients.

Psychological theories of anxiety that have been influential in investigations of emotional processing in Panic Disorder contain cognitive biases (Beck et al, 1985, Clark, 1988) and mood-specific biases (Bower, 1981) at their core. As such, psychological approaches to
studying anxiety-related biases in Panic Disorder have been employed, specifically using emotional stimuli. One task that has been used extensively is the Emotional Stroop task. Studies using the Emotional Stroop have attempted to uncover the nature and relationship of cognitive biases to the maintenance of anxiety disorders (Williams et al, 1996), however, the research into the neural mechanisms underlying the task’s performance is limited. The neurophysiology of the Emotional Stroop task forms the basis of the present thesis and the task will be discussed in detail in the next chapter, Chapter 3.

2.3 Summary

Panic Disorder has been recognised as a discrete diagnostic entity, separate from other forms of pathological anxiety, for over 20 years. Since symptoms of panic encompass both somatic and cognitive domains, biological and cognitive approaches to understanding the aetiology of Panic Disorder have been employed. The biological approaches reviewed in this chapter have described models of animal fear as well as the application of technologies to investigate the neurophysiology of both normal and pathological emotions. Some of the models of emotional processing in humans that has driven research in this field were also presented.

Models of animal fear have identified the amygdala as essential to the development and maintenance of conditioned fear. Animal research has also identified the hippocampus and the prefrontal cortex as major contributors to contextual fear and extinction of learned fear respectively. Aversive conditioning in humans appears to activate similar structures as those seen in animals, thus confirming the relevance of the study of animal fear to human emotion. Other biological investigations of anxiety have implicated the serotonin, BZD-GABAergic and NAd systems. Evidence of the involvement of the neurotransmitters has come from a variety of sources including altered metabolite levels, agonists that provoke panic, and medications that ameliorate anxiety symptoms. In addition, neuroimaging techniques identifying receptor location and density has further implicated dysregulation of the BZD-GABAergic system in Panic Disorder.

Identifying the locus of the ‘normal’ experience of emotion may reveal insights into where aberrant brain activity is likely to occur in disorders of emotion, such as Panic Disorder. Electrophysiological studies have consistently revealed patterns of anterior lateralisation for
the experience of positive and negative emotions. Other neuroimaging methodologies such as fMRI and PET have often implicated subcortical structures including the amygdala, as well as anterior regions although no consistent laterality effects have been observed. These inconsistencies may be a result of methodological and conceptual issues (Davidson, 1993). Neurophysiological evidence also suggests the parietal region may be preferentially involved in the perception of emotional information, regardless of valence, which is consistent with the notion of emotional arousal in Heller’s model (Heller, 1993). Clinical studies have suggested that resting EEG abnormalities exist in some Panic Disorder patients. Positron emission tomography studies have consistently implicated the parahippocampal and hippocampal regions in Panic Disorder patients known to be sensitive to chemically-induced panic attacks. These regions also represent an area known to be essential for contextual fear in animals. Abnormalities of the left parietal region have also been observed in Panic Disorder, and may constitute a trait abnormality involving dysregulation of serotonin. While neurophysiological investigations into emotional processing in Panic Disorder have been limited, altered brain activity has been indicated.

A number of psychological theories of anxiety have given rise to investigations of cognitive biases in Panic Disorder, however the neural mechanisms underlying these biases has not been well studied. The next chapter will introduce the cognitive approaches to understanding the cognitive biases in Panic Disorder. Specifically, in Chapter 3, the Emotional Stroop task and its use in anxiety disorders and Panic Disorder in particular will be reviewed in detail.
CHAPTER 3  Cognitive Approaches To Anxiety Disorders

The aim of this chapter is to introduce the Emotional Stroop task as a tool to assess the presence and nature of cognitive or attentional biases in anxiety, and Panic Disorder in particular. Section 3.1 will briefly review the Stroop paradigm, a colour-word task bearing the creator’s name, which has been used for 70 years to investigate attention and interference in various groups. Psychiatric disorders, where poor control of attention may be part of the symptomatology, have also been assessed using the Stroop task. More recently, neuroimaging techniques such as fMRI and PET have employed the Stroop task in order to elucidate the neural mechanisms of selective attention.

Cognitive approaches to anxiety disorders have consistently found that anxiety is strongly associated with attention to threatening stimuli (Mathews and MacLeod, 1994). The Emotional Stroop is a variation of the Stroop task, in which colour names are replaced with emotionally relevant words. The difference in the time to name the colour of emotional words and the colour of emotionally neutral words is referred to as Emotional Stroop interference. Delays in identifying the colour of emotional words have been used to infer attentional biases in subclinical and clinical anxiety, including Panic Disorder. The use of the Emotional Stroop to investigate attentional biases in anxiety will be examined in section 3.2. A number of factors have been shown to modify the degree to which Emotional Stroop interference is observed. The relationship of current mood, current concerns and valence specificity with Emotional Stroop interference will be explored in sections 3.2.2 and 3.2.3 respectively. The effects of expertise, amelioration of emotional symptoms and practice on Emotional Stroop performance have also been investigated and these factors will be examined in sections 3.2.4, 3.2.5 and 3.2.6 respectively. A small number of investigations have attempted to identify the neural mechanisms underlying Emotional Stroop performance in non-psychiatric participants. Regional brain activation associated with the Emotional Stroop, as identified by PET and fMRI techniques, will be discussed in section 3.3.
3.1 The origins of the Stroop task

In 1935, John Ridley Stroop published the results of three experiments, which investigated the interfering effect of colour stimuli on both reading names of colours and naming of colours. The first experiment consisted of colour words written in black ink and colour words written in opposing ink colours (red, blue, green, brown and purple). Each form was presented to participants on separate sheets, each consisting of 100 stimuli. In the second form, the colour words were printed an equal number of times in opposing colours, but never in the colour it named. Male and female college undergraduates participated in the study, and were required to read the names of the colours as quickly as possible, and correct any errors made. Time to complete the entire sheet was measured by a stop watch. While participants took an average of 2.3 seconds longer to read the second form (colour words written in different coloured ink), this difference was found to be unreliable.

In the second experiment, the colour words were written in different coloured ink, as used in the first experiment, and compared to coloured solid squares. However, in this experiment, participants were required to name the ink colour of the words and the squares, rather than simply read the words presented as in the first experiment. Again, this task was to be done as quickly as possible, with corrections of any errors. The mean time to name the colours of different colour words was increased 74% compared to the mean time to name the colours of solid squares. It is this experiment that is now commonly known as the classical ‘Stroop’ task. The increase in time to name the colours of different colour words, compared to a baseline (here being the naming of colours of solid squares) is known as the ‘interference effect’. Colour words, written in ink different to colour named by the word, is known commonly as the ‘incongruent Stroop’. Stroop’s influential paper motivated a great body of work using the incongruent form of the task.

The third and final experiment investigated the effect of practice over 14 days. Over the two weeks, participants became 34% faster at the incongruent Stroop, and 4% faster at the naming of coloured symbols (the solid block was changed to a swastika). However, replications of the original Stroop study have found that the interference effect remains relatively constant, even with practice (MacLeod 1991). Stroop's findings may be explained by the experimental design, which included the naming of coloured symbols on
two occasions, and the incongruent Stroop on eight occasions. The unequal proportion of
practice in the tasks may account for the participants becoming much faster at the
incongruent Stroop, compared to the baseline task.

Stroop also found that there was a trend for females to respond faster than males on naming
the colour of stimuli, which he attributed to:

“[the response] to a color stimulus by naming the color may be more common
with females than with males.[ ]... Education in color is much more intense for
girls than for boys..” p658

However, the fact that females are faster than males in Stroop's experiments may simply
have been due to females comprising 70% of the participants studied. Since then, other
studies explicitly exploring gender differences related to the Stroop interference effect have
found none (MacLeod, 1991).

3.1.1 Variations of the classical Stroop task

The classical Stroop task has been varied to accommodate advances in technology, as well
as study purposes. Variations in presentation of the task have included three main formats:
card presentation, where the whole stimulus set is presented on a large card, and the time to
complete the whole card is measured; tachistoscopic presentation, where individual
stimulus words are presented on a screen in front of the subject; and computer presentation
where individual words are presented on a computer monitor. For tachistoscopic and
computer presentation, timing is commenced at presentation of the word and concludes
when the subject initiates a response.

In the case of the card presentation, the measure of interference is found by subtracting the
time to name the colours of the stimuli on the control card from the time to name the colour
of the stimuli on the incongruent card. For tachistoscopic and computer presentation, the
interference effect is calculated by subtracting the average time to name the colours of the
individual control stimuli from the average time to name the colours of the individual
incongruent stimuli.

There have also been variations in the Stroop control stimuli that are used to compare with
the incongruent Stroop. Variations of the control task include the use of colour patches,
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non-words, unrelated words, rows of Xs or other characters, or colour words written in ink congruent with the colour name. There seems to be little difference in using unrelated or non-words in the control task, however, using colour patches or a string of characters (eg XXXX) may produce comparatively more interference (MacLeod, 1991). The use of the congruent condition (for example, where red is written in red ink) was not investigated until 30 years after the original Stroop article. In using the congruent condition, facilitation is often produced (MacLeod, 1991). ‘Facilitation’ describes the phenomenon whereby the average time to name the colour of congruent stimuli is faster than the average time to name the colour of letter-strings or neutral words. However, the interference produced by the incongruent condition is usually much larger than the facilitation produced by the congruent condition. It has been suggested that one particular drawback of the congruent Stroop is that participants may adopt a strategy of reading the word, rather than naming the ink colour, especially if the condition is presented in one block (MacLeod, 1991).

Semantic variations of words used in the Stroop task have been investigated as early as 1964 (Klein, 1964). In successive experiments, it was found that as words in the incongruent condition related less to the ink colour being used, the less interference they caused (MacLeod, 1991). This finding has been supported by another study where less frequently used colour words (eg ‘aqua’ for blue) produced a reduced interference effect (Langlois, 1974).

3.1.2 Accounting for the Stroop interference effect

One main account of the Stroop effect, relative speed of processing, corresponds to the view held by Stroop (1935) in his original article. Stroop (1935) suggested that:

“The associations that have been formed between the word stimuli and the reading response are evidently more effective than those that have been formed between the color stimuli and the naming response.” pp659-660

Stroop concludes that since strength is proportional to training, and that there is more emphasis on reading than colour naming, then:
“it seems reasonable to conclude that the difference in speed in reading names of colors and in naming colors may be satisfactorily accounted for by the difference in training in the two activities.” p660

Thus relative speed of processing refers to the suggestion that since reading is more practiced than colour-naming, it is a faster process than colour-naming. Relative speed of processing has been rejected as an explanation of Stroop interference because it fails to account for the majority of critical findings listed by MacLeod (1991) in his extensive review of the Stroop paradigm. In addition, MacLeod (1991) notes that direct manipulations of relative speed of processing also fails to confirm this hypothesis.

The automaticity account of Stroop interference arises from the skill of reading being so practised from an early age, that an individual cannot help but read words presented to him or her. Reading is reinforced by years of schooling, as well as during daily life through assessing printed media, street signs, and such. Reading therefore becomes automatic response, whereas naming of colours requires more attention (MacLeod, 1991). The hypothesis of automaticity in producing Stroop interference is considered to be a viable one, although it is in need of more precise detailing and direct testing (MacLeod, 1991).

Another explanation of the Stroop interference effect is based on Cohen and colleagues’ (Cohen et al, 1990) parallel distributed processing model. MacLeod (1991) explains that the main premise of the model is that processing occurs in the system along pathways of differing strength, and that relative speed of processing as well as strong automaticity may not be driving factors. Instead, a gradient of automaticity contributes to the strength of particular network pathways. Attentional processes, in this model, are incorporated as modulators of the processing units in a particular pathway. The effect of learning, or practice, serves to change strengths of connections on successive trials.

While speed of processing was originally thought to give rise to the Stroop Interference effect, the theory does not account for all the experimental results noted, including practice effects. Automatic reading of the word may account for the Stroop interference effect, however, attention and strength of automatic responses are likely to be modulators. The favoured theory of MacLeod (1991) is that based on the model of Cohen and colleagues
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(Cohen et al, 1990), which incorporates automaticity, attention, and learning into a network model based on strength of connections to produce a correct output.

3.1.3 The Stroop task in psychiatric populations

The Stroop task has been used in psychiatric populations presumably to elucidate some of the underlying mechanisms of psychopathology, especially where the ability to ignore distracting information is regarded as a symptom of the disorder. As such the most common groups studied using the Stroop task have been depression and schizophrenia.

Depression appears to be associated with increased Stroop interference. Trichard et al (1995) tested severely depressed patients when symptomatic and again at a later point in time when patients were asymptomatic. In comparison with the control group, depression was associated with increased Stroop interference at both occasions. While the results on the first occasion may be explained by the presence of psychomotor retardation, the increased interference persists when the depression, and psychomotor retardation has remitted. This suggests long term specific cognitive deficits in depressives. Lemelin et al (1997) also showed that symptomatic depressives have increased interference for the incongruent Stroop.

Not all studies have found increased interference in depression. The Stroop Interference Effect has been studied in studied patients suffering from seasonal affective disorder (Drake et al, 1996). In that study, subjects were tested in winter and in summer to determine whether cognitive deficits existed only during the depressive period in winter. While both patients and controls performed the Stroop better in summer than in winter, there were no differences between groups at both testing sessions. This result occurred despite the moderate depression of patients remitting during summer. Unilateral presentation of the Stroop task has also resulted in no differences between depressives and controls (David, 1993). The disparity in results may be explained by the severity of depression. While the studies showing an increased interference effect tested moderately to severely depressed patients (Lemelin et al, 1997; Trichard et al, 1995), others showing no effect either did not report level of depression (David, 1993).
The Stroop task has also been studied as a test of impairment of attention in schizophrenia (Barch et al, 1999; Carter et al, 1997; David, 1993), as well as in Attention Deficit Hyperactivity Disorder (Carter et al, 1995a). Unfortunately, there has been a paucity of studies using the Stroop task as a neuropsychological tool in anxiety disorders. In one study investigating the relationship between anxiety and Stroop performance (Newman, 1990), high trait anxiety was associated with longer latencies and reduced accuracy when subjects were relaxed.

Thus there is limited evidence that some psychopathologies, characterised by attentional disturbances, are impaired on the Stroop task. However, it is not known whether clinical anxiety is associated with impaired Stroop performance.

3.1.4 Neurophysiology of the Stroop task

Neurophysiological investigations of the Stroop task have endeavoured to uncover the neural mechanisms involved in selective attention. The majority of research in this field has employed PET and fMRI neuroimaging techniques, which will be the focus of this section.

A number of studies have assessed regional cerebral blood flow (rCBF) in non-psychiatric participants performing the Stroop task. Bench et al (1993) found that the incongruent Stroop, compared to a baseline of coloured crosses, produced increased rCBF in right orbitofrontal, cingulate and bilateral parietal structures. In the second part of the experiment, the incongruent Stroop was compared to the congruent Stroop (ie RED written in red ink), and only parietal activation was observed.

In the preliminary data of Larrue et al (1994), right frontal increases in rCBF located in the superior mesial region during the incongruent Stroop were also found. Activation of right frontal areas was also observed by Taylor et al (1997) for the incongruent Stroop minus a neutral word baseline task. This effect did not occur to the same extent in the right hemisphere for Stroop comparisons using baseline tasks consisting of false fonts and symbols. Increased rCBF was also noted by Carter et al (1995b) for the incongruent Stroop when compared with the congruent baseline task. Increases in rCBF were observed in the parietal and temporal regions as well as the right anterior cingulate. The activation of right
frontal structures is in agreement with the results of Vendrell et al (1995) who found that right frontal lesions but not left frontal lesions were associated with more errors in Stroop performance.

In contrast, Taylor et al (1997) found increased rCBF in left hemisphere regions for the incongruent Stroop was compared to symbols and irrelevant, neutral words. Compton et al (2003) also reported activation of left middle and inferior frontal gyri in an fMRI study comparing the incongruent Stroop with neutral words. In agreement with these findings, preliminary ERP data has shown task-relevant negativities to be greater in the left hemisphere, compared to the right (Aine and Harter, 1984).

However, other fMRI studies have found activation of bilateral structures during performance of the incongruent Stroop, as compared to a congruent baseline. Leung et al (2000) reported activation of bilateral frontal structures during the Stroop task, including middle and inferior frontal gyri. Activation of the anterior cingulate and temporal region were also found. Peterson et al (1999) also observed increased fMRI signals in a number of bilateral structures including the mesial, lateral and inferior frontal gyri, in addition to anterior cingulate, inferior parietal and occipital cortex activations.

Activation of the anterior cingulate appears to be the most consistent finding in Stroop studies (MacLeod and MacDonald, 2000) and appears to be independent of choice of baseline task. Pardo et al (1990) first brought the role of the anterior cingulate in the Stroop task to light. In that study, the incongruent Stroop was compared to the congruent version. While rCBF increases in a number of regions were observed, the right anterior cingulate in particular exhibited the most robust response. Carter et al (1995b) compared the incongruent Stroop to neutral and congruent baselines and found increased rCBF in the right anterior cingulate was a common feature of both comparisons. Activation of the anterior cingulate has also been observed for the Stroop task using a baseline consisting of coloured crosses (Bench et al, 1993) and the congruent Stroop (Leung et al, 2000; Peterson et al, 1999). Peterson et al (1999) conducted factor analysis on the Stroop data which revealed the anterior cingulate may have a specific role in response selection and execution. Studies of the neural mechanisms activated during the Stroop paradigm have consistently implicated the role of the anterior cingulate cortex in selective attention. However, whether
the activation of the anterior cingulate relates to the role of attention in the task or it relates to detection of informational conflict is a source of debate (MacLeod and MacDonald, 2000). There is also evidence for the involvement of frontal, parietal and occipital structures in the incongruent Stroop. These differences may be due, in part, to the different baseline tasks employed.

3.2 Attentional biases in anxiety

Over the last few decades, cognitive accounts of anxiety which contain cognitive biases at their core have been published. One theoretical account has described catastrophic thinking in anxiety disorders (Clark, 1988). In that model, panic attacks are said to occur in the anxious individual when bodily sensations are misinterpreted as evidence of imminent danger. In another model, Beck et al (1985) suggest that anxiety is characterised by hypervigilance to cues from both internal and external environments, which are interpreted as signalling impending danger. A vulnerable individual, overwhelmed with perceived danger, feels helpless and a panic attack ensues. A central theme of these cognitive models of panic is the bias towards danger cues in the environment, which actively contributes to the development and continuation of the emotional disorder (Williams et al, 1996). In this section, tasks that have investigated cognitive or attentional biases in Panic Disorder will be examined. The concept that individuals with anxiety disorders process threat information differently to those without pathological anxiety has dominated recent cognitive approaches to understanding anxiety disorders (McNally, 1995). The cognitive biases suggested to be present in anxiety disorders have been investigated experimentally using tasks employing emotionally relevant stimuli which capture the attention of the sufferer, and disrupts their performance (Williams et al, 1996; Williams et al, 1997). For example, presenting threat words to the unattended channels during a dichotic listening task has been found to impair the performance of anxious subjects during a simultaneous reaction time task (Mathews and MacLeod, 1985). Faster naming of lexically primed threat targets, compared to primed positive targets in Panic Disorder also provides evidence of preferential processing of threatening information in clinical anxiety (McNally et al, 1997).

Other approaches to biases in anxiety have included direct assessment of memory processes following Bower’s model that predicts enhanced memory for stimuli congruent to an
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individual’s mood (Bower, 1981). Bower’s theory (Bower, 1981) utilises associated networks to describe the effect of emotion on cognitive effort. The main feature of the model is the assumption that each emotion has its own node in memory, which gathers information related to that emotion. At the time of encoding, connections are biased by the current mood, so that mood-congruent biases are favoured over mood-incongruent biases. Both Bower’s network theory of mood and memory (Bower, 1981) and Beck’s schema theory (Beck et al, 1985) predict that anxious individuals will show enhanced memory for anxiety-relevant information. Cognitive biases have been explored in anxiety, and Panic Disorder in particular, using tasks that employ memory for threat-related material. Explicit memory biases have been observed in Panic Disorder, for words relating to physical threat (Lundh et al, 1997), panic symptoms (Becker et al, 1994; Becker et al, 1999) and panic-related threat (Cloitre and Liebowitz, 1991; Windmann and Kruger, 1998). In contrast, Neidhart and Florin (1999) found implicit, but not explicit, memory biases for panic-related words in Panic Disorder patients. Using a white-noise paradigm, Amir et al (1996) also observed implicit memory biases for panic-related threatening sentences in Panic Disorder patients. In contrast, a number of investigations of implicit memory biases have not observed effects in Panic Disorder (Baños et al, 2001; Lundh et al, 1997; Windmann and Kruger, 1998).

Attentional biases in anxiety disorders, and Panic Disorder in particular, have been investigated in other ways. In particular, a modification of the Stroop task, which employs emotionally relevant words, rather than colour names, has been used for over 20 years to investigate attentional biases in anxiety. The following section describes the use of the Emotional Stroop as a tool to investigate disorder-specific cognitive biases in anxiety. The application of neuroimaging techniques have provided a way of investigating the neural correlates of Emotional Stroop performance, particularly in non-psychiatric populations, and this will be explored in section 3.3. Finally, section 3.4 will summarise the use of the Emotional Stroop to explore attentional biases for threatening information in anxiety, and Panic Disorder in particular.
3.2.1 The Emotional Stroop

Biases for threatening information have been investigated in anxiety disorders using a modified version of the Stroop colour-word test. The Emotional Stroop incorporates emotional words in place of colour names. As in the classical Stroop task, the participant is required to identify the colour that the emotional word is written in, with an emphasis on speed and accuracy. Clinical groups have consistently shown slowed reaction times for colour-naming emotional words, compared to neutral words, which has been interpreted in terms of disorder-specific attentional biases (Williams et al, 1996; Williams et al, 1997).

The Emotional Stroop has been used in many psychiatric conditions such as Depressive Disorders as well as Anxiety Disorders, including GAD, Panic Disorder, Specific Phobias, OCD and PTSD. Other psychiatric conditions such as Schizophrenia and eating disorders have also been investigated, but are outside the scope of this thesis. The use of the Emotional Stroop has not been restricted to clinical populations, and has also been used in subclinically anxious and depressed participants.

This section will review the use of the Emotional Stroop task in subclinical and clinical anxiety, and how it has been used to elucidate attentional biases in these populations. In addition, the Emotional Stroop will be explained in terms of relatedness of stimuli to current concern, mood and expertise.

3.2.1.1 Subclinical anxiety

Studies examining subclinical anxiety typically use the Spielberger state/trait anxiety inventory (STAI: Spielberger et al, 1970) to divide their healthy subject sample into groups representing high and low trait anxiety. A cut-off point for the trait anxiety scale is assigned by the researchers, and is usually around 40 (eg Richards and Millwood, 1989). Above this cut-off score, subjects are deemed to have high trait anxiety, and those below this score are deemed to have low trait anxiety. The following section describes how the Emotional Stroop paradigm has been applied to groups divided into high and low trait anxiety, and how this has impacted on the Emotional Stroop interference effect.

High trait anxiety has been associated with increased time to colour name negative threat words, compared to neutral and emotionally positive words (Richards and Millwood,
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1989). Those with low trait anxiety did not show a differential response to the different types of emotional words. The high trait anxious subjects also recorded high levels of state anxiety (as measured by the STAI), which may have influenced the result, however the relation of state anxiety to Emotional Stroop interference was not reported.

Performances of high and low trait anxious subjects were compared by Dawkins and Furnham (1989) as part of a study on repression characteristics. The high trait anxious group performed more poorly for threat words compared to neutral words. The threat words (eg cry, sob) were chosen to relate particularly to repressor characteristics. Again, state anxiety, which may have been detrimental to performance, was not examined.

Mogg and Marden (1990) also examined trait, but not state anxiety. They found that the high trait anxious subjects were slower at colour naming emotional words compared to non-emotional words. However, further analysis revealed that this result was due to increased interference for positive words, and there was only a non-significant trend for a slowed response to threat words.

A further study of high and low trait anxiety (Mogg et al, 1990) revealed that colour naming of threat words was disrupted in high trait, but not low trait, anxiety. The stimuli consisted of general threat, achievement threat and neutral words. To investigate the effects of state anxiety on the Emotional Stroop, participants were underwent a low stress or high stress procedure. In the low stress condition, participants solved easy anagrams and were told not to be concerned if they could not perform the task. In the high stress condition, participants were given difficult or insoluble anagrams and told after attempting the task that their performance was well below average. The results showed that regardless of the stress condition undertaken, the high trait anxious group had higher state anxiety scores and the low trait anxious group had lower state anxiety. This suggests that trait anxiety, but not state anxiety, may contribute to the differential effects seen in the Emotional Stroop.

Subliminal presentation of the Emotional Stroop has been used to determine whether delays in colour-naming of negative words compared to neutral words are under the control of automatic, rather than strategic processes (Mathews and MacLeod, 1994). The subliminal task involves brief presentation of words on colour patches, with the colour patch
remaining on screen so that subjects can identify the colour. Subjects are unable to identify any of the words displayed on subsequent identification tasks, confirming the effectiveness of the masking procedure.

Mogg et al (1993b) compared subliminal and supraliminal presentation of the Emotional Stroop in high and low trait anxious subjects. In the subliminal condition, words were presented on a background patch of colour, and replaced by a mask after 14 msec that covered the word but not the colour patch. High trait anxiety was found to be associated with greater interference for threat words in the subliminal condition only, and not the supraliminal condition. This result supports the notion that high trait anxious subjects may be able to override the tendency to be distracted when they are consciously aware of the threatening stimuli presented (Williams et al, 1997). This study also manipulated state anxiety levels of subjects with either a stressful or relaxing mood induction procedure and showed that high state anxiety produced slower colour naming times for threat words compared to the low state anxiety group. This effect occurred for the supraliminal but not subliminal presentation, suggesting that individuals with high state anxiety may adopt strategies for performing the unmasked version of the Emotional Stroop.

MacLeod and Rutherford (1992) also compared subliminal and supraliminal presentation of stimuli in high and low trait anxious individuals during different levels of stress. University students were tested one week prior to end of semester examinations, when state anxiety was high and again in the middle of the semester when state anxiety was low. The high and low trait anxious showed a different pattern of results, depending on state anxiety and mode of presentation. Only when state anxiety was high, the high trait anxious individuals were slower to colour name threat words (eg stupidity, lonely) than non threat words (eg intelligent, identical) in the subliminal condition, despite being unable to identify the words on a subsequent identification task. The low trait anxious group did not show this pattern of colour-naming. Thus it appears that state anxiety may indeed have a role in determining Emotional Stroop interference in high trait anxiety. However, the results of the study may have been influenced not only by the stress due to exam proximity, but also perhaps by the emotional consequences of the outcome of the examinations themselves, such as parental, personal or departmental pressures and expectations (Williams et al, 1997).
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The first experiment of Dalgleish’s study (Dalgleish, 1995) compared Emotional Stroop performance in subjects divided into high and low trait anxiety groups and found that the high trait anxious group were impaired at colour naming threat compared to neutral words. In addition, both trait and state anxiety were correlated with the extent of interference due to the threat words.

In contrast, Richards et al (1992) found that trait, but not state, anxiety was correlated with Emotional Stroop interference for anxiety-related words. This effect occurred only when single-valenced blocks of stimuli were presented. For blocked (single-valenced), but not mixed-valence presentation of stimuli, high trait anxiety was associated with slower colour naming times for anxiety-related words. The authors suggest that blocked presentation may produce a mood manipulation effect, however this is not supported by the fact that positive words failed to produce a corresponding increase in reaction time.

In a study conducted by MacLeod and Hagan (1992), gynaecological patients awaiting a colposcopy appointment to diagnose suspected cervical pathology were presented threat (eg disease, inferior) and non threat (eg leisure, carefree) stimuli. Both state and trait anxiety scores were positively correlated with the degree of interference produced by the threat words, compared to the non threat words. This correlation was evident for subliminal, but not supraliminal presentation of stimuli. In women whose cervical pathology was confirmed, the level of distress which they suffered was predicted by the degree of subliminal threat interference.

Van den Hout et al (1995) replicated the findings of MacLeod and Hagan (1992) in healthy subjects who were not currently stressed. Non-stressed subjects instead rated how upset they would be if they found themselves in fifteen different stressful situations, and also rated how other people might react in the same situation, which gave a measure of vulnerability. The degree of threat interference was positively correlated with state and trait anxiety scores, as well as vulnerability. This effect was evident for subliminal presentation of stimuli only. It is of interest to note that further analysis revealed that the subjects were in fact faster to colour name threat words, compared to neutral words, in the subliminal condition.
High trait anxiety has been consistently associated with diminished performance of the Emotional Stroop when compared to low trait anxiety, suggesting that individuals with subclinical anxiety process threat differently to non-anxious participants. In addition, there is some evidence that transient or state anxiety may also mediate Emotional Stroop performance in individuals with high trait anxiety. The subliminal presentation of the Emotional Stroop has been used to determine the contribution of automatic processes to interference effects. However, there appears to be no effect of content specificity in subliminal presentations of the Emotional Stroop (Mathews and MacLeod, 1994). The relatedness of words to current concern has been shown to be an important factor in the production of Emotional Stroop interference in clinical groups (Williams et al, 1996; Williams et al, 1997) and will be discussed further in section 3.2.3.

3.2.1.2 Clinical anxiety

The Emotional Stroop has been used to assess biases for emotional information in groups showing clinically-defined emotional disturbance. Panic Disorder has been consistently associated with impaired performance of the Emotional Stroop, particularly for negatively valenced disorder-specific stimuli. The Emotional Stroop has been used to assess the presence of attentional biases for threatening information which is a feature of cognitive models of anxiety (eg Beck et al, 1985; Clark, 1988). This review will show that clinical anxiety, and in particular, Panic Disorder has been consistently associated with increases in colour-naming for words representing threat or harm.

Ehlers et al (1988) conducted one of the first investigations of Emotional Stroop performance in Panic Disorder. Stimuli consisted of physical threat (eg disease), separation threat (eg lonely) and social embarrassment (eg stupid) words and were compared to matched non threat stimuli (eg leisure), presented on six separate cards to Panic Disorder patients and controls. In two separate experiments, Panic Disorder patients exhibited slower colour-naming times for physical threat words compared to non-threat stimuli, in contrast to the non-psychiatric controls. In addition, the Panic Disorder patients did not show any effects for separation or embarrassment words. In the second part of the experiment, Ehlers et al (1988) showed impaired performance on physical threat words was also present for subclinical panickers.
Cognitive approaches

Other studies have found that Panic Disorder is associated with impaired performance on different categories of negatively valenced stimuli. Carter et al (1992) presented physical threat, anxiety-related threat, depression-related and neutral words to Panic Disorder, clinically depressed and control participants. The Panic Disorder patients exhibited slower colour-naming times for all negatively valenced words compared to the neutral words. Neither the control group nor the depressed group showed Emotional Stroop interference for any word type. Lundh et al (1999) also observed that Emotional Stroop interference was present in their Panic Disorder patients for panic-related (eg pain) and interpersonal threat (eg jealous) words, compared to neutral words. No effect for word type was found for the control group. However, when separate analyses for supraliminal and subliminal exposure conditions were conducted, only the panic-related words showed significant effects. That is, the Panic Disorder patients were slower to colour-name words related to their disorder, compared to neutral words, in both exposure conditions.

McNally and colleagues (McNally et al, 1990; McNally et al, 1992; McNally et al, 1994) have performed a series of experiments using the Emotional Stroop to investigate attentional biases in subjects with Panic Disorder. In the earliest study neutral (eg polite), fear (eg panic), negative body sensation (eg dizzy) and catastrophe (eg death) words were presented to individuals with Panic Disorder and healthy controls (McNally et al, 1990). Panic Disorder patients were found to be impaired for colour-naming all categories of stimuli, including neutral words, compared to the controls. Further analysis revealed that the catastrophe words produced more interference than bodily sensation or fear words in both the patient and control groups, however the magnitude of interference was greater in the Panic Disorder patients. Impaired performance of the Emotional Stroop in Panic Disorder was replicated in a later study using a larger number of subjects (McNally et al, 1992). In that study, the time to colour name positive (eg happiness), fear, bodily sensation and catastrophe words were compared to a simple baseline consisting of a row of Xs. The Panic Disorder patients produced more interference for all words compared to the baseline, with the greatest effect observed for catastrophe words (eg heart attack). An idiographic version of the Emotional Stroop, where participants selected the most emotionally relevant and most emotionally neutral words from a list, was employed to assess interference effects in Panic Disorder, OCD and control groups (McNally et al, 1994). The Panic Disorder
patients, but not the control or OCD groups exhibited increased interference for panic-related threat as well as general threat words.

Two features of the studies of the Emotional Stroop in Panic Disorder conducted by McNally and colleagues (McNally et al, 1990; McNally et al, 1994) are worth discussing. Firstly, one consistent finding is that Panic Disorder patients are slower on all word types, including neutral words compared to the control group. This effect has also been observed in other studies (eg Kampman et al, 2002). It has been suggested that increased general distractibility, resulting from decreased cognitive capacity in chronic anxiety may account for this finding (McNally et al, 1994). However, since non-emotional measures of attention, such as the Standard Stroop, have not been used often in clinical anxiety, it is unclear whether general distractibility is a suitable explanation of the results. The second feature observed in the experiments of McNally and colleagues (McNally et al, 1990; McNally et al, 1992) is that the control group also exhibit interference for emotional words compared to the baseline task. However, the magnitude of interference in the Panic Disorder patients is always significantly greater than that shown by the control groups.

Emotional Stroop interference has not always been observed in Panic Disorder. Van Niekerk et al (1999) found that neither Panic Disorder nor Social Phobia was associated with Emotional Stroop interference. Stimuli consisted of social threat (eg failure), physical threat (eg ambulance) and non threat control words (eg frankfurter). Although the threat stimuli were chosen to reflect the concerns of individuals with these disorders, this may not have been accurate for the subject sample. Having subjects rate the stimuli in terms of emotionality, or relevance to current concerns, is one way to determine the suitability of stimuli, which was not carried out in the study by Van Niekerk et al (1999). Kampman et al (2002) also found no interference effect for Panic Disorder patients. In that study, panic-related threat, OCD-related threat, general threat and neutral words were presented in both supraliminal and subliminal formats to Panic Disorder, OCD and control groups. While Panic Disorder patients were slower at responding to all word types, there was no difference in Emotional Stroop interference between subject groups. The words used in that study had been rated on a previous occasion by Panic Disorder and OCD patients not involved in the current Emotional Stroop study, and found to be consistent with the desired
emotionally value. The authors considered a number of experimental flaws that may have lead to lack of interference effects, however no likely explanation could be found.

Generalised Anxiety Disorder (GAD) is one other clinical group that has been studied extensively using the Emotional Stroop. Cognitive features of GAD include persistent anxiety and unfounded worry about possible future events and outcomes (DSM-IV; APA, 1994). Generalised anxiety can also be a feature of Panic Disorder, for example, high levels of anxiety may persist even in the absence of panic attacks (Hoehn-Saric and McLeod, 1988). Mathews and MacLeod (1985) found that anxious out-patients took longer to colour name both threat and non-threat words compared to the control group, but were more impaired on the threat words. Mogg et al (1989) later confirmed these findings in a replication of Mathews and MacLeod's (1985) study. Selective processing of emotional information in GAD and major depression has also been investigated (Mogg et al, 1993a). In that study, anxiety and depression relevant stimuli were presented to subjects using both subliminal and supraliminal exposure conditions. The negative stimuli were a compared to categorised neutral, uncategorised neutral and positive words. The anxiety and depression words were deemed relevant to depression and anxiety on the basis of the rating by three judges. The GAD patients showed increased interference for all negative stimuli, compared to the depressed and control subjects, which was greater for the subliminal condition. Further analysis revealed that interference scores for positive words did not differ between groups, nor did the psychiatric groups differ on disorder-relevant stimuli. The authors suggest that the lack of differences between groups on disorder-relevant stimuli may indicate that both depressed and anxious groups found the stimuli to be related to their current concern. Bradley et al (1995) also contrasted Emotional Stroop performance of patients with a diagnosis of GAD, with and without depression against that of normal controls. The paradigm was the same as described by Mogg et al (1993a) except that positive words were excluded and number of colours reduced to three, resulting in fewer trials. The results showed that the GAD group without concurrent depression showed a greater interference effect for anxiety words, compared to GAD patients with depression. This effect was evident in both exposure conditions, but greater in the subliminal condition. This result suggests that comorbidity with depression may reduce
Emotional Stroop interference in anxiety. The result may also reflect amotivational states in depression producing a general slowing for all categories of words (Bradley et al, 1995).

To determine whether the production of Emotional Stroop interference in clinical groups, as compared to controls, can be explained by differences in anxiety levels, correlational analyses are often conducted. Correlations of state anxiety with interference scores have been found in clinical anxiety (Mathews and MacLeod, 1985). Trait anxiety has also been found to be correlated with interference for threat words across combined anxiety and control groups (Mogg et al, 1989), and for GAD patients when tested before and after treatment (Mogg et al, 1995). However, correlations of anxiety levels and interference scores in Panic Disorder have not often been reported. Lundh et al (1999) found trait anxiety was associated with interference for subliminal panic-related words and supraliminal interpersonal threat words. When depression levels were partialled out, however, the correlations were no longer significant. Ehlers et al (1988) also found no association between anxiety levels in Panic Disorder patients and Emotional Stroop interference. As detailed in section 3.2.1.1, correlations with state and trait anxiety in subclinical anxious groups have also been observed for threat interference (MacLeod and Hagan, 1992; Van Den Hout et al, 1995), however this effect occurred for subliminal presentation of the Emotional Stroop only. Trait anxiety only was also found to be associated with unmasked Emotional Stroop interference for anxiety-related words (Richards et al, 1992). Thus while state and trait anxiety has been found to correlate with Emotional Stroop interference in both clinical and subclinical anxiety in some studies, the outcome is not always reliable, particularly for Panic Disorder.

Impaired performance of the Emotional Stroop appears to be a consistent feature of clinical anxiety and is particularly evident in Panic Disorder. Increased reaction times in response to presentations of negatively valenced stimuli have been interpreted as evidence of increased attention for threatening information, which disrupts the ability to name the colour of the stimuli. The Emotional Stroop interference also appears to be the greatest for stimuli related to the patients’ disorders. For example, Panic Disorder patients have exhibited the largest interference effects for catastrophe words (McNally et al, 1992) and idiographic panic-related words (McNally et al, 1994). Response to threat words relevant
to Panic Disorder, but not other types of threat words, has been shown to be impaired for clinical and subclinical panic (Ehlers et al, 1988; Lundh et al, 1999).

Another feature of Emotional Stroop performance in individuals with Panic Disorder, is the increased time for naming colours of all stimuli, compared to control groups (McNally et al, 1990; 1994; Kampman et al, 2002) which may reflect general distractibility in chronic anxiety states (McNally et al, 1994).

3.2.2 Mood induction studies

The cognitive models of Bower (1981) and Beck (Beck et al, 1985) both predict mood-congruent biases for emotional information, and as such, a number of investigations have assessed whether current mood or stress levels, rather than trait characteristics, influence Emotional Stroop performance.

To investigate whether transient mood contributes to Emotional Stroop interference, university undergraduates underwent a depression, elation or neutral mood induction procedure in a study by Gotlib and McCann (1984). Mood induction was achieved by reading, both silently and aloud, statements that progressed from being neutral to being strongly related to the inducted mood. The subsequent performance of the Emotional Stroop task did not reveal any differences in colour-naming between the three groups, despite the depression mood induction being rated as successful. This study was designed to determine whether transient mood, rather than stable patterns of depression, could explain the differences in colour-naming of emotional words seen in clinical psychiatric groups. The results suggest that transient mood does not have any bearing the Emotional Stroop interference effect. The authors note that the results may also indicate that negative cognition precedes, rather than follows depressed effect.

Richards et al (1992) manipulated the mood of subjects by exposing them to either negative or positive pictures from newspaper articles. Assessment of state anxiety following the mood induction procedure showed that the negative pictures increased anxiety while the positive pictures decreased anxiety. The high trait anxious group only showed mood congruency effects. High trait anxiety following positive mood induction was associated
with greater interference for positive words while participants who underwent negative mood induction showed greater interference for negative words.

Participants were required to recall negative and positive experiences in order to induce emotion-related moods in a study by Gilboa-Schechtman et al (2000). Participant ratings confirmed the efficacy of the mood induction procedure, before an Emotional Stroop task was performed. The results showed that the negative mood induction produced more interference for negative words, while the positive mood induction produced more interference for positive words. These findings support the notion of mood-congruent effects in the Emotional Stroop.

The effect of manipulations of stress levels on Emotional Stroop interference has also been investigated. The effect of state anxiety on the performance of high and low trait anxious individuals has been discussed in section 3.2.1.1. MacLeod and Rutherford (1992) found that increased state anxiety produced increased threat interference for subliminal presentation of the Emotional Stroop in the high trait anxious group only. Increased levels of stress did not appear to influence the interference effect in the low trait group.

Manipulation of mood and anxiety levels may not always be achievable. Riemann and McNally (1995) reported that film-induced mood manipulation procedures failed to produce a sustained effect in the participants, which may explain the lack of the expected interaction with word type. Mogg et al (1990) also found that manipulations of stress levels did not significantly alter state anxiety levels. Thus it appears from limited research, that inducing mood is not always achievable and does not appear to reliably influence Emotional Stroop interference.

3.2.3 Emotionality and relatedness to current concern

One of the issues in the Emotional Stroop is whether any strong emotional stimuli can interfere with colour naming or whether relatedness to current concern is important in producing interference in populations with emotional disturbances. If the ‘emotionality’ hypothesis is correct, then groups with emotional disturbances should show increased interference to all types of emotional words, that is, both negatively and positively valenced stimuli, compared to neutral control stimuli. The ‘personal relevance’ or ‘relatedness’
hypothesis' implies that amount of colour naming interference will reflect the degree of the semantic relatedness to the individuals' current concern of the stimuli used in the task. That is, the more a word is related to the concerns of the subject it is presented to, regardless of valence, the higher the degree of interference seen. The studies that address these concerns will be reviewed in this section.

The role of emotionality and relatedness to current concern in the Emotional Stroop was specifically investigated by Mathews and Klug (1993). Anxiety patients with mixed diagnoses, colour-named stimuli that varied in valence (positive/negative) and relatedness to anxiety (related/unrelated). Thus the negative words were either related to anxiety (eg shaking) or unrelated to anxiety (eg quarrel). Similarly, the positive words were either related to attributes that anxious patients strive for (eg fearless) or unrelated to patients' concerns (eg pride). A set of neutral control words were also used. The anxiety patients responded more slow to the anxiety-related words than unrelated words, irrespective of emotional valence. Thus the relatedness of the words to the patients’ current concerns (ie anxiety) accounted for the pattern of interference. The authors suggest that the results of other studies may be influenced by this factor, however there have been studies showing positive word interference where words are unrelated to current concerns (eg Dalgleish, 1995; Martin et al, 1991, Experiment 4).

In contrast, Martin et al (1991) found support for the emotionality hypothesis in their fourth experiment. Patients with GAD were presented with negative threat, neutral and positive words. The results showed that the GAD patients responded to both threat and positive words mores slowly than neutral words, whereas the controls showed no difference between word types. This is despite the fact that the patients and controls had rated the positive words as emotional as the negative words.

Riemann and McNally (1995) also manipulated valance and relatedness of Emotional Stroop stimuli to determine the effect on performance of the task. To obtain idiographic word lists, subjects chose two most positive and two most negative content areas from a structured questionnaire designed to assess subjects' current concerns, which lists a total of fifteen content areas including family and home, friends, physical health, education, and organisations to name a few. Participants wrote a brief explanation of the particular
negative and positive concerns they had about the content areas they chose. The authors used these explanations to select words that varied in emotional valence (positive/negative) and relatedness to current concerns (high relevance/low relevance). Participants rated each of these words on these measures. Stimuli highly related to current concerns of subjects, regardless of valence, were responded to more slowly than words of low current concern. In other words, relatedness, not valence, was responsible for the Emotional Stroop interference effect seen in that study.

Panic disorder patients have shown to be impaired at colour-naming disturbing panic words (eg fear) compared to their near antonyms (eg safe) and neutral words (McNally et al, 1994). Near antonyms were used as they may be viewed as the opposite of what patients suffer and hence be related to the patients current concerns since the words represent the type of characteristics presumably strived for. However, while the participants chose the five words that the found the most emotional from a list of twelve, the positive words may not have been highly personally relevant (Williams et al, 1996).

Gilboa-Schechtman et al (2000) also investigated relevance to current concerns. Psychiatrically healthy participants colour-named negative, positive and neutral words: one set was supplied by the experimenter, the other set was generated by the participant to represent neutral, positive and negative experiences. Words generated by the participant elicited more interference than experimenter-generated words, regardless of valence, reinforcing the concern-relevance hypothesis.

In contrast, Dalgleish (1995) found support for the emotionality hypothesis in his second experiment. Subjects with high trait anxiety showed interference for both negative (eg terror) and positive words (eg pleased) compared to neutral words. The low trait anxious showed no such pattern. This result is in contrast to the first experiment which showed interference for threat words only. The difference between the two experiments was in the method (blocked versus mixed) and mode of presentation (computer versus card). However, these factors have been reviewed by Ruiz-Caballero and Bermudez (1997) and appear not to have a consistent effect on Emotional Stroop outcome. However, the mode of response differed between the two methods of presentation: vocal response was recorded for card presentation and manual (button) response was used for computer presentation.
One criticism of the use of a button press response is that it may introduce a motor component which is not as practiced as speech. While it seems unlikely that method of response would have an effect on Emotional Stroop interference, it cannot be completely ruled out.

Relatedness to current concern, rather than emotionality, appears to be more important in the generation of the Emotional Stroop interference effect. Reviews of the Emotional Stroop paradigm have concluded that while relatedness to current concern is necessary to produce Emotional Stroop interference in clinical groups, it is not sufficient in explaining the extent to which interference is observed (Williams et al, 1996; Williams et al, 1997). In addition to the issue of current concern, it is important to explore whether this effect is not simply the by-product of participants’ expertise in the area of their emotional disturbance. This factor is discussed in the next section.

3.2.4 Expertise

It is possible that emotionally disturbed patients who constantly ruminate on certain themes, which are often a hallmark of the disturbance itself, may have become ‘experts’ in processing information related to their problems (Williams et al, 1997). This theory is often referred to as the ‘expertise’ hypothesis (eg Williams et al, 1996).

The idea of expertise was directly examined by McNally et al (1990), who compared the performance of Panic Disorder patients with a control group comprised of PhD-level clinical psychologists and doctoral candidates in clinical psychology. If expertise does indeed contribute to the Emotional Stroop interference effect, then both the patients and control group, who were experienced in processing information related to Panic Disorder, should exhibit greater interference for words related to Panic Disorder. Although both the Panic Disorder patients and clinicians took longer to name panic threat words (eg fear, dizzy) compared to neutral words, the magnitude of the difference was significantly greater for the panic patients. Expertise cannot be a complete explanation for the difference in Emotional Stroop interference between the Panic Disorder patients and psychology clinicians who are presumably both well experienced with Panic Disorder terminology, symptoms and concerns.
Active members of a rowing club showed no colour-naming interference on words related to rowing (eg sculling, oarswoman) compared to neutral words (eg teacup), in a study by Mogg and Marden (1990). However, the lack of findings may reflect infrequent usage of the words used, or the lack of tight categorisation that is associated with increased word usage (Williams et al, 1997). The rowers were amateur members of the club and therefore could not be considered genuine experts, and the results may have an interference effect if professional rowers had been studied.

Dalgleish (1995) showed that keen ornithologists were slower to identify the colour or names of rare birds, thus supporting the expertise hypothesis. However, in this study, it cannot be ruled out that names of rare birds may produce an emotional reaction in experts on the topic. Emotional ratings of the words used in the study were not reported and may have answered this question.

The issue of expertise in the Emotional Stroop has previously been considered as a form of extended practice, due to often-used concepts (Williams et al, 1996). Practice effects on the Emotional Stroop have specifically been investigated by McKenna and Sharma (1995). The researchers controlled for word length and frequency to ensure these were not confounding factors. The stimuli were neutral (eg clock), negative emotional (eg fear). The stimuli were presented in five blocks, each consisting of a random presentation of the 10 stimulus words. The results showed that amount of interference decreased over successive blocks, however the time to respond to stimuli increased over successive blocks as well which is suggestive of flagging attention.

It has previously been noted that the problem with studying ‘experts’ is that high specialist word usage encompasses material that may hold special emotional significance (Williams et al, 1996). From the studies presented above, it appears that while expertise may contribute to Emotional Stroop interference, it does not explain the levels of interference observed in clinical groups. Indeed, if expertise were to represent a form of extended practice, then decreased interference should be seen over successive repetitions as found by McKenna and Sharma (1995). In addition, if expertise were responsible for the Emotional Stroop interference effect seen in clinical populations, then studies using the paradigm before and after treatment therapy should maintain Emotional Stroop interference at
recovery. That is, as therapy progresses, patients would presumably become more expert in the material related to their condition, as their emotional symptoms subsided. The effect of treatment in clinical groups is discussed in the next section.

3.2.5 Treatment studies

Effects of recovery from emotional disturbance on the Emotional Stroop were studied by Gotlib and Cane (1987). Emotional Stroop performance of depressed inpatients with diagnosis of major depression was compared with nondepressed controls. Stimuli consisted of depression-relevant, manic-relevant and neutral words. The depression words had been rated as highly self-descriptive by an independent sample of depressed patients. The depressed patients showed greater interference for depression words, compared with the control group. When the depressed patients were tested again following sufficient clinical improvement to result in discharge, no difference in response latencies between depression, manic and neutral words was observed. The results indicated that current mood, at least in depression, might influence Emotional Stroop performance. However, it is not clear in Gotlib and Cane’s study whether the effect seen in depression was sustained over along the period of time.

Watt et al (1986) also observed therapy-related reductions in Emotional Stroop interference for spider phobics. In that study, the treatment session for spider phobics encouraged individuals to handle dead or live spiders. This process exposed phobics to greater levels of spider stimuli than they would have otherwise exposed themselves to, thus presumably becoming more ‘expert’ during treatment. Following the therapy session, the spider phobics showed a reduction in interference for spider words, compared to the testing session prior to therapy.

A similar pattern of results was seen in GAD patients after two months of behavioural therapy (Mogg et al, 1995). In that study, GAD patients without depression were followed up after receiving two months of cognitive therapy, and then tested again after 20 months. Interference for negative words was observed at the first session, prior to commencement of therapy. After two months of treatment, there was no difference in interference between controls and patients, however the reduction in Emotional Stroop interference was not maintained 20 months after treatment. These results suggest that reductions in cognitive
biases may not be maintained over time. Cautious interpretation of the results is warranted, however, given the small sample size at the final testing session. Mogg et al (1995) interpret their results in terms of anxious thoughts and worries, which may be reduced with psychological treatment, but perhaps not be sustained without it.

Thus most studies find that successful treatment reduces the Emotional Stroop interference effect, rather than maintain it as would be expected if the expertise hypothesis were true. In addition, one drawback of treatment studies is that practice effects over time cannot be ruled out.

3.3 Neurophysiology of the Emotional Stroop

Speculation about the mechanisms behind the Emotional Stroop interference effect in clinical and nonclinical samples continues between researchers. Prior to the application of neuroimaging techniques to investigations of the Emotional Stroop, McNally et al (1994) postulated that Emotional Stroop deficits seen in clinical anxiety may involve prefrontal and limbic circuits. As discussed in Chapter 2, animal and human models of fear, which approximate some symptoms of Panic Disorder, have strongly implicated subcortical structures, particularly the amygdala. The experience of emotion has been shown to involve the anterior brain regions, with lateralisation of negative and positive emotions a common feature. In contrast, the perception of emotional information, as is likely to be the case in the Emotional Stroop, has been shown to involve the parietal regions, which may have a specific role in modulating emotional arousal.

Unilateral presentations of the Emotional Stroop have suggested the presence of hemispheric asymmetries in anxious participants. Compton et al (2000) examined hemispheric asymmetry in unilateral presentations of the Emotional Stroop. Positive, neutral and threat words were presented on a background patch of colour to the left or right visual fields, which the participants verbally identified. Half the time the word and colour patch appeared in the same visual field and half the time the word and colour patch were in different visual fields. Colour-naming was faster for right visual field (RVF) presentations of colour patches compared with left visual field (LVF) presentation. However the presence of emotional words decreased this advantage the colour-naming patches in the RVF, by increasing LVF performance. Contrary to the predictions of the researchers, the
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The anxious apprehension group did not display a RVF advantage in colour-naming, which was seen in the control and anxious arousal groups.

Simply, the Compton et al (2000) study found that all subjects showed a RVF (ie left hemisphere) advantage for colour-naming which is reduced when the emotional words are present. When the findings were broken down into different comparison groups, the anxious apprehension group did not show the RVF advantage that the anxious arousal and controls exhibited. Whether this was due to an increase in right hemisphere processing or a decrease in left hemisphere processing is unclear since the anxious apprehension group was faster than both comparison groups. Compton et al (2000) concede that in the number of weeks from initial assessment to performance of the Stroop task, the anxious arousal score dropped considerably, indicating anxious arousal may only be transient, and thus similar to the control group in anxiety measures.

Hemispheric asymmetry in the processing of emotional words in high and low trait anxious subjects was also investigated by Richards et al (1995). Stimuli consisted of threat-related words (eg despair), positive words (eg relaxed) and neutral words and were presented vertically in either the left or right visual fields. All subjects responded more slowly to the emotional stimuli compared with the neutral stimuli, and there were no specific effects for trait anxiety. However the high and low trait groups showed differences in accuracy for left and right hemisphere presentations. The low trait group showed reduced accuracy for threat-related trials presented to the LVF only, thus implicating the right hemisphere in correct response selection. However the high trait anxious group showed impaired performance for LVF presentation for both threat and positive stimuli compared to neutral trials. The fact that there were enough errors to be analysed indicates is in contrast to most other Emotional Stroop studies where errors are rare (eg Gotlib and McCann, 1984; McNally et al, 1990). Emotional Stroop studies that require a vocal response find that errors are rare, whereas manual (ie button press) responses are prone to higher error rates (Mogg et al, 1993b) which may explain the high error rate found by Richards et al (1995).

of a row of hatches (ie #######) as a baseline, the incongruent Stroop and 'sad' words (eg grief) to subjects, while rCBF was measured. All stimuli were presented on the screen in columns, similar to a standard card presentation of the Emotional Stroop. The ‘sad’ Stroop produced increased rCBF in the left and mid-cingulate region, as well as in the left occipital cortex. However the cingulate region was also activated in the incongruent Stroop, suggesting that the effects in this region were not specific to the Emotional Stroop, and may reflect activation of a region involved in overriding a competing verbal response.

Functional MRI (fMRI) was used by Whalen et al (1998a) to investigate areas of brain activation during an Emotional counting Stroop paradigm. The Emotional counting Stroop requires the participant to indicate how many times a single word is repeated at each presentation. For example, if the word 'murder' is three times on a screen, the subject presses the third of four buttons to indicate his/her response. General negative words (eg painful) and OCD-related words (eg filthy) were compared to neutral words (eg table). Negative and neutral stimuli were alternated throughout the task. The normal controls showed activation of the left anterior cingulate area, for the negative words compared to the neutral words. This area is only slightly anterior to the area of activation found by George et al (1994) in the sad Stroop task. Since the anterior cingulate is commonly activated for studies of the Standard Stroop (MacLeod and MacDonald, 2000), the activation of the anterior cingulate observed in the Whalen et al (1998a) study may simply indicate its general role in selective attention.

Other regions, implicated in human and animal models of fear have shown activation during an Emotional Stroop task. Isenberg et al (1999) measured rCBF in volunteers while performing an Emotional Stroop task consisting of threat and neutral words. Comparisons revealed significant activation of the bilateral amygdala, the left premotor cortex and a region incorporating the left parahippocampal gyrus. Both the amygdala and hippocampal structures have been implicated in models of animal and human fear. In addition, abnormalities of the parahippocampal region have been observed in Panic Disorder (see Chapter 2).

In a comprehensive study of the Emotional Stroop using fMRI, Compton et al (2003) reported increased activation in frontal, parietal, occipital and temporal regions. In that
study, negative words (e.g., danger, gloom) were compared to neutral words (e.g., data, equal) in twelve participants. Increased activity was observed in left middle inferior and medial frontal gyri, as well as bilateral temporal and parietal sites, and also in the right occipital cortex. However, activations within the left frontal and left parietal regions were also observed for the incongruent Stroop task compared to neutral words, suggesting a general cognitive role for these regions, rather than an emotional one.

The left prefrontal areas have also been implicated in attentional bias for angry faces during a pictorial version of the Emotional Stroop task (d'Alfonso et al., 2000). Repetitive transcranial magnetic stimulation (rTMS) was applied to the left and right prefrontal cortices of healthy women, while they performed the pictorial Emotional Stroop. The task consisted of random presentation of neutral and angry faces on a transparent coloured background. When rTMS is applied to a cortical area, local processing in brain neural networks is briefly disrupted. When rTMS is of the slow type, this disruption tends to result in decreased cortical activation. When rTMS was applied to the right prefrontal cortex (PFC), thus increasing relative activation in the left PFC, angry faces were responded to more slowly than neutral faces. When rTMS was applied to the left PFC, the result was reversed; neutral faces were responded to more slowly.

It is of note that rTMS deactivation of the right PFC in the d'Alfonso et al. (2000) study, may have also included the underlying cingulate area or its connections, thus producing relatively greater activation of not only the left PFC but also the left anterior cingulate. This is in agreement with other studies observing anterior cingulate activation during different versions of the Emotional Stroop (George et al., 1994; Whalen et al., 1998a).

To date, there have been no studies investigating the neurophysiology of the Emotional Stroop in Panic Disorder. The limited literature on emotional processing in Panic Disorder suggests abnormalities within prefrontal regions. Windmann et al. (2002) investigated whether associations between attending to emotional information and prefrontal dysfunction in Panic Disorder can be measured using ERPs. The task presented to patients and controls required the participant to indicate whether neutral (e.g., protract) or negative (e.g., destroy) words had been presented in an earlier list. In the early time window, 300-500 msec following stimulus presentation, the control group showed significant decreases in
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anterior ERPs for negative compared to neutral words. The Panic Disorder group failed to show differentiation between the stimuli suggesting impaired processing of differently valenced material. That is, neutral and negative stimuli were processed in a similar way, which is consistent with over-reactive automatic threat detection systems (McNally, 1995; Williams et al, 1997). In contrast, Pauli et al (1997) demonstrated enhanced positive slow waves (600-800 msec following stimulus presentation) for body-related words, compared to nonsomatic words in Panic Disorder patients. The ERP effect was most pronounced within the right hemisphere and at central and parietal sites, but not frontal sites. The authors interpret their findings as evidence of altered processing of stimuli related to bodily sensations. Increased attention to bodily sensations as a prelude to panic is a feature of Clark’s cognitive account of anxiety disorders (Clark, 1988).

Neurophysiological investigations of the Emotional Stroop in nonpsychiatric groups have indicated a particular role for the left frontal regions as well as the anterior cingulate, in processing emotionally threatening information. Activation has also been observed in other cortical and subcortical structures, although no consistent results have emerged. This may simply be due to conceptual and methodological differences, and the general limitations of having only a small number of studies to compare.

3.4 Summary

The original Stroop task has been used for a number of decades as a measure of selective attention in a number of different groups. The Stroop task involves overriding the tendency to read the colour-word presented in order to name its ink colour, and has been used in psychiatric populations as an index of the ability to ignore distracting information. There is some evidence that attentional disturbances exist in some psychopathologies such as depression and schizophrenia, however it is unclear as to whether this extends to anxiety disorders. Neurophysiological investigations of the Stroop in nonpsychiatric groups have consistently implicated the anterior cingulate.

Whether the activation of the anterior cingulate reflects a role in attentional control or informational conflict detection is unclear (MacLeod and MacDonald, 2000). The application of the Standard Stroop task to anxiety disorders may help to clarify whether observed attentional biases are limited to emotional information, or whether a general
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distractibility exists, particularly in Panic Disorder, as has been suggested previously (McNally et al, 1994).

Attentional biases in anxiety disorders have been predicted by a number of cognitive accounts of emotional psychopathology (eg Beck et al, 1985; Bower, 1981; Clark, 1988). One method of investigating attentional biases in clinical and subclinical anxiety uses a modified version of the Stroop task. The Emotional Stroop uses differently valenced emotional and neutral words, in place of colour names, while still requiring participants to indicate the ink colour of the words presented. The Emotional Stroop has been presented to patients and psychiatrically healthy controls using a variety of presentation and response methods, with word stimuli generated in a number of ways. Within clinical anxiety disorders such as Panic Disorder and GAD, the Emotional Stroop has consistently shown impaired colour-naming of negative words. To obtain Emotional Stroop interference, evidence from previous research suggests that the stimuli used must be either threatening in nature or relate to the current concerns of the participant. Limited neurophysiological data have implicated the anterior cingulate and left prefrontal regions in Emotional Stroop performance. While there has been much speculation of the theoretical mechanisms that give rise to the Emotional Stroop interference in clinical anxiety (eg Williams et al, 1996), there has been very little empirical research to elucidate the neural mechanisms of attentional biases in these groups. The limited evidence available suggests that altered processing of negative and somatic words in Panic Disorder can be detected with neurophysiological measurements (Pauli et al, 1997; Windmann et al, 2002). The ERP studies also highlight the presence of time-varying processes in emotional processing, which may be obscured in fMRI and PET investigations in particular, where the data collection time is in the order of seconds to minutes. The Emotional Stroop has been used extensively in anxiety to demonstrate attentional biases, but there have been no studies to date investigating the neural mechanisms of these attentional biases nor the time-varying processes associated with Emotional Stroop performance specifically in Panic Disorder.
CHAPTER 4 Theory And Hypotheses

The brain regions involved in emotion, and in particular, emotions that are relevant to the study of Panic Disorder have previously been highlighted in Chapter 2. Also highlighted were the regions which may be dysfunctional in Panic Disorder. Chapter 3 highlighted the use of the Emotional Stroop to investigate emotional biases in psychiatrically healthy groups as well as sub-clinical and clinically anxious groups. It has already been noted that very few studies of the Emotional Stroop have utilised brain imaging techniques to elucidate underlying mechanisms of the observed attentional biases, with most studies making inferences based on behavioural measures. This chapter outlines and compares the most commonly used brain imaging techniques and their suitability to the present study, in section 4.1. In addition, section 4.2 will introduce Steady-State Probe Topography (SSPT) techniques and methodology as used in the present study. Finally, the aims and the hypotheses of the present study will be outlined in section 4.3.

4.1 Currently available brain imaging techniques

There currently exists a wide range of brain-imaging techniques that each has their own unique potential for contributing to the understanding of the functional organisation of the human brain. The use of Positron Emission Tomography (PET) to elucidate functional brain activity has been occurring since the 1980s and its methodology is by now well understood. The advantage of PET is its in vivo, high spatial resolution. However, one drawback is that its temporal resolution is limited by the half-life of the isotope used, typically a couple of minutes for 15-Oxygen and 110 minutes for 18-Fluorodeoxyglucose (FDG). Neurons communicate in the order of milliseconds, and as such, the cognitive activation of certain cortical regions, which may occur only briefly, may be grossly underestimated in PET imaging.

Functional MRI (fMRI) is now becoming the preferred method for imaging functional brain activity, due to its high spatial resolution and its improved temporal resolution, in the order of a few seconds (Rosen et al, 1998). Functional MRI signals originate from the haemodynamic responses presumed to be secondary to neural activity in the brain which
are generally regarded as due to excitatory neuronal processes but may also represent inhibitory processes (Raichle, 1998). While the temporal resolution of fMRI is far better than that of PET, it may still underestimate transient fluctuations in the order of a few milliseconds related to cortical processing. Non-invasive ways to map millisecond cortical changes, such as those seen in cognitive processing of stimuli, include electroencephalography (EEG), magnetoencephalography (MEG) or evoked response potential (ERP) techniques.

4.1.1 Traditional ERP/EEG

Electroencephalography and ERPs have superior temporal resolution compared to fMRI and PET. However this benefit is tempered by diminished spatial resolution which is in part due to the non-invasive nature of the recording, but also due to the number of recording sites traditionally used. Clinical and experimental studies have typically employed no more than 21 electrodes, used in the standard 10-20 configuration. The limited number of electrodes makes it difficult to determine the neurophysiological and neuroanatomical substrates of disorders or cognitive processes under investigation by EEG alone. In addition, current EEG and ERP studies use a variety of techniques that make it difficult to directly compare the studies’ outcomes. Another drawback, particular to traditional ERP, is that it requires high stimulus repetition to gain a reasonable signal to noise ratio and thus cannot be used to investigate time varying processes.

4.2 Steady state probe topography (SSPT)

Steady state probe topography (SSPT) is a neuroimaging method that combines the steady state visual evoked potential (SSVEP) with the probe-ERP paradigm to identify regions of brain activity, that may be represented as a dynamic sequence of topographic maps reflecting the distribution of cerebral activation in response to a cognitive task.

4.2.1 The probe-ERP paradigm

The probe-ERP paradigm is based on the premise that regional increases in cortical activity associated with cognitive processes will give rise to smaller potentials evoked by an irrelevant or ‘probe’ stimulus (Papanicolaou and Johnstone, 1984). The probe-ERP
Theory and hypotheses

paradigm assumes a limited-resources model in that brain regions involved in performing the operations associated with the cognitive task will have fewer resources available for the processing of the probe stimulus, thus results in the attenuation of the ERP arising from the response to the irrelevant probe (Papanicolaou et al, 1987). The main advantage of this method is that it permits a more natural investigation of cognitive process (Papanicolaou and Johnstone, 1984). Thus it can be used to study cerebral activity in the absence of external stimuli, as well as the effects of time-varying processes, which are traditionally beyond the ability of standard ERP methods (Papanicolaou and Johnstone, 1984).

4.2.2 Task related changes in the SSVEP

The steady-state probe topography (SSPT) technique, in conjunction with the probe-ERP paradigm, takes advantage of the task-related modulation observed in the steady-state visually evoked potential (SSVEP), to provide a dynamic topographic representation of cerebral activation. The SSVEP is the probe stimulus, such as that described in section 4.1.1 that is distinct from and irrelevant to the cognitive task being performed, and its components, amplitude and phase (or latency), are altered in regions of the brain engaged in the cognitive processes being investigated.

4.2.2.1 Steady state visual evoked potentials

Steady-state evoked potentials (EPs) are elicited when the evoking stimuli are presented at a repetition rate that is high enough to prevent the EP from returning to baseline. This is in contrast to transient EPs which are elicited in response to discrete or discontinuous stimuli. While transient EPs are well suited for investigating rapid brain processes due to their high temporal resolution, the advantage of using steady-state EPs in conjunction with the probe-ERP method is that the temporal continuity of steady-state EPs offers a continuous, or dynamic, measure of time varying processes (Silberstein, 1995).

A diffuse, unstructured, sinusoidal flicker stimulus superimposed over the visual field can be used to elicit a SSVEP response in the EEG that is comprised of sinusoidal components at the stimulus frequency and its harmonics (Silberstein, 1995). The amplitude and phase of the SSVEP may be estimated using Fourier techniques. Applying coherent demodulation yields sine and cosine Fourier coefficients which can be used to determine
the amplitude and phase time series of the SSVEP. Coherent demodulation is effectively equivalent to narrow band pass filtering at the stimulus frequency (Regan, 1989), and involves integrating the product of the EEG signal with sine and cosine waveforms phase locked to the sinusoidal stimulus waveform (Silberstein, 1995).

4.2.2.2 Functional interpretation of task-related SSVEP amplitude and phase (latency) changes

Support for the SSPT technique has been provided by a number of studies which have demonstrated strong cognitive task effects on the SSVEP. This has been achieved by superimposing the eliciting stimulus, a uniform visual flicker, onto the computer monitor which presents the cognitive task. Previous studies have observed SSVEP amplitude and phase fluctuations during simple visual vigilance tasks (Silberstein et al, 1990), the Wisconsin Card Sort (WCS) (Silberstein et al, 1995), the Continuous Performance Task (CPT) (Silberstein et al, 1996a; Silberstein et al, 1996b; Silberstein et al, 1998), as well as during auditory hallucinations in schizophrenic patients (Line et al, 1998).

In an early study using the SSPT technique, Silberstein and colleagues (Silberstein et al, 1990) demonstrated a correlation between the SSVEP magnitude and visual vigilance. In the study, subjects viewed a series of 180 geometrical shapes for three trials. On the third trial, a third of the shapes were modified, and subjects were challenged to detect this modification. The results of the study demonstrated a distinction between the cortical activation patterns occurring at different stages of the task, thus supporting the use of SSPT technique. A later study confirmed similar patterns of reciprocal anterior and posterior SSVEP amplitude attenuation during performance of the CPT (Silberstein et al, 1996b). It was also noted that prefrontal phase advances (latency reductions) were associated with faster responses. These and other studies have shown that the fluctuations in the amplitude and phase (latency) of the SSVEP are cyclic and appear to be synchronised to the temporal demands of the task (Silberstein et al, 1990; Silberstein et al, 1995; Silberstein et al, 1996b; Silberstein et al, 1998).

These task related regional amplitude attenuations and phase advances have generally been interpreted as reflecting regional activation, and are in keeping with combined probe-ERP and regional cerebral blood flow measurements which have demonstrated a reduction in the
Theory and hypotheses

Probe-ERP is associated with an increase in regional cerebral blood flow (Papanicolaou, 1987). Reductions in 13 Hz SSVEP amplitude are generally considered to correspond with increases in regional brain activity (Silberstein, 1995) in much the same way as the concept of event-related desynchronisation (ERD) where regional reductions in alpha power are associated with cognitive or motor processing tasks (Pfurtscheller and Klimesch, 1990; Pfurtscheller and Lopes da Silva, 1999). However, SSVEP amplitude increases related to cognitive tasks have also been observed, particularly for tasks involving working memory (Silberstein, 1998; Silberstein et al, 2001). Specifically, during the memory component of an object working memory task, SSVEP amplitude exhibited load-dependent increases at frontal and occipital-parietal sites (Silberstein et al, 2001). Studies of alpha activity during memory tasks have also observed task-dependent alpha increases (Klimesch et al, 1999; Krause et al, 1996; Ray and Cole, 1985). Therefore task-related SSVEP amplitude alterations are generally interpreted in a similar way as alterations in EEG alpha activity.

Simple calculations applied to the SSVEP phase changes give measures of the relative increases or decreases in the latency of the SSVEP response. The latency of SSVEPs elicited by an unstructured flicker in the 8-20 Hz frequency range as applied in the SSPT technique has been estimated to be approximately 200-275 msec (Silberstein, 1995). A relative phase advance thus reflects a relative reduction in the latency of the SSVEP response with respect to the stimulus waveform. A phase lag is interpreted as a relative latency increase. Variations in SSVEP latency have been interpreted as an index of changes in neural information processing speed, which are likely to result from alterations in the loop transmission time of local cortico-cortical feedback loops (Silberstein et al, 1995). Specifically, excitatory and inhibitory neuromodulation of regional cortico-cortical resonances give rise to alterations in SSVEP latency (Regan, 1989), with latency reductions associated with normal excitatory processes (Silberstein et al, 1998). Conversely, increases in latency are likely to be a result of inhibitory neuromodulation of cortico-cortical feedback loops.

Thus the SSVEP offers a unique perspective in assessing cortical activity: latency alterations may reflect an enhancement of excitatory or inhibitory dynamic linkages between neural networks, and amplitude fluctuations may index the level of activation of involved network components (Silberstein et al, 1996b). Furthermore, the cyclic nature of
the fluctuations in the amplitude and latency of the SSVEP and its synchronicity with the temporal demands of the task suggest that SSPT is uniquely suited to observing the dynamics of time varying processes.

### 4.2.3 Features of the SSPT technique

The main feature of SSPT is its ability to offer a continuous measure of time varying brain processes over a period extending from seconds to hours. With SSPT, it is possible to index tonic activations that are sustained throughout a task (Silberstein et al, 1990) as well as transient regional activations in response to specific processing demands of a task (Silberstein et al, 1995). Such effects would not be detected with other methods not possessing the appropriate temporal resolution and continuity (Silberstein, 1995).

Another advantage of the SSPT which appears to be specific to SSVEP is that it is relatively unaffected by noise and common artifacts such as EOG, EMG and eye blinks (Regan, 1989). This is due to the power of these artifacts being distributed over a range of frequencies whereas the SSVEP signal power is concentrated at the stimulus frequency (Silberstein, 1995).

An additional feature of the SSVEP as used in the present study is the large number of recording electrodes. As mentioned previously, spatial resolution has been limited in previous EEG studies by the number of scalp electrodes. The typical 19 electrodes, placed according to standard 10-20 convention (Jasper, 1958) gives an inter-electrode distance of about 6cm on an average adult head. This spacing may be sufficient for detecting gross pathology or differentiating gross topography of Evoked Potential components, it is not sufficient for detecting finer topographical components that are important for studying the dynamic patterns of cognitive brain function (Gevins et al, 1995). The number of recording sites in the current study is 64, yielding an average inter-electrode separation of 3.2cm (Silberstein et al, 1990). While this value is slightly larger than the optimum values previously recommended by researchers (eg Gevins, 1987), it still greatly reduces the possibility of missing some of the smaller topographic features of the EEG (Silberstein et al, 1990).
Therefore, it has been suggested that the features of the SSPT technique make it an extremely useful tool in the investigation of brain activity associated with extended time varying processes such as attention (Silberstein et al, 1996b) and thus biases that may be associated with attentional tasks.

4.3 Present study’s aims and hypotheses

Many inferences about attentional and emotional processes have been made based on participants’ performances on the Emotional Stroop task, without brain activity having been recorded (eg McNally et al, 1994; Mogg et al, 1993a). There have to date, been limited studies of the Emotional Stroop using fMRI and PET (eg Compton et al, 2003; George et al, 1994; Isenberg et al, 1999; Whalen et al, 1998a), however while these methodologies have excellent spatial resolution, the poor temporal resolution means that these methods cannot provide information concerning the duration or sequence of the activation process. Studies of emotional processing utilising EEG or ERP have provided important information, but have used tasks other than the Emotional Stroop. The present study aims to investigate the brain processes involved in performing the Emotional Stroop task while providing high temporal and spatial resolution. Since patient groups, especially those with anxiety disorders, have been shown to demonstrate increased interference for the Emotional Stroop compared to non-patient groups, the present study included participants with Panic Disorder. In the present study, the Standard Stroop was also performed to determine whether a gross cognitive deficit in exists Panic Disorder, or whether the deficit is specific to processing stimuli of an emotional nature, such as that in the Emotional Stroop task.

The present study’s hypotheses are separated into those for the Standard and Emotional Stroop tasks and are outlined below:

Standard colour-word Stroop:

1. It is hypothesised that the Panic Disorder group is specifically sensitive to emotional information and as such will show similar mean reaction times to the Control group for the standard colour-word Stroop task. Similar performances as measured by reaction time data are likely to be associated with similar brain activity. Thus the inclusion of
the Standard Stroop is to confirm that Panic Disorder is not associated with a general cognitive deficit.

2. The performance of the incongruent Stroop, compared to the congruent Stroop, will show anterior or temporal SSPT changes, which are likely to be a reflection of the activity of the anterior cingulate.

The Emotional Stroop:

1. It is hypothesised that the Panic Disorder group is sensitive to emotional information, and in particular, emotional words relevant to their anxiety. Therefore it is suggested that the Panic Disorder group will show an interference effect for anxiety-related words. It is hypothesised that this interference effect will not be present for other emotional, non-relevant, categories. The altered processing of anxiety-related words will be reflected in regional SSPT differences and is likely to be localised to the right hemisphere.

2. It is hypothesised that the Control group is not sensitive to emotional information and thus will show no interference for any emotional category when compared to neutral words. A lack of interference for emotional words infers that emotional and neutral words are processed similarly and hence it is likely that no regional SSPT differences will be observed.
CHAPTER 5  Methods

This chapter describes the methods that were used to record brain electrical activity while subjects performed the Standard Stroop and Emotional Stroop tasks. Although both of these paradigms have been used extensively in the past, there are no standardised versions of either task. The considerations given to the construction of the Standard Stroop and Emotional Stroop tasks, will be detailed in section 5.1. Considerations given to the choice of stimuli for the Emotional Stroop task in particular, including physical and lexical attributes of the stimuli selected and timing considerations will also be specified. Section 5.2 will describe the application of the SSPT method to the study of the Standard and Emotional Stroop tasks in the present study. Following this, section 5.3 details the subject recruitment procedure, including the inclusion and exclusion criteria for the study. The questionnaires used for the assessment of eligible participants are also detailed. Finally, section 5.4 describes the complete experimental procedure undertaken by all participants.

5.1  Development of the Standard and Emotional Stroop tasks

The following sections discuss the development of the tasks used in the present study. Section 5.1.2, details the development of the Emotional Stroop task and outlines the adaptation of the paradigm to suit the SSPT technique. In the present study, the term ‘Standard Stroop’ encompasses the incongruent and congruent Stroop tasks which are used as the activation and baseline tasks respectively. The development of the Standard Stroop tasks will be discussed in section 5.1.1.

5.1.1  Standard Stroop task

As discussed in a previous chapter, the standard version of the Stroop task assesses an individual’s ability to selectively attend to the colour of the word stimulus, while ignoring its semantic content. In the incongruent Stroop, the subject is required to verbally respond to the ink colour of a different colour name.
For example, if the following stimulus was presented:

\textbf{green}

the subject would be required to respond by saying ‘red’ aloud.

In the present study, the baseline task was chosen to be the congruent Stroop, which consists of colour names written in the same ink colour, thus an example would be:

\textbf{green}

with the subject required to respond by saying ‘green’ aloud. Some concern has been raised over the use of congruent Stroop stimuli whereby a participant might adopt the strategy of reading the word, rather than naming its colour (McLeod, 1991). However, there are advantages to using the congruent Stroop as a comparison task for the incongruent Stroop. The main advantage of using the congruent and incongruent forms of the Stroop task is that the stimuli are physically identical, and differ only in the colour ink they are matched with. The other advantage is that the lexical and semantic aspects of each task are identical. The benefits of using the congruent Stroop as a comparison task have been outlined in other neuroimaging studies of the Stroop interference effect (Peterson et al, 1999). In addition, a number of other studies investigating the neurophysiology of the Stroop task have utilised the congruent Stroop (eg Leung et al, 2000; Pardo et al, 1990; Peterson et al, 1999) which makes comparisons with the present study more meaningful.

One of the major concerns during the development of the Standard Stroop was in selecting appropriate colours, since the steady-state flicker required for the SSVEP may alter the perceived colour of the stimuli. The original study by Stroop (1935), used brown, red, purple, blue and green, however these colours may be altered when viewed under the pink flicker of the steady-state visual stimulus. It was decided that there were no shades of brown that could be easily distinguished from red under the steady-state visual stimulus, hence the colour brown was not used. After consulting with a number of colleagues, who viewed different colours under the steady-state visual stimulus, the colours chosen for the Standard Stroop task were red, green, blue, purple and white. All words were presented in lowercase letters on a black background.
The Standard Stroop was not designed to constitute a major portion of the experiment, but was included for the main reason of being able to determine the presence of general cognitive deficits in the Panic Disorder subjects.

5.1.2 Emotional Stroop Task

As discussed in detail in Chapter 3, the Emotional Stroop task is based on the original Stroop task, whereby colour names are substituted with emotional or neutrally valenced words, while retaining the use of different coloured ink. In the Emotional Stroop task, the time to name the colour of emotional words is compared to the time to name the colour of emotionally neutral words. For example, an Emotional Stroop task might consist of the word afraid, written in green ink as shown below:

afraid

In this case, the subject would be required to say ‘green’ aloud.

Many studies have used their own version of the Emotional Stroop task, with various considerations made while constructing the task, including the relationship of the stimuli to the concerns and fears of the individuals studied (Williams et al, 1997). As such, there is no standardised version of the Emotional Stroop paradigm. The following section describes the development of an Emotional Stroop task that would be suitable for both the SSPT methodology and relevant to the subject groups investigated in the present study.

5.1.2.1 Word selection for the Emotional Stroop task

The words to be incorporated into the Emotional Stroop in the present study were chosen to represent one of four categories. These categories consisted of depression-related, anxiety-related, positive, and categorised neutral words. As discussed in Chapter 2, investigations of the Emotional Stroop have employed words related to the concerns of the subject group studied. The depression-related category was selected since it was originally intended in the present study to include patients with major depression, however this did not eventuate. The anxiety-related category was chosen to reflect words related to Panic Disorder. The positive category was included to determine whether any observed Emotional Stroop interference effects were associated with emotionality rather than valence type (see section
3.2.3). Since the emotional words used in the Emotional Stroop fall into particular categories, the neutral words used in the Emotional Stroop paradigm were chosen to form a category also, namely ‘household items’. While there appears to be no effect of categorising the neutral words on the outcome of the Emotional Stroop (Mogg et al, 1993b), it was considered necessary for the present task. In the present study, subtraction techniques will be used to investigate the areas of the brain actively involved in producing the Emotional Stroop interference effect, and therefore the neutral words should be categorised to match all other ‘categorised’ emotional stimuli.

Suggestions for suitable Emotional Stroop words were obtained from a number of different sources including previous studies of the Emotional Stroop that had published word lists, thesauri and psychologists particularly familiar with anxiety disorders. Lists of words with emotional connotations have been published (John, 1988; Johnson-Laid and Oatley, 1989) and these also served to provide choices for Emotional Stroop stimuli. The final list of stimuli chosen for the Emotional Stroop was approved by a practising psychologist. Other considerations for choice of stimuli included physical and lexical characteristics, such as number of syllables, part of speech and word length and which are detailed in section 5.1.2.2. To ensure that the participants found the stimuli suitable emotional (or non-emotional in the case of the neutral words), participants assessed each word used in the experiment in terms of personal emotional value. These findings are presented in section 6.1.3.2.

5.1.2.2 Physical and lexical characteristics of the Emotional Stroop words

The lengths of the words used in the Emotional Stroop were given first consideration. There is evidence that word length is a factor in differences seen in some aspects of word processing (Bruyer and Janlin, 1989; Young and Ellis, 1985). As a starting point, the Emotional Stroop stimuli were matched in length (3, 4, 5 and 6 characters) to the colours they were written in (red, blue, green, white and purple). It was reasoned that words containing smaller numbers of characters are easier to read at a glance and therefore may be more difficult to ignore. It is also possible that increased word length may result in lateral eye movements as the participant reads the stimulus presented, even though they are
In addition, matching for length means that the Emotional Stroop stimuli contain physical similarities with the Standard Stroop stimuli.

The words used for the Emotional Stroop in the present study were also matched for number of letters and syllables. Words were also matched for frequency of usage in the English language, as far as possible, using a publication of word frequencies in British English texts (Johansson and Hofland, 1989) as no Australian versions could be found. Previous studies of the Emotional Stroop have used similar literature in developing their word lists, quoting word frequencies in American English texts (e.g., Mogg et al., 1993a). Frequency matching may be important in two ways. Firstly, it is a variable that is easily controlled for, and therefore facilitates its inclusion. Secondly, it has been found that less commonly used colour names, for example, ‘aqua’ in place of ‘blue’ produce a greatly reduced Stroop interference effect compared to commonly used colour names (Langlois, 1974). This suggests that there may be differences in cognitive processing between high frequency and low frequency words. The word frequencies of the emotional words (anxiety-related, depression-related and positive) were compared to the word frequencies of the neutral words using $t$-tests. Analysis using Student’s $t$-tests revealed that there was no difference between the emotional and neutral words in terms of frequency of usage, as listed by Johansson and Hofland (1989), \[ t(18) = 0.852, p = 0.4 \].

Words were also matched for part of speech, as much as possible, while adhering to the other requirements listed above. All words could be used as nouns, however, for some words, the noun-form has no emotional connotation. For example ‘die’ as a noun denotes a forge or a press. In this way, three of the words have no emotional connotation if considered as nouns. These three words have emotional connotations as adjectives (two words) and as a verb (one word). All of the neutral words selected are nouns, as it was difficult to select verbs or adjectives that were solely related to the ‘household’ category. Since it was difficult to exactly match the words in each emotional category to the neutral words, categorised neutral words were chosen for their match to the average frequency of the emotional words.

The final list of words chosen for the Emotional Stroop task is listed in Table 5.1.
Methods

Table 5.1 Emotional Stroop Task Word List

<table>
<thead>
<tr>
<th>Anxiety-related</th>
<th>Positive</th>
<th>Depression-related</th>
<th>Categorised neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>die</td>
<td>joy</td>
<td>cry</td>
<td>cup</td>
</tr>
<tr>
<td>38, v</td>
<td>35, n</td>
<td>33, n,v</td>
<td>49, n</td>
</tr>
<tr>
<td>pain</td>
<td>ease</td>
<td>doom</td>
<td>pots</td>
</tr>
<tr>
<td>52, n</td>
<td>30, n,v</td>
<td>6, n,v</td>
<td>29, n</td>
</tr>
<tr>
<td>terror</td>
<td>tender</td>
<td>sorrow</td>
<td>kettle</td>
</tr>
<tr>
<td>18, n</td>
<td>17, j</td>
<td>5, n</td>
<td>8, n</td>
</tr>
<tr>
<td>scare</td>
<td>cheer</td>
<td>gloom</td>
<td>spoon</td>
</tr>
<tr>
<td>3, n,v</td>
<td>10, n,v</td>
<td>9, n</td>
<td>7, n</td>
</tr>
<tr>
<td>tense</td>
<td>bliss</td>
<td>grief</td>
<td>plate</td>
</tr>
<tr>
<td>10, j</td>
<td>5, n</td>
<td>15, n</td>
<td>37, n</td>
</tr>
</tbody>
</table>

Note: The numbers below each word indicates frequency per million. Part of speech is indicated by n (noun), v (verb), j (adjective). Where words can be used in different parts of speech, those with emotional connotations are indicated.

Thus each word used in the Emotional Stroop task was matched for word length, number of syllables, part of speech (as far as possible) and frequency of usage. Words were presented in lower case, which has been employed by previous Emotional Stroop studies (e.g. Lundh et al., 1999; George et al., 1994). The Emotional Stroop task has been designed such that any interference effect seen in the subject groups should be due only to the differences in emotional value of the words, and thus activity of the cortical areas involved in the emotional aspects of the task should be evident.

5.1.3 Timing considerations for the Standard and Emotional Stroop tasks

For each of the congruent and incongruent Stroop trials twenty lists of words ordered in a semi-randomised fashion were generated. The limitations imposed on the lists were that no word was presented more than three times in a row, and no colour was presented more than two times in a row. Occasionally, the same word-colour pair was presented successively,
but this did not occur often. The congruent trial consisted of 75 stimuli, with each colour name presented 15 times in the ink colour it named. The incongruent trial consisted of 80 stimuli, with each colour name presented in one of four ink colours (i.e., excluding the colour it named) a total of four times. All stimuli were presented on a black background.

The Emotional Stroop task was presented in a blocked format. That is, words from only one category (anxiety-related, depression-related, positive and neutral) were presented in an individual trial. There were 75 stimuli in each trial, and within each category, every word was presented 3 times in each of the 5 colours, on a black background. Twenty-five lists of randomised words were generated for each category of words, with the restriction that the same word was never presented more than twice in a row, and no colour was ever presented more than twice in a row.

Each stimulus in both the Standard and Emotional Stroop trials was presented on the screen for 1400 msec. In between each target stimulus, a ‘blank’ screen was presented for 600 msec, thus providing an interstimulus interval of 2000 msec. The blank screen provided an interval in which subjects’ incorrect responses could be logged accurately. The ‘blank’ screen in fact contained a luminance control, which consisted of a row of 4 grey-coloured hatches (# # # #) presented on a black background, which the subject was not required to respond to. The row of hatches were used in place of a characterless blank screen to control for any effect related to changes in luminance as the stimuli appeared or disappeared from screen.

Thus the incongruent Stroop trial was 160 seconds long, while all other trials (excluding the practice trials) were 150 seconds long. Representations of the congruent, incongruent and Emotional Stroop tasks are presented in figures 5.1, 5.2 and 5.3 respectively.

A reference task was required for normalising the data (see section 5.2.4.1). The reference task was a low demand visual vigilance condition and consisted of the presentation of the first 5 letters of the alphabet, ‘a, b, c, d, e’ appearing in that order repeatedly, using the same presentation rate, luminance, and number of stimuli as the Emotional Stroop task. Subjects were required to respond with a button press upon presentation of the letter ‘e’. A luminance control of a solid circle was presented in between stimulus presentations. The reference task consisted of 75 stimuli and took 150 seconds to complete.
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Figure 5.1 Representative Segment Of The Congruent Stroop

- 80 Stimulus presentations
- Stimulus duration = 1400 msec
- Interstimulus interval = 600 msec
- Task length = 160 sec
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Figure 5.2 Representative Segment Of The Incongruent Stroop

- 75 Stimulus presentations
- Stimulus duration = 1400 msec
- Interstimulus interval = 600 msec
- Task length = 150 sec
Methods

Figure 5.3 Representative Segment Of The Emotional Stroop: Anxiety-Related Words Trial

- 75 stimulus presentations
- Pseudorandom presentation order
- Stimulus duration = 1400 msec
- Time between stimuli = 600 msec
- Task length = 150 sec
5.1.4 Delivery of task and presentation parameters

The Standard and Emotional Stroop tasks were presented on a 14 inch computer monitor, with the horizontal centre of the monitor sitting approximately at the subject’s eye level. The monitor was set at a distance of 1 metre to the subject. The words were written in lower case, and the physical length of the stimulus words ranged from 8.75 cm to 3.5 cm, subtending a horizontal visual angle of 1.5 degrees to 3.7 degrees. The word images were produced with 256 colours, and the presentation of each word image was synchronised to the screen refresh. This enabled the word images to appear without flickering or scrolling down the monitor screen.

Subjects were instructed to respond to the stimuli presented on the monitor by stating aloud the colour the word was written in. The identification of the ink colour of the word was duly emphasised. Participants were told to not correct any mistakes they made, otherwise they may lose concentration. Participants were given the opportunity to practice naming the ink colour of congruent and incongruent colour words before each respective trial. Prior to commencement of the first trial of the Emotional Stroop, participants were given a practice, which contained neutral words not contained in the task proper. Practice was monitored to ensure the participants understood the task requirements. Participants wore a microphone, connected to a relay switch that recorded the time of onset of a vocal response following stimulus presentation. Incorrect responses were flagged by the investigator pressing a hand held microswitch, which was logged onto the presentation computer and identified the corresponding word-colour stimulus for later identification and analyses purposes.

The task protocol consisted of the following trials:

1. Naming the colour of congruent colour words (practice)
2. Naming the colour of congruent colour words
3. Naming the colour of incongruent colour words (practice)
4. Naming the colour of incongruent colour words
5. Naming the colour of neutral words (practice)
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6. Naming the colour of positive words
7. Naming the colour of depression-related words
8. Naming the colour of neutral words
9. Naming the colour of anxiety-related words
10. Simple visual vigilance task

Trials of the Emotional Stroop, that is, naming the colour of positive, depression-related, neutral and anxiety-related words (parts 6, 7, 8 and 9 above) were ordered in a Latin square design such that there were four ways that the Emotional Stroop was presented. The four ways the Emotional Stroop could be delivered were as follows:

a) Anxiety-related, neutral, depression-related, positive;
b) Depression-related, anxiety-related, positive, neutral;
c) Neutral, positive, anxiety-related, depression-related;
d) Positive, depression-related, neutral, anxiety-related.

For each participant, a unique task pattern was constructed, using different orders of the 20 congruent, 20 incongruent, 25 anxiety-related, 25 depression-related, 25 neutral and 25 positive semi-randomised word lists outlined in section 5.1.3. In addition, the Emotional Stroop task was ordered according to a Latin square design. This ensured that no participant received the same complete task presentation.

5.2 Steady State Probe Topography

The following sections detail the technical aspects of the application of the SSPT technique to the present study.

5.2.1 Delivery of the steady-state visual stimulus

The SSVEP was evoked using a 13 Hz sinusoidal flicker, which subtended a horizontal angle of 160° and a vertical angle of 90°. The modulation depth of the stimulus was 45% when viewed against the background. The stimulus was presented using a set of goggles, which were worn by the participant, and permitted the sinusoidal flicker to be
superimposed over the viewing field without obstructing the line of sight (Silberstein et al, 1990). The goggles consisted of two light emitting diode (LED) arrays held in place near the outer canthus of each eye. Light from the array is reflected into the eyes using two half mirrored lenses, placed at a 45° angle to the line of sight. This is shown in Figure 5.4. The light intensity generated by the LED arrays was controlled by a 13 Hz sinusoidal voltage waveform and the non-linearity between voltage input and light intensity was less than 0.5%.

Figure 5.4 is a diagrammatic representation of experimental set-up, including the delivery of the steady-state flicker.
5.2.2 Data recording equipment

The standard in-house (Brain Sciences Institute (BSI), Swinburne University) system for recording SSPT data was used. Hardware was developed by BSI to enable control of the task presentation computer, via the operating computer. A Voice Operated Relay (VOR) was developed at BSI for measuring time to respond vocally or manually to a specified target appearing on the computer monitor. This specialised hardware collected reaction time data by recording the time of stimulus presentation and the subsequent onset of a vocal response during the task, thus enabling calculations of reaction times. The VOR recorded vocal reaction time to an accuracy of 1 msec.

Following application of the recording electrodes, and prior to the commencement of the experimental procedure, a small microphone was attached to the subject to record vocal reaction time. The sensitivity of the microphone was tested by asking the subject to count slowly from 1 to 10 repeatedly, using a tone and volume that they would be able to sustain throughout the task. During this time, the microphone sensitivity dial was adjusted so that it would trigger at voice onset only.

A microswitch, held by the investigator, was connected to the hardware so that incorrect responses could be flagged by a simple button press for later identification. So that the investigator would not have to observe the task monitor during the experiment, software was written to display a symbol to indicate the colour of the word presented at the time of presentation on the 8-bit display on the VOR hardware. This enabled the investigator to determine whether there was a match between the colour the subject was voicing and the display. If the display and the subject’s response differed, the button microswitch was pressed.

A hard link to the amplifiers enabled the Stroop trial and the data collection to begin simultaneously. To achieve this, each trial in the experimental procedure was activated by a pulse from the data acquisition. Once data acquisition was commenced (via key press), a pulse was sent via a cable to the VOR which in turn launched the experimental trial.
5.2.3 Recording parameters

An electrode cap (Electro-cap International, Eaton, USA) with 64 electrodes was used to record the SSVEP. Electro-caps are made of an elastic material with recessed, tin electrodes attached to the fabric. The Electro-cap is held in place with adjustable elasticised bands that connect the cap to an elasticised brace fitted around the upper chest of the participants. The elastic material allows for easy and rapid fitting of the Electro-cap, resulting in relatively consistent electrode placement across participants. The 64 electrodes included twenty electrodes placed according to the International 10-20 system, with additional electrodes placed at intermediate points. EEG data was referenced to linked earlobes, and a nose electrode served as a ground. Figure 5.5 shows the recording montage used for these experiments. An attempt to keep electrode impedances to a minimum was made, however, impedance values were not recorded.

Ongoing EEG could not be displayed during experimental trials, but could be visually inspected in between trials to determine any faults. If any faults were found, the offending electrodes were checked and gel added if needed.

Bandpass filters were set at 0.2 Hz and 90 Hz, and EEG data were acquired with a gain of 2000 at a rate of 500 Hz. Data were digitised to 16-bit accuracy and saved to (removable) hard disk for later off-line SSPT analysis.
Figure 5.5 represents the 64 electrode placements on the scalp. Additional electrodes on the nasion and ears served as ground and linked-ears reference respectively. Standard 10-20 sites are indicated with a solid square.

5.2.4 Signal processing

A method known as coherent demodulation was used to extract the amplitude and phase time series from the 13 Hz component of the SSVEP (Reagan, 1989). This method was applied to each of the 64 EEG recording sites. The 13 Hz sine and cosine Fourier coefficients were evaluated over an integration period of 10 cycles (769 msec), which acts as a narrow bandpass filter centred on the stimulus frequency (Silberstein et al, 1990). The integration window was shifted by one stimulus cycle and the Fourier coefficients re-evaluated. This process was repeated for the entire EEG segment, at all 64 recording sites.
5.2.4.1 Normalising data

To account for intersubject variability in the SSVEP response, data was normalised using the simple visual vigilance task (consisting of presentations of the sequence ‘a, b, c, d, e’). The procedure for normalising the data involved obtaining the mean SSVEP amplitude during the reference task for each of the 64 recording sites. The 64 values were then averaged to produce a single factor for each subject. The amplitude measures for individual time series were therefore normalised by dividing through by the normalisation factor prior to cross subject averaging. All phase data was rotated with respect to the average phase during the reference task.

SSVEP time series epochs of 10 seconds were centred on the presentation of correctly identified Stroop stimuli for each subject and each condition. Cross subject averaging produced representative amplitude and phase time series for both the baseline and the activation tasks.

5.2.5 Mapping and statistics

Time averaged and dynamic sequences of maps were created using a spherical spline interpolation routine (Cadusch et al, 1992). This enables investigations of the time invariant and transient aspects of the SSVEP response. Time averaged maps were constructed by calculating the mean SSVEP level over the entire duration of each task condition, for each electrode. These maps indicate the overall processes occurring during the performance of each task in terms of the SSVEP amplitude and phase (hence latency). Subtraction between baseline and activation conditions for the time averaged maps shows the overall differences between the two conditions. The phasic (task-related) processes associated with performance of the standard and emotional Stroop, sequences of topographic maps were generated at 77 msec intervals (the period of one stimulus cycle) for the baseline, activation and difference time series. Animations were generated from the topographic map sequences, showing amplitude and phase variations covering the time from the appearance of the Stroop stimulus to the appearance of the blank (luminance control).
Statistical parametric mapping (SPM) was adapted to the SSVEP. This technique measures the statistical strength of the topographic distribution of the amplitude and latency differences. Hotelling’s measures were based on multiple bivariate $T^2$ tests that are used in this methodology to account for the SSVEP being expressed as real and imaginary components, represented as amplitude and phase in the SSVEP response (Silberstein et al, 1995). It was possible to produce animated time sequences of the topographic distribution of the square root of the Hotelling’s $T^2$ parameter ($T$) for the same time interval described above for the time averaged data. Uncorrected p values were used for exploratory purposes, while Bonferroni-corrected values were used for specific points in time.

### 5.3 Details of subject recruitment

This section describes the recruitment of suitable psychiatric and control subjects for the study. This study was approved by the Committee of Human Ethics in Research, Austin and Repatriation Medical Centre in Victoria, where the experiments were conducted, as well as by the Swinburne Research Ethics Committee as per university policy. The experimental procedures including the SSVEP recording and questionnaire assessments were explained to each subject at the initial interview, and a plain English description of the study was read by all participants before written consent was obtained. Participants were told that the study was investigating perceptual processes, and were not informed of the emotional aspects of the task until after the participant had concluded the experimental procedure. For the current experiment, only female subjects were recruited. Since Panic Disorder is more common in females than males (DSM-IV; APA, 1994), a greater number of females were likely to be recruited. Thus the possible inclusion of a small number of male subjects was seen as a source of variability, which may have an impact on the electrophysiological results. While investigations of gender differences may have clarified such issues, the anticipated paucity of male data may have engendered problems of its own. In addition, the approach of using single gender populations has been somewhat justified by recent studies which have confirmed significant gender differences in the processing of emotional stimuli (eg Kemp et al, 2004; Shirao et al, 2005) which may be due to differences in brain volumes in areas of the brain associated with such processing (Gur et al, 2002).
5.3.1 Control subjects

Thirty six psychiatrically healthy women, with no major medical problems were recruited as the control population for this study. Subjects were included if there was no previous personal history of psychiatric disorder and no history of psychiatric disorder in first degree relatives. First degree relatives include immediate family such as siblings, parents or children. Those with previous head injury, previous history of seizure, epilepsy or who were left handed were excluded. Women were also excluded if they were colour-blind. Participants were recruited from hospital staff, friends and colleagues of the investigator. Thirty-six women were recruited, but three were excluded from analysis because of hardware failure and one woman was excluded because reaction times were greater than two standard deviations from the mean. Thus the data from thirty-two control participants were analysed. The participants’ ages ranged between 21 and 55 years, with a mean of 38.72 ± 11.9 (sd) years. Subjects were right-handed as assessed by the Simplified Hand Preference Questionnaire (SHPQ: Bryden, 1982)

5.3.2 Panic Disorder subjects

Female participants suffering DSM-IV defined Panic Disorder with spontaneous panic attacks were obtained from private referrals to Professor Graham Burrows at the Austin and Repatriation Medical Centre, Heidelberg, Victoria. Participants were excluded if they had suffered previous head injury, had a history of seizures or epilepsy, if they were left-handed or had colour-blindness. All Panic Disorder subjects were right-handed as assessed using the SHPQ (Bryden, 1982). Fifteen women with panic disorder were recruited, but one was excluded from analysis due to technical failure. The ages of the panic disordered women ranged between 22 and 51 years, with a mean of 37.93 ± 10.2 (sd) years.

Patients who were taking medications for anxiety symptoms were required to refrain for antidepressant medication for at least 5 days prior to testing, and were excluded if they had received fluoxetine (Prozac or Lovan) in the previous 6 weeks. Short-acting benzodiazepines were allowed, but not less than four hours before assessment.

The Composite International Diagnostic Interview (CIDI-Auto, WHO, 1997), conducted by a registered psychologist at the Austin and Repatriation Medical Centre, Heidelberg,
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Victoria to screen out participants that might have a co-morbid diagnosis of clinical depression. The CIDI-Auto is a computer program that assists in the assessment of mental disorders using standardised interview techniques. All fifteen women met criteria for Panic Disorder, but none met the criteria for clinical depression.

Within Panic Disorder, a comorbid diagnosis of another anxiety disorder is common (Barlow, 2002, p337). Of the fifteen women in the present group, eight had a sole diagnosis of Panic Disorder with no other comorbid diagnosis. The seven remaining women shared nine comorbid diagnoses; four of Agoraphobia, two of Specific Phobia and three of Social Phobia.

5.3.2.1 Other assessments

Prior to entry into the study, the Control and Panic Disorder participants were interviewed to determine whether the individual was eligible to participate in the study. Participants who met all inclusion criteria were required to complete the following assessments:

1. Life history questionnaire, detailing age and past and current health.

2. The Simplified Hand Preference Questionnaire (SHPQ) (Bryden, 1982) which determines the level of handedness using five items.

3. Beck Depression Inventory (BDI), which is used to determine depressive symptoms (Beck, 1961)

4. Spielberger State/Trait Anxiety Scale (STAI), which measures trait anxiety as well as current anxiety (Spielberger et al, 1970).

5. Hamilton Depression Scale (Ham-D), which is used to determine the severity of depression in an individual (Hamilton, 1960)

6. National Adult Reading Test (NART), which is used as an estimate of verbal IQ, and can be used to estimate premorbid intelligence in psychiatric patients (Nelson, 1978; Crawford et al, 1991).
5.4 Experimental procedure

This section describes step by step the experimental procedure followed for each subject. This includes the procedure prior to, during and following the experimental session.

On the day of testing, prior to the commencement of EEG recording, the questionnaires relating to mood (STAI and BDI), the SHPQ and the life history questionnaire were completed by the participant. The Ham-D and the NART were also administered by one of the experimenters on the day of testing. In addition, participants were reminded of the procedure for recording SSVEP, and were given an opportunity to re-read the subject information sheet or ask questions. Subjects also completed a questionnaire detailing the time of their last consumption of caffeine and nicotine products, as well as the stage of their menstrual cycle. No participant consumed caffeine less than two hours or tobacco less than one hour prior to testing. Although stage of menstrual cycle was not controlled for, it was noted.

Participants were then accompanied into the room where the experiment was to be conducted. The electrode cap (Electro-cap International, Eaton, USA) was fitted and prepared. The delivery system for steady-state sinusoidal flicker was placed so that the flicker covered a field that included the task monitor which was placed at a fixed distance of one metre in front of the subject. The subject was instructed that she would see words appearing in the middle of the monitor, and that they would be in one of five colours: green, blue, white, purple and red. Her task would be to identify the colour that the word was written in, out loud, as fast as possible. Each participant was told to ignore the hatch marks (####) that appeared after every word, and only to respond to the colour of the words. If she made a mistake, she was not to correct it, but to concentrate on the next stimulus. It was made clear that subjects should respond as fast as possible, and while accuracy was important, it was more important that the subject not lose concentration. Subjects were also reminded to keep their head as still as possible during each trial. If the subject experienced any problems during the task, they were asked to raise their hand, otherwise, short breaks could be taken in between each trial if required. Subjects were informed that they would be allowed a short practice before testing commenced. A
microphone was attached to the Electro-cap to record voice onset. The experiment proper was conducted in the darkened room.

In the first practice trial, participants were told that the colour and words to be presented were written in a congruent colour, that is, blue written in blue etc and that this practice, was intended for them to get used to the colours. Following the practice, the congruent Stroop trial was presented. Prior the incongruent Stroop trial, participants were advised that the ‘words and colours will be mixed up’ but that they were still to respond only to the colour the word was written in, and a short practice was given. Participants were informed that they may find this task more difficult, and reminded not to correct themselves if they gave an incorrect response. Subjects were advised that the next part of the task used different words to what they had previously seen and to get used to seeing different words, another short practice task would be given. The practice task consisted of neutral words, not presented in the task itself. The Emotional Stroop task was then presented in four trials, each trial consisted of a semi-randomised block of neutral, positive, anxiety-related and depression-related words. The Emotional Stroop was presented in a counterbalanced order across subjects. The participants were not informed of the nature of the Emotional Stroop until well after the experiment had ceased. Any incorrect responses during the Standard or Emotional Stroop tasks were electronically flagged by the experimenter.

Following the last Emotional Stroop trial, subjects were asked if they remembered any features of the words (without being prompted as to their emotional nature) that were presented in the various trials, despite being required to attend to the colour of the words. The comments obtained during this part of the experimental session are detailed in Appendix 2. Following the last trial of the protocol, which consisted of a simple vigilance task, participants were shown a folder containing all the words presented in the Emotional Stroop. All words were presented in white on a black background with two words per page. Anxiety-related and depression-related words were always paired with a neutral or positive word in the display folder. The subject was instructed, upon viewing the words, to give a rating on how emotional she considered the words to be. The rating was based on a scale of 1 to 5, where 1 was a word conveying no emotion at all, while 5 was a very emotional word. The same rating scale was applied to both positively and negatively
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valenced words. The rating scale was verbally explained as well as having a visual analogue consisting of a straight line with the numbers 1 to 5 marked at equal increments.

The rating of each of the words presented in the Emotional Stroop marked the conclusion of the experimental procedure for the study presented in this thesis. The Emotional Stroop was one of two experimental protocols given to most participants. In 25 of the 32 subjects with usable data, an imagery task was also administered, as part of another student’s PhD project. The imagery experiment required the same inclusion and exclusion criteria as described in the current experiment for both the Panic Disorder and control groups. Where the imagery task was also administered, half of the subjects performed the Emotional Stroop task protocol first, the other half performed it after the imagery task.
CHAPTER 6  Results

This chapter is divided into two major sections, 6.1 and 6.2, which describe the behavioural and electrophysiological statistical findings of the current study respectively. With regard to the behavioural findings, the issue of interest was whether the Panic Disordered subjects performed the Standard and Emotional Stroop tasks differently, in terms of mean reaction times, compared to the Controls. An additional issue not directly related to the original hypotheses was also investigated. Specifically, the presence of an interference effect for anxiety-related words was noted for a subgroup of the Controls, and the effect of interference on the associated electrophysiology was investigated further.

Analysis of the electrophysiological data was carried out in three stages and is reported in Section 6.2. Initially, in order to have an overall view of any differences, or modal effects, which distinguished Panic Disorder from Controls within each of the tasks, time-averaged maps were generated for the two groups. These maps were generated by subtracting the mean electrophysiological activity for the entire duration of the Stroop task from the mean value of activity during the relevant baseline task. While time-averaged maps give a valuable overview of sustained effects associated with each of the tasks, they have a low temporal resolution, and lack information regarding transient or phasic changes occurring at various stages during the task. In order to investigate transient changes, dynamic maps were generated and are shown in Section 6.2.2. These maps provide information regarding the transient differences between the Panic Disorder and Control groups within each task. Finally, Section 6.2.3 focuses on specific electrode sites, which from the dynamic maps, appeared to differentiate the Controls and Panic Disordered subjects within the Standard and Emotional Stroop Tasks. In addition, specific electrode sites for the subgroup of Controls who showed interference for anxiety-related words (Interferers) and those who did not (Non-Interferers) were also examined.

6.1  Behavioural data

The following section details the participants’ behavioural data including subject characteristics as well as mean reaction times obtained for the Standard Stroop and the
Emotional Stroop tasks. Initially, behavioural data is presented for both the Panic Disorder group and the Control group. As explained in section 6.13, mean response latency from the Control group was used to further separate the participants into groups who showed increased mean reaction times for anxiety-related words compared to neutral words and those who did not. Statistical analysis of this data is also presented.

As outlined in section 5.1.1, 36 women were recruited for the Control group, but 3 were excluded from further analysis due to technical failure and one due to excessive reaction times, thus the data of thirty-two women were analysed. As outlined in section 5.1.2, 15 women with Panic Disorder were recruited for the patient group, however one was excluded from further analysis due to technical failure, resulting in the data of 14 Panic Disorder patients being analysed.

### 6.1.1 Subject characteristics

The means and standard deviations for general demographic data and questionnaire scores are presented in Table 6.1. This table represents data from 32 Control subjects and 14 Panic Disorder patients whose SSPT data were analysed.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>Panic Disorder</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.72</td>
<td>11.9</td>
<td>37.93</td>
<td>10.2</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>115.57</td>
<td>5.6</td>
<td>108.71</td>
<td>7.4</td>
</tr>
<tr>
<td>BDI</td>
<td>2.63</td>
<td>2.8</td>
<td>14.21</td>
<td>6.8</td>
</tr>
<tr>
<td>State Anxiety</td>
<td>29.63</td>
<td>9.3</td>
<td>47.21</td>
<td>9.6</td>
</tr>
<tr>
<td>Trait Anxiety</td>
<td>31.75</td>
<td>8.5</td>
<td>49.64</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Table 6.1 represents the subject characteristics of the Panic Disorder and Control groups. M = mean, SD = standard deviation; ns = not significant.
A series of $t$-tests revealed that the Panic Disorder group differed from the Control group in terms of state anxiety [$t(44) = 5.86, p<0.001$], trait anxiety [$t(44) = 5.97, p<0.001$], and BDI scores [$t(14.9) = 6.16, p<0.001$], but not in terms of age [$t(44) = 0.216, p = 0.83$]. The $t$-tests also revealed that the Panic Disorder group had a lower average estimated IQ compared to the Control group [$t(44) = 3.47, p = 0.001$].

6.1.2 Standard Stroop

The Standard Stroop paradigm was conducted to determine whether patients differed from Controls in their mean reaction times. It was hypothesised that Panic Disordered patients would not differ from Controls for the Standard Stroop since there is no emotional component in the task. The following analyses relate to the mean reaction times of the present study, which is defined as the time to name the colour of the word following its presentation.

The mean reaction times for the Standard Stroop were submitted to a 2 (Group: Controls, Panic Disorder) x 2 (Word Type: Congruent, Incongruent) repeated measures analysis of variance. The results show that there was a significant difference in the reaction times for each word type [$F(1,44) = 213, p<0.001$], but no significant interaction [$F(1,44) = 2.07, p = 0.16$] and no difference between patients and Controls in their mean reaction times for each word type [$F(1,44) = 3.37, p = 0.073$]. Thus the results indicate that both Controls and Panic Disorder patients are slower at naming the colours of incongruent words compared to naming the colours of congruent words. Table 6.2 shows the mean reaction times for the Standard Stroop.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Panic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Congruent (msec)</td>
<td>501.60</td>
<td>93.4</td>
</tr>
<tr>
<td>Incongruent (msec)</td>
<td>731.72</td>
<td>84.8</td>
</tr>
</tbody>
</table>

Note: M=mean, SD = standard deviation. Data are presented in milliseconds.
6.1.3 Emotional Stroop

In the Emotional Stroop paradigm, a comparison of the time to name the colour of emotionally neutral words and the time to name the colour of emotionally charged words, was undertaken. Mean response latencies for the Emotional Stroop were submitted to a 2 (Group: Controls, Panic Disorder) x 4 (Word Type: neutral, positive, anxiety-related, depression-related) repeated measures analysis of variance.

The analysis revealed no significant differences in mean reaction times for word type \( F(2.9, 126.4) = 1.54, p=0.21 \). There was no significant interaction between diagnosis and word type \( F(2.9,126.4) = 0.76, p = 0.5 \). However, there was a main effect for diagnosis, which showed that the panic patients were significantly slower in naming all types of words compared to the Controls \( F(1.44) = 8.1, p<0.01 \). Table 6.3 shows the means and standard deviations for the reaction times for the Emotional Stroop.

<table>
<thead>
<tr>
<th>Table 6.3 Mean Reaction Times For The Emotional Stroop</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Word type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Neutral</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Anxiety-related</td>
</tr>
<tr>
<td>Depression-related</td>
</tr>
</tbody>
</table>

Note: M=mean, SD = standard deviation. Data are presented in milliseconds.

The finding that the patients were slower than Controls in colour-naming all stimuli is consistent with previous research (eg Kampman et al, 2002; McNally et al, 1990; McNally et al, 1994; Mathews and MacLeod, 1985). In line with McNally et al, 1990, three Emotional Stroop interference indices were calculated by subtracting the mean reaction times for neutral words from the mean reaction times for positive, anxiety-related and depression-related words. Creating interference indices controls for differences in colour-naming speed and enables comparisons of relative Emotional Stroop interference for each
emotional category. The construction of interference indices in this way has been previously used in a number of other Emotional Stroop studies (eg Lundh et al, 1999; McNally et al, 1990; McNally et al, 1994).

Emotional Stroop interference data were submitted to a 2 (Group: Controls, Panic Disorder) x 3 (Word Type: positive, anxiety-related, depression-related) repeated measures analysis of variance. The means and standard deviations for the interference indices are presented in Table 6.4. Results showed no main effect for word type \(F(1.9, 83)=0.79, p=0.45\) or for Group \(F(1, 44)=1.24, p=0.27\). No significant interaction between Group and Word Type was observed \(F(1.9, 83)=0.51 p=0.59\). Therefore, even by controlling for group differences in mean reaction times using interference indices, neither the Control nor Panic Disorder groups showed any differential effects for the Emotional Stroop.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Panic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word type</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Positive</td>
<td>8.24</td>
<td>27.4</td>
</tr>
<tr>
<td>Anxiety-related</td>
<td>12.87</td>
<td>33.8</td>
</tr>
<tr>
<td>Depression-related</td>
<td>19.08</td>
<td>37.6</td>
</tr>
</tbody>
</table>

Note: M=mean, SD = standard deviation. Data are presented in milliseconds. Positive values indicate slower response for emotional words; negative values indicate faster response for emotional words.

It is worth noting that the paucity of significant effects may be due to the increased size of the standard deviations observed in the Panic Disorder group compared to the Controls, for both the mean reaction times and mean interference indices. Similar standard deviations effects have been documented for other Panic Disorder groups performing the Emotional Stroop (eg Lundh et al, 1999; McNally et al, 1994). Despite this, a significant statistical interaction between group and word type is still achieved. To combat differences in the size of the standard deviation, the mean reaction times can be log transformed (eg Kampman et al, 2002; Lemelin et al, 1997). Despite the use of the log transformed data,
Kampman et al (2002) failed to find any differences in Stroop interference between Panic Disorder patients and the Control group. To ensure that the size of the standard deviations in the Panic Disorder group did not bias the previous analysis of variance results, the mean reaction time data for the Emotional Stroop was transformed using the natural logarithm. This data was submitted to a 2 (Group: Controls, Panic Disorder) x 4 (Word Type: neutral, positive, anxiety-related, depression-related) repeated measures analysis of variance. No significant differences in the mean log-transformed reaction times for word type \[F(2.8,124.4)=1.68, p=0.18\] was found, nor was there a significant interaction between group and word type \[F(2.8,124.4)=0.65, p=0.6\]. However, there remained a significant main effect for group, indicating that the panic patients were slower in naming all word types, compared to the Controls \[F(1,44)=7.6, p<0.01\]. These results reflect the findings observed in the analysis of the absolute mean reaction times in section 6.1.3, and demonstrate that the results of the statistical analysis were not influenced by the large standard deviations seen for all Emotional Stroop word types in the Panic Disorder group.

### 6.1.3.1 Matching for differences in estimated verbal IQ

To ensure that the observed differences in mean reaction times for the Emotional Stroop were not due to differences in estimated IQ between the two groups, the following analysis was conducted. The 6 control subjects with the highest estimated IQ and one Panic Disorder patient with the lowest IQ were removed from analysis. The resultant control subgroup (n=26) had a mean estimated IQ of 113.7 ± 4.5 SD, the resultant Panic Disorder subgroup (n=13) had a mean estimated IQ of 109.7 ± 6.5 SD. T-tests confirmed that the two subgroups did not differ in estimated IQ \[t(17.9) = 2.02, p=0.06\]. Analysis of variance was then conducted on the Emotional Stroop data, as outlined in section 6.1.3. As for the whole group, the subgroups showed no effect for type of word \[F(2.8,102.4)=2.17, p=0.1\], nor was there an interaction between type of word and diagnosis \[F(2.8,102.4)=1.2, p=0.3\]. However there remained an effect for diagnosis \[F(1,37)=6, p=0.02\] indicating again that the Panic Disorder group were slower to name all types of Emotional Stroop words, compared to the Control group. Thus it appears that estimated IQ does not affect the outcome of the Emotional Stroop performance.
6.1.3.2 Emotionality ratings of the Emotional Stroop

Following the performance of the Emotional Stroop task, all subjects rated how emotional they perceived all the words presented in task to be. The scale ranged from 1 (not emotional) to 5 (highly emotional). The mean rating for each word type are presented in Table 6.4.

<table>
<thead>
<tr>
<th>Word type</th>
<th>Controls</th>
<th></th>
<th>Panic Disorder</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>Neutral</td>
<td>1.08</td>
<td>0.3</td>
<td>1.21</td>
<td>0.4</td>
</tr>
<tr>
<td>Positive</td>
<td>3.60</td>
<td>0.6</td>
<td>3.74</td>
<td>0.6</td>
</tr>
<tr>
<td>Anxiety-related</td>
<td>4.03</td>
<td>0.5</td>
<td>4.33</td>
<td>0.8</td>
</tr>
<tr>
<td>Depression-related</td>
<td>3.90</td>
<td>0.7</td>
<td>4.09</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Note: M=mean, SD = standard deviation. Scores ranged from 1 to 5.

The mean ratings were submitted to a 2 (Group: Controls, Panic Disorder) x 4 (Word Type: neutral, positive, anxiety-related, depression-related) repeated measures analysis of variance. The analysis revealed a main effect for word type [F(2.5,112.1) = 371.4, p<0.001], indicating that the words were rated differently, however the Panic Disorder and Control groups did not differ in their ratings [F(1,44) = 2.3, p=0.14]. There was no significant interaction between word type and group [F(2.5, 112.1) = 0.27, p=0.82]. Post Hoc Scheffé analyses (p<0.05) were conducted to determine how word emotionality ratings differed. The results indicated that the neutral words were significantly rated as least emotional compared to the positive, depression-related and anxiety-related words. The anxiety-related and depression-related words were rated equally emotional, however, the positive words were rated equally emotional as depression-related words but less emotional than the anxiety-related words. The Panic Disorder and Control groups’ ratings for the neutral, anxiety-related, depression-related and positive words are shown in Figure 6.1.
Results

Figure 6.1 represents the ratings for each of the word types within the Emotional Stroop task. The Control ratings are indicated by the solid squares. The Panic Disorder ratings are indicated by the open squares.

6.1.3.3 Individual differences within the Control group

It was observed that there were individual differences within the Control group in regard to the reaction times for neutral and anxiety-related words. In particular, it was observed that 19 Control subjects showed slower mean response latencies for anxiety-related words compared to neutral words, while the remaining 13 Control subjects showed faster mean response latencies for anxiety-related words compared to neutral words. This observation was analysed further to determine whether these differences were due to State or Trait levels of anxiety. In section 6.2 the electrophysiological findings are discussed.

For each Control subject, an interference score was obtained by subtracting the mean response latency for neutral words from the mean response latency for anxiety-related words. Subjects with a positive interference score were labelled as ‘Interferers’ while...
subjects obtaining a negative score were labelled ‘Non-Interferers’. Table 6.6 shows mean reaction times and interference scores for these two groups.

<table>
<thead>
<tr>
<th>Table 6.6 Mean Reaction Times And Emotional Stroop Interference Score For Control Group Separated Into Interferers And Non-Interferers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Word Type</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Neutral words</td>
</tr>
<tr>
<td>Anxiety-related words</td>
</tr>
<tr>
<td>Interference score</td>
</tr>
</tbody>
</table>

**Note:** M=mean, SD = standard deviation. Data are presented in milliseconds.

A series of *t*-tests revealed that the Interferers and Non-Interferers did not differ in age [40.26 ± 11.2 and 36.46 ± 13.0 respectively; *t*(30) = 0.89, *p* = 0.38] or estimated IQ [115.51 ± 5.3 and 115.58 ± 6.3 respectively; *t*(30) = 0.03, *p* = 0.97]. Previous research has suggested that state or trait anxiety may relate to the presence of an interference effect (eg Dalgleish, 1995; MacLeod and Rutherford, 1992; Mogg et al, 1990). Students’ *t*-tests revealed that there was no difference between the Interferers and Non-Interferers in terms of State Anxiety measures [27.84 ± 6.6 and 32.23 ± 12.0 respectively; *t*(17) = 1.2, *p* = 0.25] or Trait Anxiety measures [30.21 ± 5.8 and 34.00 ± 11.2 respectively; *t*(16.5) = 1.1, *p* = 0.28]. Tests were conducted to determine whether there were correlation between State and Trait Anxiety and mean reaction times. The results showed no correlation between State or Trait Anxiety with reaction time for neutral words or anxiety-related words (Pearson correlation < 0.24, *p* > 0.1 for all correlations). However, there was a borderline significant correlation for State Anxiety and Interference score (Pearson correlation = -0.349, *p* = 0.05), indicating that State Anxiety decreased as the Interference score increased. A similar negative correlation between trait anxiety and Interference score almost reached significance (Pearson correlation = -0.328, *p* = 0.067).
To confirm the separation of the two groups by presence or absence of an interference effect for the anxiety-related words, a Students’ $t$ test was conducted. The results confirmed a significant difference between the interference score for the Interferers and Non-Interferers [35.09 ± 22.5msec and -19.59 ± 16.4msec respectively; $t(30) = 7.5$, $p < 0.001$].

To determine whether the presence of a positive Interference score was due to the anxiety-related words being perceived as more emotional, a 2(Group: Interferers, Non-Interferers) x 2(Word Type: anxiety-related, neutral) repeated measures analysis of variance was conducted for the emotionality ratings of the two word groups. There was a significant effect for Word Type [F(1,30) = 1077.9, $p<0.001$] indicating that the words were rated differently, and a significant difference between the two groups [F(1,30) = 12.8, $p=0.001$]. This interaction was significant [F(1,30) = 5.7, $p=0.024$]. As can be seen from Figure 6.1, the Non-Interferers rated the anxiety-related words as more emotional than the Interferers.

A similar analysis of data was not conducted for the Panic Disorder group due the small number (n=14) of participants.
Figure 6.2 shows the ratings for anxiety-related and neutral words for the Interferers and Non-Interferers. The solid circles represent the Non-Interferers and the open circles represent the Interferers.

### 6.2 Electrophysiological data

The analysis of the electrophysiological data was carried out in three stages, each of which will be discussed in turn. It is important to note that the following electrophysiological data is associated with correct performance of the task, since only correctly performed trials were analysed. Furthermore the data presented is thought to represent the cognitive processing associated with avoiding distracting information so as to produce a correct response. The data thus corresponds to time frame that begins at presentation of the individual word up to 1 second, which includes response.

Despite the simplicity of the words used in the Emotional Stroop task, it is possible that the differences in estimated verbal IQ between the Control and Panic Disorder groups may give rise to differences in the electrophysiological data. However, previous research using
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SSVEP has shown that electrophysiological data is not affected by differences in full-scale IQ (Silberstein et al, 1998). In addition, the use of the entire data set allowed for greater statistical power and better signal to noise ratio within the electrophysiological data. In order to determine whether the electrophysiological effects apparent in the entire group persisted when IQ was matched between groups, the following procedure was adopted. The SSVEP amplitude differences between the anxiety-related words and the mean of neutral words were calculated for the entire Control group (n=32) and Panic Disorder group (n=14). The anxiety-related words portion of the Emotional Stroop was chosen as a representative task, and one most relevant to the present study. This procedure was repeated for the IQ matched Control group (n=21) and Panic Disorder group (n=13) described in section 6.1.3.1. The Control group waveform was then subtracted from the Panic Disorder group waveform for both the entire group and the IQ-matched subgroups, yielding one difference waveform for the whole group and one difference waveform for the IQ-matched subgroup. A correlation coefficient for each of the 64 recording sites was then calculated between the entire group difference waveform and the IQ-matched difference waveform.

A high correlation coefficient would indicate that the differences observed in the entire group were also apparent in the IQ-matched subgroups and that the SSVEP differences between the comparison groups were unlikely to be due to differences in mean estimated IQ. When this procedure was conducted, a mean correlation coefficient of 0.71 for SSVEP amplitude, suggesting that the observed effects for the entire group are not a consequence of the differences in mean IQ between the Control and Panic Disorder groups. Previous research using this method has demonstrated that when SSVEP amplitude waveforms correlate between the two groups, the SSVEP latency shows a similar correlation (Silberstein et al, 1998) and as such, only correlations for SSVEP amplitude measures were conducted for the current paradigm.

6.2.1 Time-averaged maps

In order to receive an overall view, or modal effects, of the differences which distinguished Panic patients from the Control group, time-averaged maps were generated for each group and can be seen in Figures 6.3 and 6.4. In order to facilitate comparison between the two
groups within each task, maps for the two groups are shown together. These maps were constructed by subtracting the mean electrophysiological activity for the entire duration of the cognitive task from the mean value of activity during the baseline task and as such had a low temporal resolution. As previously noted, in the SSPT technique, SSVEP differences are reflected in amplitude and latency variations. Thus, each row of maps shows the SSVEP amplitude in the left column and latency differences in the central column, for each of the cognitive tasks being investigated. Measures of relative SSVEP amplitude and latency reductions are represented by warmer colours and a negative scale. Reductions in SSVEP amplitude are interpreted as increased regional activation. Typically, latency reductions are interpreted as indexing increased neural excitation, while latency increases index increased inhibitory neural processes.

Statistical Probability Mapping (SPM; Duffy et al, 1981) based on Hotelling’s $T^2$ parameter was used to illustrate the topography of the statistical strength of the amplitude and latency effects. The Hotelling’s $T^2$ parameter is shown in the right hand column. The four adjacent iso-$T$ contours superimposed onto the Hotelling’s $T$ maps correspond to single comparison p-values of 0.05, 0.025, 0.01 and 0.001 and are shown for exploratory purposes only.
Figure 6.3 Time-Averaged Maps For The Control And Panic Disorder Groups - Standard Stroop Task

Control Group

Panic Group

The maps in Figure 6.3 reveal sustained SSVEP amplitude reductions about the occipital pole for the Control group, which is skewed to the right, and extends to the parietal region.
The associated SPM shows that this effect is significant. With respect to SSVEP latency, a sustained reduction in the right frontal region which extends to the left posterior temporal region is present. The associated SPM shows that the SSVEP latency reduction in a discrete area of the right frontal region is significant.

The Panic Disorder group show a sustained SSVEP amplitude reduction in the occipital region, similar to the Control group, however, the Panic group also show a reduction in SSVEP amplitude bilaterally in the frontal area. The associated SPM shows that only the left frontal and right occipital SSVEP amplitude reductions are significant. The Panic group also exhibit strong and sustained SSVEP latency reductions in the left temporo-parietal region, which is significant in the temporal region only. In contrast to the Control group, the Panic Disorder group fail to exhibit right anterior SSVEP latency reductions.
Figure 6.4 Time-Averaged Maps For The Control And Panic Disorder Groups - The Emotional Stroop
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Figure 6.4 represents the time-averaged maps for Emotional Stroop task, which was constructed by subtracting the mean activity during the neutral words task from the mean activity of each of the positive, depression-related and anxiety-related words task. The maps on the left represent relative amplitude differences, the middle maps represent relative latency differences and the maps on the right represent the SPM.

With regard to the Emotional Stroop tasks displayed in Figure 6.4, the Controls show no marked changes in SSVEP amplitude, with the exception of a general bilateral decrease in the posterior area for depression-related words. The SPM demonstrates that this was statistically significant in the region of the occipital pole, and at a right parietal site. In contrast, the Panic Disorder group show SSVEP amplitude decreases in the frontal regions, which are particularly salient within the left frontal region for anxiety-related words. In addition, SSVEP amplitude is decreased bilaterally in the occipital regions for anxiety-related words. The associated SPM shows a significant effect in these regions, but it must be noted that latency decreases in this area may also be contributing to this.

Figure 6.4 shows that in terms of latency, the Control group display SSVEP changes mainly in the temporal region. For the positive words there is a SSVEP latency decrease in the right temporal region, which does not reach significance. For the depression-related words, there is a SSVEP latency decrease in the left temporal region, as well as within right frontal sites, which again does not reach significance. However, the SPM for depression-related words indicates a significant effect in the right central area. This is probably due to the slight increase in SSVEP latency in this region. The anxiety-related words were associated with a latency decrease in the left temporal area, which extended frontally. In addition, the SPM shows an effect in the right parietal area, which is likely to be due to either the SSVEP amplitude decrease or the SSVEP latency increase in this region, or a combination of both.

The most prominent features of the Panic Disorder group as seen in Figure 6.4, is the bilateral SSVEP latency decreases in the parietal areas for all categories of words. The SPMs indicate that this effect was significant for the anxiety-related words only. Both the positive and depression-related words were also associated with SSVEP latency decreases in the left frontal regions but the observed effects were not significant. The SPM for positive words also reveal a significant effect at a right central-frontal site and is likely to
be associated with a SSVEP latency increase. The SPM for anxiety-related words also shows a right temporal effect, however it is not clear whether SSVEP amplitude or latency alterations are responsible.

Figure 6.5  Time-Averaged Maps For The Interferers and Non-Interferers – Anxiety-Related Words

Figure 6.5 represents the time-averaged maps for anxiety-related words condition of the Emotional Stroop task for the Interferer and Non-Interferer groups. The maps were constructed by subtracting the mean activity during the neutral words task from the mean activity during the anxiety-related words.
In Figure 6.5, the Interferers display small sustained SSVEP amplitude decreases bilaterally in frontal regions, which extend to central areas as well as to left parietal sites, although these effects are not significant. In terms of SSVEP latency, there are no outstanding sustained effects.

The Non-Interferers show small sustained SSVEP amplitude decreases mainly in the right hemisphere, and particularly in the right frontal area, extending to right posterior temporal regions. SSVEP latency increases are also noted in the same region. The associated SPM shows that the SSVEP alterations in the right hemisphere are significant.

6.2.2 Dynamic maps

While time-averaged maps are valuable as an overview of the modal effects associated with each of the cognitive tasks under investigation, they do not provide an insight into the transient or phasic changes occurring as various stages of task performance. As such, dynamic maps were generated for the Panic and Control groups, and are shown in Figure 6.6 to Figure 6.11.

For the Standard Stroop Task, the dynamic maps represent the difference between the mean levels of amplitude and latency time series in the baseline task (congruent Stroop) and the time series of the incongruent Stroop. Only correct responses were analysed, and the maps were centred on the presentation of the word. For the dynamic maps, as was the case for the time-averaged maps, regions of relative SSVEP amplitude and latency reductions are indicated by a negative scale and warmer colours.

For the Emotional Stroop task, the dynamic maps represent the difference between the mean levels of amplitude and latency in the baseline task (neutral words) and the time series of the activation tasks (positive, anxiety-related and depression-related words). Only correct responses were used in the final analyses, and the maps were centred on the presentation of the word. As mentioned in the previous paragraph, regions of relative SSVEP amplitude and latency reductions during the task of interest are indicated by a negative scale and warmer colours.

For the Interferers and Non-Interferers, the dynamic maps represent the difference between the mean levels of SSVEP amplitude and latency in the baseline task (neutral words) and
the time series of the anxiety-related words task of the Emotional Stroop. Only correct
responses were analysed, and again the maps were centred on presentation of the word.
The amplitude and latency scales are identical to those mentioned above.

The first row of maps labelled “Presentation” illustrates the SSVEP amplitude (left column)
and latency (central column) differences as well as the corresponding Hotelling’s $T$
parameter at the time of word presentation. The four iso-T contours correspond to single
comparison p-values of 0.05, 0.025, 0.01 and 0.001 and are shown for exploratory purposes
only. The next five rows illustrate the equivalent set of three maps at specified times
following presentation. To facilitate comparison, the dynamic maps for the Panic Disorder
and Control groups within each of the three different emotional categories of the Emotional
Stroop appear on two consecutive pages. The most prominent features of these two groups
for each condition are then summarised on the subsequent page.
Figure 6.6 Dynamic Maps For The Control Group, Standard Stroop Task
Figure 6.7 Dynamic Maps For The Panic Disorder Group, Standard Stroop Task
Figures 6.6 and 6.7 represent the dynamic maps for the Standard Stroop condition for the Control and Panic Disorder groups respectively, at presentation up to 1000 msec following presentation. The maps were constructed by subtracting the mean activity of the congruent Stroop from the time series of the incongruent Stroop.

Figure 6.6 displays the dynamic maps for the Standard Stroop condition in the Control group. A general posterior SSVEP amplitude reduction, extending to the left temporal area is noted initially at word presentation. This is significant about the occipital pole, as well as in the left temporal region. The posterior SSVEP amplitude reduction continues until 462 msec, and the associated SPMs indicate the most prominent effect is located in the right hemisphere. The occipital SSVEP amplitude reduction continues to 923 msec, but with less strength. Between 462 msec and 769 msec, general anterior SSVEP amplitude reductions are noted and reach significance mainly in the right central and frontal regions. Right temporal SSVEP amplitude reductions also reach significance during this time.

With regard to SSVEP latency, at presentation, a general anterior reduction is noted, which extends into the temporal region, and may be contributing to the associated significance at this point. Anterior SSVEP latency reductions continue in strength up to 462 msec, after which the effect diminishes, and is no longer significant in the associated SPMs. However, the left temporal SSVEP latency reduction is present from word presentation up to 923 msec, and appears to be contributing to the significance in this region. It is interesting to note that posterior SSVEP latency and amplitude reductions occur in similar areas and may both be contributing to the significant effects in this area, particularly from time of presentation up to 462 msec.

Figure 6.7 displays the dynamic maps for the Standard Stroop condition for the Panic Disorder group. At word presentation, SSVEP amplitude reductions are apparent in bilateral prefrontal regions as well as about the occipital pole. The associated SPM shows the occipital effect is significant. Central SSVEP amplitude increases extending to the right posterior temporal region are also noted, where significance is reached. At 385 msec, the SSVEP amplitude reductions become generalised to the anterior regions. This effect continues throughout but does not reach significance.

In terms of SSVEP latency, the most prominent effect is the sustained reduction, initially involving the left temporo-parietal region, but then extending occipitally from 385 msec to
Results

cover the left posterior region. This effect reaches significance at temporo-parietal sites from 385 msec onwards. Other SSVEP latency effects include a latency increase in the right parieto-occipital region that appears to be contributing to the significance in this area at the time of word presentation and 385 msec. Bilateral anterior increases in SSVEP latency are also apparent from 385 msec onwards, reaching significance at 769 msec where the effect is has a right fronto-central distribution.

The Panic Disorder group appear to have large SSVEP amplitude reductions from the time of presentation to 462 msec, which the Control group do not show. In addition, the Panic Disorder group appear to lack the sustained anterior SSVEP latency reductions exhibited by the Control group.
Results

Figure 6.8 Dynamic Maps For The Control Group, Positive Words

Presentation

231 msec

385 msec

615 msec

769 msec

1000 msec

+0.3
Amplitude Difference

-0.3

+9.8
Latency Difference
(msec)

-9.8

0.0
Hotelling's T

4.0
Results

Figures 6.8 and 6.9 represent the dynamic maps for the positive words Emotional Stroop condition for the Control and Panic Disorder groups respectively, at presentation up to 1000 msec following presentation. The maps were constructed by subtracting the mean activity of the neutral words condition from the time series of the positive words condition.

Figure 6.8 displays the dynamic maps for the positive words component of the Emotional Stroop for the Control group. At word presentation, the Control group demonstrate SSVEP amplitude decreases in the left frontal region as well as bilaterally in the occipito-parietal regions. The bilateral reduction of SSVEP amplitude in the occipito-parietal region is sustained until 385 msec. At 385 msec, anterior SSVEP amplitude reductions develop and become most prominent in the map immediately prior to response (615 msec), reaching significance in bilateral fronto-central and temporal sites. This anterior effect abates following response. At 615 msec, mild bilateral SSVEP amplitude increases are evident, and contribute to the significance of the left occipito-parietal region in the associated SPM at this point and at 769 msec.

In terms of SSVEP latency, at the time of word presentation, The Control group display SSVEP latency increases in bilateral anterior regions which is maximal prefrontally. This effect is not sustained and at 385 msec, anterior SSVEP latency reductions are observed which remain until 615 msec. Left occipito-parietal SSVEP latency reductions are also observed and contribute to the significance in the associated SPMs.

Figure 6.9 displays the dynamic maps for the positive words component of the Emotional Stroop for the Panic Disorder group. At presentation, the Panic Disorder group demonstrate prefrontal SSVEP amplitude decreases, as well as bilateral SSVEP amplitude decreases in the occipital region. As the task progresses, generalised frontal SSVEP amplitude reductions are noted, which extend to include left temporal sites where the effect reaches significance. After 615 msec, the frontal SSVEP amplitude effects diminish, while the left occipito-parietal reduction remains, contributing to the significance in the associated SPMs.

For the Panic Disorder group, SSVEP latency reductions in the left and right occipito-parietal regions are prominent throughout the task from word presentation until 1000 msec. In the first two maps, (presentation and 231 msec), an area of SSVEP latency increase in the parietal region is apparent. It should be explained that this effect is due to ‘wrap
around’ and in fact is a large latency reduction indicative of a phase advance of greater than $2\pi$. Other reductions in SSVEP latency occur prior to response at right temporal sites, and at left frontal sites from 615 msec onwards.
Figure 6.10 Dynamic Maps For The Control Group, Depression-Related Words

Presentation

231 msec

385 msec

615 msec

769 msec

1000 msec

Legend:

Amplitude Difference

Latency Difference (msec)

Hotelling's T

Values:

+0.3

0.0

-0.3

+9.8

0.0

-9.8

+4.0

-4.0
Results

Figure 6.11  Dynamic Maps For The Panic Group, Depression-Related Words
Results

Figures 6.10 and 6.11 represents the dynamic maps for the depression-related words Emotional Stroop condition for the Control and Panic Disorder groups respectively, at presentation up to 1000 msec following presentation. The maps were constructed by subtracting the mean activity of the neutral words condition from the time series of the depression-related words condition.

Figure 6.10 displays the dynamic maps for the depression-related words component of the Emotional Stroop for the Control group. At word presentation, SSVEP amplitude reductions are apparent at prefrontal, left anterior, and bilateral posterior regions. The associated SPM indicates significant effects at prefrontal, left temporal, left occipital and right posterior temporal regions. At 231 msec, the SSVEP amplitude reduction is most prominent in bilateral posterior regions and this is reflected in the SPM. At 385 msec, general anterior SSVEP amplitude reduction is seen in addition to posterior effects, however significance is reached only at two discrete frontal sites. Immediately prior to response (615 msec), the posterior SSVEP amplitude reductions are diminished, although the associated SPM indicates significant occipital effects, which extend parietally. Following response (769 msec), a right anterior SSVEP amplitude increase is noted, and its significance is indicated in the SPM. SSVEP amplitude reductions are also noted at left posterior and temporal regions, contributing to the significant effects in this area.

In terms of SSVEP latency changes in the Control group, left prefrontal increases are noted at the time of word presentation, contributing to the associated significance in this area. No other outstanding features are noted until immediately prior to response (615 msec) where bilateral prefrontal and right temporal and parietal SSVEP latency reductions are exhibited. Mild SSVEP latency decreases in the occipital region may be contributing to the significance in this area. Following response, at 769 msec, right frontal SSVEP latency reductions may be contributing to the significance indicated in the associated SPM.

Figure 6.11 represents the dynamic maps for the depression-related words component of the Emotional Stroop for the Panic Disorder group. At word presentation, significant right temporo-parietal SSVEP amplitude increases are noted, along with mild anterior SSVEP amplitude reductions. At 231 msec, general anterior and bilateral occipital SSVEP amplitude reductions are noted, with significance achieved at temporal and central sites. At 385 msec, prefrontal SSVEP amplitude increases are noted, which becomes prominent at
left prefrontal sites at 615msec, but does not reach significance. This effect is diminished following response as can be seen at 769 msec.

With regard to SSVEP latency, mild but significant increases are noted in the left temporal area, along with right temporo-parieto-occipital SSVEP latency decreases at word presentation. In addition, SSVEP latency reductions in the left parietal area are noted, which increase in prominence and expand to include temporal and occipital areas, remaining significant from 385 msec up to 1000 msec. In two maps, at 231 msec and 385 msec, an area of SSVEP latency increases in the temporo-parietal region are apparent. As mentioned earlier, this effect is due to ‘wrap around’ and in fact is a large SSVEP latency reduction indicative of a phase advance of greater that $2\pi$. 

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Figure 6.12 Dynamic Maps For The Control Group, Anxiety-Related Words

Presentation

231 msec

385 msec

615 msec

769 msec

1000 msec

Amplitude Difference

Latency Difference (msec)

Hotelling's T
Figure 6.13 Dynamic Maps For The Panic Group, Anxiety-Related Words
Figures 6.12 and 6.13 represent the dynamic maps for the anxiety-related words Emotional Stroop condition for the Control and Panic Disorder groups respectively, at presentation up to 1000 msec following presentation. The maps were constructed by subtracting the mean activity of the neutral words condition from the time series of the anxiety-related words condition.

Figure 6.12 represents the dynamic maps for the anxiety-related words component of the Emotional Stroop for the Control group. The Control group maps are characterised by generalised and sustained SSVEP amplitude reductions from presentation until response. The reductions are most prominent at left fronto-temporal sites at the time of presentation, which the SPMs indicate are significant. Following presentation, the SSVEP amplitude reductions are most prominent in the left temporal and bilateral occipito-parietal regions. The SPMs show significant effects in left fronto-temporal, left occipital and right parieto-temporal regions, which occur at 231 msec and 385 msec. At 615 msec, immediately prior to response, anterior SSVEP amplitude reductions are significant at a number of frontal and central electrodes, as well as within the left posterior region. As can be seen at 769 msec and 1000 msec, the anterior SSVEP amplitude effects abate following response.

In terms of SSVEP latency, prefrontal increases are evident at word presentation, and continue to develop up to 385 msec, particularly at right prefrontal sites, and contribute to the significance at these sites in the associated SPMs. At 231 msec and 385 msec, left temporal SSVEP latency reductions contribute to the significance in the associated SPMs. Left anterior SSVEP latency reductions are apparent at 615 msec, immediately before response, and appear to contribute to the significant effects at left fronto-central sites. In addition, at 615 msec and 769 msec, left posterior latency reductions appear to contribute to the significance in the associated SPM. At 769 msec, significant right temporo-parietal latency reductions are also noted.

Figure 6.13 represents the dynamic maps for the anxiety-related words component of the Emotional Stroop for the Panic Disorder group. SSVEP amplitude is reduced at bilateral prefrontal and occipito-parietal sites. The associated SPM suggests the right prefrontal effect is significant. As the task progresses, the occipito-parietal SSVEP amplitude reductions becomes more prominent as seen at 231 msec and 385 msec. From 231 msec onwards, a band of amplitude reduction encompassing central sites and extending to the
right fronto-temporal area is evident, and persists becoming most prominent at 769 msec. At 769 msec and 1000 msec, occipital SSVEP amplitude increases, skewed to the right, become evident, contributing to the significance in the associated SPMs. Throughout the task, left parieto-temporal SSVEP amplitude reductions are evident, and appear to be contributing to the significance in this area.

With regard to SSVEP latency, the Panic Disorder group show large sustained left and right parieto-temporal reductions that encompass occipital sites. This effect is significant at parieto-occipital sites throughout the task. Other significant effects include right anterior SSVEP latency increases, which are focussed in the right frontal and central areas at word presentation and 231 msec respectively. At 615 msec, left fronto-temporal SSVEP latency reductions are evident, and this effect becomes prominent at 769 msec.
Figure 6.14 Dynamic Maps For The Interferers, Anxiety-Related Words
Figure 6.15  Dynamic Maps For The Non-Interferers, Anxiety-Related Words
Results

Figures 6.14 and 6.15 represent the dynamic maps for the anxiety-related words Emotional Stroop condition for the Interferers and Non-Interferers respectively, at presentation up to 1000 msec following presentation. The maps were constructed by subtracting the mean activity of the neutral words condition from the time series of the anxiety-related words condition.

Figure 6.14 displays the dynamic maps for the anxiety-related words component of the Emotional Stroop for the Interferer group. At word presentation, general SSVEP amplitude reductions are observed at anterior and posterior sites, reaching significance at bilaterally at prefrontal electrodes and at left parietal, occipital and temporal sites. At 231 msec, the anterior SSVEP amplitude reductions diminish, and posterior SSVEP amplitude reductions attain additional significance at right parietal sites. This effect is maintained at 385 msec. In the map immediately prior to response (615 msec), SSVEP amplitude reductions are maximal at fronto-central sites. Following response (769 msec) these effects abate, along with the associated significance.

With regards to SSVEP latency, at word presentation, significant right prefrontal latency increases are noted, which persist until 385 msec. At 231 msec, significant right posterior temporal latency increases are apparent, which persist until 385 msec. In the map immediately prior to response (615 msec), left anterior SSVEP latency reductions emerge contributing to the significant effects in the associated SPM. Following response (769 msec) significant left posterior SSVEP latency reductions occur.

Figure 6.15 represents the dynamic maps for the anxiety-related words component of the Emotional Stroop for the Non-Interferer group. At word presentation, SSVEP amplitude reductions are noted at left prefrontal and right posterior areas. Significant effects are noted mainly in the left anterior region. At 231 msec, non-significant central SSVEP amplitude increases are noted. At 385 msec, general SSVEP amplitude reductions are present and contribute to the significance indicated in the associated SPM in the right posterior temporal and left occipital region. Prior to response (at 615 msec), the most notable effects are non-significant left prefrontal and right occipital SSVEP amplitude increases. Following response (769 msec), general SSVEP amplitude reductions are present, reaching significance at right prefrontal, temporal and central sites as well as in the left occipital area.
In terms of SSVEP latency, the Non-Interferers display increases within left prefrontal and right central areas and these effects appear to contribute to the significance indicated in the SPM, at the time of word presentation. At 231 msec, left temporal SSVEP latency reductions extending frontally and centrally are noted, with associated significant effects in the left fronto-central area. Prominent significant posterior temporal SSVEP latency increases are noted in conjunction with mild prefrontal increases. At 385 msec, left prefrontal and temporal SSVEP latency reductions are apparent, however, these effects do not reach significance. At this time, right posterior temporal SSVEP latency increases appear to contribute to the significance noted in the associated SPM. Prior to response (615 msec), right anterior SSVEP latency increases which are maximal at central sites, and posterior SSVEP latency reductions which are maximal at right posterior temporal and left occipital sites are apparent. Following response, right anterior SSVEP latency increases diminish but remain significant at prefrontal sites.

**6.2.3 Single electrode time series**

The dynamic maps provide an overview of the transient effects occurring at various stages during the task. The dynamic maps also provide topographical information on how these effects differ between the Panic Disorder and Control groups within each task of the Emotional Stroop. The final stage of analysis involves focusing on specific electrode sites, which supplements the information provided by the dynamic maps. The single electrode time series graphs show both SSVEP latency and amplitude with respect to the mean latency or amplitude during the baseline task, as a function of time. The mean SSVEP latency and amplitude during the baseline task has been arbitrarily set to zero for both groups, and represented by a solid line. Two vertical lines indicate the point in time at which the task word was presented and then disappeared from screen. A dashed vertical line represents the mean reaction times for the particular task of interest, averaged over the sample displayed, to give an indication of when verbal responses were recorded. These single electrode time series are illustrated in Figures 6.16 to 6.20. The specific electrodes displayed in the following sections (6.2.3.1 and 6.2.3.2) have been selected whereby significant SSVEP amplitude or latency changes were observed in the dynamic maps. In particular, the electrodes represented in Figures 6.16 to 6.20 displays the maximal
significant differences between the comparison groups, that is, between the Control and Panic Disorder groups, as well as between the Interferers and Non-Interferers.

6.2.3.1 Standard Stroop

The following graphs represent the time series at selected electrodes for SSVEP latency and amplitude variations during the incongruent Stroop task, compared to the mean SSVEP activity during the congruent Stroop task, which has been arbitrarily set to zero. The position of the electrode displayed in the time series graph is presented to the right of each graph respectively.

Figure 6.16 Time Series Graphs For The Standard Stroop Task

A

B
Figure 6.16 displays SSVEP amplitude and latency differences for the Control and Panic Disorder groups during the Standard Stroop task at selected electrode sites. Both SSVEP latency and amplitude variations are shown with respect to the mean latency or amplitude during the baseline task which is arbitrarily set to zero for both groups and is marked with a solid line. The vertical lines marked ‘Presentation’ and ‘Word off’ indicate the time that the word appeared on screen and the time the word was removed from screen, respectively. The dashed line indicates the reaction time for incongruent words averaged over the Panic Disorder and Control groups. Note the individual scales for SSVEP latency and amplitude of each graph.

In Figure 6.16, graph A and B illustrate SSVEP latency differences at specific temporal and parietal sites. Graph A represents the SSVEP latency variations at electrode 37, which is an intermediate site between T3 and T5 according to the 10-20 system. The SPMs of the
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associated dynamic maps show that this site reaches significance for both the Control and Panic Disorder groups. At presentation of the incongruent Stroop word, the Panic group exhibit a small increase, followed by a reduction, reaching a maximum at 1.6 seconds. In contrast, the Control group shows a sustained SSVEP latency decrease, which is maximal 0.5 seconds following word presentation.

Graph B shows a sustained SSVEP latency difference between the Control and Panic Disorder groups at electrode 45, which is situated adjacent to P3 and T5 sites according to 10-20 system convention. The dynamic maps indicate that the Panic Disorder group exhibit large SSVEP latency reductions within this area. As can be seen in Graph B, the Panic Disorder group exhibits a large and sustained reduction following presentation of the word, which varies only after 1.4 sec which corresponds to the stimulus word disappearing from the screen. In contrast, the Control group show only relatively small variations in SSVEP latency about the mean.

Graphs C and D illustrate SSVEP amplitude differences at right frontal and right parieto-occipital sites, respectively. Note the different amplitude scale for each graph. Graph C shows SSVEP amplitude variations at electrode 3, which corresponds to Fp2 in the 10-20 system. The dynamic maps indicate nonsignificant, sustained prefrontal SSVEP amplitude reductions in the Panic Disorder group only. Graph C illustrates an SSVEP amplitude reduction that is sustained throughout the task for the Panic Disorder group. In contrast, the Control group exhibits fluctuations about the mean, with a maximum reduction at 0.74 msec. Graph D shows SSVEP amplitude at electrode 56, which is adjacent to the electrode O2 in the 10-20 system convention. The dynamic maps indicate occipital SSVEP amplitude reductions during the task, which are more pronounced in the Control group. In Graph C, it can be seen that the Control group exhibit a sustained reduction, peaking around 0.4 seconds following word presentation. The Panic Disorder group show a similar pattern of SSVEP amplitude reduction to the Control group, but to a lesser extent. The dynamic maps confirm that the occipital SSVEP amplitude reduction in the Panic Disorder group does not reach significance.
6.2.3.2 Emotional Stroop

The following graphs represent the time series at selected electrodes for SSVEP latency variations during the positive words component of the Emotional Stroop task, compared to the mean SSVEP latency during the neutral words component of the Emotional Stroop task, which has been arbitrarily set to zero. The position of the electrode displayed in the time series graph is presented to the right of each graph respectively.

Figure 6.17 Time Series Graphs For The Emotional Stroop Task: Positive Words
Figure 6.17 displays SSVEP latency (Graphs A, B and C) for the Control and Panic Disorder groups during the positive words component of the Emotional Stroop task. The graphs of SSVEP latency are shown with respect to the mean latency during the baseline task which is arbitrarily set to zero for both groups and is marked with a solid line. The vertical lines marked ‘Presentation’ and ‘Word off’ indicate the time that the word appeared on screen and the time the word was removed from screen, respectively. The dashed line indicates the reaction time for positive words averaged over the Panic Disorder and Control groups.

Figure 6.17 shows a number of differences between the Panic Disorder and Control groups in terms of SSVEP latency changes for the positive words component of the Emotional Stroop. Graph A represents the SSVEP latency variation at electrode 11, a right frontal electrode which is adjacent to the electrode F4 in the 10-20 system. At word presentation, the Control group exhibit a SSVEP latency increase, which reaches a maximum at 0.12 sec, which is followed by a large reduction, peaking at 0.58 sec. The dynamic maps indicate that this effect was significant around the time of word presentation. The Panic Disorder group follow a similar pattern to the Controls but with a delay of approximately 100 msec, and do not exhibit a SSVEP latency reduction as large as the Control group.

Graph B illustrates SSVEP latency differences between the Panic Disorder and Control groups at electrode 45, in the left parieto-temporal region. The most outstanding feature is the large reduction shown by the Panic Disorder group following word presentation, which is sustained for most of the task. The Control group do not exhibit this effect. As discussed previously in section 6.2.2, the dynamic maps for the positive words in the Panic Disorder...
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group (Figure 6.8) show what appears to be a SSVEP latency increase about electrode, which is in fact a ‘wrap around’ effect. The time series graph of electrode 45 displays the SSVEP latency as it should be.

Graph C displays the SSVEP latency differences between the two groups at electrode 57, which is a right occipito-parietal point located at the mid point of P4 and O2 as placed in the 10-20 system. The Panic Disorder and Control groups show remarkably similar patterns of SSVEP latency, however, unlike the Control group, the reduction shown by the Panic Disorder group is sustained throughout the task.

The following graphs represent the time series at selected electrodes for SSVEP latency and amplitude variations during the depression-related words component of the Emotional Stroop task, compared to the mean SSVEP activity during the neutral words component of the Emotional Stroop task, which has been arbitrarily set to zero. The position of the electrode displayed in the time series graph is presented to the right of each graph respectively.

Figure 6.18 Time Series Graphs For The Emotional Stroop Task: Depression-Related Words
Results

B

C
Figure 6.18 displays SSVEP latency (Graphs A, B and C) and SSVEP amplitude (Graph D) time series for the Panic Disorder and Control groups during the depression-related words task of the Emotional Stroop. Both SSVEP latency and amplitude are shown with respect to the mean latency or amplitude during the baseline task is arbitrarily set to zero for both groups and is marked with a solid line. The vertical lines marked ‘Presentation’ and ‘Word off’ indicate the time that the word appeared on screen and the time the word was removed from screen, respectively. The dashed line indicates the reaction time for depression-related words averaged over the Panic Disorder and Control groups.

In Figure 6.18, graphs A, B and C illustrate a number of SSVEP latency differences between the Panic Disorder and Control groups during the depression-related words task of the Emotional Stroop. Graph A represents SSVEP latency differences at electrode 1, a left prefrontal electrode which corresponds to Fp1 in the 10-20 system. This area shows significant effects for the Control group in the dynamic maps (Figure 6.9). After word presentation, the Control group exhibit a large increase, followed by a reduction, which is maximal at 0.58 sec, just prior to response. In contrast the Panic Disorder group shows smaller variations in SSVEP latency about the mean.

Graph B illustrates SSVEP latency differences between the Panic Disorder and Control groups at electrode 45, in the left parieto-temporal region situated between P3 and T5 according to the 10-20 system. The most outstanding feature is the large reduction shown by the Panic Disorder group following word presentation, which is sustained for most of the task. The Control group do not exhibit this effect. As discussed previously in section
6.2.2, the dynamic maps for the depression-related words in the Panic Disorder group (Figure 6.10) show what appears to be a SSVEP latency increase about electrode, which is in fact a ‘wrap around’ effect. The time series graph of electrode 45 displays the SSVEP latency as it should be.

Graph C illustrates the SSVEP latency changes in the Panic Disorder and Control groups at electrode 57, a right occipito-parietal point located at the mid point of P4 and O2 as placed in the 10-20 system. The Panic Disorder and Control groups show similar patterns of SSVEP latency difference, however, unlike the Control group, the reduction shown by the Panic Disorder group is sustained throughout the task.

Graph D illustrates SSVEP amplitude differences between Panic and Control groups for the depression-related words at electrode 28, a left temporal electrode corresponding to T3 in the 10-20 system. The dynamic maps (Figure 6.9 and Figure 6.10) demonstrate SSVEP amplitude effects are significant for both groups at different points during the task. As can be seen in Graph D, the Control group exhibit strong SSVEP amplitude reductions at word presentation, and again after approximately 0.58 sec. The Panic Disorder group show SSVEP amplitude reductions in the time following presentation, which is no longer apparent after approximately 0.58 sec.

Graph E illustrates SSVEP amplitude differences in the left temporal region. The most prominent feature is that at word presentation, the Control group exhibit a SSVEP amplitude increase, while the Panic Disorder group show no marked alterations. However, following presentation, the Panic Disorder group exhibit a SSVEP amplitude increase, while the Control group show a relative decrease.

The following graphs represent the time series at selected electrodes for SSVEP latency and amplitude variations during the anxiety-related words component of the Emotional Stroop task, compared to the mean SSVEP activity during the neutral words component of the Emotional Stroop task, which has been arbitrarily set to zero.
Figure 6.19 Time Series Graphs For The Emotional Stroop Task: Anxiety-Related Words

A

B
Figure 6.19 SSVEP latency (Graphs A and B) and SSVEP amplitude (Graphs C and D) time series for the Panic Disorder and Control groups during the anxiety-related words task of the Emotional Stroop. Both SSVEP latency and amplitude are shown with respect to the mean latency or amplitude during the baseline task is arbitrarily set to zero for both groups and is marked with a solid line. The vertical lines marked ‘Presentation’ and ‘Word off’ indicate the time that the word appeared on screen and the time the word was removed from screen, respectively. The dashed line indicates the reaction time for anxiety-related words averaged over the Panic Disorder and Control groups.

In Figure 6.19, graphs A and B illustrate a number of SSVEP latency differences between the Panic and Control groups during the anxiety-related words component of the Emotional Stroop task. Graph A represents SSVEP latency differences at electrode 45, in the left parieto-temporal region situated between P3 and T5 according to the 10-20 system. The outstanding feature is the large reduction shown by the Panic Disorder group following
word presentation, which is sustained for most of the task. The Control group do not exhibit this effect, showing variations of SSVEP latency about the mean.

Graph B displays the SSVEP latency differences between the Panic Disorder and Control groups at electrode 57, a right occipito-parietal point located at the mid point of P4 and O2 as placed in the 10-20 system. The Panic Disorder group demonstrates a reduction that is sustained throughout the task, while the Control group exhibit variations about the mean.

Graph C represents SSVEP amplitude differences related to anxiety-related words at electrode 1, a left prefrontal site that corresponds to Fp1 in the 10-20 system. The Control group demonstrates significant effects in this region as shown in the dynamic maps (Figure 6.11) at presentation and the subsequent map. Graph C shows that at presentation, the Controls exhibit a sustained SSVEP amplitude reduction, which is most prominent following word presentation. In contrast, the Panic Disorder group demonstrate a SSVEP amplitude increase shortly after word presentation, followed by a reduction after 0.97 sec.

Graph D demonstrates SSVEP amplitude differences at electrode 22, a left fronto-temporal site, which is situated in between the electrodes corresponding to C3 and F7 in the 10-20 system. The dynamic maps of the Control group (Figure 6.11) indicate that the SSVEP amplitude reductions within this area are significant from word presentation until after response. Graph D shows a sustained SSVEP amplitude reduction for the Control group, which is maximal from presentation until approximately 0.6 sec. In contrast, the Panic Disorder group display maximal SSVEP amplitude reductions at 0.81 sec, which is likely to have contributed to the significant effects seen in the dynamic maps (Figure 6.12).

The following graphs represent the time series for the Interferer and Non-Interferer groups at selected electrodes for SSVEP latency and amplitude variations during the anxiety-related words component of the Emotional Stroop task. The task-related SSVEP activity is compared to the mean SSVEP activity during the neutral words component of the Emotional Stroop task, which has been arbitrarily set to zero.
Figure 6.20  Time Series Graphs For The Interferers and Non-Interferers: Anxiety-Related Words

A

B
Figure 6.20 SSVEP latency (Graphs A, B and C) and SSVEP amplitude (Graph D) time series for the Interferer and Non-Interferer groups during the anxiety-related words task of the Emotional Stroop. Both SSVEP latency and amplitude are shown with respect to the mean latency or amplitude during the baseline task is arbitrarily set to zero for both groups and is marked with a solid line. The vertical lines marked ‘Presentation’ and ‘Word off’ indicate the time that the word appeared on screen and the time the word was removed from screen, respectively. The dashed line indicates the reaction time for anxiety-related words averaged over the Interferer and Non-Interferer groups.

In Figure 6.20, graphs A, B and C illustrate a number of SSVEP latency differences between the Interferers and Non-Interferers during the anxiety-related words component of the Emotional Stroop. Graph A represents SSVEP latency at electrode 4, a right frontal site which is intermediate to Fp2 and F8 in the standard 10-20 system. The dynamic maps
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indicate significant SSVEP latency increases for the Interferer group in the lead up to response (Figure 6.13). In Graph A, the Interferers show a large SSVEP latency increase which extends from the time of word presentation until approximately 0.43 sec, after which the SSVEP latency reduces. In contrast the Non-Interferer group show SSVEP latency increases, which peak at approximately 0.5 sec and 1.2 sec. The dynamic maps (Figure 6.14) indicate the early SSVEP latency increases in the Non-Interferer group are significant up to 231 msec.

Graph B demonstrates SSVEP latency differences at electrode 28, which is equivalent to T3 in the 10-20 system. The Non-Interferers show a marked SSVEP latency reduction following word presentation, which does not reach significance in the dynamic maps (Figure 6.14), but nevertheless appears to be an important feature. This effect is not present in the Interferer group.

Graph C represents SSVEP latency differences at electrode 52, in the right posterior temporal region, which corresponds to T6 in the 10-20 system. Graph C demonstrates the opposite patterns of SSVEP latency variation by the Interferer and Non-Interferer groups. The Non-Interferers display SSVEP latency increases following word presentation, while the Interferers show mild reductions, which are sustained to some extent throughout most of the task. The Non-Interferer group also exhibit a SSVEP latency reduction, which peaks at approximately 0.66 sec. The dynamic maps (Figure 6.14) display significant SSVEP latency changes for the Non-Interferers in the maps from presentation to 385 msec.

Graph D illustrates SSVEP amplitude differences at electrode 1, in the left prefrontal region, which corresponds to Fp1 in the 10-20 convention. Both the Interferer and Non-Interferer groups demonstrate significant effects at this site at the time of word presentation (Figure 6.14 and Figure 6.15 respectively). However, Graph D demonstrates that at approximately 0.58 sec, the Non-Interferers demonstrate a relatively large SSVEP amplitude increase.
CHAPTER 7  Discussion

This thesis aimed to investigate the behavioural and neurophysiological correlates of the performance of the Emotional Stroop task in Panic Disorder patients and psychiatrically healthy controls. Ultimately, it was expected that the present study would help to clarify a number of issues. Firstly, whether there was a general cognitive deficit in Panic Disorder as indicated by slower reaction times for the Standard Stroop, compared with the Controls. Second, whether there existed a deficit in performance of the Emotional Stroop for Panic Disorder patients, and whether any deficits were particular to an emotional category. Third, whether any differences in performance of the Emotional Stroop were reflected in regional SSPT differences between the Panic Disorder and Control groups.

In this chapter, behavioural findings, including mean reaction times and interference index results are discussed in section 7.1. Neurophysiological findings are then discussed in section 7.2. In each section, both the Standard Stroop and Emotional Stroop tasks will be discussed separately, with focus on the Emotional Stroop.

7.1  Behavioural findings

The Standard Stroop task, which also involves inhibition of automatic responses, has long been used to investigate the components of selective attention. The difference in reaction times between congruent and incongruent colour words arises because word reading is more automatic than is colour naming (MacLeod and MacDonald, 2000). To investigate selective attention related to emotion and its disorders in particular, the Emotional Stroop has been employed. The increase in time to name the colour of emotionally laden words, compared to neutral words, particularly in clinical groups, has been interpreted as evidence of a relationship between psychopathology and attention (Williams et al, 1996).

7.1.1  Subject characteristics

As expected, the Panic Disorder group were significantly more anxious than the Control group on measures of both state and trait anxiety. In addition, the Panic Disorder group exhibited a higher score on the BDI compared to the Control group, and so must be
regarded as mildly depressed. However, the Panic Disorder patients were screened for
depressive disorders and none were found, and in addition, the BDI scores indicate only
mild to moderate depression (Beck and Steer, 1987).

The results also showed a significant difference between the Panic Disorder and Control
groups’ estimated verbal IQ. This finding is difficult to explain, since care was taken to
include Control subjects with differing levels of education and thus presumably verbal IQ.
However, the participants for the Control group were mainly drawn from general hospital
staff and associates of the investigator, who may have had higher levels of education
compared to the patient group. It is interesting to note that measures of IQ are not routinely
reported for clinical groups in studies using the Emotional Stroop (eg Kampman et al,
2002; McNally et al, 1992). In one study that investigated whether familiarity with words
associated with Panic Disorder contributed to the production of Emotional Stroop
interference, the control group were drawn from a pool of PhD-level clinicians and
postgraduate students in the psychology field (McNally et al, 1990). While it is not
reported in that study, it is reasonable to presume that in such a case, the level of education
was higher in the control group compared to the patient group. Even so, the Panic Disorder
patients in that study produced more interference for panic-related words compared to
neutral words, than did the control group. In addition, analyses on a subgroup of Controls
that matched the IQ of the Panic Disorder group in the present study showed that IQ had no
bearing on the presence or absence of interference for both Stroop tasks.

7.1.2 Reaction time comparisons for the Standard Stroop

Both the Panic Disorder and Control groups exhibited interference for the Standard Stroop
task. Mean reaction times were longer for the incongruent Stroop task compared to the
congruent Stroop task for both groups, with no group differences evident. This result is
consistent with the study’s hypothesis that Panic Disorder patients do not exhibit deficits on
general attentional tasks. There has been very little published regarding the Standard
Stroop performance in anxious groups, so comparison is difficult. However, a number of
studies of the incongruent Stroop in psychiatrically healthy populations have recorded both
faster (Bench et al, 1993) and slower (Carter et al, 1995b) times suggesting that the current
findings are within an acceptable range. It has been shown that deficits in Stroop
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Performance exist in some psychiatric disorders, including current depression (Lemelin et al, 1997; Trichard et al, 1995), schizophrenia (Barch et al, 1999; Carter et al, 1997; David, 1993) and Attention Deficit/Hyperactivity Disorder (Carter et al, 1995a). In contrast, other research has demonstrated that reaction times for the Stroop task do not always distinguish depression from nonpsychiatric groups (David, 1993), even when regional brain activation differs (George et al, 1997). Unfortunately, it is unknown as to whether these results can be extended to anxiety disorders.

The use of the congruent Stroop (ie the word ‘blue’ written in blue ink) as a comparison to the incongruent Stroop (ie the word ‘blue’ written in red ink) was not part of the original Stroop study (Stroop, 1935), and its use is now further discussed. The use of the congruent Stroop has been used in a number of imaging studies investigating the neural circuits involved in the production of Stroop interference (Bench et al, 1993; Carter et al, 1995b; Leung et al, 2000; Pardo et al, 1990; Peterson et al, 1999). The main advantages of using the congruent Stroop are that its physical characteristics, and the lexical and semantic demands of the task, are identical to the task of interest, namely the incongruent Stroop.

The main disadvantage of such a comparison is that the congruent Stroop has been shown to facilitate colour naming, that is, enhance the speed at which the stimuli is responded to (MacLeod, 1991). If facilitation, which is brought about by reading the word rather than naming the colour, is employed by the participant, this then would potentially engage cognitive processes not used for colour-naming in the incongruent Stroop. However, facilitation is much less robust than the interference produced by the incongruent Stroop (MacLeod, 1991) and a parallel distributed processing model of word-colour interference suggests that differences in pathway strengths may be responsible for facilitation and interference effects, and not necessarily involve separate processing mechanisms (Cohen et al, 1990). The advantages of matching stimulus characteristics between congruent and incongruent Stroop stimuli, especially for the current study where neuroimaging subtraction techniques are employed, outweighs the potential disadvantages (Peterson et al, 1999). An additional advantage is that direct comparisons with previous neuroimaging studies that also utilised the congruent Stroop as a baseline task are possible.
7.1.3 Reaction time comparisons for the Emotional Stroop

Contrary to the study’s hypothesis, Panic Disorder patients did not exhibit specific sensitivity to emotional information, and in particular, showed no bias for anxiety-related material. Instead, Panic Disorder patients were slower to name the colour of both emotional and neutral words compared to the Control group. To control for differences in colour naming speed, a mean interference index was created for each emotion category, the Emotional Stroop interference index. This measure failed to show any differences between positive, anxiety-related or depression-related categories for either subject group. This result occurred despite the positive, anxiety-related and depression-related words being rated as significantly more emotional than the neutral words, by both the Control and Panic Disorder groups.

The Panic Disorder group rated the anxiety-related, depression-related and positive words as more emotional than the neutral words, with anxiety-related words receiving the highest rating (see Table 6.4). Despite this, they failed to show increased Emotional Stroop interference, suggesting that high emotional significance may not be a factor in producing an Emotional Stroop interference effect. This result is consistent with that of McNally et al (1992), who found that while the control group rated positive words as having higher ‘personal emotional significance’ than catastrophe, bodily sensation or fear words, they demonstrated interference for all words equally, relative to a simple control condition. In addition, Panic Disorder patients took longer to name the colour of catastrophe words even though the positive words were rated as more emotional than the other types. Therefore, emotional significance may not be an important factor in creating an Emotional Stroop interference effect.

Relevance to current concern, rather than emotional significance, may be necessary to produce an interference effect (Williams et al, 1997). In the present study, participants were asked to judge the emotional value of words, and not the relevance to their current concerns. While personal emotional value of each word was recorded, the relation of the words to current concerns was not directly assessed. Therefore the anxiety-related words may not have been directly related to the Panic Disorder patients’ current concerns and thus reduced the amount of Emotional Stroop interference. The issue of relatedness to current
A striking effect in the present study was the overall increased colour-naming reaction times in Panic Disorder patients for all Emotional Stroop categories, including the neutral words. This effect has been noted to occur in anxiety (Mathews and MacLeod, 1985; Williams et al, 1997) and particularly in Panic Disorder (Kampman et al, 2002; McNally et al, 1990; McNally et al, 1994). McNally et al (1994) suggest that cognitive capacity is diminished by chronic anxiety which leads to increased general distractibility and slower reaction times for all words. If poor performance for the Emotional Stroop task in the present study is related to general distractibility in the Panic Disorder patients, then the Panic Disorder group should also do poorly on other tasks requiring increased attention, such as the Standard Stroop. As previously discussed in section 7.1.2, the Panic Disorder group’s performance of the Standard Stroop was not statistically different to that of the Control group, which is at odds with the suggestion of McNally et al (1994). However, increased vigilance for threatening stimuli in the environment, which is a common feature of psychological accounts of pathological anxiety (Beck et al, 1985) may account for the present results. Beck et al (1985) suggest that scanning the environment for threatening stimuli severely limits the anxiety patient’s ability to focus on other demands. In addition, the sensitivity to threat may lead the patient to perceive danger where it is not actually present. Thus it is possible that the Panic Disorder patients, in scanning the experimental environment for threatening stimuli, may be inclined to interpret the positive and neutral words in a threatening way. Another possibility is that the experimental procedure itself
may have rendered all presented stimuli in a threatening way. It is not difficult to perceive that a Panic Disorder patient, in a darkened room with a 64-channel electrode cap and goggle apparatus flickering with the steady-state visual stimulus may have felt to be in a somewhat threatening environment. However, if the experimental procedure was perceived as threatening, then it is not unreasonable to expect that a debilitated performance of the Standard Stroop would have ensued, which did not occur. Thus the slowed reaction times for all words of the Emotional Stroop in the Panic Disorder group is likely to be due to insufficient relevance to current concern or hypervigilance for any stimuli which may be threatening, or a combination of both.

7.1.3.1 Reaction time differences within the Control group

Inspection of the mean reaction times for the Emotional Stroop within the Control group revealed that approximately two-thirds of subjects exhibited a positive interference score for anxiety-related words (the Interferers). The other third showed a negative interference score, indicating speeded responses for anxiety-related words (the Non-Interferers).

Previous research investigating Emotional Stroop biases in non-clinically anxious subjects has shown that increased in state or trait anxiety produces increased interference for anxiety words (Dalgleish, 1995; MacLeod and Rutherford, 1992; MacLeod and Hagan, 1992; Mogg et al, 1990). In the present study, neither state nor trait anxiety differed between the Interferers and Non-Interferers. In fact, state anxiety was negatively correlated with the interference score. Thus, decreased state anxiety was associated with greater Emotional Stroop interference. Mogg and colleagues (Mogg et al, 1993b) found increased state anxiety was related to decreased reaction times for threat words. Specifically investigating the effect of stress on the reaction times of high and low trait anxious students, they found that state anxiety correlated negatively with Emotional Stroop threat interference, regardless of trait anxiety. The authors suggest that such a result is possibly the product of controlled strategies. MacLeod and Rutherford (1992) also found that increased state anxiety was related to a decrease in interference for threat words, whereby the threat words were related to participants’ current concerns. They suggest that the high trait subjects in particular, who were expected to show increased interference, use particular strategies to reduce the impact of automatic biases for relevant emotional information.
De Ruiter and Brosschot (1994) postulated that ‘cognitive avoidance’ may explain why certain groups, such as ‘repressors’, who have low state and trait anxiety, and who would be expected to show the least interference for the Emotional Stroop, actually show increased interference (Dawkins and Furnham, 1989). The cognitive avoidance theory suggests that increased reaction times are due to the subjects’ effortful avoidance of cognitively processing the stimulus because it contains emotional information. While attentional biases may explain why certain groups show increased interference, the results of the Interferers are consistent with the notion of cognitive avoidance. This is supported by the finding in the present study that the Interferers rated the anxiety-related words as less emotional compared to the Non-Interferer group, indicating that even when prompted on a conscious and deliberate level, the Interferers minimise the emotional impact of the stimuli.

It is suggested that the Non-Interferer group have a different, and possibly more effective strategy for rapid colour-naming compared the Interferer group. If the Interferers cannot avoid processing emotional information, then their pattern of brain activation should be different to the Non-Interferer group, who possibly employ different strategies to deal with emotional information in order to ensure rapid colour-naming of stimuli as instructed. The separation of the Control group into Interferers and Non-Interferers provides an opportunity to investigate the neurophysiological correlates of Emotional Stroop interference. This will be discussed further in section 7.2.2.1.

In summary, the Panic Disorder patients and Control groups exhibit similar mean reaction times for the Standard Stroop task, suggesting that, as hypothesised, there are no general cognitive deficits in the Panic Disorder group. Contrary to the present study’s hypothesis, the Panic Disorder patients exhibited no difference in the time to name the colour of anxiety-related words compared to neutral words. The mean reaction times for the Standard and Emotional Stroop do not appear to be affected by the difference in estimated verbal IQ between the two comparison groups. Similar to previous studies of the Emotional Stroop in Panic Disorder, the Panic Disorder group demonstrated slower mean reaction times for all categories of words. Thus Panic Disorder may be associated with increased vigilance for any possibly threatening material in the external environment. On the other hand, the results for the Panic Disorder group may also indicate that the stimuli used were not directly relevant to the current concerns of the group. A subgroup of
Controls did show increased Emotional Stroop interference for anxiety-related words that could not be attributed to increased anxiety levels or increased emotional significance of the words. Instead, the Interferer group appears to have displayed evidence of ‘cognitive avoidance’ for anxiety-related words, while the Non-Interferers may be employing effective strategies to override the impact of the emotional words. The separation of the Control group into Interferers and Non-Interferers provides an opportunity to investigate the neurophysiological correlates of Emotional Stroop interference.

7.2 Neurophysiological findings

Previous studies of the Emotional Stroop have made assumptions about the type of processes involved in creating attentional biases. While no attentional biases were apparent in the analysis of mean reaction times for the Emotional Stroop for each group, the Panic Disorder group exhibited longer reaction times for all word types indicating that the pattern of regional brain activation might prove to be specific to each group. Previously, in section 4.2.2.2, the functional interpretation of SSVEP changes in amplitude and latency were discussed. Briefly, SSVEP reductions in amplitude are interpreted in a similar way to EEG alpha, and are generally interpreted as cortical activation for cognitive tasks. Variations in SSVEP latency are understood to result from the excitatory and inhibitory neuromodulation of regional cortico-cortical resonances (Silberstein et al, 2000).

7.2.1 Neurophysiological findings for the Standard Stroop

The pattern of activation for the Standard Stroop for the Panic Disorder and Control groups contained similar components, particularly relative activation of occipital regions, as evidenced by SSVEP amplitude reductions. In addition, both groups showed SSVEP latency decreases at temporal sites. Differences between the groups, evident in the time-averaged maps (Figure 6.3) include sustained right anterior SSVEP latency reductions that were observed in the Control group, but that the Panic Disorder group did not display, as well as left posterior SSVEP latency reductions which were evident in the Panic Disorder group, but not in the Controls. The discussion of the neurophysiological findings for the Standard Stroop task will be divided into two parts. The first will focus on anterior findings and their implications, the second will focus on posterior regions and relevant
implications. The Standard Stroop was not the main focus of the present study, and was used as a measure of general cognitive ability. As such, the discussion of the Standard Stroop findings will be limited to a general discussion within the context of previous research within the same area.

### 7.2.1.1 Anterior findings

The Stroop task has traditionally been considered as a measure of frontal lobe function in neuropsychology, following the findings of Perret (1974). In particular, right frontal lesions, but not left frontal lesions have been associated with more errors in Stroop performance (Vendrell et al., 1995). It has also been used to imply frontal dysfunction in various psychiatric patient groups particularly depression (Lemelin et al., 1996; Trichard et al., 1995). With the advent of neuroimaging techniques, the role of frontal lobe structures such as the anterior cingulate, has been highlighted (MacLeod and MacDonald, 2000).

In the present study SSVEP alterations were observed in the frontal region during the Standard Stroop task. One effect comprised a sustained prefrontal SSVEP amplitude reduction in the Panic Disorder group. The other effect involved sustained right anterior SSVEP latency reductions, which were present in the Control group only. These differing patterns of SSVEP variations occurred despite similar times for colour-naming of stimuli between the groups.

SSVEP latency reductions were observed in the right anterior region in the Control group and the time-averaged maps (Figure 6.3) show this effect is sustained. In contrast, the Panic Disorder group does not exhibit such SSVEP latency reductions, however non-significant anterior SSVEP latency increases are noted. The dynamic maps (Figure 6.6) show that for the Control group, the right anterior SSVEP latency reduction was most prominent from 462 msec until 769msec, approximately corresponding the time of response for the incongruent Stroop.

The incongruent Stroop has been found to consistently activate frontal regions, compared to a variety of baseline tasks including coloured rectangles (Larrue et al., 1994), coloured crosses (Bench et al., 1993), false font and non-colour neutral words (Taylor et al., 1997), and congruent colour words (Carter et al., 1995b; Leung et al., 2000; Peterson et al., 1999).
The right frontal region in particular appears to be important during Stroop performance. Increased rCBF in a number of right frontal areas has been reported (Bench et al, 1993; Larrue et al, 1994; Taylor et al, 1997, experiment 1). Peterson et al (1997) performed factor analysis on the fMRI signal alterations observed during the incongruent Stroop, in comparison to the congruent condition. The results of the factor analysis suggest that right hemispheric alterations, which included a number of frontal regions as well as portions of the cingulate, were involved in vigilance and error response monitoring aspects of the Stroop task. The pattern of SSVEP latency reductions within frontal electrodes in the Control group, may be interpreted as evidence of an increase in excitatory cortical activity, and occurs during the formation of colour response. These results suggest that previously reported right frontal increases in rCBF and fMRI signals may be associated with increased localised excitation.

The most consistent finding across most studies of the incongruent Stroop compared to a control condition is activation of the anterior cingulate (MacLeod and MacDonald, 2000). Macleod and MacDonald (2000) propose that the function of the anterior cingulate may be to maintain goal-oriented attention and response to colour. Anterior cingulate activation has been observed in a number of different Stroop studies (Bench et al, 1993; Carter et al, 1995b; Leung et al, 2000; Pardo et al, 1990; Taylor et al, 1997). The anterior cingulate has also been implicated in error detection, as well as conflict processing and memory processes, which is consistent with the formation of correct colour response for the incongruent Stroop (Bush et al, 2000). Considering the efferent connections between the anterior cingulate and numerous frontal and prefrontal areas (Pandya et al, 1981), the anterior cingulate may exert some control over frontal areas. Since the SSVEP technique cannot directly assess cingulate activity, its connection to frontal SSVEP alterations must remain speculative.

The Standard Stroop time-averaged maps (Figure 6.3) demonstrate sustained anterior SSVEP amplitude reductions in the Panic Disorder group. The dynamic maps (Figure 6.7) indicate the SSVEP amplitude reductions at word presentation are most prominent within prefrontal sites, although the effect remains non-significant. At 385msec, the SSVEP amplitude reductions are significant at discrete mid-frontal and right frontal sites. Concurrent SSVEP latency increases within these areas are also likely to contribute to the
statistical significance. In contrast, the Controls exhibit significant SSVEP amplitude reductions at right fronto-central locations at a time corresponding to the formation and execution of verbal response, and can be clearly seen in Graph C of Figure 6.16. This suggests that the early SSVEP amplitude reductions shown by the Panic Disorder group may not be related to performance of the Standard Stroop task. Anterior brain asymmetries, measured by EEG alpha activity, have been shown to relate to affective style. Specifically, Tomarken et al (1992) reported that subjects with left anterior activation reported greater positive and less negative affect than subjects with right-sided activation. Sutton and Davidson (1997) also found that greater left than right alpha brain asymmetries were associated with greater approach behaviour, while greater right than left asymmetries were associated with greater withdrawal-inhibition behaviour. In addition, negative affect, accompanied by withdrawal-type behaviour has been related to increased right anterior alpha activation (Davidson, 1995). Models of regional brain activity in pathological emotion have incorporated the findings of anterior asymmetries on the basis that avoidance behaviour is a feature of anxiety (Heller, 1993). Thus the frontal SSVEP amplitude reductions in the right hemisphere may be evidence of negative affect and avoidance behaviour that is characteristic of Panic Disorder.

7.2.1.2 Posterior findings

During the Standard Stroop task, the Control and Panic Disorder groups exhibit sustained SSVEP amplitude reductions in the occipital region, and sustained SSVEP latency effects in the left temporal region (Figure 6.3). A striking difference between the two groups is the marked sustained SSVEP latency reduction in the Panic Disorder group which extends to include a large portion of the left posterior region.

Left posterior temporal SSVEP latency decreases were noted for both the Control and Panic Disorder groups. Figure 6.16, Graph A shows that for the Controls, the effect is sustained for the entire task albeit reduced following verbal response. While the Panic Disorder group also exhibited SSVEP latency reductions, although it did not maintain significance throughout the entire task (Figure 6.7). The pattern of SSVEP latency reductions within the left posterior temporal region occurs in an area known to be associated with language and is consistent with processing word meaning (Liotti et al, 2000). Specifically, activation of the
left posterior temporal region, as evinced by increased rCBF, has been consistently reported during simple language tasks including passive viewing of words (Beauregard et al, 1997), active silent reading of single words (Perani et al, 1999), and listening to words (Wise et al, 2001). The left temporal area has also been implicated in implicit reading (Brunswick et al, 1999, experiment 2). In that study, subjects were instructed to attend to particular letter features of presented words, and not explicitly instructed to read the stimuli, resulting in increased rCBF in the left middle temporal and superior temporal regions, suggesting reading of the word occurred anyway.

Thus the posterior temporal SSVEP latency reductions observed in both the Control and Panic Disorder groups, which are interpreted as evidence of increased localised excitatory activity, are consistent with general activation of language centres. It is worth noting that SSVEP amplitude reductions also occur in both Panic Disorder and Control groups, and possibly contribute to the significant effect in the left temporal area.

Another feature of the Panic Disorder group are the strong left parietal SSVEP latency reductions throughout the task, however, only from time of congruent word response does the effect become significant (Figure 6.7). Inspection of Figure 6.16, Graph B shows that the SSVEP latency reduction observed in the Panic Disorder group is large compared to the Control group. The SSVEP latency reduction occurs in a region in which abnormalities have previously been observed in Panic Disorder. Decreased rCBF in the left posterior parietal/superior temporal cortex was observed in Panic Disordered women compared to healthy subjects, and this area underwent the greatest increase in activity following administration of a serotonin agonist (Meyer et al, 2000). Meyer et al (2000) suggest that increased rCBF is indicative of serotonin abnormalities but whether the abnormality was due to serotonin hypersensitivity or tonic reductions in serotonin release could not be determined. Decreased glucose metabolism has also been observed in the inferior parietal cortex in Panic Disorder patients (Nordahl et al, 1990). The metabolism in this area was also reported to normalise in separate group of Panic Disorder patients following imipramine therapy (Nordahl et al, 1998), which affects both serotonin and NAd uptake. Thus the increased excitation at left parietal sites in Panic Disorder in the present study may be a consequence of a synaptic inhibitory deficit, which is consistent with decreased metabolism and blood flow observed within this region in Panic Disorder.
The relationship between certain components of the auditory ERP and stimulus intensity are known to be influenced by central serotonin levels (Hegerl and Juckel, 2000). Specifically, low serotonin levels are associated with a larger increase in ERP magnitude for a given stimulus intensity. In contrast, higher central serotonin levels are associated with reduced ERP amplitude for a given stimulus intensity. It has previously been argued that SSVEP latency reductions may be the consequence of increased localised neurochemically modulated cortical excitation or relatively decreased cortical inhibition.

GABA is the major inhibitory neurotransmitter in the human central nervous system, and it is known to interact clinically with serotonin (Nutt and Cowen, 1987) and may also work to modulate medial prefrontal pyramidal neurons (Puig et al, 2005).

Serotonergic neurons have been shown to synapse on GABAergic interneurons (Jakab and Goldman-Rakic, 2000; Yan, 2002), and appears to act through the 5-HT$_{2A}$ receptor (Abi-Saab et al, 1999; Jakab and Goldman-Rakic, 2000). In particular, administration of a serotonin agonist that specifically targets the 5-HT$_{2A}$ receptor, increases cortical levels of GABA (Abi-Saab et al, 1999). Conversely, reduced cortical levels of serotonin may result in reduced GABA activity, producing relatively less local inhibition and thus relatively greater excitation. This may then give rise to the reduction in SSVEP latency seen in the Panic Disorder group in the left parietal area. Deficits in GABAergic function have previously been suggested as a causative mechanism in anxiety (Crestani et al, 1999). In addition, GABA and related BZD abnormalities have been frequently reported in Panic Disorder (Brandt et al, 1998; Goddard et al, 2001; Kuikka et al, 1995; Malizia et al, 1998; Roy-Byrne et al, 1990). Since there is no way of determining whether serotonin-mediated GABA abnormalities exist in the Panic Disorder group in the present study, it is stressed that this theory must remain highly speculative.

The Control group showed significant sustained posterior SSVEP amplitude reductions prominent within the occipital cortex for the Standard Stroop task (Figure 6.6). The Panic Disorder group also showed a similar effect, however significance was limited to a smaller area in the right hemisphere, and present only up to the time of response. The difference between the Panic Disorder and Control groups is clearly displayed in Graph D, Figure 6.16. Activations of the occipital cortex may be related to early visual processing (Price et al, 1999), and are also observed in many neuroimaging studies of the Stroop task (George
The activation of the occipital cortex during the Stroop task appears to occur regardless of the baseline task used, and is also present during variations of the Stroop task. Taylor et al. (1997) reported activation of the left occipital lobe for a Stroop task using the standard incongruent words and taboo words, compared to a baseline task of coloured symbols. Left occipital activation has also been observed during both incongruent and sad word Stroop tasks, compared to coloured hatches (George et al., 1994). In addition, SSVEP amplitude reductions within extrastriate visual areas have previously been associated with increased visual vigilance during continuous performance attentional tasks (Nield et al., 1998; Silberstein et al., 1990). This suggests that the activation of the occipital cortex demonstrated by reductions in SSVEP amplitude is likely to be related to visual processing as well as attentional demands of the task.

The Panic Disorder group also display occipital SSVEP amplitude reductions during the Standard Stroop task, however, the effect is significant only from word presentation until 462 msec. Figure 6.16, Graph D shows that the Panic Disorder and Control groups show remarkably similar pattern of occipital SSVEP amplitude reduction, however the effect is more prominent in the Control group. A possible explanation of the reduced occipital significance in the Panic Disorder group is that the small number of subjects increased the variability of the signal, thus reducing its significance. Another explanation is that the lack of significant occipital activation is related to cognitive factors, namely, poor attention or vigilance. If lower attention were responsible, longer mean reaction times for the Standard Stroop task would possibly ensue, as well as higher error rates. Neither of these effects was found, and so poor attention is unlikely to be the cause of reduced occipital activity.

In summary, investigation of the neurophysiology of the Standard Stroop task in the present study has revealed both similarities and marked differences between the Control and Panic Disorder groups. The Panic Disorder and Control groups both exhibited SSVEP amplitude reductions in the occipital cortex, which is consistent with visual processing and attentional demands related to the task. Both groups also exhibited localised excitation within left posterior temporal sites, consistent with processing language components of the task. The most prominent difference between the Panic Disorder and Control groups was the large left parietal SSVEP latency reduction demonstrated by the Panic Disorder group. This
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Effect may reflect dysregulation between excitatory and inhibitory neural mechanisms involving serotonin and GABA within the region. The Panic Disorder group also showed frontal SSVEP amplitude reductions which appear to be consistent with theories of negative affective style and behaviour.

7.2.2 Neurophysiological findings for the Emotional Stroop

The Emotional Stroop has been used as a tool to examine automatic processing biases that appear to be central to a number of psychopathologies (Williams et al, 1996), and Panic Disorder in particular (McNally, 1995). As mentioned in section 7.1.3, the Panic Disorder group demonstrated increased colour-naming times for all categories of the Emotional Stroop, despite performing the Standard Stroop as well as the Control group. The Control and Panic Disorder groups displayed different patterns of SSVEP latency and amplitude alterations for the Emotional Stroop, which will be discussed in sections 7.2.2.1 and 7.2.2.2 which deal with anterior and posterior findings respectively.

7.2.2.1 Anterior findings

Anterior SSVEP alterations in latency and amplitude were observed for the Control group for all word categories of the Emotional Stroop. The time-averaged maps (Figure 6.4) show no sustained effects for any Emotional Stroop task. However, the dynamic maps (Figures 6.8-6.13) show significant anterior SSVEP alterations within the Control group, particularly at the time of word presentation, while the Panic Disorder group display only a limited number of significant anterior SSVEP variations within a similar time frame.

The Control group exhibited significant anterior reductions in SSVEP amplitude and concurrent increases in SSVEP latency which were most notable at word presentation, for all categories of the Emotional Stroop. The frontal electrodes represented in the Time-Series graphs (Figures 6.17, Graph A; Figure 6.18, Graph A; Figure 6.19, Graph C) indicate that the relevant SSVEP latency and amplitude effects were developing prior to word presentation, and peaked shortly after. This suggests anticipation by the Control group for the stimulus about to be presented, and the possible initiation of neural mechanisms to ignore the stimulus meaning in order to successfully name the colour of the word as directed. Participants were likely to be aware of the emotional content of the task,
and its emotional category since the word remained on screen after verbal response was recorded. In addition, when debriefed following the experimental procedure, subjects often reported noticing the stimuli were categorised by emotional valence (see Appendix 2).

In the Control groups’ dynamic maps following presentation (at 231 msec), it is apparent for the positive and depression-related words in particular, that the SSVEP latency and amplitude effects are diminished. The anxiety-related words task appears to engender a different pattern of SSVEP changes than the other word types. For the anxiety-related words, the right prefrontal SSVEP latency increases strengthen and extend to anterior temporal regions, in addition to the left anterior SSVEP amplitude reduction which also remains prominent.

Early SSVEP effects may relate to selective attention for threatening information. Weinstein (1995) found that the N100 amplitude of visual ERPs discriminated between high and low anxious subjects for a threat priming condition, and were most evident mid-frontally. Thus the left anterior SSVEP amplitude reductions seen in the Control group for anxiety-related words may be an indication of early attention to threat stimuli. Left anterior activation has also been observed for threat and general negative words conditions of the Emotional Stroop (Compton et al, 2003; Isenberg et al, 1999). Specifically, increased rCBF for threat words compared to neutral words occurred in the left premotor cortex (Brodmann Area 6) (BA 6: Isenberg et al, 1999) and fMRI activation of a number of left anterior structures (BA 6, 9, 10/11, 45) including the left temporal region occurred for general negative words (Compton et al, 2003). Activation of these regions is consistent with the significant pattern of SSVEP amplitude reductions in left frontal, central and temporal regions seen in the dynamic maps for the anxiety-related words (Figure 6.12), particularly in the time prior to response. However, the left anterior region may have a more general role in attention to stimuli since it is also activated by the incongruent Stroop (Compton et al, 2003). In the present study, the Control group exhibited no significant reductions in SSVEP amplitude in the left anterior region for the Standard Stroop in a similar early time frame, suggesting the left anterior activation for the anxiety-related words is specific to processing of negative stimuli.
Similar to the Control group, the Panic Disorder group display anterior SSVEP amplitude reductions evident in the dynamic maps (Figures 6.9, 6.11, 6.13) prior to response. However, while the Controls exhibited the strongest and most sustained anterior SSVEP amplitude reductions for the anxiety-related words, the Panic Disorder group exhibited the strongest SSVEP amplitude reductions for the positive words task. The anterior SSVEP amplitude decreases in the Panic Disorder group do not appear to be as widespread as in the Control group.

Anterior SSVEP latency increases observed in the Control group also contributed to the significance within this region in the associated SPMs. For the positive words (Figure 6.8), the SSVEP latency increases encompassed bilateral frontal sites and were most prominent at word presentation. For the depression-related words (Figure 6.10), the SSVEP latency increase was also prominent at word presentation, but was lateralised to mainly left prefrontal sites. In contrast, the SSVEP latency increases associated with anxiety-related words was prominent in the dynamic maps at 385 msec (Figure 6.12), and focussed at right lateral prefrontal sites.

Performance of the Emotional Stroop is dependant on suppressing the tendency to read the presented word in order to name its ink colour as fast as possible. As mentioned earlier, the effects observed at word presentation are suggestive of anticipation of the stimulus and may involve preconditioned initiation of neural mechanisms specifically employed to ignore stimulus meaning. Increased SSVEP latency at frontal electrodes within the present study may be interpreted as evidence of increased inhibitory cortical activity. Regions within the prefrontal cortex have been understood to play a role in the modulation and inhibition of subcortical structures, including the amygdala (Davidson, 2002), which is well known for its role in conditioned fear (LeDoux, 1992, 1995a, 1996). In particular, glutamatergic projections from the PFC are believed to project to GABAergic neurons which synapse on the amygdala, allowing reciprocal modulation between the PFC and amygdala during emotional processing in the cognitive domain (Davidson, 2002; LeDoux, 1996). The role of the amygdala in cognitive-based emotional evaluation (Halgren, 1992) is supported by PET and fMRI studies in humans showing activation of the amygdala for fear conditioning (Büchel et al, 1998; Morris et al, 1997) and Emotional Stroop (Isenberg et al, 1999) paradigms. Increasing the GABA-modulated inhibitory output of the amygdala is known to
retard aversive conditioning, as well as producing anxiolytic effects (Davis et al, 1994). Thus it is postulated that the increases in SSVEP latency observed in the Control group at the time of word presentation, particularly for positive and depression-related words may indicate the activation of inhibitory neural mechanisms to reduce the impact of the emotional stimuli. For the anxiety-related words, the emotional salience of the stimuli may be greater such that reducing the impact of the emotional stimuli requires sustained implementation of neural mechanisms described above. However, without the ability to image amygdala function in the present study, its role in modulating frontal SSVEP latency must remain purely speculative.

In contrast to the pattern of SSVEP latency alterations in the Control group which appeared to differentiate each emotional category, the Panic Disorder group exhibited mild right anterior SSVEP latency increases for all Emotional Stroop words. This effect was significant only for the anxiety-related words, suggesting activation of inhibitory neural mechanisms to reduce the impact of salient emotional stimuli. However, non-significant anterior SSVEP latency increases were also noted for the Standard Stroop task within the Panic Disorder group, indicating the effect may be related to cognition in general or a characteristic of Panic Disorder itself.

An interesting feature of the Panic Disorder group with regard to anxiety-related words is the anterior SSVEP latency reductions evident in the dynamic maps at 769 msec (Figure 6.13). The associated SPM indicates the effect is most prominent at left frontal sites, and encompassing electrodes F7 and F3. This effect occurs after verbal response has been recorded, and while the stimulus word is still on the computer screen. The SSVEP latency reduction occurs approximately over Brodmann areas 44 and 45, which are areas well known for their role in language and speech production in particular (Uylings et al, 1999). Left frontal activation has been consistently observed for studies investigating language function in healthy participants (Beauregard et al, 1997; Perani et al, 1999; Rumsey et al, 1997). In investigating the differences between lexical and semantic processing, Perani et al (1999) found increased rCBF in left inferior frontal regions during a simple lexical decision task involving silent reading of words, compared to viewing a letter-string baseline. Increased rCBF in these areas were also observed in a lexical-decision task in
which the subjects responded to the correct phonological or orthographic versions of word pairs (Rumsey et al, 1997). For the phonological decision task, participants were implicitly required to silently pronounce the word pairs in order to determine which sounded like real words (eg ‘gaim’, ‘joak’). Passive viewing of emotional words (eg sex, murder), compared to viewing a flashing symbols, has also produced increased rCBF in the left inferior frontal gyrus (Beauregard et al, 1997). The significant reductions in SSVEP latency, which are interpreted as increased neural excitation, occur in similar regions where increased rCBF has been observed. Thus decreases in SSVEP latency appear to be related to the processing of a written stimulus and is particularly strong for Panic Disorder patients performing the anxiety-related words task of the Emotional Stroop. This suggests that the Panic Disorder patients produce greater activation of language centres, after they have performed the task of colour-naming, and are afforded more opportunity to read the stimulus word. Interestingly, SSVEP latency reductions within the same area are noted for depression-related and positive words, but the effect is reduced and does not reach significance. The effect is also observed for the Control group for anxiety-related and depression-related words at the same time, but does not reach the same level of significance.

The prefrontal SSVEP latency increases in the Controls may indicate activation of inhibitory mechanisms for reducing the emotional impact of the Emotional Stroop stimuli, which is not evident to the same degree in the Panic Disorder group. In addition, marked anterior SSVEP amplitude reductions observed in the Control group are not observed in the Panic Disorder patients, and this effect is particularly apparent for anxiety-related and depression-related stimuli.

7.2.2.2 Posterior findings:

The most prominent posterior SSVEP effects are the marked sustained SSVEP latency reductions in bilateral temporo-occipito-parietal regions of the Panic Disorder patients. This reduction is not observed in the Controls. As previously discussed in section 7.2.1.2, the SSVEP latency reductions of the left temporal-parietal region also occur for the Standard Stroop task. While the effect fails to reach significance in the temporo-parietal region, its sheer size merits a discussion. Evident in the Panic Disorder dynamic maps for all word types (Figures 6.9, 6.11, 6.13), the SSVEP latency reduction is maximal between
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615 msec and 769 msec, occurring about the time of response. That a similar effect is observed during the Emotional Stroop task supports the suggestion that the left temporo-parietal SSVEP latency reductions are likely to be characteristic of Panic Disorder. Focal abnormalities of this region have been previously discussed in section 7.2.1.2, and as stated previously, may be a result of the interaction of GABA with serotonin.

For the Emotional Stroop tasks, marked SSVEP latency reductions involving the right temporo-parieto-occipital region are noted for the Panic Disorder group. The results indicate that the effect maintained significance at parieto-occipital sites throughout the anxiety-related words task. The Control group also exhibit right posterior SSVEP latency reductions, although the distribution is more towards the posterior temporo-parietal region. In addition, the effect is maximal within the Controls around the time of verbal response, and reaches significance for anxiety-related and depression-related words only.

The right posterior region has been implicated in emotional processing. Lang et al (1998) assessed posterior contributions to processing of emotional pictures using fMRI. In that study, activation of the right fusiform gyrus and the parietal lobule was observed, in addition to bilateral occipital areas, which is consistent with the present study. The right hemisphere activation was also noted to be greater in women than in men. Reiman et al (1997) also observed increased rCBF within these regions during viewing of emotional and neutral films although the activation was bilateral. From these results, the authors postulate that specific sensory association areas of the brain, such as the visual cortex, preferentially attends, evaluates and responds to visually presented, emotionally arousing stimuli. Thus the right posterior regions may have a specific role in processing highly arousing emotional information. This view is supported studies investigating high emotional arousal conditions. Compton et al (2003) found increased activation of the occipital and parietal areas as well as the right temporal region during the negative high arousal condition of an Emotional Stroop task, compared to a negative low arousal condition. Büchel et al (1998) also noted right medial parietal activation during presentation of a conditioned stimulus, which had been previously paired with an unpleasant loud tone, in their study of aversive conditioning in humans. The reductions in SSVEP latency in the right posterior region in the Panic Disorder group is consistent with Heller and colleagues (Heller, 1993; Heller et al, 1998) who postulate that the right parieto-temporal regions have a specific role in the
experience of emotion as well as emotional processing, and in mediating autonomic arousal. In particular, it has been observed that a high arousal state in anxious individuals is characterised increased activity of the right parietal region (Heller et al, 1997). The present findings of marked reductions of SSVEP latency within right posterior regions for the Panic Disorder group are interpreted as evidence of increased neurochemically modulated excitatory cortical activity. These results suggest that emotional arousal may be associated with localised excitation. Panic Disorder may be characterised by high arousal for emotional stimuli, and may explain the increased reaction times for all Emotional Stroop categories. High emotional arousal may be reciprocally related to hypervigilance for possible threats within the environment in anxiety disorders (Beck et al, 1985), which was discussed as a possible mechanism for producing delayed reaction times for the Emotional Stroop in the Panic Disorder group compared to the Controls in section 7.1.3. In contrast to the Panic Disorder group, the Controls exhibit SSVEP latency increases within the right posterior temporal region, and this effect is evident in the dynamic maps for all word types at 231msec (Figures 6.8, 6.10, 6.12). This suggests that the Control group utilised neural inhibitory processes possibly in response to emotional arousal engendered by the Emotional Stroop stimuli.

The present finding of reduced SSVEP latency within the right posterior regions in the Panic Disorder group, which extends to include occipital areas, may be interpreted as evidence of an increased localised excitation, or as relative decreases in localised inhibition. Decreased neural inhibition may arise from abnormalities in posterior GABA systems in Panic Disorder. Preliminary reports suggest GABA levels in the occipital cortex in Panic Disorder are decreased by 22% compared to controls (Goddard et al, 2001) in addition, general global reductions in \( \text{GABA}_\alpha \)-BZD receptor binding in Panic Disorder have been observed (Malizia et al, 1998). Thus reduced localised neural inhibition may result in relative increased excitation, contributing to the decreases in right posterior SSVEP latency in the Panic Disorder group. In addition, the reductions in SSVEP latency observed within occipital electrodes in the Panic Disorder group is also consistent with increased modulation of visual processing by regions of the limbic system including the amygdala (LeDoux, 1996).
The Control group displayed significant posterior SSVEP amplitude reductions during each of the Emotional Stroop tasks. Similarities between all tasks include activation of the right parieto-temporal region, particularly evident in the lead up to verbal response. In addition, bilateral occipito-parietal SSVEP amplitude reductions occurred prior to response for positive and depression-related words. However, during performance of the anxiety-related words, the Controls showed sustained left posterior SSVEP amplitude reductions. In contrast to the Control group, the Panic Disorder group showed strong posterior SSVEP amplitude reductions for the anxiety-related words only.

Sustained occipital SSVEP amplitude reductions were also observed for the Standard Stroop task within both groups. As previously discussed in section 7.2.1.2, activation of the occipital cortex is likely to reflect visual processing and attentional demands of the task. Reductions in SSVEP amplitude in extrastriate visual areas have been associated with visual vigilance during a continuous performance attentional task (Nield et al, 1998; Silberstein et al, 1990). The SSVEP amplitude reductions of the left occipital region seen in the Control group during anxiety-related words in particular are also consistent with reports of increased rCBF during Emotional Stroop tasks using taboo words and sad words (George et al, 1994; Taylor et al, 1997).

The SSVEP amplitude reductions within the posterior temporal and parietal areas in the Control group are also consistent with ERP recordings during the processing of emotional stimuli. Roschmann and Wittling (1992) observed posterior ERP negativities during viewing of emotionally negative and neutral pictures in psychiatrically healthy participants. The effect was most prominent over the right hemisphere and evident from approximately 671 msec following onset of picture presentation for negative pictures. Using a similar set of stimuli, Kayser et al (1997) also found augmentation of the N2-P3 amplitude for negative stimuli over the right parietal region. Thus right parietal activation has been observed during processing of emotionally negative stimuli which is consistent with the present study negative words within the Controls in which SSVEP amplitude reductions were greater in the right hemisphere. The studies of Roschmann and Wittling (1992) and Kayser et al (1997) failed to investigate ERPs for positive stimuli and so cannot be compared with the positive words task in the present study, where significant SSVEP amplitude reductions, particularly in the right hemisphere were also noted. Mini et al
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(1996) recorded ERPs from students during viewing of pleasant, unpleasant and neutral pictures and observed larger ERPs at the parietal electrode for both the P3 and N4 components. Unfortunately the study only employed midline electrodes, so any laterality effects could not be detected, however the results of Mini et al (1996) suggest that the parietal region may be involved in emotional processing, regardless of valence.

In contrast to the Controls, the Panic Disorder group do not display significant right posterior temporo-parietal SSVEP amplitude reductions, and in fact display slight increases in SSVEP amplitude for positive words. The Panic Disorder group show the strongest SSVEP amplitude reductions within this region for anxiety-related words, however the extent to which the SSVEP latency reductions are contributing to the significance within the parietal region cannot be determined. While the lack of associated significance for the SSVEP amplitude reductions for the Panic Disorder group may be a function of the small sample size, it may also indicate that the processing of emotional stimuli was similar to that of the neutral stimuli. There is converging evidence that the posterior regions, and the parietal region in particular, are involved in attentional processes (Cabeza and Nyberg, 2000; Posner et al, 1984). The inability of anxiety sufferers to focus attention, in the face of perceived threat has also been suggested (Beck et al, 1985), which may result in decreased regional cortical activity and thus explain the lack of posterior SSVEP amplitude reductions within the Panic Disorder group.

In summary, the Panic Disorder and Control groups display distinct differences in SSVEP alterations during the Emotional Stroop task. The most outstanding effects in the Panic Disorder group were the prominent left and right posterior SSVEP latency reductions, which were not observed in the Control group. Right hemisphere SSVEP latency reductions of the posterior temporal and parietal regions reflect increased localised neural excitation in an area previously associated with emotional arousal, which may contribute to the emotional disturbance in Panic Disorder. The Panic Disorder group also exhibit marked left posterior SSVEP latency decreases, which were also evident for the Standard Stroop. This effect may reflect a serotonin-mediated GABA disturbance in Panic Disorder. The Panic Disorder group also displayed left frontal SSVEP latency reductions in a region known for language processing, which occurred following verbal response, indicating a conscious appreciation of anxiety-related stimuli. The Control group displayed significant
anterior SSVEP alterations which were not present in the Panic Disorder group. Anterior SSVEP amplitude reductions exhibited by the Controls are consistent with early processing of negatively valenced stimuli. Increases in anterior SSVEP latency in the Control group, which were the strongest for anxiety-related words, suggests neural inhibitory mechanisms were employed, possibly to suppress the emotional salience of the Emotional Stroop stimuli. Posterior SSVEP amplitude alterations appeared to differentiate the Panic Disorder and Control groups. Reductions in SSVEP amplitude within the occipital region is likely to reflect visual demands of all Emotional Stroop tasks in the Controls, and in anxiety-related words task only for the Panic Disorder group. SSVEP amplitude reductions in the parietal region in Controls are consistent with the processing of emotionally valenced stimuli as well as attention in general. This effect appeared to be diminished in the Panic Disorder group, possibly suggesting a reduced ability to focus attention on non-threatening aspects of the task such as colour-naming.

7.2.3 Neurophysiological findings for the Interferers and Non-Interferers

The production of interference for the Emotional Stroop has been argued to arise from the emotional salience of a given word disrupting the ability to name the ink colour of the word (Williams et al, 1996). While this paradigm has been used extensively to investigate biases in anxiety disorders (as reviewed in Chapter 3) Emotional Stroop interference also occurs in psychiatrically healthy control groups. McNally and colleagues (1990; 1994) have noted that Emotional Stroop interference occurs in both control and patient groups, but the interference effect is greatest in the clinical population.

The present study provides an opportunity to explore differences in SSVEP brain activity related to the production of interference for the Emotional Stroop. In explaining why some Emotional Stroop studies do not find the expected interference in non-clinical anxiety, Williams et al (1996) suggest that participants may adopt a conscious strategy to override the effect of the salient stimulus word in order to name the colour. At the simplest level, the pattern of SSVEP alterations for the Non-Interferers may be considered as related to effective overriding of the emotional salience of the stimulus word in order to name its ink colour. Conversely, the SSVEP alterations for the Interferers may be considered as related to bias for emotional material which disrupts the task of colour-naming.
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In the present study, the Non-Interferers were characterised by SSVEP latency increases, involving the right posterior temporal and right fronto-central regions during the anxiety-related words component of the Emotional Stroop task. The right posterior-temporal SSVEP latency increases seen in the Non-Interferers are evident prior to verbal response, and are most prominent at 231msec. In section 7.2.2.2, it was argued that SSVEP latency reductions of the right posterior-temporal region, indicative of increased localised neural excitation, is consistent with suggestions that the right posterior region has a specific role in emotional processing and mediating autonomic arousal (Heller, 1993; Heller et al, 1998) and is supported by findings of increased rCBF and BOLD signals during emotional processing tasks (Büchel et al, 1998; Compton et al, 2003; Lang et al, 1998; Reiman et al, 1997). Conversely, increased localised neural inhibition as evinced by SSVEP latency increases within the region, are consistent with the notion of inhibition of emotional processing and autonomic arousal. Thus it appears that the Controls who do not show interference for anxiety-related words (the Non-Interferers) employ neural inhibitory processes in order to avoid processing the emotional content of the stimuli.

The Non-Interferers also exhibit marked SSVEP latency increases which are prominent immediately prior to response within the right central sites and extending frontally (Figure 6.15). This is in contrast to the Interferer group who show SSVEP latency reductions within the region for the same point in time. While the effect does not reach statistical significance in the Non-Interferer group, which may be a function of the small sample size (13 subjects), it may also relate to control of emotional arousal. Compton et al (2003) found a number of right frontal regions (BA 6, 8 and 45) were activated during an Emotional Stroop task using high arousal negative words, contrasted with low arousal negative words, despite no difference in reaction time between each word group. These Brodmann’s areas lie approximately within the regions bounded by electrode placements F4, F8 and C4 (Homan et al, 1987). Again, this may indicate the application of neural inhibitory mechanisms in order to ignore the emotional salience of the stimuli in order to name its ink colour. The time frame in which the SSVEP latency increases occur, that is, immediately prior to verbal response, suggests participants may have adopted a strategy for performing the task.
If increased neural inhibition reduces Emotional Stroop interference in the Non-Interferer group, then increased local excitation within the right posterior-temporal region may facilitate processing of emotionally arousing stimuli to an extent that it interferes with colour-naming. SSVEP latency reductions are observed for the Interferer group, which is sustained from word presentation until after verbal response, but is most prominent in the lead up to response (Figure 6.14). Thus in contrast to the Non-Interferers, the Interferer group exhibit a pattern of right posterior neural excitation which may indicate greater emotional arousal and thus give rise to the longer reaction times for anxiety-related stimuli.

The Non-Interferer group exhibit marked SSVEP amplitude increases within the right occipital region immediately prior to response (Figure 6.15). In contrast, the Interferer group show occipital SSVEP amplitude reductions, significant in the right hemisphere in the time from presentation until response. SSVEP amplitude reductions within the occipital region have also been observed in healthy males during anticipatory anxiety (Gray et al, 2003). Since reductions in SSVEP amplitude within extrastriate regions have been previously associated with increased attention during a visual vigilance task (Nield et al, 1998; Silberstein et al, 1990), increases in SSVEP amplitude may indicate a shift in attentional focus away from the visually presented emotional stimuli for the Non-Interferer group. This is reflected in the faster reaction times for emotional stimuli which have previously been interpreted as shifting attention away from emotional material (eg Wilson and MacLeod, 2002). Conversely, the occipital SSVEP amplitude reductions in the Interferer group appear to reflect attention towards emotional stimuli, which may give rise to the longer reaction times seen in the present study.

The right prefrontal SSVEP latency increases that were noted within the Control group for anxiety-related words appear to be due to the Interferers, who exhibit this pattern between word presentation and response (Figure 6.14). This effect was discussed in section 7.2.2.1, where it was argued that the SSVEP latency increases may represent implementation of neural inhibitory mechanisms, possibly involving the amygdala, to reduce the impact of the emotional nature of the stimuli. Since this effect was observed in the Interferer group more strongly than in the Non-Interferer group, it is speculated that while the emotional impact of the stimuli may have been reduced, it was not eliminated, and interference for anxiety-related words did occur. In addition, the effect was evident at the time of word
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presentation, and this suggests that it may be a reflection of anticipation of the stimulus. The stimulus word remained on screen for 1400 msec, while average verbal response occurred at 649 msec, allowing a brief opportunity to read the stimulus word after responding to its colour.

Another feature of the Non-Interferer group is the left temporal and prefrontal SSVEP latency reductions which appear to be most prominent around the time of verbal response. While this effect did not reach statistical significance, which may be a function of a small number of subjects, it represents a visible difference between the Interferers and Non-Interferers. Figure 6.20, Graph B demonstrates that this effect was present in both groups, however it was much stronger in the Non-Interferers compared to the Interferer group. Left temporal SSVEP latency reductions were observed in the Control group during the Standard Stroop task, and may reflect neural excitation related to word processing as discussed in section 7.2.1.2. Left frontal regions also appear to be important in language function (Beauregard et al, 1997; Perani et al, 1999; Rumsey et al, 1997). The results of the present study suggest that neural excitation within regions known to be involved in language processing occurs in the Non-Interferer group.

In summary, the Interferer and Non-Interferer groups displayed distinct differences in their respective pattern of SSVEP activation. The Non-Interferer group exhibited evidence of increased neurochemically modulated inhibitory cortical activity of the right hemisphere regions thought to be associated with emotional arousal. In contrast, while the Interferer group displayed right prefrontal SSVEP latency increases, indicative of increased neurochemical inhibitory cortical activity, the group also displayed evidence of increased neurochemical excitation within the right posterior temporal region, which is noted for its role in emotional arousal (Heller, 1993; Heller et al, 1998). The SSVEP amplitude alterations in the occipital area may reflect attention towards anxiety-related stimuli in the Interferer group and attention away from anxiety-related stimuli in the Non-Interferers, also contributing to the differences in mean reaction times. These factors imply the use of strategic cognitive processes to reduce emotional arousal and shift attention from anxiety-related stimuli within the Non-Interferer group. The Interferer group, on the other hand, is characterised by excitation within areas associated with emotional arousal, presumably contributing to attentional bias for such stimuli. It is important to note that since the
number of subjects within the Interferer and Non-Interferer groups are relatively small (19 and 13 respectively), the results must be regarded as preliminary.

### 7.4 General conclusion and future directions

The aim of the present study was to investigate the brain processes involved in performing the Emotional Stroop task in both Panic Disorder and psychiatrically healthy participants. In addition to the Emotional Stroop task, participants performed the Standard Stroop task to determine whether general cognitive deficits existed in the Panic Disorder group or whether effects were specific to tasks containing emotional stimuli. As predicted in the first hypothesis, the Panic Disorder and Control groups did not display any differences in the mean reaction times for the incongruent and congruent Stroop, thus confirming the absence of general cognitive deficits in Panic Disorder. However, the SSPT data showed that, while both groups displayed some similarities in SSVEP amplitude and latency alterations, there were also some patent differences. The Panic Disorder and Control groups displayed SSVEP latency reductions, indicative of increased localised excitation, in the left posterior temporal region. This effect possibly reflects language processing aspects of the task. In addition, the occipital SSVEP amplitude reductions seen in both groups may reflect visual processing and attentional demands of the Standard Stroop task. The most striking difference between the Panic Disorder and Control groups was the large SSVEP latency reduction located in the left parietal region in the Panic Disorder group. It was speculated that the increased neural excitation within the left parietal region may reflect reduced inhibitory GABAergic activity, mediated by inherent abnormalities of the serotonin system.

The hypotheses for the Standard Stroop also predicted anterior SSPT effects, which may reflect anterior cingulate activity, which is a common finding of Stroop studies (MacLeod and MacDonald, 2000). In agreement with this hypothesis, sustained right anterior SSVEP latency reductions, indicative of increased neural excitation, was observed for the Control group only. That efferent connections between the anterior cingulate and anterior regions exist (Pandya et al, 1981) suggests that the anterior cingulate may exert some control over the frontal area. Since the SSPT technique cannot directly assess deep cortical structures, the association between effects on frontal SSVEP latency and anterior cingulate activity must remain speculative. The mid frontal and right frontal SSVEP amplitude reductions
noted in the Panic Disorder group were interpreted in terms of negative affective style and avoidance behaviour, which is characteristic of Panic Disorder.

With regard to the Emotional Stroop task, it was hypothesised that the Panic Disorder group would show increased interference for anxiety-related words, whereas the Control group would show no Emotional Stroop interference effect. In agreement with this hypothesis, the Control group showed no overall difference in the mean reaction times for anxiety-related, depression-related, positive and neutral words within the Emotional Stroop task. Contrary to the expectations of the present study, the Panic Disorder group also displayed similar mean reaction times for all categories of the Emotional Stroop task. However, the Panic Disorder group were significantly slower than the Control group for all Emotional Stroop categories. It was suggested that the overall increased reaction time for the Emotional Stroop may reflect hypervigilance in Panic Disorder for any stimuli that may represent latent threat, including positive and neutral words. It was also asserted that the absence of an interference effect in Panic Disorder may be a result of the stimuli having insufficient relevance to the patients’ current concerns.

The SSPT data showed that the Panic Disorder and Control groups displayed distinct differences in SSVEP amplitude and latency measures during the Emotional Stroop task. The most outstanding effects in the Panic Disorder group were the reductions in SSVEP latency in the left and right temporo-parieto-occipital regions for all Emotional Stroop categories. With this effect also observed during the Standard Stroop task, the suggestion that the effect is likely to represent a neurochemically-modulated trait abnormality in Panic Disorder, is reinforced. It has been suggested that the impairments in the aminergic systems in Panic Disorder, which normally play a part in effortful behaviour, might be responsible for the behavioural and cognitive patterns in individuals with Panic Disorder (Middleton, 1998).

The prominent SSVEP latency reductions in the right posterior region of the Panic Disorder group were consistent with the present study’s hypothesis of regional brain differences localised to the right hemisphere. However, these effects were not specific to the anxiety-related words, but were observed for all emotional categories. The SSVEP latency reductions reflect increased excitatory cortical activity in a region previously associated
with increased emotional arousal, and may contribute to the emotional disturbance in Panic Disorder.

It was also hypothesised in the present study that no regional SSPT differences would be observed for each category of the Emotional Stroop in the Control group. Contrary to this, the Controls exhibited increased in anterior SSVEP latency, which was greatest for the anxiety-related words, and is suggestive of the utilisation of cortical inhibitory mechanisms to suppress the emotional salience of the stimuli. SSVEP amplitude measures further differentiated the Control and Panic Disorder groups. Of particular note, the Control group displayed SSVEP amplitude reductions in the parietal region, which was discussed in terms of emotional processing and general attention to stimuli. This effect was diminished in the Panic Disorder group and possibly indicates a reduced ability to focus attention in the presence of threatening information, which may be characteristic of pathological anxiety (Beck et al, 1985).

An unexpected finding was the observation that a subgroup of Controls, the Interferers, exhibited Emotional Stroop interference for anxiety-related words. The SSVEP patterns for the Interferers were compared to the Controls who did not show an interference effect, the Non-Interferers. The Interferers were characterised by neural excitation within an area associated with emotional arousal (Heller, 1993; Heller et al, 1998). In addition occipital SSVEP amplitude effects suggest the Interferer group oriented attention towards anxiety-related stimuli. These factors appear to have contributed to an attentional bias for the anxiety-related words, thus resulting in increased interference. In contrast, the Non-Interferer group exhibited neural inhibition of right hemisphere regions previously associated with emotional arousal, as well as occipital SSVEP amplitude alterations consistent with shifting attention away from negative stimuli. These preliminary results suggest that the presence or absence of Emotional Stroop interference is reflected in the corresponding brain activity in non-psychiatric participants.

While the present study has highlighted the differences in brain activity between Panic Disorder and Control participants performing the Emotional Stroop, a number of important issues remain unresolved. Firstly, the absence of an interference effect within the Panic Disorder group highlights the importance of choosing Emotional Stroop stimuli relevant to
the current concerns of the patient group. At the time when the present study was conducted, it was not possible to quickly and easily construct an idiographic version of the Emotional Stroop for the participants. With the recent advent of more sophisticated presentation software, it is possible for future investigations of the Emotional Stroop to more easily produce tasks consisting of personally relevant stimuli. Personalised versions of the Emotional Stroop task containing relevant negative stimuli are much more likely to produce the expected interference in patient groups (Williams et al, 1996). Another limitation of the present study is that the SSVEP technique cannot directly record activity in subcortical or limbic structures. Thus the effect of such structures on cortical activity must remain speculative. These issues may be resolved by combining other neuroimaging techniques such as fMRI and PET with SSPT. In addition, the role of serotonin in modulating the SSVEP effects observed in Panic Disorder patients is also speculative. This issue may be addressed in the future by repeating the paradigms detailed in the present study subsequent to successful treatment with pharmacological interventions, such as SSRIs, which have a direct effect on serotonin levels. The reduced levels of significance for apparent SSVEP effects in the Panic Disorder group may be resolved in the future by increasing the number of participants.

Thus the SSPT technique appears to be a useful approach for investigating the brain activity associated with both the Standard Stroop and Emotional Stroop performances in both clinical and psychiatrically-healthy groups. The use of SSVEPs enables a continuous measure of time-varying processes, and provides the ability to index both sustained and transient alterations in regional brain activation during the Standard and Emotional Stroop tasks. The SSPT technique is also suited to address the issues of the effects of successful treatment on the pattern of activation in Panic Disorder, and the use of personally relevant emotional stimuli within the Emotional Stroop task.
References


