THE PSYCHOPHYSIOLOGY OF SOCIAL ANXIETY

THE PSYCHOPHYSIOLOGY OF SOCIAL ANXIETY:

AN INTEGRATIVE APPROACH

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Abstract

Social fears gain in prominence among higher primates, including humans, where threats associated with other conspecifics become more common. Social fearfulness is expressed on a continuum, ranging from shyness to a diagnosable psychiatric disorder. Despite the wide prevalence and considerable distress associated with social anxiety, our understanding of its neural and cognitive correlates remains in its infancy and remains an imperative for future translational research. The current dissertation examined social anxiety by utilizing multiple experimental approaches and employing a broad range of measures involving neural, cognitive, behavioural and clinical assessments.

Chapters 2 to 4 relied on nonclinical samples of adults selected for social anxiety from a large adult population. Chapters 2 and 3 employed event-related brain potentials to index distinct aspects of perceptual and cognitive processing in tasks that manipulated novelty under socio-emotional and affectively neutral contexts. The aim was to provide a fine-grained characterization of the information processing stages that are biased by social anxiety. Chapter 4 measured reaction times in a selective attention task that independently varied the temporal and energetic aspects of affective stimulus delivery to provide convergent evidence into how affective processing is perturbed by social anxiety. Chapter 5 employed a novel method of quantifying continuous EEG to examine large-scale brain activity during rest and symptom provocation in patients diagnosed with social anxiety disorder. The aim was to examine, for the first time, whether there are treatment-related changes in a measure that putatively indexes communication across different (cortical and subcortical) neuronal systems.

Findings suggest that social anxiety is associated with a sensitization of (bottom-up) systems reacting to social threat and that these biases appear during the early, relatively automatic stages of information processing. Some of these systems may be susceptible to evidence-based psychological treatments that are correlated with changes in brain activity detectable in EEG patterns.

Preface

This thesis contains a total of six chapters. Chapters 2 through 5 are written as empirical journal articles, while Chapters 1 and 6 provide background context for the work and discuss the theoretical and clinical implications of the main findings.

Abbreviated versions of Chapters 2 and 5 have been accepted for publication in *Cognition and Emotion*[1] and *Psychological Science*[2], respectively. Materials from Chapters 2 and 5 are reproduced here with permission from Taylor & Francis and American Psychological Society for non-commercial educational usage as outlined on their websites:

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Figures 1.1 and 1.2 from Chapter 1 were images in the public domain and therefore not under copyright.

For Chapters 2 through 4, I oversaw all aspects of research. I was assisted in data collection by our research coordinator, Sue McKee, and two honours students: Laurel Pickel and Maria Ierullo. The computer generated morphed faces in Chapter 5 were created by Dr. Xiaoqing Gao and used with his permission. I was responsible for experimental design and programming, as well as psychophysiological data reduction/analysis and writing.

For Chapter 5, the experimental design was conceived by Drs. David Moscovitch and Louis Schmidt. I assisted in EEG data acquisition and was also responsible for EEG data reduction, analysis and writing.

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[1]Miskovic, V., & Schmidt, L.A. (2011). Early information processing biases in social anxiety. *Cognition & Emotion, in press*.

[2]Miskovic, V., Moscovitch, D.A., Santesso, D.L., McCabe, R.E., Antony, M.M., & Schmidt, L.A. (2011). Changes in EEG cross-frequency coupling during cognitive behavioural therapy for social anxiety disorder. *Psychological Science, 22*, 507-516.

research was also supported by an Alexander Graham Bell scholarship from NSERC to myself for years 1 and 2, and a Vanier doctoral NSERC fellowship awarded to me for years 3 and 4 under the direction of Dr. Louis Schmidt. Portions of this work were presented at the 2009 Society for Neuroscience Meeting in Chicago, IL and the 30th Annual Conference of the Anxiety Disorders Association of America in Baltimore, MD.

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I would like to thank Sue McKee for her help and support, not only with the actual studies themselves, but also in countless other instances. I am also grateful to many members of the Child Emotion Laboratory, including Louis and Sue, for helping me to find the humour in many a situation. I thank Karen Mathewson for her kind support, encouragement and willingness to listen to all of my scientific ideas, no matter how silly or underdeveloped. I was fortunate to have had the opportunity to work with excellent undergraduate students, especially Laurel Pickel and Maria Ierullo, who helped immensely with running many of the studies that are reported here.

My parents and my brother have been a constant source of support to me and have figured prominently in so many of the goals that I have set for my self. A lion's share of any success that I ever have or will achieve surely belongs to them. Finally, I would like to thank Diana Carbone for her friendship and understanding without which I would have been much impoverished.

I remain grateful and humbled by my entire circle of friends and supporters. If I have achieved anything worthy, it is because of their presence in my life.

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Chapter 1

General Introduction

Psychologists and psychiatrists have long recognized that the varieties of human fears and phobias are not entirely arbitrary but rather seem circumscribed to a limited group of categories (Marks, 1969) including natural/situational triggers (e.g., darkness, heights), dangerous predators (e.g., snakes, spiders) and threatening conspecifics (American Psychiatric Association, 2000). Not surprisingly these categories consistently emerge as stable factors in structural analyses of human fears (Arrindell, Pickersgill, Merckelbach, Ardon, & Cornet, 1991) and are also anticipated by ethological perspectives on animal behaviour (Öhman, Dimberg & Öst, 1985). Taken together, the sum of these considerations suggest that phobic content is at least partially constrained by the evolution of core brain circuits that influence what qualifies as an 'emotionally competent stimulus'[1] (Damasio, 2003) capable of activating fear-related circuitry.

The present set of studies is devoted to a consideration of social anxiety, both in terms of its clinical and subsyndromal manifestations. A characteristic feature of social anxiety involves fear and avoidance of interpersonal interactions, especially those with

[1]Damasio (2003) introduced the term emotionally competent stimulus to indicate an object or event (actual or recalled/imagined) that is necessary and sufficient to engage specific brain circuits and trigger an emotional response. The notion of an emotionally competent stimulus was conceived as a (loose) analogy to antigen-antibody interactions in the immune system.

potential for scrutiny and evaluation. As with many other kinds of fear, the experience of social anxiety can range in intensity from relatively mild to severely disabling, producing responses that are increasingly dysfunctional in their effects (Rosen & Schulkin, 1998). Although some individuals with social anxiety may be able to endure social interactions with a degree of discomfort and distress, for others the fears may be sufficiently powerful to induce active behavioral avoidance of almost all such encounters, resulting in marked disability and psychiatric impairment. A phylogenetic perspective suggests that the extreme manifestations of social anxiety represent maladaptations of a behavioural system that evolved as a means of regulating dominance/submissiveness hierarchies in primate societies (Hermans & van Honk, 2006; Öhman, 1986, 2009). Among higher primates, there is an increasing danger to survival associated with threats from conspecifics, including the threat of disapproval, rejection and ostracism from one's community. In this way, social fears have become incorporated into the human psychological repertoire, alongside fears of predators (e.g., snakes and spiders) and other potentially harmful stimuli.

As a diagnostic entity, social anxiety disorder (SAD) constitutes one of the most common psychiatric illnesses, with lifetime prevalence rates estimated to be as high as 12% of the general population (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005). While SAD is highly distressing in itself, it also constitutes a risk factor for the development of additional psychiatric problems, including depression, substance abuse, and suicidal behaviours (Weiller, Bisserbe, Boyer, Lepine, & LeCrubier, 1996). Social anxiety also frequently accompanies other chronic psychiatric disorders such as

schizophrenia where it appears to be predictive of worse patient outcomes (Goldberg & Schmidt, 2001; Pallanti, Quercioli, & Hollander, 2004). Clearly, much stands to be gained from increasing our understanding of pathogenic mechanisms, including the psychobiological processes that may underlie and maintain social anxiety. A growing number of research studies have recently emerged[2], that have considerably expanded our knowledge concerning the neural and cognitive foundations of social anxiety (see Pérez-Edgar & Fox, 2005;Schmidt & Schulkin, 1999; Shin & Liberzon, 2010). Despite several promising developments over the past two decades, our understanding about the psychobiology of social anxiety remains in its infancy and continues to represent an imperative for future translational research (Charney, 2004). The aim of the introductory chapter is to provide a brief overview of what is currently known about the psychophysiology of social anxiety and draw an outline for the subsequent chapters.

The introductory chapter is divided into four parts. The first section involves an abridged summary of the neural circuitry that supports complex socioemotional functions, the dysregulation of which may contribute to social anxiety. The second section charts the developmental precursors of adult social anxiety as reflected in a particular temperamental style of responding that emerges within the first few months of post-natal life. The third section reviews a series of studies concerning neural and cognitive activity during resting conditions and in response to either acute symptom activation or more subtle forms of cognitive/affective activation in socially anxious

[2]The focus of this chapter is largely on studies conducted with human participants. Several promising animal models (e.g., subordination stress in nonhuman primates) of social anxiety are currently available, but those findings will not be reviewed here (see Mathew, Coplan, & Gorman, 2001, for a brief summary).

adults. Finally, a research strategy is outlined, describing how the subsequent chapters will probe the multiple components of social anxiety.

1.1 Functional Neuroanatomy of Emotion and its Relation to Social Anxiety

This section will review the functional neuroanatomy underlying the experience, expression, and regulation of emotion in the human brain, since the same regions are involved in any discussion about the neurobiological bases of social behaviours, including social anxiety (Adolphs, 2003). Much of the current knowledge about the so-called emotional brain originates from nonhuman animal studies, which permit invasive procedures such as the placement of selective lesions, the application of focal electrical stimulation, as well as the use of molecular biology techniques to examine tissue-dependent patterns of gene expression (see Panksepp, 1998, for a substantive summary). Since the neural structures and pathways shown to be important for implementing emotion in nonhuman animals are highly conserved throughout mammalian brain evolution, many of the findings can be reasonably extended to humans. At the same time, the development of functional neuroimaging methods (PET, fMRI, EEG/MEG) has led to an explosion of knowledge about how human brains implement emotions, with added emphasis on the role of neocortical regions in affective functions[3].

[3]A cursory read of the affective neuroscience literature may foster the impression that the emotional brain of nonhuman animals consists of an aggregate of subcortical (limbic and brainstem) systems while human emotions are elaborated by neocortical and cingulate regions. However, this apparent difference is largely artifactual and can be attributed, in considerable part, to methodological and theoretical differences employed by the researchers rather than being grounded in neurobiology (Berridge, 2003).

Figures 1.1 and 1.2 presents midsaggital and ventral aspects of the human brain, highlighting some of the key regions that collectively help to mediate socioemotional functions.

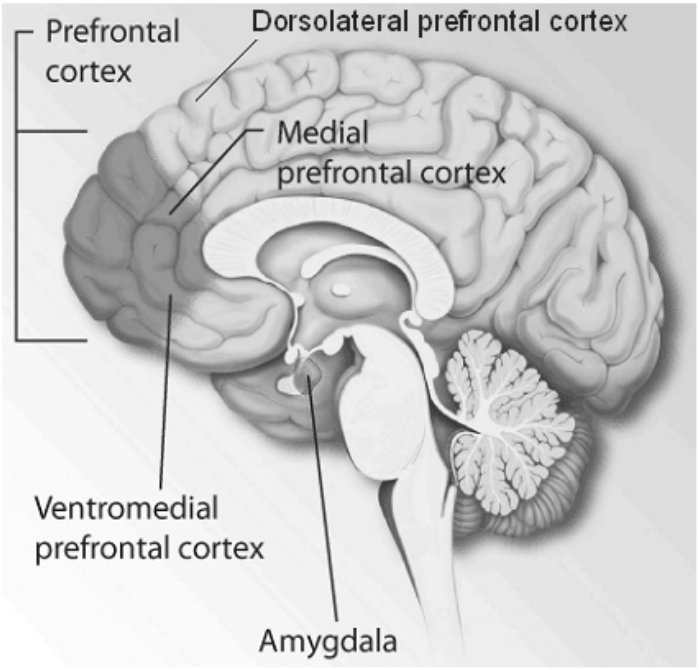

Figure 1.1: A midsaggital view of the human brain highlighting some of the key regions involved in emotional reactivity, expression and regulation. Many of the regions highlighted here appear to be dysregulated in social anxiety.

Given that the emotion of fear[4] is a focus of this chapter, the amygdala represents a cogent starting point for discussion. The amygdala is a complex of functionally distinct nuclei that reside deep within the anterior temporal lobes of the human forebrain. Numerous lines of evidence indicate that the amygdala is implicated in fear learning and

[4]It is important to note that a fear state can be the final outcome of multiple causes or inducers (e.g., innate releasers versus aversively conditioned stimuli). The extent to which there is a common neurophysiological profile subserving all of these different kinds of fear states versus several distinct pathways is still a matter of some debate (Kagan & Schulkin, 1995) that awaits additional empirical evidence.

memory, rapid threat appraisals and emotional inhibition (Phelps & LeDoux, 2005). Due to its multifaceted roles, the amygdala is pivotal for understanding both normal and abnormal aspects of primate social cognition (Emery & Amaral, 2000).

A broad functional-anatomical distinction can be made between the lateral, basal and central divisions of the amygdala. The basolateral division receives afferent connections from the thalamus, hippocampal formation and various regions of the cerebral cortex. Some of these connections convey highly processed and multimodal sensory information (e.g., representations of salient species-specific stimuli, such as emotional facial expressions). Patterns of intrinsic connectivity route the incoming sensory information from the lateral to the basal cell groups, extracting affective value and stimulus context along the information processing stream (Amaral, 2002). In turn, the basolateral division reciprocates many of its incoming connections. For example, anatomical tracing studies in primates have demonstrated that the basal nucleus sends dense feedback projections to cortical sensory areas, including all levels of the ventral ("object based") visual pathway (Amaral, 2002). A potential functional role of these re-entrant connections is to prime cortical sensory pathways and potentiate the perceptual representation of motivationally significant stimuli (e.g., threatening faces of conspecifics in the case of social anxiety). Another important source of output from the basolateral amygdala is to the central nucleus. The central nucleus interfaces, either directly or indirectly, with multiple downstream targets, including the lateral hypothalamus (which is involved in orchestrating wide ranging autonomic and endocrine adjustments), the locus coeruleus and basal forebrain nuclei (which provide energizing noradrenergic and

cholinergic inputs to the cerebral cortex) and periaqueductal gray (which is involved in highly stereotyped motor programs such as freezing and flight). Collectively, these neural systems prepare the organism to cope with the source of threat by providing the metabolic support for motivated actions and simultaneously fostering a cognitive/perceptual framework for fear via relatively slow endocrine mechanisms and more rapidly via broadly distributed activations of the cerebral cortex.

A second major region that contributes to the neural instantiation of emotions necessary for social behaviours is the prefrontal cortex (PFC). The PFC is the most anterior brain region whose chief function appears to be implementing complex behavioural goals by orchestrating the flow of information in structures that receive and process sensory information and control motor output (Miller & Cohen, 2001). While debate continues concerning the precise role of PFC in emotion (Davidson, 2002), it is well established that its function is important for understanding representations of affective value as well as the capacity to exert regulatory control over more basic motivational reflexes centered around the amygdala. Much like the amygdala, the PFC is structurally and functionally heterogenous: (i) in terms of its ventromedial and dorsolateral sectors and also (ii) in terms of hemispheric lateralization.

The ventromedial aspect, including the cingulate cortex, lies on the underside of the PFC convexity and contains numerous reciprocal connections with the amygdala and other limbic centers (see Figure 1.2). By contrast, the dorsolateral aspect encompasses more superior PFC regions and generally lacks direct connections with the 'lower' emotional regions, instead interfacing only through indirect pathways. There is steadily

increasing evidence, derived from both human and nonhuman animal studies, that the PFC (in particular, the ventromedial sector) can dampen or inhibit the activation of fear-related circuits centered around the amygdala and its connections (Ochsner & Gross, 2007; Sotres-Bayon & Quirk, 2010). In human brains, the ventromedial PFC portion may be involved in outcome-based forms of fear regulation (e.g., as occurs after learning that a conditioned stimulus previously paired with an aversive outcome no longer predicts threat) while the dorsolateral system is more important for description-based regulatory processes that involve a strategic reappraisal of stimuli using symbol-based representations (Ochsner & Gross, 2007).

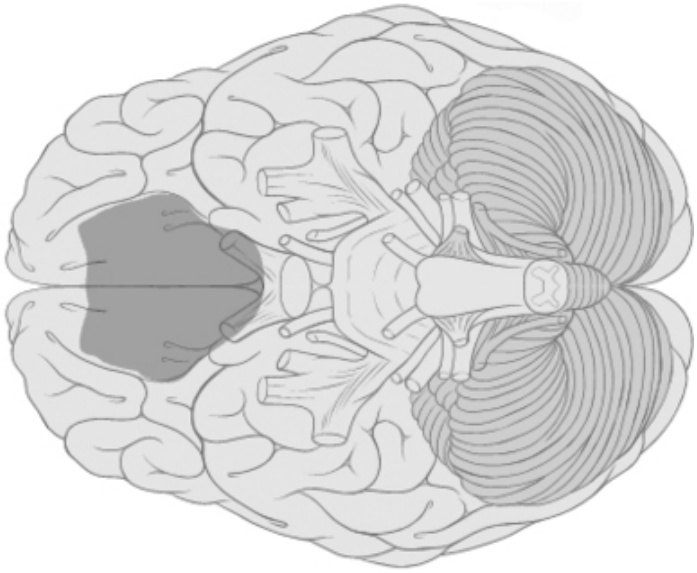

Figure 1.2: A ventral view of the human brain with the ventromedial portion of the PFC highlighted.

When considering hemispheric lateralization, there is evidence that the left PFC is an important component of a system that mediates appetitive, approach tendencies (along

with the consequent positive emotions), while the right PFC appears to form a major component of a circuit that instantiates defensive withdrawal and negative emotions (Fox, 1991). Interestingly, the left and right PFC sectors appear to be differentially associated with amygdalar metabolism, such that the left PFC mediates a functional 'brake' over fear-related circuitry while the right PFC is associated with its release (Davidson, 2002).

Given the important role that prefrontal and amygdala regions play in socio-emotional functions, it is enlightening to note that primate brain evolution has been accompanied by a conspicuous enlargement of these very structures (Barton & Aggleton, 2000; Bickart, Wright, Dautoff, Dickerson, & Feldman-Barrett, 2010). This fact suggests that as the size and complexity of societies inhabited by anthropoid primates increased, there was a corresponding need to accommodate the heightened information processing demands and the consequent neural infrastructure necessary to secure inhibitory control over motivational reflexes. The increased density of connections between the PFC and amygdala allowed for more refined, context-dependent modifications of emotional expressions and controlled responses to the affective states of other conspecifics – an important requirement for dynamic social interactions (Emery & Amaral, 2000).

The neural origins of social anxiety may be traced to dysfunctional patterns of prefrontal-amygdala interactions, resulting in activations of fear-related circuitry in inappropriate contexts or to a degree that seems disproportionate with the eliciting situation. Dysregulation of amygdala function (in particular, that of its central component) has long been hypothesized to underlie high social anxiety (Kagan, 1994; Schmidt & Fox, 1999) – a prediction that has been largely borne out by functional

neuroimaging evidence (Freitas-Ferrari et al., 2010). However, whether amygdala dysregulation can be accounted for primarily on the basis of enhanced bottom-up (hyperexcitability intrinsic to amygdala circuits) or deficient top-down (neocortical) mechanisms (or some combination of the two; Liao et al., 2010) remains to be determined.

A final note of caution should be issued regarding the limits of functional localization. Although the preceding section has reviewed some of the important structures that are consistently implicated in socio-emotional processes, there is no evidence for the simplistic notion that function *resides* directly within those structures (Cohen, 2011). Rather, there is an increasing appreciation that complex functions (emotions being one example) are the emergent products of dynamic and reciprocal neural interactions among interconnected elements (Başar, 2006; Kagan, 2007; Pessoa & Adolphs, 2010). Accordingly, understanding the neural substrates of social anxiety will require appreciation for a wide range of cortico-cortical and cortico-subcortical interactions. In methodological terms, selected aspects of cortico-cortical and cortico-subcortical interactions may be captured by the application of novel measures to neural time series data (see Section 1.5 below).

1.2 Developmental Considerations

There is considerable interest in clarifying the developmental course and precursors to clinical manifestations of social anxiety, since anxiety disorders in general are increasingly being conceptualized as developmental in nature (Leonardo & Hen,

2008). The ability to detect early precursors of anxiety disorders holds promise for offsetting the development of pathological trajectories (Pine, 2007). Temperamental shyness (or behavioural inhibition[5]) constitutes the earliest antecedent of subsequent social anxiety (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). Temperamental shyness refers to an early appearing and extreme form of shyness which is observed in approximately 5 to 10% of typically developing children (García Coll, Kagan, & Reznick, 1984; Kagan, Reznick, & Snidman, 1987). When followed longitudinally, those children who are classified as temperamentally shy show increased risk for development of adolescent and adult anxiety disorders, especially SAD (Biederman, Hirshfeld-Becker, Rosenbaum, Perenick, Wood, & Faraone, 2001; Hirshfeld-Becker et al., 2007; Schwartz, Snidman, & Kagan, 1999) – at times amounting up to a fourfold increase in diagnosis likelihood (Hayward, Killen, Kraemer, & Taylor, 1998). Interestingly, physiological and behavioural markers of temperamental shyness emerge within the first four months of post-natal life (Kagan & Snidman, 1991). These infant predictors include patterns of high motor activity (e.g., limb trashing, spastic back arching) and emotional distress (e.g., crying, fussing) in response to the presentation of novel sensory stimuli. Moreover, a subset of the highly motoric and easily aroused infants also exhibit elevated fetal heart rates and elevated heart rates during sleep, when held erect, within the first two weeks following birth (Kagan, 1994). A significant proportion of infants selected for early temperamental shyness continue to display

[5]This literature has often used the terms *shyness* and *behavioural inhibition* synonymously, sometimes to the detriment of conceptual clarity. The term temperamental shyness is preferred here because it is more precise (i.e., specific to social fears), while the usage of behavioural inhibition may denote a more general fear reaction (see Schmidt & Buss, 2010).

peripheral (Schmidt & Fox, 1998; Schmidt, Fox, Rubin, Sternberg, Gold, & Smith, 1997; Schmidt, Fox, Schulkin, & Gold, 1999) and central (Calkins et al., 1996; Fox, Calkins, & Bell, 1994; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Schmidt, 2008; Schmidt & Fox, 1994; Schmidt et al., 1999; Theall-Honey & Schmidt, 2006) markers associated with heightened limbic arousal across the lifespan. Behaviourally, these children exhibit quiet, restrained and overly cautious styles of responding to novel social situations (e.g., Rubin, Burgess, & Hastings, 2002). Even a brief overview of the literature on temperamental shyness suggests the operation of biological constraints on the experience and expression of social anxiety –a subset of children enter the social arena predisposed to respond in fearful ways.

Heritability studies reinforce the hypothesis that there is a considerable genetic contribution to social phobias (e.g., DiLalla, Kagan, & Reznick, 1994; Kendler, Karkowski, & Prescott, 1999), although precise gene linkage attempts have been elusive thus far. For example, the heritability estimate for social phobia is around 51% according to large epidemiological samples (e.g., Kendler et al., 1999). The inherited quality appears to be a predisposition to exhibit fearfulness towards novel social situations, rather than fully developed social anxiety disorder per se (Kendler et al., 1999; Stein, 1998). As with the majority of complex phenotypic expressions, genes do not operate in isolation but are continuously intertwined with environmental inputs that operate throughout ontogeny (Segalowitz & Schmidt, 2008). Compared to agoraphobia on the one end (with the highest heritability estimates) and specific phobias on the other (with the lowest heritability), social phobias seem to be characterized by comparable contributions from

genetics and unique person-specific experiences (Kendler, Neale, Kessler, Heath, & Eaves, 1992).

When examining early precursors to severe forms of adolescent and adult social anxiety, it is important to consider the concept of equifinality (Cicchetti & Rogosch, 1996) which postulates that identical clinical outcomes could result from multiple originating pathways. There is more than one way of becoming a socially anxious individual. Recent findings from our laboratory indicate that social anxiety in adulthood may be linked to adverse prenatal influences as indexed by proxy markers of low birth weight and/or prematurity (Schmidt et al., 2008). Ultimately, it may be discovered that the different etiological pathways towards the development of social anxiety share common molecular mechanisms, potentially involving early overexposure to glucorticoid hormones that are known to have organizational effects on amygdalar excitability[6] (Takahashi & Kalin, 1999).

1.3 Studies with Adults

The psychophysiological correlates of social anxiety in adults can be profitably studied by recording biological responses under a variety of different paradigms: (i) during periods of rest and relaxed wakefulness, (ii) during the completion of more controlled laboratory tasks designed to capture specific components of affective

[6]Here, it is interesting to note that some of the relevant preclinical models (e.g., variable foraging demands in primates, handling in rodents) that result in socially inhibited phenotypes also involve dysregulation of the limbic hypothalamic-pituitary-adrenal axis, including perturbed corticotrophin-releasing factor (CRF) signalling in amygdalar circuits.

processing (e.g., viewing of threatening faces), and/or (iii) during periods of acute symptom provocation induced by the anticipation of an actual or simulated social interaction (e.g., public speech in front of a panel of judges). A large number of social anxiety studies employing one or more of the above paradigms are summarized in Table 1 and a summary of selected findings is provided below. Other studies that have involved the administration of pharmacological probes and/or indices of peripheral markers will not be reviewed in the present chapter and are covered elsewhere (e.g., Brunello et al., 2000; Mathew, Coplan, & Gorman, 2001).

Table 1.1: Summary of existing studies on the neural correlates of social anxiety

Reference	**Paradigm**	**Method**	**Principal Findings (related to social anxiety)**
Hahn et al. (2011)	Resting/Functional	fMRI	Decreased functional coupling of left amygdala with medial prefrontal cortex and posterior cingulate; reduced connectivity between medial prefrontal cortex and the anterior cingulate.
Liao et al. (2010a)	Resting/Functional	fMRI	Decreased connectivity in somatomotor and visual networks; increased in a network including the medial prefrontal cortex; both increases and decreases in the default mode network, dorsal attention network and the core network.
Liao et al. (2010b)	Resting/Functional	fMRI	Decreased directed influence from inferior temporal gyrus to amygdala and bidirectional amygdala/visual cortex increased.
Phan et al. (2005)	Resting/Functional	MRS	Increased glutamate (relative to creatine) levels in the anterior cingulate cortex.
Potts et al. (1994)	Resting/Structural	MRI	No group differences in total cerebral, caudate, putamen, and thalamic volumes; age-related reduction in putamen volumes observed in social phobics, but not controls.
Schmidt (1999)	Resting/Functional	EEG	Shyness associated with greater relative right frontal EEG activity; sociability associated with greater relative left frontal EEG activity.

Schneier et al. (2000)	Resting/Functional	SPECT	Reduced mean dopamine D_2 receptor binding potential in the striatum.
Tiihonen et al. (1997)	Resting/Functional	SPECT	Lower striatal dopamine reuptake site densities.
Warwick et al. (2008)	Resting/Functional	SPECT	Increased perfusion in the frontal cortex and right cerebellum, decreased perfusion in pons, left cerebellum and right precuneus.
Ahs et al. (2009)	Provocation	PET + ECG	Positive correlations between stress induced regional cerebral blood flow in right supra genual anterior cingulate, right head of caudate nucleus, bilateral medial prefrontal cortex and high frequency heart rate variability.
Ahs et al. (2006)	Provocation	PET	Positive correlations between stress induced cortisol and blood flow in hypothalamus; negative correlations with the medial prefrontal cortex and motor/premotor cortices.
Beaton et al. (2008)	Provocation	EEG	No group differences in resting or reactive frontal brain electrical activity; controlling for depression reveals association between right frontal resting activity and shyness.
Davidson et al. (2000)	Provocation	EEG + ECG	Stress induced increase in right-sided activation in the anterior temporal and lateral prefrontal scalp regions, along with elevated heart rate.
Furmark et al. (2002)	Provocation	PET	Treatment associated reductions of stress induced regional cerebral blood flow in bilateral amygdalae, hippocampus, periamygdaloid, rhinal and parahippocampal cortices. Degree of amygdalar-limbic attenuation associated with clinical improvements one year later.
Guyer et al. (2008)	Provocation	fMRI	Greater amygdala activation, and positive functional connectivity with ventrolateral prefrontal cortex, when anticipating evaluation from peers previously rated as undesired for interaction.
Lorberbaum et al. (2004)	Provocation	fMRI	Greater stress induced subcortical, limbic, and lateral paralimbic activity; less cortical activity in the dorsal anterior cingulate/prefrontal cortex.
Miskovic et al. (in press)	Provocation	EEG	Significant reductions in slow/fast EEG cross-frequency coupling following group cognitive behavioral therapy for social anxiety.

Miskovic et al. (2010)	Provocation	EEG + ECG	Greater stress induced slow/fast EEG cross-frequency coupling in the right midfrontal region; no heart rate differences.
Tillfors et al. (2002)	Provocation	PET	Greater regional cerebral blood flow within the right dorsolateral prefrontal cortex, left inferior temporal cortex and left amygaloid-hippocampal region during public speech anticipation.
Tillfors et al. (2001)	Provocation	PET	Greater regional cerebral blood flow in the amygdaloid complex accompanied by decreased cortical blood flow (orbitofrontal and insular cortex, temporal pole) during public versus private speaking.
van Ameringen et al. (2004)	Provocation	PET	Significant stress induced deactivations in the right lingual gyrus and right medial frontal gyrus.
Amir et al. (2005)	Face viewing	fMRI	Increased anterior cingulate cortex activity during processing of disgust (versus neutral) faces.
Beaton et al. (2010)	Face viewing	fMRI	Heightened neural activation across a range of brain regions during implicit processing of emotional (versus neutral) faces.
Beaton et al. (2009)	Face viewing	fMRI	Less bilateral activation in the fusiform face area during processing of strangers' neutral faces, but greater activation during processing of personally familiar faces.
Beaton et al. (2008)	Face viewing	fMRI	Greater bilateral amygdala activation during the presentation of stranger faces and greater left amygdala activation during processing of personally familiar faces.
Birbaumer et al. (1998)	Face viewing	fMRI	Selective amygdala activation during passive viewing of neutral faces.
Blair et al. (2008)	Face viewing	fMRI	Increased amygdala activation for fearful (versus neutral) faces; presence of generalized anxiety abolishes the effect.
Cooney et al. (2006)	Face viewing	fMRI	Increased left (rather than right) amygdala activity during processing of neutral faces.
Danti et al. (2010)	Face viewing	fMRI	Altered patterns of functional connectivity across brain regions within the core and the extended systems for face perception and the default mode network.
Evans et al. (2008)	Face viewing	fMRI	Enhanced right amygdala activation for angry (relative to neutral)

			schematic line drawing faces.
Furmark et al. (2005)	Face viewing	PET	Increased left amygdala activation for angry (versus neutral) faces in both anxious and non-anxious groups; serotonin transporter allelic variation explained more variance than diagnosis.
Gentili et al. (2009)	Face viewing	fMRI	Lower deactivation in network of precuneus and posterior cingulate regions during viewing of faces (versus scrambled visual stimuli).
Gentili et al. (2008)	Face viewing	fMRI	Increased activity in left amygdala, insula, bilateral superior temporal sulcus and weaker activation in the left fusiform gyrus, left dorsolateral prefrontal cortex, and bilateral intraparietal sulcus during viewing of faces (versus scrambled visual stimuli).
Goldin et al. (2009)	Face viewing	fMRI	Increased activity in multiple emotion-related regions (medial orbitofrontal cortex, subgenual anterior cingulate, bilateral hippocampal gyri) during viewing of harsh faces (relative to neutral scenes), but not physical threat scenes.
Jetha et al. (in press)	Face viewing	ERP	Faster latency of P1 responses for fearful (versus angry, happy, neutral) faces; smaller P1 amplitude for fearful (versus neutral) faces.
Kolassa & Miltner (2006)	Face viewing	ERP	Greater right-temporoparietal N170 component during angry face processing. Social fears associated with higher P1 amplitudes for angry faces.
McTeague et al. (2011)	Face viewing	SSVEP	Sustained amplitude enhancement for occipital evoked potentials during viewing of emotional (relative to neutral) faces.
Moser et al. (2008)	Face viewing	ERP	Negative face bias indicated by the parietally maximal attention- and memory-related P3/late positive potential.
Mueller et al. (2009)	Face viewing	ERP	Enhanced amplitude of early sensory component (P1) for angry-neutral than happy-neutral pairs; increased fusiform gyrus activation for angry-neutral pairs; better behavioural performance for angry-neutral than happy-neutral pairs and shorter reaction times for probes replacing angry versus happy faces.

Mühlberger et al. (2009)	Face viewing	ERP	Enhanced emotional modulation of the early posterior negativity in response to fearful and angry facial expressions (for both natural and artificial faces). Late positive potential elevated for both emotional and neutral faces.
Phan et al. (2006)	Face viewing	fMRI	Greater amygdala activation in response to harsh (versus happy) faces; strength of amygdala activation positively related to social anxiety severity.
Schwartz et al. (2003)	Face viewing	fMRI	Greater bilateral amygdala activation for novel (versus familiar) faces among adults previously categorized as temperamentally shy.
Shah et al. (2009)	Face viewing	fMRI	Enhanced bilateral amygdala activation to negative (versus neutral) images; strength of amygdala activation positively related to social anxiety severity.
Stein et al. (2002)	Face viewing	fMRI	Enhanced activation of the left allocortex (amygdala, uncus, and parahippocampal gyrus) during viewing of contemptuous (versus happy) and angry (versus happy) faces.
Straube et al. (2005)	Face viewing	fMRI	Increased activation of extrastriate visual cortex regardless of facial expression; angry (versus happy or neutral) faces produced more insular activation; both angry and happy faces led to more amygdala activation.
Straube et al. (2004)	Face viewing	fMRI	Greater insular responses to angry (versus neutral) faces in both explicit and implicit task modes; greater amygdala, parahippocampal gyrus, and extrastriate visual cortex activation to angry (versus neutral) faces during implicit task mode only.
Wieser et al. (2010)	Face viewing	SSVEP	Angry (relative to neutral and happy) faces associated with electrocortical facilitation over visual regions.
Yoon et al. (2010)	Face viewing	fMRI	Greater bilateral amygdala activation to high versus low intensity of emotional faces (angry, fearful, disgusted, sad, happy).

Note: Abbreviations (ECG, electrocardiogram; EEG, electroencephalogram; ERP, event-related potential; fMRI, functional magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single photon emission computed tomography; SSVEP, steady state visual evoked potential).

Resting Activity Because resting conditions are often employed for purposes of computing task reactivity difference scores, relatively few studies have directly examined the links between spontaneous brain activity and social anxiety. Several studies from our laboratory (Beaton, Schmidt, Ashbaugh, Santesso, Antony, & McCabe, 2008; Schmidt, 1999) have noted a relation between social anxiety (in the nonclinical range) and greater relative EEG activation of the right PFC region at rest. As already mentioned, such a pattern of frontal brain activity is associated with poor regulation of limbic arousal (see Section I) and appears among temperamentally shy infants and children (see Section II). Recently, our research group (unpublished data) has demonstrated that resting frontal brain electrical asymmetry remains stable across time in patients with social anxiety disorder.

The past decade has heralded a "paradigm shift" in the PET/fMRI neuroimaging field, with a resurgence of interest in studying the functional significance of spontaneous brain activity in normal and pathological states (Zhang & Raichle, 2010). Large-scale brain networks typically exhibit organized patterns of connectivity at rest that appear to be selectively perturbed in patients with social phobia (Liao et al., 2010a) as reflected in decreased functional connectivity within some networks (somatomotor and visual), but increased connectivity in others (default mode and dorsal attention networks). A recent study employed sophisticated data processing methods that rely on temporal precedence cues to infer directed interactions between distributed brain regions during relaxed wakefulness (Liao et al., 2010b). The findings suggested that socially phobic patients exhibit increased directed influences deriving from the amygdala and impinging onto the

visual cortices as well as decreased regulatory influences from several neocortical regions, including the frontal cortex, to the amygdala. Abnormalities of functional connectivity between the frontal cortex and the amygdala have been replicated by others (Hahn et al., 2011) indicating that this a relatively consistent brain profile. An implication of the recent fMRI connectivity findings is that socially anxious individuals show disinhibition of emotionally reactive centers and are predisposed to detect threat in their social environments.

Other studies have employed resting brain measurements to examine structural or neurochemical differences between high and low socially anxious populations. Potts and colleagues (1994) found no evidence of structural abnormalities in patients diagnosed with social anxiety disorder, although they did observe an age-related decline of putamen brain volume in the patient group. Neurochemical imaging has demonstrated reduced levels of dopamine D_2 receptor binding in the striatum of patients with social anxiety disorder (Schneier, Liebowitz, Abi-Dargham, Zea-Ponce, Lin, & Laruelle, 2000), as well as fewer dopamine reuptake site densities (Tiihonen, Kuikka, Bergstrom, Lepola, Koponen, & Leinonen, 1997).

Cognitive Activation Since angry facial expressions signal negative evaluation and represent the prototypical stimulus for activating the social submissiveness system (Öhman, 1986, 2009), numerous social anxiety studies have examined the neurocognitive correlates of threat-related processing using visual stimuli (see Staugaard, 2010, for a comprehensive review). Neuroimaging data indicate that adults with SAD show enhanced amygdala (and often insular) activity in response to hostile and contemptuous

faces (Stein, Goldin, Sareen, Zorrilla, & Brown, 2002; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004). Moreover, the magnitude of amygdala activation to threatening faces is positively related specifically to the severity of social – not generalized – anxiety (Phan, Fitzgerald, Nathan, & Tancer, 2006). Amygdala hyperresponsivity to angry expressions persists in socially anxious individuals when processing schematic (i.e., line drawing) faces where the confounding effects of gender, age and race are eliminated (Evans, Wright, Wedig, Gold, Pollack, & Rauch, 2008).

Electrocortical studies have largely corroborated findings of increased reactivity to threatening faces among clinical and sub-syndromal socially anxious populations (Kolassa & Miltner, 2006; Moser, Huppert, Duval, & Simons, 2008; Mühlberger, Wieser, Herrmann, Weyers, Troger, & Pauli, 2009; Wieser, McTeague, & Keil, 2010), with uncertainty as to whether the early or late stages of visual processing are affected.

Other evidence indicates that socially anxious individuals show hyper-reactivity of amygdala nuclei even in response to neutral faces (Birbaumer et al., 1998; Cooney, Atlas, Joorman, Eugene, & Gotlib, 2006). An fMRI study from our research group (Beaton, Schmidt, Schulkin, Antony, Swinson, & Hall, 2008) showed that adults selected for shyness and social anxiety exhibit greater amygdalar activation when viewing strangers' neutral faces. Indeed, left amygdala activation in the high compared to the low shy group persisted during the viewing personally familiar faces. Taken together, these findings suggest that social anxiety is associated with heightened responses of a threat-evaluative system in situations that could be classified as interpersonally 'ambiguous'; social scenarios that might be perceived as relatively innocuous by non-anxious

individuals are perceived by socially anxious individuals as replete with potential for harm. This latter interpretation is consistent with predictions derived from cognitive models (Mathews & Mackintosh, 1998) that individual differences in anxiety level increase the strength of activation for threat-related attributes during stimulus processing.

Acute Symptom Provocation Experimental designs that involve anticipation of or direct confrontation with a feared event (e.g., public speaking in socially anxious populations) allow the researcher to examine the psychophysiological correlates of anxiety "in the moment".

Evidence derived from nuclear and magnetic imaging of socially anxious populations shows that anticipation of public speaking is consistently associated with hyper-activity in subcortical/limbic regions (amygdala, insula) related to threat processing (Furmark et al., 2002; Lorberbaum et al., 2004; Tillfors, Furmark, Marteinsdottir, & Fredrikson, 2002). Increased right prefrontal cortex perfusion during speech anticipation was observed in one PET study (Tillfors et al., 2002), which is also supported by EEG findings of greater relative right cortical activation (Davidson, Marshall, Tomarken, & Henriques, 2000; but see Beaton et al., 2008, for null findings in a non-clinical sample).

A PET study that examined patterns of brain activation during public versus private speaking (as opposed to during anticipatory periods) replicated exaggerated amygdala responses in socially phobic patients, combined with reduced blood flow in multiple neocortical regions (Tillfors et al., 2001). The authors interpreted their findings to imply that an evaluative interpersonal situation leads to engagement of

phylogenetically older 'alarm' systems in socially phobic individuals, while non-anxious individuals engage a phylogenetically newer assembly of brain regions associated with higher-level cognitive/analytic processes, allowing them to remain calm and focused in the identical context.

Summary Across the majority of studies reviewed in this section the most consistent brain-based correlate of social anxiety is amygdala hyperexcitability, accompanied by over-responsiveness to social threat cues. This conclusion is strengthened by two recent formal meta-analyses (Etkin & Wager, 2007; Freitas-Ferrari et al., 2010). Unfortunately, the resolution of contemporary PET and low-field fMRI[7] imaging precludes the possibility of discriminating activations in individual amygdaloid nuclei (e.g., basolateral versus central divisions) and testing more refined theoretical hypotheses. Studies of human social anxiety are therefore confined, for the time being, to making broad statements about the excitability of a functionally heterogenous complex of amygdaloid nuclei. It is also worth noting that the psychophysiological correlates reviewed here appear to be very similar regardless of whether the study samples involved clinically diagnosed patients or adults selected from the extreme ends of the normal population reinforcing the suggestion that SAD can be viewed as a dimensional – rather than a categorical – disorder, that exists on a continuum of severity.

Given the multifaceted roles that the amygdala plays vis-à-vis affective functions (Phelps & LeDoux, 2005), especially its important role in primate social cognition

[7]More general differentiation between ventral and dorsal activations is possible. High-field fMRI protocols could potentially provide greater spatial resolution, but to date, have failed to generate more insight into the neurobiology of social anxiety. The activation of more medial affective brain structures, such as the hypothalamus and brainstem nuclei (e.g., periaqueductal gray) can also be difficult to resolve using current imaging techniques.

(Emery & Amaral, 2000), one may well wonder about the relative specificity of the amygdala findings to social anxiety. Although the majority of anxiety disorders may share a common pathophysiological mechanism involving exaggerated fear responses, there is some evidence for more subtle psychobiological differences between them. An obvious difference derives from the fact that each of the anxiety disorders is distinguished by a unique theme of concern. For example comorbidity of SAD and generalized anxiety disorder seems to mask the relation between social anxiety and amygdala hyperactivity for threatening faces, providing some support that these are two distinct disorders (Blair et al., 2008). As will be discussed in Chapter 6, unique learning experiences and conditioning may be what transforms a common biological profile (a hyperexcitable amygdala) into a specific anxiety disorder such as a social phobia, an animal phobia or panic disorder.

Future insights into the neurobiology of social anxiety are likely to be maximized by increasing the effort aimed at characterizing links between systems involved in processing social cues (e.g., threatening facial expressions) and the neurocircuits that are involved in fear and anxiety (Shin & Liberzon, 2010). Additionally, while SAD, specific phobias and post-traumatic stress disorders share in common a hyperexcitable amygdala, they likely differ in ways that become more obvious when considering extended patterns of co-activation in cortical and subcortical areas (Etkin & Wager, 2007). When attempting to carve anxiety disorders at the joints, increased insight comes from taking into account a range of cortico-cortical and cortico-subcortical interactions rather compared to studying individual component activations in isolation.

1.4 An Outline of Study

The set of studies collected here will attempt to examine the phenomenon of social anxiety by applying multiple experimental paradigms and utilizing a broad range of measures, including subjective and clinician-administered assessments, brain electrical activity (event-related and continuous) and simple behaviours. A schematic outline of the program of study is illustrated in Figure 1.3.

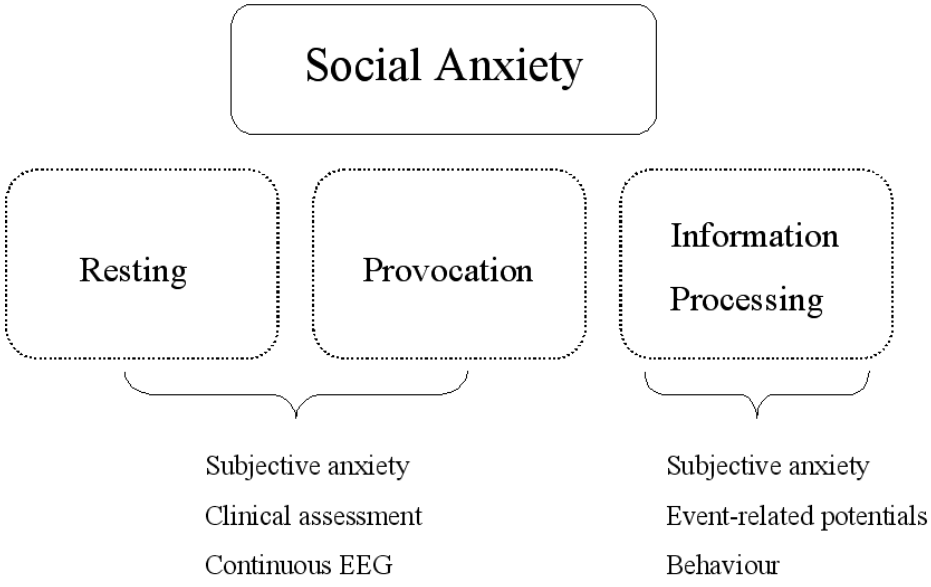

Figure 1.3: Multi-method approach to the study of social anxiety adopted in the present set of studies.

When considered individually, each of the study approaches carries both strengths and limitations. For example, acute symptom provocation mimics real life situations encountered by socially anxious individuals, but does not always permit researchers to make inferences about why socially anxious individuals react the way that they do under

conditions of evaluative threat. By contrast, controlled laboratory studies of information processing can generate new insights into precisely what aspects of affective information processing are perturbed in social anxiety, but these insights are sometimes gained at the expense of ecological validity. A combination of all of the aforementioned paradigms may provide the most in terms of illuminating the many functional domains impacted by social anxiety.

The initial studies (Chapters 2 to 4) relied on non-clinical samples of adults who were selected for high and low social anxiety from a large population of undergraduate students. The studies described in Chapters 2 and 3 relied on event-related brain potentials to index distinct aspects of perceptual processing in tasks that manipulated stimulus novelty in socio-emotional (e.g., rare affective faces) and affectively neutral contexts (e.g., rare geometric shapes). The aim of those studies was to provide a more fine-grained characterization of the information processing stages that are biased in socially anxious individuals and to examine the relative content specificity of the biases. Chapter 4 measured reaction times in a selective attention task that independently varied both the temporal and energetic aspects of affective stimulus delivery in order to extend prior literature and provide convergent evidence into how affective information processing is perturbed in social anxiety. In particular, a chief aim of Chapter 4 was to examine whether there are simple behavioural (reaction time) differences between high and low socially anxious individuals when processing social threat signals under conditions of stimulus competition.

The final study described in Chapter 5 employed a novel method of measuring continuous EEG signals in order to examine large-scale aspects of brain activity during rest and symptom provocation in a group of patients diagnosed with generalized SAD. The aim of this study was to examine, for the first time, whether there are treatment-related changes in an EEG measure that putatively indexes communication across different (cortical and subcortical) neuronal systems. The patients were undergoing 12-weekly sessions of group cognitive behavioural therapy for their anxiety and received EEG assessments at four separate testing periods. Since SAD is estimated to be grossly under-treated in the clinic (Cuthbert, 2002), having a potential brain-based correlate of standardized treatment has several important theoretical and practical implications.

A brief overview of the different psychophysiological measures used in this set of studies is provided below.

1.5 Psychophysiological Methods

Event-Related Potentials Event-related potentials (ERPs) were employed as a key psychophysiological measure in the present set of studies in order to examine the ways in which perceptual processing of social and non-social forms of novelty is altered among socially anxious individuals. ERPs consist of minute voltage fluctuations that are derived from the ongoing EEG signal trace by averaging multiple stimulus-locked data segments[8]. Signal averaging leads to a preservation of the time and phase-locked oscillations (stimulus evoked brain responses) while cancelling out the background EEG

[8]ERPs can also be response-locked, but these types of ERP waveforms are not of interest here.

that is assumed to have a random phase distribution with regard to event onset. In its most simple interpretation, positive and negative deflections in the resultant Voltage x Time function are referred to as ERP components, each of which has a specific functional significance and is further characterized by its unique latency and scalp topography. A chief advantage of ERPs is that they provide millisecond temporal resolution of stimulus-evoked brain responses. The contribution of ERPs to the present set of studies relies on their ability to provide a continuous index of information processing at several distinct stages. The components that are of particular interest here are those that have been associated with early sensory-perceptual encoding on the one hand and others associated with controlled stimulus processing and working memory representation (Schupp, Flaisch, Stockburger, & Junghofer, 2006). The quantification of these neural components allows for more accurate characterization of threat-related processing biases in adults with high social anxiety. Figure 1.4 illustrates the basic principles of ERP measurement.

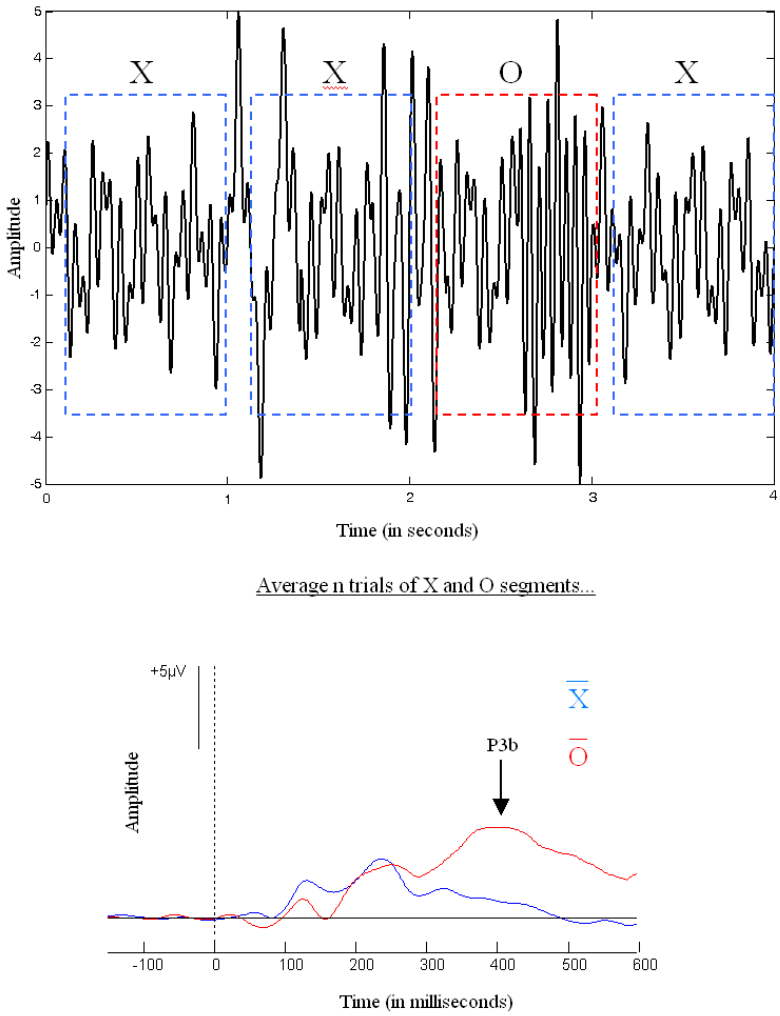

Figure 1.4: Basics of event-related brain potential measurement, beginning with stimulus-locked raw EEG traces (top) and ending with the averaged Voltage x Time function (bottom). The black arrow in the bottom panel highlights the so-called P3b wave, a large positive voltage deflection produced in response to target stimuli.

Continuous EEG As previously mentioned, emotions are likely to involve widespread interactions between cortical and subcortical systems. However, the majority of neuroimaging studies of emotion, to date, have focused almost exclusively on

regionally occurring group and/or condition differences. One way to study communication between different neuronal systems is by applying novel cross-frequency approaches to the analysis of EEG signals (Young & Eggermont, 2009). For example, measuring the strength of correlations between the amount of spectral power residing in slow and fast EEG frequency bands provides some sensitivity to gross changes in the amount of cortico-subcortical interaction (Knyazev & Slobodskaya, 2003; Schutter, Leitner, Kenemans, & van Honk, 2006).

Slow neuronal oscillations (in the δ frequency range) primarily reflect the arousal of phylogenetically older, subcortical regions while fast electrical rhythms (in the β and γ range) relate mostly to activities of the neocortex (Knyazev, 2007; Uhlhaas & Singer, 2006). When the amount of spectral power generated in the slow and fast frequency bands becomes positively correlated, it is hypothesized to reflect a state of increased cortico-subcortical information transfer (Schutter et al., 2006) and heightened anxiety (Knyazev, Schutter, & van Honk, 2006).

We (Miskovic & Schmidt, 2009) and others (Schutter & van Honk, 2004, 2005; van Peer, Roelofs, & Spinhoven, 2008) have shown that EEG cross-frequency power interactions are affected in predictable ways by natural and synthetic steroid hormones (cortisol and testosterone) that are differentially associated with anxiogenic and anxiolytic properties and exhibit functional antagonism between one another (Viau, 2002).

Cortisol (the end product of the hypothalamic-pituitary adrenal axis) predicts high positive δ/β correlations while testosterone (the end product of the hypothalamic-

pituitary-gonadal axis) predicts decoupling of EEG δ/β spectral power. Converging evidence concerning the role that steroid hormones like testosterone play in regulating cortico-subcortical interactions has come from the application of fMRI methodology (van Wingen, Mattern, Verkes, Buitelaar, & Fernandez, 2010), which has superior spatial resolution to EEG recordings derived from the scalp.

In one recent study, we demonstrated that when adults who were selected for high social anxiety anticipated the performance of a public speech, they showed enhanced amounts of positively correlated power between the slow and fast EEG frequencies compared to low anxious participants (Miskovic, Ashbaugh, Santesso, McCabe, Antony, & Schmidt, 2010). The neural signatures agreed with self-report measures derived from the same participants, who indicated greater anxiety during anticipation of the public speech compared to their low anxious counterparts. Although speculative, the EEG results may indicate that part of the increased cortico-subcortical communication observed in high socially anxious individuals during symptom provocation is associated with enhanced bottom-up transmission of threat-related signals, conveyed by subcortical regions to the neocortex (van Honk, Harmon-Jones, Morgan, & Schutter, 2010). This latter hypothesis has been supported, most recently, by a study demonstrating a direct link between high positive δ/β coupling and selective attention to threat (Putman, 2011). Chapter 5 will examine whether this measure of EEG cross-frequency coupling is sensitive to standardized treatment for social anxiety disorder and whether the metric can be used as a putative neural correlate of treatment-related effects.

The perspective adopted in this chapter is that the experience and expression of social anxiety manifests itself on a sliding continuum that can range in intensity from relatively mild to severely disabling. The dysfunctional aspects of social anxiety may be traced to a hyperexcitability of core fear and regulatory circuits, especially those involving prefrontal-amygdala interactions – the same neurobiological substrates may be involved in the elaboration of social submissiveness behaviours observed among the higher primates (Öhman, 1986, 2009).

As this chapter has hopefully illustrated, fruitful research on the psychophysiology of social anxiety involves the integration of multiple experimental paradigms and methods. The set of studies collected here will seek to obtain converging evidence about the pathogenic mechanisms underlying social anxiety, on the basis of task-related neural processing, behavioural indices of selective attention as well as measures of continuous brain electrical activity, self-report and clinician derived measures.

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Chapter 2

Abstract

While previous work has shown that social anxiety is associated with heightened responses to socially threatening stimuli, little is known about the temporal dynamics of processing biases or how they unfold in response to fluctuating socio-emotional contexts. This study recorded event-related cortical electrophysiology while high and low socially anxious individuals performed a three-stimulus oddball experiment that involved repetitive presentations of a neutral face (probability = 80%) combined with rare emotional faces (threatening and friendly; probability 10% per expression). Analyses focused on two broad components of the electrocortical response: (i) a relative negative voltage shift over the occipito-temporal cortex in an early processing stage (240 to 280 msec post-stimulus), associated with affective salience detection and (ii) a midline distributed cortical positivity that onsets roughly 300 msec. post-stimulus onset and is associated with sustained attentional processing and memory-encoding. Results showed that the early negative potential over secondary visual cortex was slightly enhanced among high socially anxious adults when detecting contextually novel threatening faces. No differences emerged in the electrocortical signatures associated with later, controlled processing stages. Findings suggest that high socially anxious adults are hyperresponsive to threat-related changes in socio-emotional contexts, at least at the early stages of information processing.

2.1 Introduction

The ability to detect change or discrepancy in the sensory environment is an adaptive phenomenon that is highly conserved across phylogeny[9] (Campbell, Wood, & McBride, 1997; Knight & Nakada, 1998; Sokolov, 1963). The most established way to study this aspect of selective attention involves the use of repetition-change (or oddball) experimental paradigms. The oddball paradigm, in its simplest formulation, consists of presenting a repetitive stimulus train that is infrequently punctuated by presentation of an anomalous stimulus, called the "oddball" (Knight & Nakada, 1998; Sokolov, 1963). The anomalous, low probability stimulus may or may not require a response on the part of the experimental subject or participant.

The majority of neuroscience studies that have explored change detection and orienting phenomena have relied on tracking low-level sensory inputs, such as pure auditory tones that differ in frequency or high contrast visual patterns. Few studies have examined neural responses to change in more complex, socially relevant stimuli like faces, despite the fact that changes of this sort carry considerable biological significance (Astikainen & Hietanen, 2009; Campanella, Gaspard, Debatisse, Bruyer, Crommelinck, & Guerit, 2002; Susac, Ilmoniemi, Pihko, & Supek, 2004; Zhao & Li, 2006). Facial expressions of emotion have communicatory functions that can rapidly transmit vital information[10] about the valence of objects and situations to observers (Adolphs, 2003;

[9]Even the relatively 'simple' nervous system of the nematode worm, *C. elegans*, orchestrates reflexive responses to abrupt changes in its sensorimotor input (Kagan, 2002).

[10]The information conveyed by facial expressions of emotion is just as important (or even more so) as the information conveyed by the kinds of highly controlled stimuli employed in traditional studies of orienting. The distinct kinds of information that can be conveyed by emotional expressions appear to be mirrored at

Blair, 2003). Some expressions, such as disgust, serve primarily to signal information about the contamination of physicochemical substances in the environment, while others, such as anger, serve as prototypical stimuli of social transgression and negative evaluation (Öhman, 1986, 2009). Expressions of the latter sort – namely those that communicate information about one's social standing – gain prominence in higher primates and especially in humans, where safety concerns are increasingly defined with respect to other conspecifics rather than merely elements of the physical world. The detection of change that is embedded within a socio-emotional environment (e.g., an expression changing from a neutral to a threatening or friendly one) is a salient event. Attentional processing of socially relevant changes is likely to be implicated in the origins and maintenance of social anxiety, since socially anxious individuals are hypersensitive to changes in others' approval, especially in cases where a partner's expression in an interaction shifts from neutral to threatening. However, the psychophysiological studies of threat-related processing in social anxiety that were reviewed in the first chapter have mostly measured biological responses under conditions of passive face viewing, where the probability of threatening and neutral expressions remains constant.

The purpose of the present study was to examine how the brains of high and low socially anxious adults respond to sensory changes that are embedded within a socio-emotional context. To this end, event-related cortical electrophysiology was recorded during a modified three-stimulus visual oddball sequence that involved a frequent,

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the level of distinct neurotransmitters and circuits that are involved in processing different expressions (Blair, 2003).

repetitive presentation of a neutral face interspersed with rare presentations of threatening and friendly faces.

Event-Related Brain Potential Measures of Affective Information Processing

Two ERP indices of affective information processing were of special interest to this study: an early posterior negativity recorded over the extrastriate visual cortex, and a later occurring P3b/late positive complex recorded over posterior parietal sites. The unique involvement of the aforementioned ERP components in emotion and attention processing is attested to by a large ERP literature (see Schupp, Flaisch, Stockburger, & Junghöfer, 2006, for a review) as well as recent evidence from data-driven principal component approaches to ERP analysis (Foti, Hajcak, & Dien, 2009).

Early Posterior Negativity Several studies have documented increased amplitude of a relative negative-going waveform recorded over temporo-occipital cortex during the presentation of infrequent, low probability emotional expressions (Astikainen & Hietanen, 2009; Campanella et al., 2002; Zhao & Li, 2006). Although there is variance across studies, this neural response seems to appear *ca*. 200 ms and can be sustained up to 320 ms post-stimulus onset[11]. The negative potential over the posterior scalp is most clearly observed by computing a difference waveform that subtracts potentials evoked by a frequent stimulus (e.g., a neutral face) from those evoked by a rare item (e.g., an angry face). A relative negativity with a similar time course and scalp distribution is also observed when participants are selecting a specific (non-affective)

[11]A somewhat earlier (120 to 160 ms) visual mismatch negativity over posterior recording sites has been reported in studies that assessed ERPs sensitive to preattentive detection of change in lower-level visual categories such as colour, motion direction, orientation, and spatial frequency (Czigler, 2007; Pazo-Alvarez, Cadaveira, & Amenedo, 2003).

target from a complex visual array (Potts & Tucker, 2001) or when performing explicit categorization of natural scenes (Codispoti, Ferrari, Junghöfer, & Schupp, 2006). Similarly, the passive viewing of emotional compared to neutral images (where the probability of each is balanced) is associated with an enhanced early posterior negativity during rapid (Junghöfer et al., 2001) and prolonged (Schupp et al., 2003) presentations. An enhanced posterior negativity is also observed when viewing affective faces (Lee et al., 2009; Marinkovic & Halgren, 1999; Sato, Kochiyama, Yoshikawa, & Matsumura, 2001; Schupp, Öhman, Junghöfer, Weike, Stockburger, & Hamm, 2004) and symbolic emotional gestures (Flaisch, Häcker, Renner, & Schupp, 2011).

One potential interpretation of these disparate findings is that the posterior negativity in the 200 to 300 ms interval corresponds to the outcome of a process by which certain stimuli (e.g., those that are spatially or temporally unexpected, emotionally engaging and/or relevant to the performance of an experimental task) are selected for additional processing (Schupp et al., 2006). The hypothesis that the emotion-related amplitude modulation of the early posterior component corresponds to increased visual information processing is supported by results from source analyses, suggesting the involvement of occipito-temporo-parietal areas in the generation of this ERP signature (Junghöfer et al., 2001; Schupp, Stockburger, Codispoti, Junghöfer, Weike, & Hamm, 2006). Similarly, the increased posterior negativity that is observed during the feature-based selection of low-level (non-affective) visual stimuli reflects the activation of neural generators in the ventral ("object-based") regions of the extrastriate cortex (Martinez, Di Russo, Anllo-Vento, & Hillyard, 2001).

P3b/Late Positive Complex The P3b/late positive complex is a posterior parietal midline component that onsets *ca*. 300 ms post-stimulus and may persist up to 600 ms or longer (see Sutton, Braren, Zubin, & John, 1965, for the original description of this ERP component). The P3b waveform is one of the most studied ERP responses in the selective attention literature, and yet there is still no consensus in the field about precisely what neurocognitive operation is reflected by this component (Luck, 2005). The P3b brain electric response is consistently observed in oddball and target detection paradigms (Friedman, Cycowicz, & Gaeta, 2001; Polich, 2007) and is found not only in humans, but also in rats, cats, rabbits, dolphins, and monkeys (Knight & Nakada, 1998). The most tractable current hypothesis is that this waveform is related to stimulus integration into working memory, following an upstream call for increased processing resources (Friedmanet al., 2001; Polich, 2007). Evidence from source localization, intracranial recordings, functional neuroimaging and brain lesion studies indicates that the P3b is generated by a distributed neuroelectric circuit that involves multi-modal parieto-temporal regions as well as the hippocampal/parahippocampal, anterior cingulate, and insular areas (Herrmann & Knight, 2001; Knight & Nakada, 1998; Ranganath & Rainer, 2003). In addition, the P3b that is recorded over parietal regions may result, in part, from long distance cortico-cortical interactions with the prefrontal cortex (Polich, 2007; Ranganath & Rainer, 2003).

In humans, a cortical positivity with a similar topography and latency to the P3b is observed during the passive viewing of emotional images (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Hajcak, MacNamara, & Olvet, 2010), including faces

(Liddell, Williams, Rathjen, Shevrin, & Gordon, 2007; Schupp et al., 2004), suggesting that affectively salient stimuli automatically recruit attentional and memory resources even in the absence of explicit task instructions (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Hajcak, MacNamara, & Olvet, 2010). The late cortical positivity engendered by the viewing of affective material seems to share similar neural generators as the P3b that is observed in traditional selective attention studies (e.g, Sabatinelli, Lang, Keil, & Bradley, 2002). The extent to which these multiple cortical positivities reflect independent neurocognitive modules is a subject of some empirical debate (Foti, Hajcak, & Dien, 2009; Hajcak, MacNamara, & Olvet, 2010). The approach adopted here will be to use the term late positive complex to encompass the broad family of brain evoked-potentials that relate to stimulus representation in working memory and sustained, elaborate processing that occurs following the early sensory-perceptual stages.

Some authors (Schupp et al., 2006) have considered the early posterior negativity and the subsequent broad cortical positivity within the context of a two-stage model of affective information processing (Öhman, 1986; Robinson, 1998). According to two-stage models, incoming stimuli first pass through a large capacity sensory-perceptual scanning stage, where items that are particularly salient are "tagged" for continued processing. In this case, the early posterior negativity, which corresponds to a boost in perceptual resources following an initial selection mechanism may represent an electrophysiological correlate of such a tag. One pathway that could potentially account for the initial sensory-perceptual amplification consists of the dense feedback projections from the amygdala to the extrastriate cortices (Amaral, 2002). A plausible function of

these reentrant anatomical connections is to prime cortically based representations of biologically significant stimuli[12]. Subsequently, items may pass into a second, capacity-limited stage that provides a gateway to working memory, conscious recognition and more elaborate processing operations. This second, post-perceptual stage is assumed to be indexed by the P3b/late positive complex whose amplitude varies with the extent to which a given stimulus receives sustained analysis. The hypothesis that the P3b response reflects a late, post-perceptual stage of information processing in the visual system is further supported by evidence from the attentional blink paradigm. The attentional blink refers to a phenomenon where the ability to consciously report the second of two visual targets is impaired when the preceding target is in close temporal proximity (e.g., occurring ~200 ms prior). Vogel and colleagues (1998) demonstrated that items falling within the putative "blink" elicit robust perceptual ERP components, but no P3b responses. The two-stage model offers a reasonable theoretical framework from which to generate further hypotheses about perturbations in the neurodynamics of threat-related processing among socially anxious populations.

Studies of Socially Anxious Populations Event-related potential studies of processing biases in social anxiety are surprisingly scarce. The majority of experiments to date have relied on evidence derived from other functional neuroimaging methods (fMRI, PET) with good spatial, but poor temporal, resolution (Staugaard, 2010). As a result, our understanding of the temporal course of threat-related processing biases in social anxiety remains poorly understood. However, such findings can play an important

[12]Recent evidence (Wendt, Weike, Lotze, & Hamm, 2011) suggests that this physiological pathway might be moderated by the relative novelty of the stimuli.

role in advancing models of anxiety-relevant pathology and informing issues concerning clinical treatment.

The first ERP study to employ an oddball paradigm with a non-clinical socially anxious population (Rossignol, Anselme, Vermeulen, Philippot, & Campanella, 2007) involved the frequent presentation of an emotional face (anger or disgust) with rare faces that either belonged to the same emotional category, but differed in intensity (within-trials) or belonged to a different category altogether (between-trials). The electrocortical results showed that high and low socially anxious individuals differed when processing both negative emotions as evidenced by negative-polarity shifts (N2b) recorded over the visual cortex roughly 250 ms post-stimulus. On within-trials, the high socially anxious group was more efficient in processing subtle changes in the expressed intensity of angry faces, whereas on between-trials they required more attentional resources to disengage from frequent angry faces and orient to disgust expressions.

In another recent study, Sewell and colleagues (2008) employed an oddball paradigm in which rare threatening (angry) and friendly (happy) faces were presented among frequent neutral faces. The authors discovered that social anxiety, within the normative range, first became associated with neural processing of threatening faces *ca*. 440 ms post-stimulus. Individuals scoring higher on a self-report measure of social anxiety showed greater P3b amplitudes for threatening faces in the 440 to 500 ms interval – an effect that disappeared when measuring responses to neutral-friendly changes and also, when the threatening faces were inverted, thereby disrupting perception of the threat.

Studies using alternate task paradigms have largely confirmed the hypothesis that threatening faces are processed by socially anxious individuals to a greater extent, but they have differed with respect to whether the locus of this anxiety-related effect lies in the late, post-perceptual stages (P3b/late positive complex; Moser et al., 2008[13]) and/or early, perceptual stages indexed by posterior sensory potentials (Kolassa & Miltner, 2006; Mueller, Hofmann, Santesso, Meuret, Bitran, & Pizzagalli, 2009; Mühlberger et al., 2009)[14]. However, none of these studies examined sensitivity to contextual change – in this regard, oddball paradigms may represent a more ecologically valid situation that better approximates real-world scenarios where the evaluative context remains in flux. Most daily social encounters consist of unexpected changes in evaluation (e.g., a rare threatening expression) that emerge against a more predictable background of neutral expressions.

Other Studies of Anxious Populations Late positive slow-wave potentials are reliably enhanced in small animal (spider and snake) phobics when processing their feared items, indicating that attentional biases are present at the post-perceptual stages of consolidation (Kolassa, Musiel, Mohr, Trippe, & Miltner, 2005; Kopp & Altmann, 2005; Michalowski, Melzig, Weike, Stockburger, Schupp, & Hamm, 2009; Miltner, Trippe, Krieschel, Gutberlet, Hecht, & Weiss, 2005; Trippe, Hewig, Heydel, Hecht, & Miltner, 2007). In addition, some studies find that processing biases emerge even at the sensory-

[13]Interestingly, the study by Moser and colleagues (2008) found that there were differences between high and low anxious groups in an earlier temporal window, but this consisted of a *lack* of a positive emotion bias displayed by the high socially anxious individuals, rather than the presence of a threat-related bias.
[14]Some of the reported relations between social anxiety and the early posterior potentials are not specific to threatening faces, but are evident across all affective face categories (Kolassa & Miltner, 2006; Mühlberger et al., 2009).

perceptual stages indexed by the early posterior negativity (Kopp & Altmann, 2005; Michalowski et al., 2009; Van Strien, Franken, & Huijding, 2009). Taken together, the evidence from these studies suggests that specific phobias are associated with persistent alterations in attentional functions, involving increased resource allocation to feared items, perhaps beginning within the early stages of the cortical processing stream and present during executively-controlled stages.

The Present Study The present study aimed to study the detection of novel, socially relevant changes in emotional expressions among a group of high and low socially anxious adults, with the aim of developing a finer characterization of biased processing. On the basis of the extant literature, several hypotheses were formulated. The first hypothesis was that high socially anxious adults would exhibit a greater increase in processing resources than low socially anxious adults when detecting a change in context from neutral to threatening. It was predicted that group differences would emerge at the sensory-perceptual stages of stimulus analysis (as indexed by an enhanced early posterior negativity) and would be sustained during later, more elaborate stages (as indexed by the P3b/late positive complex). A further hypothesis was that social anxiety would influence brain responses to rare threatening items differently, depending on whether those items were being actively attended (designated as targets) or not (designated as deviants). Differences between high and low socially anxious groups were expected to be particularly pronounced on trials where threatening faces were designated as deviants in line with previous neuroimaging work where social phobics are most reliably distinguished from non-anxious controls during task-irrelevant experimental

conditions (Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004). No specific predictions were made regarding group differences in neural responses to changes of context from neutral to friendly.

2.2 Method

Participant Demographics Participants were selected from 229 (*M* age = 19.21 years, range 17 to 31; 137 females, 92 males) undergraduates who completed the Social Phobia Inventory (SPIN; Connor et al., 2000). The SPIN threshold scores for inclusion into the high (> 30) and low (< 10) social anxiety groups were based on previous analyses of receiver operating characteristic curves (Connor et al., 2000). In total, 20 high (*M* age = 20.68 years, range = 18 to 31; 12 females, 8 males) and 18 low (*M* age = 19.44 years, range = 18 to 22; 10 females, 8 males) socially anxious participants were successfully recruited for the laboratory portion of the study. All of the participants reported normal or corrected-to-normal vision.

Self-Report Measures

Social Phobia Inventory (SPIN; Connor, Davidson, Churchill, Sherwood, Foa, & Weisler, 2000). The SPIN is a 17-item self-report measure of fear, avoidance, and physiological symptoms associated with social anxiety. In a clinical sample of people with social phobia, the SPIN has demonstrated strong psychometric qualities, including test-retest reliability, internal consistency, convergent validity, discriminant validity, and construct validity (Connor et al., 2000). The Cronbach's αs for the present study were as follows: total $\alpha = 0.96$; fear subscale $\alpha = 0.91$; physiological arousal subscale $\alpha = 0.81$; avoidance subscale 0.92.

Beck Depression Inventory (BDI; Beck & Steer, 1987). The BDI is a 21-item self-report scale of current depressive symptomatology, with sound psychometric properties in non-psychiatric populations (Beck & Steer, 1987). We decided to include the BDI given evidence that attention biases among socially anxious adults might be confounded by concurrent dysphoria (Mogg & Bradley, 2002). The Cronbach's α for the BDI scale was 0.91.

Experimental Stimuli and Procedure Participants were seated in a dimly lit, sound attenuated room. All participants were positioned ~ 100 cm from the monitor screen (75 Hz vertical refresh rate). The visual stimuli were neutral, threatening (angry) and friendly (happy) pictures of a single male model drawn from the NimStim set (Tottenham et al., 2009). A single model was used so as to keep the non-affective physical features of the face constant across trials. All of the visual stimuli were digitally modified to exclude extraneous features (ears, hair) and were matched for luminance and contrast using Photoshop (Version 10.0). Picture complexity, as measured by file size, was constant across the three expressions. The pictures were shown in full RGB colour with 284 x 407 pixel resolution.

The facial pictures were presented at fixation for 600 ms. The stimulus-onset asynchrony (SOA) varied randomly between 1,500 and 2,000 ms. An example stimulus sequence is illustrated in Figure 2.1. The neutral face served as a high probability standard ($p_{standard} = 0.8$) with infrequent presentations of the threatening ($p_{angry} = 0.1$) and friendly ($p_{happy} = 0.1$) faces. The presentation sequence was pseudo-random.

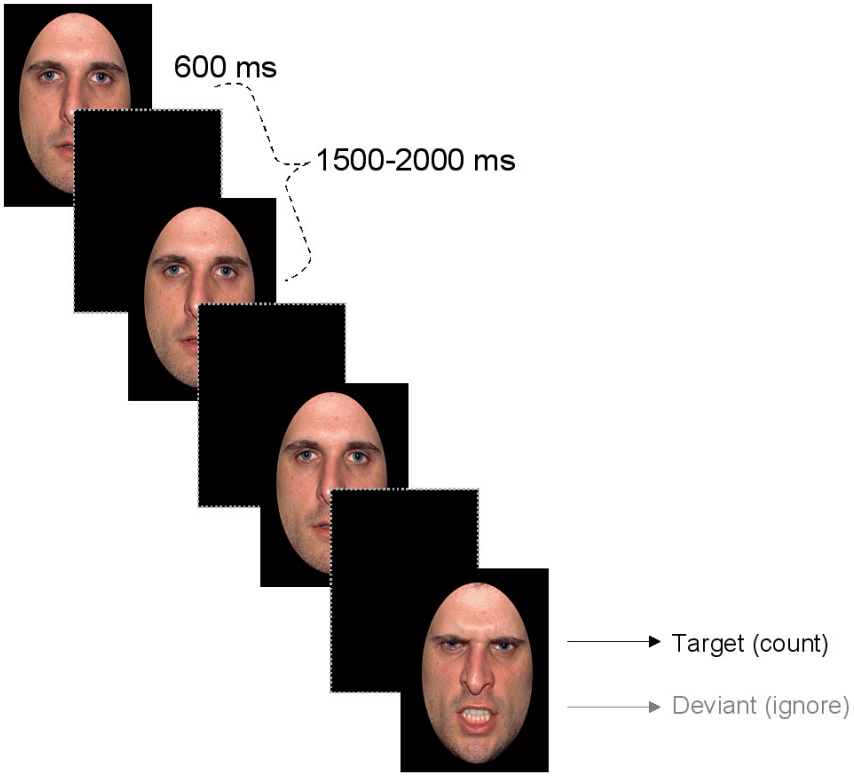


Figure 2.1: A schematic depiction of the experimental design.

Each block started with at least three neutral face presentations, before the first emotional presentation. A minimum of two, and a maximum of six, successive neutral faces were presented before any of the emotional face presentations. Participants were asked to either silently count threatening/friendly faces (targets) or to ignore them (deviants) in counterbalanced experimental runs. Participants were subsequently asked to recall the number of threatening and friendly faces that they had counted during the experiment. The initial practice block was followed by four experimental blocks (160 trials each) for a total of 640 trials.

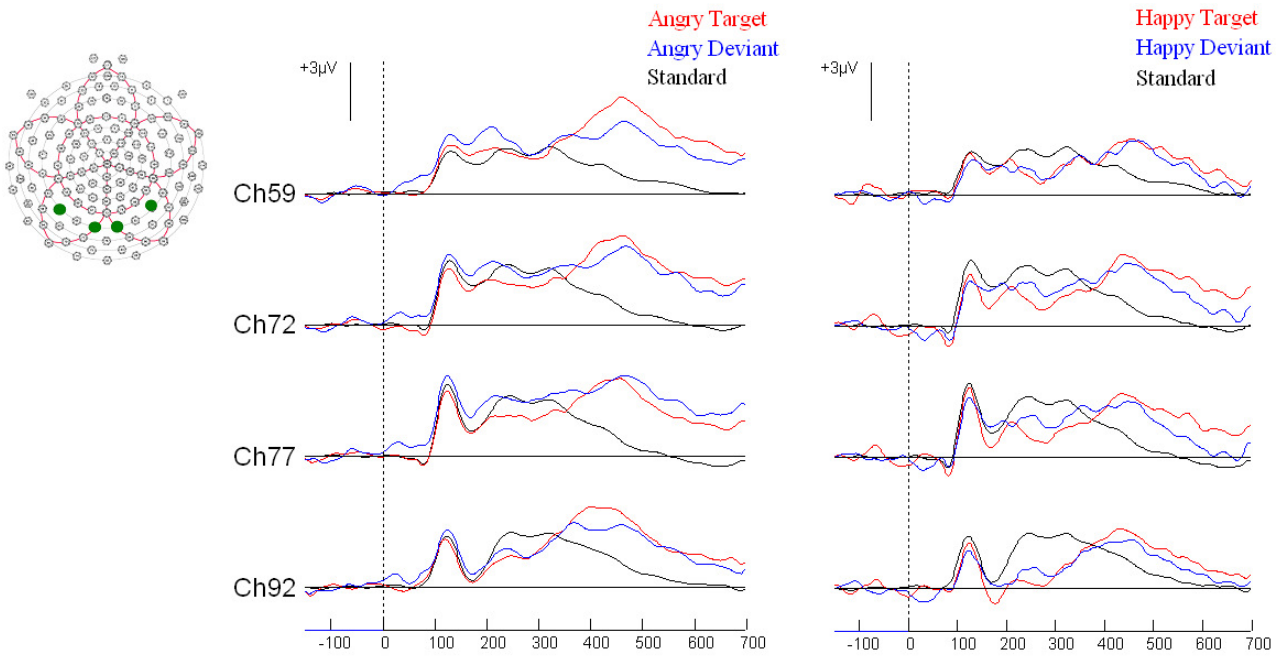
Participants were encouraged to take short breaks between blocks and were monitored for compliance via a closed circuit television in an adjoining room. The experiment was programmed and controlled using E-Prime Version 1.2 software.

EEG Data Recording and Reduction Cortical electrophysiology was recorded continuously from the scalp using a 129-channel Electrical Geodesics System (EGI Inc., Eugene, OR). Impedance of all sensors was kept below 100 kΩ, which is well under the 200 kΩ threshold for accurate (~ 0.1% error) signal acquisition using high input impedance amplifiers (Ferree, Luu, Russell, & Tucker, 2001). The EEG data were digitized at a 500 Hz sampling rate using 0.1 to 100 Hz analog filtering. The vertex sensor served as the on-line reference.

The EEG data were digitally low pass filtered at 40 Hz and stimulus-locked epochs were extracted from 150 ms before to 1,000 ms after picture onset. A semi-automated artifact detection approach was used to screen the raw EEG epochs using Net Station Version 3.0 software. First, the EEG data were passed through an algorithm that identified bad sensors within segments as those where the fast average amplitude exceeded 200 μV, differential average amplitude exceeded 100 μV, or there was zero variance. A sensor was marked bad for all segments if it was contaminated in more than 20% of epochs. Individual segments were marked bad if they contained more than 12 bad channels or if ocular artifacts were detected in excess of a 80 μV criterion. No ocular corrections were performed since trials with artifact were simply excluded from the averaging process. Second, the individual segments were manually edited to ensure that sensors of interest to the present study (see below) were uncontaminated. An averaged

mastoids reference was computed offline on the basis of artifact-free data. The re-referenced data were then averaged to derive five ERP categories (threatening face target, threatening face deviant, friendly face target, friendly face deviant, and neutral standard). To ensure adequate signal-to-noise ratio a minimum of 15 artifact-free trials were required for computing individual ERPs in response to the rare emotional faces. The percentages of artifact-free data included in the grand average waveforms were as follows: threatening face target, 67.1%; threatening face deviant, 66%; friendly face target, 64%; friendly face deviant, 71.2%.

ERP Quantification Visual inspection of the grand averaged ERP waveforms (see Figure 2.2) as well as prior research (e.g., Mühlberger et al., 2009; Schupp et al., 2004) was used to score the early posterior negativity over left and right hemispheric temporo-occipital sensors (59, 72, 77, and 92) in a 240 to 280 ms temporal interval; the P3b/late positive complex was scored over parietal midline sensors (55, 62, 68, and 73) in a 350 to 600 ms interval. Additional analyses focused on more temporally compact definitions of the positive component encompassing initial (350 to 550 ms) and later aspects (550 to 650 ms) of the waveform.


Angry Target
Angry Deviant
Standard
Happy Target
Happy Deviant
Standard
+3μV
+3μV
Ch59
Ch72
Ch77
Ch92
-100
0
100
200
300
400
500
600
700

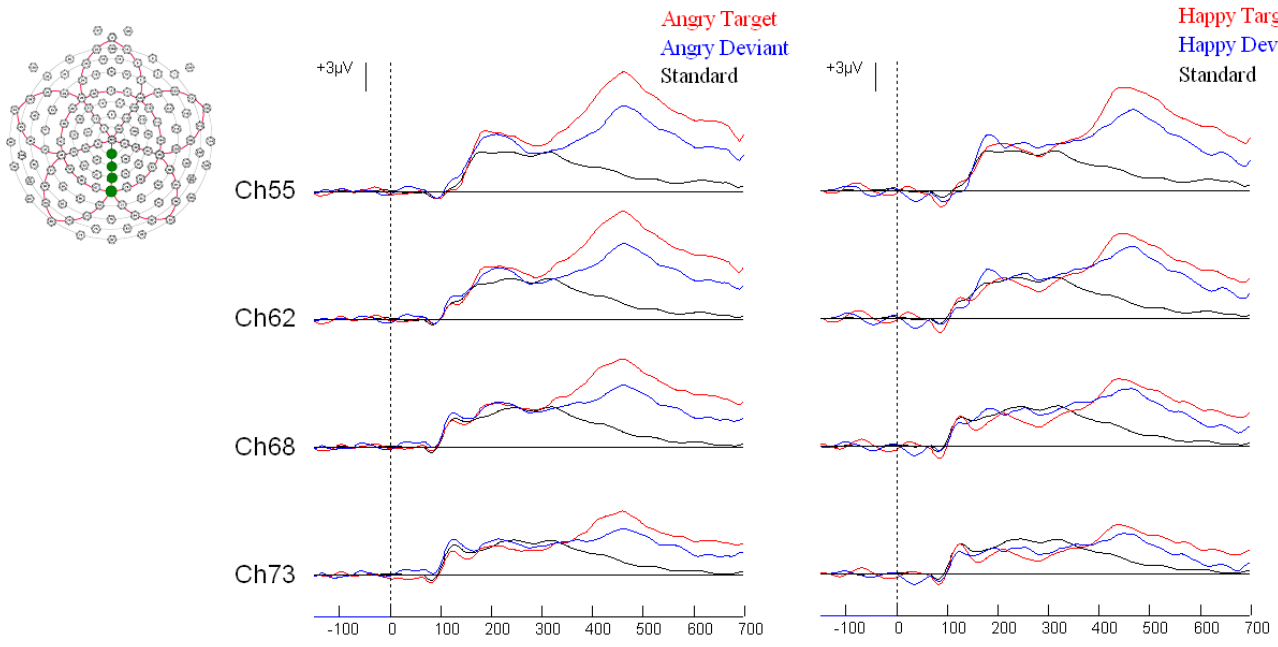

Angry Target
Angry Deviant
Standard
Happy Target
Happy Deviant
Standard
+3μV
+3μV
Ch55
Ch62
Ch68
Ch73
-100
0
100
200
300
400
500
600
700

Figure 2.2: Grand averaged ERP waveforms for the occipito-temporal (top panel) and parietal midline (bottom panel) sensors. Stimulus-locked electrocortical activity is depicted for the sensors highlighted in green.

The topographic distribution of electrical difference potentials (target minus standard) shows both the early occipito-temporal negativity and a subsequent midline positivity (see Figure 2.3) associated with processing the rare items.

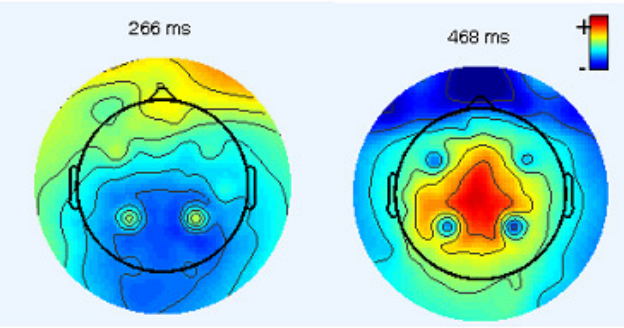


Figure 2.3: Topographic map depicting the grand averaged distribution of electrical potential differences (Target minus Standard). The map illustrates the posterior negativity occurring in the early time period (left) as well as the midline positivity during the stage of the P3b (right).

The mean area amplitude of each ERP component was calculated (in μV) using a computer ERP analysis program (Segalowitz, 1999). An advantage of using mean area amplitude (rather than peak amplitude) measures is that the former are not biased by differences in the number of trials used to derive stimulus-locked average waveforms for the separate experimental categories (Luck, 2005).

Data Loss and Analyses ERPs were unavailable for analysis from three (2 high socially anxious, 1 low socially anxious) participants due to technical difficulties or for personal reasons (refusal to participate in EEG collection). In addition, ERPs from another participant (low socially anxious) were excluded from analyses due to an insufficient number of artifact-free trials required for signal extraction.

Since the early posterior negativity is most clearly observed as a difference wave[15], several distinct difference scores were employed for analyses of this component – Threatening minus Neutral; Friendly minus Neutral and Friendly minus Threatening (see Herrmann et al., 2007 for a similar analytic approach to quantification of the early posterior negativity). An additional advantage of using difference waveforms to isolate the early posterior negativity is that difference waves are less confounded by other, overlapping ERP components occurring within the same temporal window (Luck, 2005). To test hypotheses concerning the early posterior negativity, a series of mixed-model ANOVAs were conducted, using Group (high/low social anxiety) as the between-subjects factor and Emotion (Friendly, Threatening), Hemisphere (Left, Right) and Stimulus Type (Target, Deviant) as within-subject factors. To examine P3b/late positive complex responses, separate mixed-model ANOVAs were evaluated for target and deviant threatening and friendly trials, using Group as the between-subjects factor and Stimulus Type (Standard, Target, Deviant) as the within-subjects factor. Two-tailed *p*-values were used at all times.

[15]One concern with using difference scores is the uncertainty over whether subsequent effects are due to a greater negativity for the rare emotional faces or an increased cortical positivity for frequent neutral faces. Paired sample t-tests confirmed that rare friendly faces elicited a greater extrastriate negativity compared to the frequent neutral expression (ps < 0.05). Rare threatening faces produced a greater negativity compared to the neutral ones (ps < 0.05) but only among high socially anxious individuals.

2.3 Results

Demographic and Clinical Characteristics There was no difference in age (p > 0.25) or sex composition (p > 0.75) between the high and low socially anxious groups. A one-way ANOVA was used to confirm the intended anxiety grouping at the time of the ERP visit. The results showed that the high socially anxious group exhibited greater SPIN scores than the low anxious group and also more depression-related symptoms on the BDI (ps < 0.032, η^2s = 0.15). Although a clinical diagnosis was not formally confirmed for any of the cases, the high socially anxious individuals who participated in this ERP experiment showed SPIN scores (M = 39.69, SEM = 1.68) that are within the range (32.6 to 43) previously reported among populations meeting clinical criteria (Connor et al., 2000).

Behavioural Accuracy Although the high socially anxious group had more recall errors for both threatening (M = 1.06, SEM = 0.31) and friendly (M = 1.12, SEM = 0.44) targets than the low socially anxious group (M = 0.31 and 0.73, SEM = 0.44 and 0.27, respectively), these differences failed to reach statistical significance (ps > 0.12). Across the entire sample, increased P3b/late positive complex amplitude in response to the friendly targets was associated with increased recall of friendly targets (r = 0.36, p = 0.046). No significant relations with ERP measures emerged for recall of threatening targets (ps > 0.54) or between behavioural accuracy and the amplitude of the early posterior negativity (ps > 0.38). The overall accuracy rate of recalling affective targets was high, reaching a mean of 95% correct, confirming that the task was relatively simple.

Event-Related Brain Potentials

Early Posterior Negativity (240 to 280 ms) There was a significant Group x Emotion x Hemisphere interaction [$F(1, 31) = 4.76$, $p = .037$, $\eta^2 = 0.13$] when examining the Affective minus Neutral differential ERP waveforms. Follow-up analyses revealed significant main effects of Emotion [$F(1, 31) = 5.94$, $p = .021$, $\eta^2 = 0.16$] and Group [$F(1, 31) = 8.22$, $p = .01$, $\eta^2 = 0.21$], but no Group x Emotion interaction ($p > 0.26$) for sensors in the left hemisphere. The main effect of Emotion was accounted for by an increased early posterior negativity for friendly (*vs*. neutral) rather than threatening (*vs*. neutral) faces (*M*s = -1.25 and –0.12 μV, *SEM*s = 0.30 and 0.32, respectively). The main effect of Group was explained as follows: independent of emotion, the high socially anxious group showed greater negative amplitudes in response to affective (*vs*. neutral) faces compared to the low socially anxious group (*M*s = -1.28 and –0.09 μV, *SEM*s = 0.29 and 0.30, respectively). The group differences for the left hemisphere sensor clusters are illustrated in Figure 2.4.

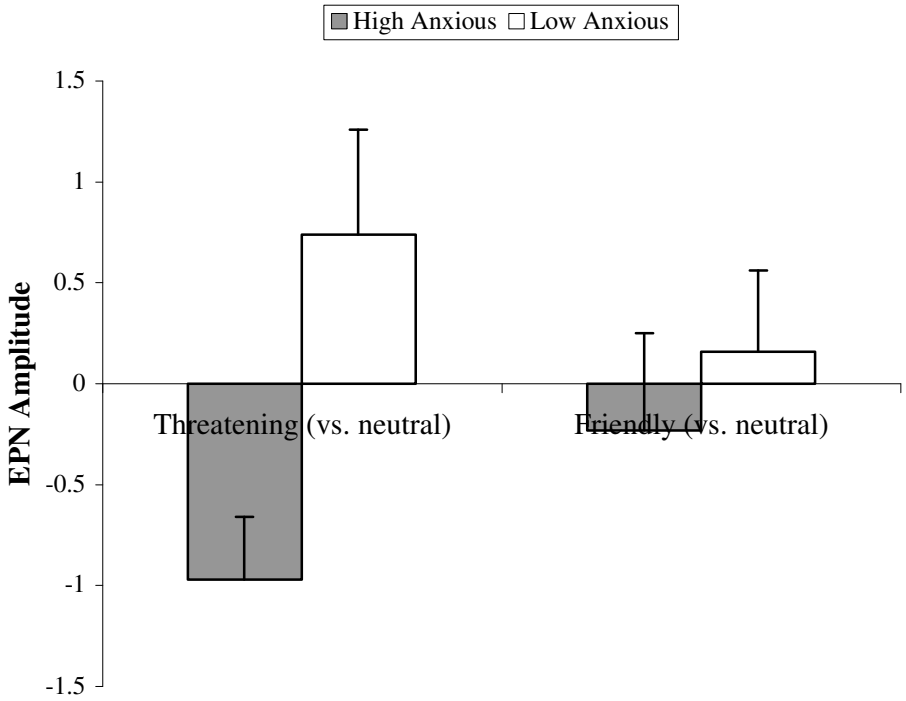


Figure 2.4: Mean left hemisphere area amplitudes of the threatening *vs*. neutral and friendly *vs*. neutral difference waveforms (240 to 280 ms) shown separately for the high and low socially anxious groups. Bars depict S.E.M. Greater negativity indicates enhanced response for affective face.

The Group x Emotion interaction also reached significance in occipito-temporal sensors over the right hemisphere, [$F(1, 31) = 4.65$, $p = .039$, $\eta^2 = 0.13$]. The high socially anxious group showed greater negative ERP amplitudes in response to threatening (*vs*. neutral) faces when compared to the low socially anxious group (see

Figure 2.5), collapsing across the target and deviant status of the face stimuli[16] [$F(1, 31) = 4.28$, $p = .047$, $\eta^2 = 0.12$].

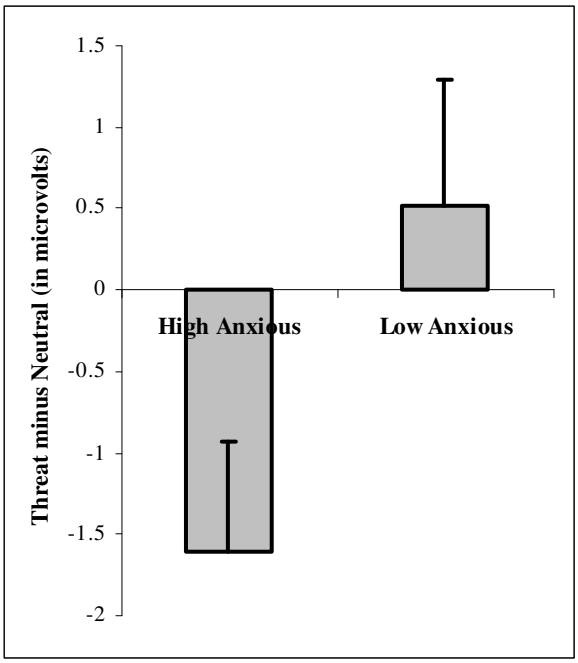


Figure 2.5: Mean right hemisphere area amplitudes of the threatening *vs*. neutral difference waveform (240 to 280 ms). Bars depict S.E.M. Greater negativity indicates enhanced response for threatening face.

There were no significant between-group differences for the early posterior negativity in response to friendly (*vs*. neutral) faces[17] (*p*s > 31).

[16]This group difference diminished slightly ($p = 0.075$) when removing two (low socially anxious) participants who could be considered potential outliers in terms of threatening (*vs*. neutral) waveform amplitudes, suggesting that the effect in question was weak to modest. Results from non-parametric tests (Mann-Whitney) performed on the entire sample revealed significant group differences for threatening (*vs*. neutral) amplitudes in sensors over the left (p=0.014), but not right (p=0.09) hemisphere.

[17]However, across all participants, friendly (*vs*. neutral) faces elicited a significantly greater posterior negativity in the right hemisphere when they were presented as targets (M = -2.29 μV, SEM = .47) rather than ignored deviants (M = -1.27 μV, SEM = 0.41).

When examining the posterior negativity derived from Friendly minus Threatening difference scores, there was a significant Group x Hemisphere interaction, [$F(1, 31) = 4.26$, $p = .048$, $\eta^2 = 0.12$]. Separate analyses within each hemisphere revealed that the low social anxiety group showed a greater posterior negativity for friendly relative to threatening faces, when compared to the high social anxiety group within the right hemisphere ($p = 0.045$, $\eta^2 = 0.12$)[18]. This effect is illustrated below, in Figure 2.6.

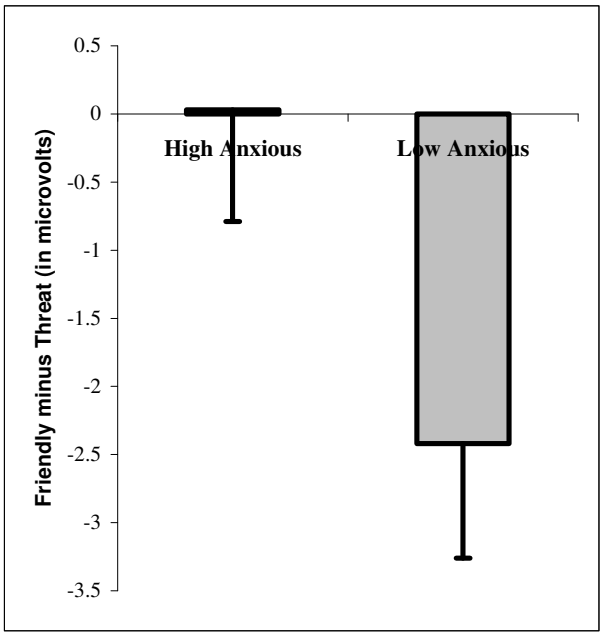


Figure 2.6: Mean right hemisphere area amplitudes of the friendly *vs*. threatening difference waveform (240 to 280 ms). Bars depict S.E.M. Greater negativity indicates enhanced response for friendly face.

P3b/late positive complex Analyses for the amplitude of late midline positivities failed to reveal any significant main or interaction effects involving Group, either for a

[18]Some caution is urged in interpreting this effect, as removal of two potential outliers mentioned before led to a marginal effect of group ($p = 0.092$).

broad temporal definition of the P3b/late positive complex (350 to 600 msec) or more restricted definitions focused on the early (350 to 550 msec) and late (550 to 650 msec) processing windows (ps > 0.39).

As expected, there was a strong main effect of stimulus type, both when examining response to targets [$F(2, 30) = 45.37$, $p = .0001$, $\eta^2 = 0.75$] and deviants [$F(2, 30) = 18.05$, $p = .0001$, $\eta^2 = 0.55$]. Regardless of anxiety group status, greater P3b/late positive complex amplitude was associated with processing rare faces (see Figures 2.2 and 2.7), confirming that the present experimental design elicited a reliable P3b brain electric response[19]. There were no differences in P3b amplitude between friendly and threatening targets ($p > 0.24$) or between friendly and threatening deviants ($p > 0.65$). Therefore, P3b was not affected by the emotional valence of stimuli, but by their probability of occurrence. Additional exploratory tests revealed no significant effects of Group when examining P3b/late positive complex target/deviant minus standard reactivity scores (ps > 0.34).

[19]Additional confirmatory evidence was provided by the expected regional differences (Polich, 2007) where the target positivity was stronger over posterior, parietal sensors than sensors covering the frontal-central regions, reflected by a significant Stimulus Type x Region interaction, ($p = .004$, $\eta^2 = 0.31$).

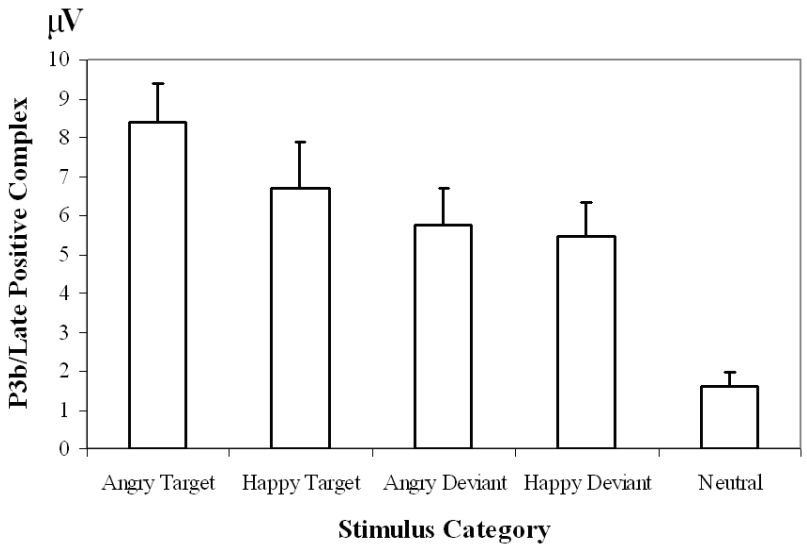


Figure 2.7: Mean area amplitude of the posterior midline P3b/late positive complex component (350 to 600 ms), collapsed across all participants and shown separately for each of the stimulus categories. Bars depict S.E.M.

Correlational Analyses Table 2.1 summarizes the Pearson zero-order correlations between the SPIN, BDI and early posterior negativity amplitudes. Importantly, these analyses added some specificity to the suggestion that social anxiety (and not depression) is related to increased processing resources devoted to threatening (*vs*. neutral) faces. Similar analyses with the P3b/late positive complex indicated no significant associations either with SPIN (rs > -0.03 and < 0.24, ps > 0.19) or BDI (rs > 0.02 and < 0.10, ps > 0.58) scores.

When BDI scores were partialled out, SPIN continued to significantly correlate with threat-related early posterior negativity amplitudes in the left (partial r = - 0.49, p = 0.004), but not right (partial r = -0.30, p = 0.10) hemispheres. Taken together, these results suggest that social anxiety is associated with threat-related biases that emerge

relatively early in the processing stream and then dissipate during more controlled processing stages.

Table 2.1: Pearson zero-order correlations among self-report measures of social anxiety (SPIN), dysphoria (BDI) and early posterior negativity (EPN) ERP amplitudes in the left and right cerebral hemispheres

	1	2	3	4	5	6
1. SPIN Total	--					
2. BDI Total	.48**	--				
3. Threat EPN Amplitude_Left	-.44*	-.01	--			
4. Threat EPN Amplitude_Right	-.34*	-.18	.81**	--		
5. Frinedly EPN Amplitude_Left	-.01	.24	-.07	-.13	--	
6. Friendly EPN Amplitude_Right	.19	-.07	-.11	-.05	.61**	--

Note: ** $p < 0.01$, * $p = 0.05$. The EPN amplitudes are threat minus neutral and friendly minus neutral difference scores. The *df* for all analyses was 31.

2.4 Discussion

This study used stimulus-locked cortical electrophysiological measures to examine how the brains of high and low socially anxious adults respond to sensory changes that are embedded within a socio-emotional context. One advantage of the oddball paradigm used here is that it more closely resembles realistic settings of fluctuating socio-emotional contexts, compared to other paradigms that involve blocked presentations of affective and neutral faces. Some, but not all, of the initial hypotheses were supported. Subclinical social anxiety was associated with threat-related biases in the sensory-perceptual stages of information processing (as indexed by the early posterior

negativity). However, contrary to the initial predictions, differences between high and low socially anxious individuals were not moderated by the task relevance of facial stimuli, and there was no evidence of group differences during the later, post-perceptual processing stages (as measured by the P3b/late positive complex). The positive relation between P3b/late positive complex amplitude and recall of friendly target items provides additional evidence that the later positivity indexed aspects of stimulus integration into working memory. The lack of group differences in accuracy recall most likely reflects the cognitively simple nature of the task.

Early posterior negativity findings When contrasting visual cortical responses to rare affective faces versus repetitive presentations of a neutral face, the high socially anxious group showed increased responsiveness to threatening faces in sensors covering the temporo-occipital cortex. The dimensional analyses provided evidence for a specific relation between social anxiety (rather than general dysphoria) and the amplitude of the early posterior negativity elicited during threatening (*vs*. neutral) stimulus changes, with some evidence of a stronger effect in the left hemisphere[20]. There were no significant correlations between social anxiety and the amplitude of electrocortical responses elicited during friendly (*vs*. neutral) contextual changes. While the effect size was small to modest, involving a < 2 μV neuroelectric difference, the findings suggest that social anxiety begins to impact threat-related processing relatively early (beginning 240 ms post-stimulus). Moreover, the statistical effect size obtained in this ERP study, although

[20]It is interesting that the magnitude of the correlations observed here is similar to those reported between spider phobia and the early posterior negativity elicited by spider pictures (*r* range = -0.37 to –0.47; Van Strien et al., 2009).

not large, seems to be roughly comparable with observations culled from behavioural studies using other anxious populations (Bar-Haim et al., 2007).

An increased relative negativity in sensors overlying the occipito-temporal cortex, during the 240 to 280 ms time range, presumably corresponds to the outcome of a process by which salient stimuli are selected for additional processing (Junghöfer et al., 2001; Schupp et al., 2006). The relative 'saliency' of stimuli could result from low spatial or temporal expectancy (novelty), affective resonance and/or arbitrary task-specific instructions. Several independent lines of evidence support this claim. First, studies that have recorded brain potentials to affective faces, either in oddball (Astikainen & Hietanen, 2009; Campanella et al., 2002; Zhao & Li, 2006) or balanced probability (Lee et al., 2009; Sato et al., 2001; Schupp et al., 2004) designs, have noted a neuroelectric response with a similar topography and latency. Second, studies of feature-based selective attention (Potts & Tucker, 2001) and scene categorization (Codispoti, Ferrari, Junghöfer, & Schupp, 2006) using non-affective stimuli have identified an analogous ERP signature. The hypothesis that the negative-going ERP responses in this time range reflect neural activity arising from extrastriate visual cortex is supported by source localization results from previous studies (Junghöfer et al., 2001; Martinez et al., 2001; Schupp, Stockburger, Codispoti, Junghöfer, Weike, & Hamm, 2006). It is interesting to note that Wieser and colleagues (2010) also observed augmented early posterior negativity amplitudes (but no differences in P3b/late positive complex waveforms) in normal participants who viewed threatening faces following a state induction of social anxiety.

One potential mechanism that has been suggested to produce affective augmentation of the early posterior negativity involves feedback projections from the amygdala to the extrastriate areas of the visual cortex (see Lee et al., 2009; Sato et al., 2001). The amygdala is known to be involved in initial salience tagging and subsequent enhancement of responses in sensory association areas (Vuilleumier & Pourtois, 2009). It is important to emphasize that the early posterior negativity is not assumed to originate from the amygdala itself. Indeed, given the closed-field electric configuration of the amygdala, it seems unlikely that scalp ERPs are sensitive to voltage fluctuations evoked in this brain region. Rather, the amygdala could be the source of an enhancement effect that is expressed at the level of the extrastriate visual cortex. An anatomical basis for a functional amygdala-extrastriate pathway is suggested by tract tracing studies in rhesus monkeys (Amaral, 2002). Additional evidence is provided by a recent study from Catani and colleagues (2003), who used *in vivo* diffusion tensor imaging to reveal a large fiber bundle (the inferior longitudinal fasciculus) in human brains. This fiber bundle connects ventral portions of extrastriate visual areas and the amygdala. Functional neuroimaging studies of emotional perception reliably demonstrate the activation of an extended amygdala-extrastriate-inferior temporal cortex system when processing affective cues in faces and naturalistic scenes (Sabatinelli et al., 2011). Interestingly, sensitization of amygdala circuits to social threat cues appears to be well established by functional neuroimaging studies of socially anxious populations (see Freitas-Ferrari et al., 2010, for a recent review). Therefore, the early posterior negativity findings obtained here suggest

that there is at least a plausible neurobiological mechanism that could contribute to the ERP differences observed between the groups.

Temporal considerations further suggest that an amygdala-based augmentation of the early posterior negativity (which onsets *ca*. 240 to 280 ms post-stimulus) is physiologically plausible. Intracranial ERPs recorded in epileptic patients (Krolak-Salmon, Hénaff, Vighetto, Bertrand, & Mauguiére, 2004) reveal that amygdala responses to fearful expressions peak around 200 ms. Moreover, the timing of the ERP component is consistent with the tentative suggestion that it reflects modulation of the visual cortex via a *direct* associative pathway rather than indirect amygdala efferents to the brainstem noradrenergic and forebrain cholinergic systems. Although noradrenergic and cholinergic neurotransmitter systems do increase the signal-to-noise ratio of cortical neurons (Gu, 2002), modulation of sensory processing by these means operates on the scale of seconds to minutes (Parikh & Sarter, 2008) and would not agree with effects in a 240 to 280 ms time window.

In addition to the subcortical-cortical pathway implicated here, facilitation of sensory-perceptual responses in visual association areas might be explained by modulatory signals emanating from other regions, including the prefrontal cortex (Miskovic & Schmidt, 2010; Pessoa & Adolphs, 2010; Vuilleumier & Pourtois, 2007). Indeed, a recent fMRI study has demonstrated that although the amygdala might be necessary to initially trigger enhanced extrastriate responses for emotional stimuli, other (presumably, neocortical) pathways are involved in response maintenance (Wendt et al., 2011).

Since the early posterior negativity findings obtained here potentially confound two separate neurocognitive processes -- one related to the emotional significance of the faces and another related to differences in stimulus novelty -- another possibility is that high socially anxious individuals are simply more sensitive to novelty (e.g., Susac et al., 2004). There is a growing ERP literature on the visual mismatch negativity – a component that responds to violations of environmental regularities in visual input[21] (Czigler, 2007; Pazo-Alvarez, Cadaveira, & Amenedo, 2003). However, since the threatening and friendly faces were balanced for probability, and given that social anxiety seemed to be more strongly associated with threatening (*vs*. neutral) stimulus changes, it is considered unlikely that the results obtained here are due solely to expectancy violations. Moreover, since the same individual's face was used for all of the stimulus categories, differences in basic structural characteristics were kept constant, with emotional expressions being the only source of variance. From these considerations, it appears that social anxiety influences responses to changes with a specific socio-emotional connotation (i.e., those that involve a change from a neutral to a threatening social context). Nevertheless, the alternative hypothesis – that novelty itself is sufficient to produce differences between socially anxious and non-anxious populations – remains a plausible one and will be subject to empirical test in the next chapter.

The P3b/late positive complex findings The lack of social anxiety group differences on the P3b/late positive complex suggests that threat-related biases dissipate

[21]There are at least two reasons that the effects obtained here are not likely to solely reflect a simple mismatch negativity: (i) the visual mismatch negativity typically onsets before 240 ms, and (ii) it has been attributed to the operation of a very transient storage buffer with typical stimulus onset asynchronies in such experiments being well below the 1.5 to 2 secs used in the present study (Czigler, 2007).

during controlled processing stages. The most popular current hypothesis (Polich, 2007) holds that the P3b, along with its associated family of potentials, is a neural signature of working memory updating and the subsequent memory storage processes elicited by rare items in repetitive stimulus trains. The P3b response is associated with conscious recognition of stimuli and post-perceptual processing steps related to stimulus integration into working memory (Kok, 2001). For example, cognitive experiments have shown that stimuli falling within the "attentional blink" produce strong sensory-perceptual ERP components, but fail to elicit P3b responses (Vogel, Luck, & Shapiro, 1998).

The ERP literature on social anxiety is in its nascence. Although some studies report no effects of social anxiety on the late positive components (Kolassa & Miltner, 2006; Mueller et al., 2009; Mühlberger et al., 2009; Rossignol et al., 2007), others have produced confirmatory findings (Moser et al., 2008; Sewell et al., 2008). Moser and colleagues (2008) employed a modified flanker paradigm to assess the effects of social anxiety on effortful processing stages, so it is possible that their results reflect the engagement of different neural processes. However, a previous oddball study (Sewell et al., 2008) appeared to establish a link between subclinical social anxiety and P3b responses to threatening faces within a 440 to 500 ms interval. It is important to note that the study from Sewell and colleagues (2008) did not make use of a pre-selected sample and the severity of social anxiety in the sample tested was relatively mild to moderate. Also, the authors did not examine a potential relation between social anxiety and the early posterior negativity.

A considerable number of studies with small-animal phobics report differences between anxious and non-anxious individuals for the P3b/late positive complex, when phobics confront images of their feared objects (Kolassa et al., 2005; Michalowski et al., 2009; Miltner et al., 2005; Trippe et al., 2007). None of the small-animal phobic studies, to date, have employed the oddball paradigm.

There are at least three reasons for the lack of significant group differences in terms of the late positive components. The first, and most obvious, explanation is that threat-related biases in subclinical social anxiety do not persist during controlled processing stages. A second reason might be that static photographs of threatening faces do not have adequate potency to trigger sustained biases, but more arousing forms of social threat might be adequate. One way to increase the experimental arousal of the facial stimuli might have been to inform participants that they would subsequently engage in a real life interaction with the model shown in the oddball paradigm. Yet another way to increase arousal could have been the use of a clinically diagnosed group, with more severe levels of social anxiety. A third reason for the null findings might be that the addition of an explicit task demand (i.e., count the number of angry and happy faces) produced strong P3b responses in all participants that may have overpowered more subtle differences. However, the last explanation appears unlikely since the groups did not differ even on those trials during which the affective faces were irrelevant to task performance.

Implications for understanding social anxiety Although statistically modest, the present ERP findings suggest that subclinical social anxiety can facilitate sensory-

perceptual responses to contextually novel threatening faces, within a relatively early (240 to 280 ms) time frame. It is possible to conceive of the early posterior negativity and the P3b/late positive complex within the theoretical framework of two-stage affective processing models (Öhman, 1986; Robinson, 1998; Schupp et al., 2006). According to such a framework, incoming stimuli are first subject to (crude) evaluation of significance or salience in a large-capacity system that operates preattentively. Those stimuli that are deemed relevant in the first stage are "tagged" for further processing. The "tag" corresponds to a selective facilitation in the sensory-perceptual representation of the relevant item, which may then enter into a second stage associated with sustained, elaborate processing. At all times, there is a trade-off between automaticity and flexibility, such that the initial processing stage proceeds largely involuntarily, but remains relatively unaffected by elaborate, conscious strategies. For example, the early posterior negativity is augmented by affective stimuli even under experimental contexts where those stimuli are completely irrelevant to the participant's primary task (Schupp, Junghöfer, Weike, & Hamm, 2003b; Schupp, Stockburger, Codispoti, Junghöfer, Weike, & Hamm, 2007).

The ERP findings obtained here, though preliminary, may be tentatively interpreted to mean that social anxiety increases reactivity to socially relevant changes associated with interpersonal threat. However, the anxiety-related bias seems to be transient and is not evident during those stages that permit conscious, controlled integration of the stimuli into a cognitive context. It is encouraging that a similar conclusion has been reached by a recent literature review that collated findings from

behavioural, subjective, cognitive and psychophysiological studies of social anxiety (Staugaard, 2010). After considering this broad literature, Staugaard (2010) notes a general tendency for social anxiety to be associated with early hyper-reactivity to social threat, with between group effects becoming increasingly unreliable for those task components that require elaborate cognitive processes.

Limitations The present study had several limitations, some of which have been previously mentioned (e.g., limited ecological validity associated with still photographs of human faces and the confounding affective quality with more general novelty effects). A further limitation that should be mentioned is that of the ERP technique. The process of deriving ERPs from signal averaging procedures preserves only the phase invariant neural oscillations, while remaining effectively silent to neural responses that are not phase locked to stimulus onset. Accordingly, ERPs should be viewed only as rough approximations of the brain's response to experimental stimuli (Başar, Schürmann, Demiralp, Başar-Eroglu, & Ademoglu, 2001). It is highly probable that social anxiety affects neural responses to threat-related stimuli in other brain regions and time periods, in ways that remain inaccessible to the traditional "ERP-view."

Conclusions This study provides a contribution to the scant literature on the temporal dynamics of threat-related processing in social anxiety. Increased knowledge about the temporal aspects of processing biases may play an important role in advancing future models of anxious pathology.

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Chapter 3

Abstract

Several cortico-limbic regions, including the amygdala, have been demonstrated to form a generic novelty detection circuit that responds to multiple forms of stimulus novelty. Hyperexcitability of the amygdala, and several other regions that form this cortico-limbic system, have been theorized to underlie social anxiety. An emerging literature suggests that infants and children at risk for social anxiety in adulthood evidence patterns of heightened reactivity to simple forms of sensory novelty. Event-related brain potentials were recorded while a group of high and low socially individuals performed a three-stimulus visual oddball experiment employing geometric shapes. Contextually novel shapes produced increased orienting responses as indexed by early (N2) and later (P3b/late positive complex) ERP responses. However, contrary to theoretical predictions, there was no evidence that social anxiety moderated any of the ERP responses to sensory novelty. Responding to non-social forms of novelty may represent a neurocognitive process that is relatively unaffected by anxiety-related individual differences. The relevance of different kinds of sensory novelty for the study of social anxiety is discussed.

3.1 Introduction

The previous chapter provided preliminary evidence that subclinical social anxiety is associated with enhanced sensory-perceptual processing of rare threatening faces interspersed between more frequent, neutral expressions. However, the possibility

still remains that high socially anxious individuals are simply more sensitive to novelty in general. That is, socially anxious individuals may simply be more sensitive to stimuli that have low expectancy, regardless of whether those stimuli are social in nature (e.g., facial expressions) or non-social (e.g., simple geometric shapes). Some authors have theorized (Fox, 2010; Reeb-Sutherland, et al., 2009) that attention biases for threat-related stimuli in anxiety originate from the lowered thresholds of more basic novelty detection circuits. According to this view, socially anxious individuals are predisposed to show vigilance for any signals in the environment that violate one's expectations or have a low probability of occurrence, independent of the actual stimulus content (Kagan & Snidman, 2004). The increased reactivity to novelty is presumably explained by the increased excitability of amygdalar cells.

Novelty Detection Circuits and the Amygdala Theories about the role of the amygdala in social anxiety originally drew from emerging research programs within non-human animal (and to a lesser extent, human) affective neuroscience, combined with descriptive approaches of personality and developmental psychology and psychiatry (Kagan, 1994). Studies of Pavlovian fear conditioning in rodents (see LeDoux, 1996, for a summary) provided strong evidence that the amygdala was a key component of a "fear centre", involved in associating stimuli with aversive qualities and the organization of defensive responses. Subsequently, other researchers, working primarily with human participants, including phobic individuals, postulated the existence of an amygdala based "fear module" (Öhman & Mineka, 2001). The fear module concept entailed the operation of specific information processing constraints: input selectivity, automaticity

and encapsulation. According to this view, the amygdala responds only to stimuli with threat-related meaning (selectivity criterion); moreover, amygdala responses to threat stimuli are considered to be obligatory (automaticity criterion) and resistant to functional modulation (encapsulation criterion).

Over-emphasizing the amygdala as a fear centre/module ignores other long standing non-human animal evidence implicating the same brain region in appetitive motivational processes and cognitive functions like attention (Holland & Gallagher, 1999). An early review of human neuroimaging studies concluded that a more accurate characterization of the amygdala's function was in terms of a continuous vigilance system that responds to ambiguity and initiates calls for continued processing (Davis & Whalen, 2001; Whalen, 1998). A related suggestion was that the amygdala detects biological relevance and signals to other brain regions that more information needs to be obtained about the objects/events in question (Sander, Grafman, & Zalla, 2003). As might be expected, amygdala activation has been shown to increase in situations that are unpredictable (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005), even when the unpredictability is not explicitly associated with threat to self (Herry, Bach, Esposito, Di Salle, Perrig, Scheffler et al., 2007). The most recent theoretical accounts of amygdala function (e.g., Pessoa, 2010) have recast the role of this brain region from that of a fear centre to a more domain-general system that helps to orient limited-capacity information processing resources to biologically significant stimuli[22] – whether the latter are aversive,

[22]Nevertheless, the fear centre/module hypothesis remains a populist notion. Kagan and Snidman (2004) provide an insightful discussion of the philosophical and historical context that has helped to maintain the view that the amygdala represents the brain's fear region and not a more generic relevance-detection system. Pessoa (2011) suggests that evolutionary changes in the structure of amygdala-neocortical

appetitive or salient because of lower-level features (e.g., appearing suddenly or unexpectedly, being unevenly distributed in space and time). In its broadest sense, the amygdala may be said to instantiate quick "what is it?" responses. Investigators interested in anxiety and individual differences have only recently begun to fully integrate these revised views of amygdala function in their research programs (Kagan & Snidman, 2004).

Stimulus novelty is a basic feature of sensory input that has clear biological significance to organisms (Knight & Nakada, 1998; Sokolov, 1963). Orienting responses toward novel stimuli have remained conserved across animal evolution (Campbell, Wood, & McBride, 1997), since such responses are directly related to an organism's likelihood of survival (Sokolov, 1963). At least two types of stimulus novelty can be distinguished. Categorical novelty refers to stimuli that are highly unusual and unlikely to have been previously encountered during an individual's lifetime. By comparison, contextual novelty is associated with stimuli that are not unusual in principle, but are unexpected or have a low probability in a given context (e.g., an oddball stimulus in a repetition-change experiment).

Recent fMRI studies have shown that the human amygdala shows a robust response to both categorical (Blackford, Buckholtz, Avery, & Zald, 2010a; Hamann, Ely, Hoffman, & Kilts, 2002) and contextual (Balderston, Schultz, & Helmstetter, 2011; Weierich, Wright, Negreira, Dickerson, & Barrett, 2010) novelty. Direct recordings from amygdalar nuclei in monkeys have shown a subgroup of cells that are tuned to respond to

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connections from rodents to primates could have inaugurated a shift in function from more domain-specific (fear) to more domain-general (relevance) role of the amygdala.

unfamiliar stimuli, independent of motivational context (Wilson & Rolls, 1993). Affectively neutral stimuli, such as rare high frequency auditory tone pips interspersed with low frequency pips elicit increased multi-unit and local field potential responses from the human amygdala and surrounding hippocampal formation (Halgren et al. 1980; Stapleton & Halgren, 1987). Some of the novelty-evoked potentials recorded from these limbic regions are extremely large (e.g., up to 200 μV in size). Functional neuroimaging scans obtained during the completion of oddball experiments indicate that the amygdala forms part of a generic novelty detection circuit that encompasses multiple cortico-limbic sites (Kiehl, Stevens, Laurens, Pearlson, Calhoun, & Liddle, 2005). A comprehensive review of the literature shows that the amygdala, along with the surrounding hippocampal and parahippocampal formation, is required to detect different forms of novelty (Knight & Nakada, 1998; Ranganath & Rainer, 2003).

Anxiety and Sensitivity to Novelty It is interesting to note that temperamental shyness – an early appearing risk factor for the development of social anxiety disorder (Schwartz, Snidman, & Kagan, 1999) – is associated with behavioural hyperreactivity (crying, distress) to categorical novelty (Kagan & Snidman, 1991; Moehler et al., 2008). At 9 months of age, infants in this temperamental category begin to show electrocortical signatures of enhanced reactivity to contextually novel auditory tones (Marshall, Reeb, & Fox, 2009). Heightened electrocortical responses to rare oddball stimuli continue to characterize the temperamentally shy group into childhood (Kagan & Snidman, 2004). Moreover, socially withdrawn children appear to show different electrocortical correlates of sensory change detection even during preattentive processing (Bar-Haim, Marshall,

Fox, Schorr, & Gordon-Salant, 2003). Among the individuals classified as temperamentally shy in childhood, those who also showed greater ERP responses to contextual novelty in adolescence exhibited a greater risk for the diagnosis of an anxiety disorder (Reeb-Sutherland et al., 2009). In an fMRI study, Schwartz and colleagues (2003) demonstrated that when temperamentally shy infants reached adulthood, they demonstrated increased amygdala BOLD responses to novel non-threatening faces. The latter result has been extended to show enhanced amygdala responses to novel neutral faces in adults selected for shyness (Beaton, Schmidt, Schulkin, Antony, Swinson, & Hall, 2008) as well as atypical temporal dynamics of amygdala responses to unfamiliar non-threatening faces among adults who were temperamentally shy children (Blackford, Avery, Cowan, Shelton, & Zald, 2010; Blackford, Avery, Shelton, & Zald, 2009).

Enhanced reactivity to sensory novelty, independent of the motivational context, is also apparent in other anxiety-related conditions[23]. For example, children selected for high trait anxiety show increased amplitude of novelty ERP responses in an auditory oddball task (Hogan, Butterfield, Philips, & Hadwin, 2007). A similar pattern is observed in ERP studies of combat soldiers with PTSD (Kimble, Kaloupek, Kaufman, & Deldin, 2000) and patients with panic disorder (Iwanami, Isono, Okajima, & Kamijima, 1997).

Taken together, the findings reviewed above suggest that anxious populations may evidence abnormal attentional capture by novel stimuli, even in situations where the

[23]The studies differ as to whether they report early novelty processing differences between anxious and non-anxious samples (e.g., Hogan et al., 2007; Iwanami et al., 1997; Kagan & Snidman, 2004) or late, P3 responses (e.g., Kimble et al., 2000).

stimuli are not overtly threatening. Hyperreactivity to novelty may, in part, be influenced by a lowered threshold for activation in a distributed cortico-limbic circuit that involves the amygdala as one of its crucial structures.

The Present Study The aim of the present study was to discover whether social anxiety is associated with enhanced electrocortical responses to non-social forms of contextual novelty. Event-related cortical electrophysiology was recorded during a modified three-stimulus visual oddball sequence that involved infrequent presentations of targets (stars) and deviants (three-dimensional shapes) amid frequently presented standards (rectangles). Although ERP measures cannot directly index electrical responses of the amygdala, there is evidence that some of the scalp derived novelty modulated components are sensitive to the excitability of a distributed cortico-limbic circuit (Knight & Nakada, 1998; Linden, 2005). On the basis of existing evidence, it was predicted that the high compared to the low socially anxious group would show greater ERP amplitudes of two attention-related components (the early posterior negativity and the P3b/late positive complex) in response to the oddball stimuli. Such findings would suggest a lack of stimulus specificity in the information processing biases of socially anxious individuals and instead point to the involvement of a more generic novelty detection mechanism.

3.2 Method

Participant recruitment procedures and self-report measures were identical to those described in Chapter 2.

Experimental Stimuli and Procedure Participants were seated in a dimly lit, sound attenuated room. All participants were positioned ~ 100 cm from the monitor screen (75 Hz vertical refresh rate). The visual stimuli were simple white rectangles (standards; $p_{standard} = 0.8$), white stars (targets; $p_{target} = 0.1$) and complex, multi-coloured three-dimensional shapes (deviants; $p_{deviant} = 0.1$). The pictures were shown in full RGB colour and measured 4.5 x 5 cm in size.

The images were presented at fixation for 150 ms. The stimulus-onset asynchrony (SOA) varied randomly between 1,500 and 2,000 ms. An example stimulus sequence is illustrated in Figure 3.1. The presentation sequence was pseudo-random. Each block started with at least three standard presentations, before the first rare presentation. A minimum of two, and a maximum of six, successive standards were presented before any rare item. Participants were instructed to silently note to themselves the star shapes (targets) and to ignore the multi-colored three-dimensional shapes (deviants). The initial practice block was followed by four experimental blocks (80 trials each) for a total of 320 trials. Participants were encouraged to take short breaks between blocks and were monitored for compliance via a closed circuit television in an adjoining room. The experiment was programmed and controlled using E-Prime Version 1.2 software.

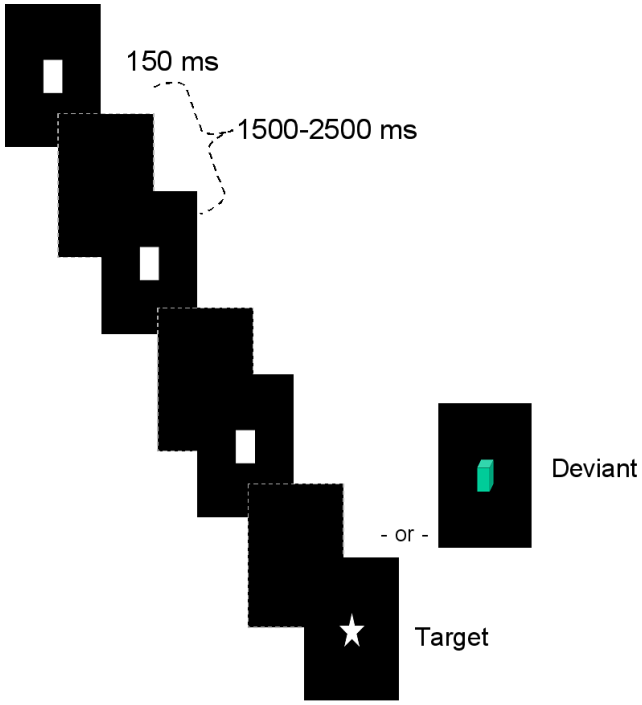
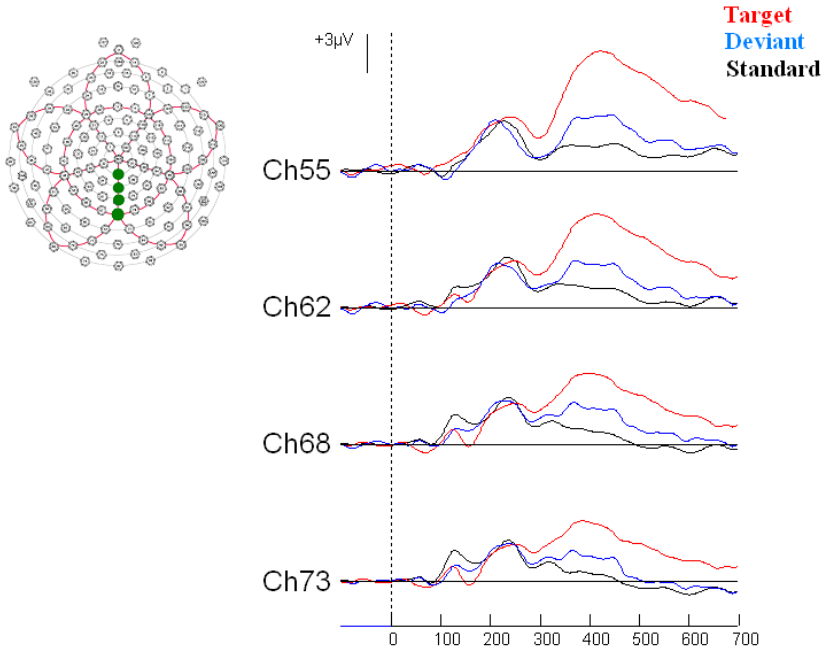


Figure 3.1: A schematic depiction of the experimental design.

EEG Data Recording and Reduction EEG recording parameters were identical to those described in Chapter 2. ERPs were averaged across trials to derive three ERP categories (standard, target, and deviant) for each participant. To ensure adequate signal-to-noise ratio a minimum of 12 artifact-free trials were required for computing individual ERPs in response to the rare stimulus items. The percentages of artifact-free data included in the grand average waveforms were as follows: targets (60%), deviants (61%), and standards (54%).

ERP Quantification Visual inspection of the grand averaged ERP waveforms (see Figure 3.2) and previous research was used to score the early posterior negativity over left and right hemispheric temporo-occipital sensors (59, 72, 77, and 92) during two separate intervals: 200 to 300 ms (broad) and 230 to 260 ms (narrow). The P3b/late

positive complex was scored over parietal midline sensors (55, 62, 68, and 73) in a 350 to 600 ms interval (see Figure 3.2 top). Additional analyses focused on a posterior N2 component (130 to 190 ms; Figure 3.2 bottom) that preceded the early posterior negativity by several milliseconds and appeared as a prominent voltage deflection in the grand averaged waveform. The mean area amplitude of each ERP component was calculated (in μV) using a computer ERP analysis program (Segalowitz, 1999).



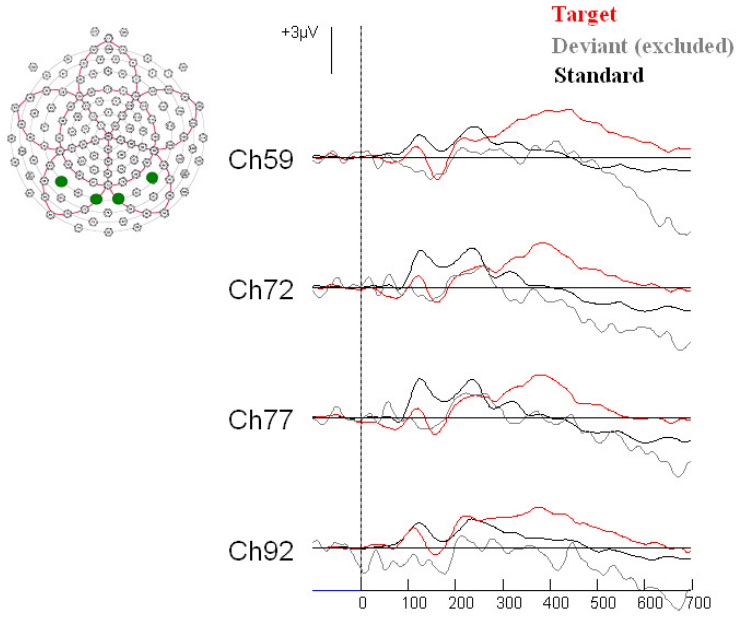


Figure 3.2: Grand averaged ERP waveforms for the parietal midline (top panel) and occipito-temporal (bottom panel) sensors. Stimulus-locked activity is depicted for the sensors highlighted in green.

Data Loss and Analyses Three (2 high socially anxious, 1 low socially anxious) participants did not have ERPs collected due to technical difficulties or for personal reasons (refusal to participate). In addition, ERPs from two other participants (low socially anxious) were excluded from analyses due to an insufficient number of artifact-free trials.

In order to test hypotheses concerning the early posterior negativity component, a Target minus Standard waveform score was computed and entered as a dependent variable into a mixed-model ANOVA with Group (high/low social anxiety) as the between-subjects factor and Hemisphere (Left, Right) as the within-subjects factor. Since the grand average waveform for the deviant trials appeared excessively noisy at the

posterior sensors (see Figure 3.2 bottom), deviant trials were not included in the posterior sensor analyses. To examine the N2 and P3b/late positive complex responses, separate mixed-model ANOVAs were evaluated using Group as the between-subjects factor and Stimulus Type (Standard, Target and Deviant) as the within-subjects factor. Two-tailed *p*-values were used at all times.

3.3 Results

Demographic and Clinical Characteristics There was no difference in age ($p > 0.36$) or sex composition ($p > 0.92$) between the high and low socially anxious groups. A one-way ANOVA was used to confirm the intended anxiety grouping for the participants who had complete ERP data for the current study. The results showed that the high socially anxious group exhibited greater SPIN scores than the low anxious group, [$F(1, 31) = 255.85$, $p < 0.001$, $\eta^2 = 0.90$]. There was no significant difference in BDI symptoms for the present sub-sample, although there was a trend ($p = 0.07$, $\eta^2 = 0.11$) for the high socially anxious group to report increased dysphoria compared to the low anxious group.

Event-Related Brain Potentials

N2 (130 to 190 ms) There was a main effect of Stimulus Type ($p = 0.01$, $\eta^2 = 0.22$), with targets eliciting a greater posterior N2 component ($M = -0.53$ μV, $SEM = 0.59$) compared to standards ($M = 1.03$ μV, $SEM = 0.35$). However, there were no main or interaction effects involving Group (ps > 0.72).

Early posterior negativity There were no Group differences for the Target minus Standard difference waveform, both when examining the broad ($p > 0.53$) and narrow ($p > 0.31$) time windows. Regardless of Group, stimulus probability did not seem to affect voltage in this temporal range ($ps > 0.26$), suggesting that the early posterior negativity (unlike the preceding N2 component) was not influenced by contextual novelty.

P3b/late positive complex Analyses revealed a main effect of Stimulus Type, [$F(2, 28) = 11.48$, $p < 0.001$, $\eta^2 = 0.45$]. As illustrated in Figure 3.3 and as determined by follow up paired-samples *t*-tests, targets elicited a greater cortical positivity than either standards or deviants ($ts > 3.69$, $ps < 0.002$). Somewhat surprisingly, there was no significant difference between the P3b amplitudes elicited by deviants versus that elicited by standards. More importantly, there were no main or interaction effects involving Group ($ps > 0.17$).

A so-called distractor P3a brain electrical response can be reliably observed in about 15% of young adults during the performance of auditory oddball tasks (Polich, 2007). The distractor P3a is elicited by deviant items in a three-stimulus oddball design and is typically characterized by an earlier latency and more anterior cortical distribution, covering the prefrontal areas.

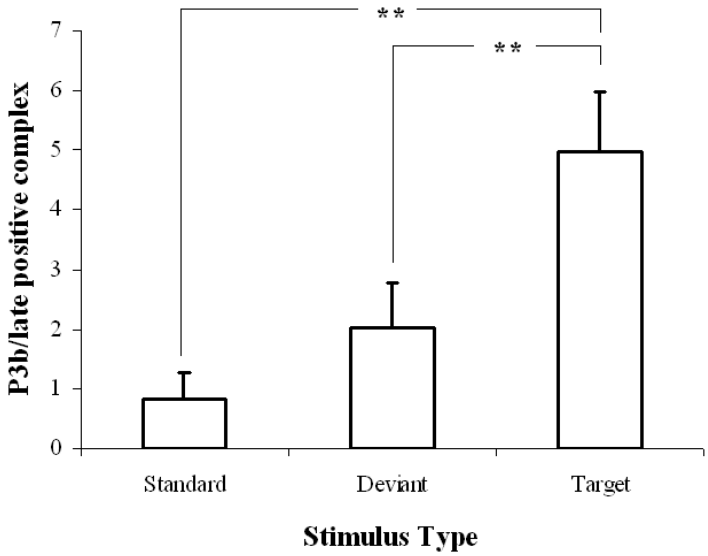


Figure 3.3: Mean area amplitude of the posterior midline P3b/late positive complex component (350 to 600 ms), collapsed across all participants and shown separately for each of the stimulus categories. Bars depict S.E.M. Note: ** p <0.01.

However, as illustrated in the grand averaged waveform of the anterior sites in Figure 3.4, there was no reliable distractor P3a response obtained in the present study. An investigation of the same time range as the P3b (350 to 600 ms), but using the anterior midline sensors as the dependent variable, revealed a main effect of Stimulus Type, [F(2, 28) = 3.63, p = 0.04, $\eta^2 = 0.21$], that mirrored the pattern observed at the parietal midline (i.e., targets elicited the greatest positivity, followed by deviants and then standards). There were no significant effects of Group (ps > 0.70).

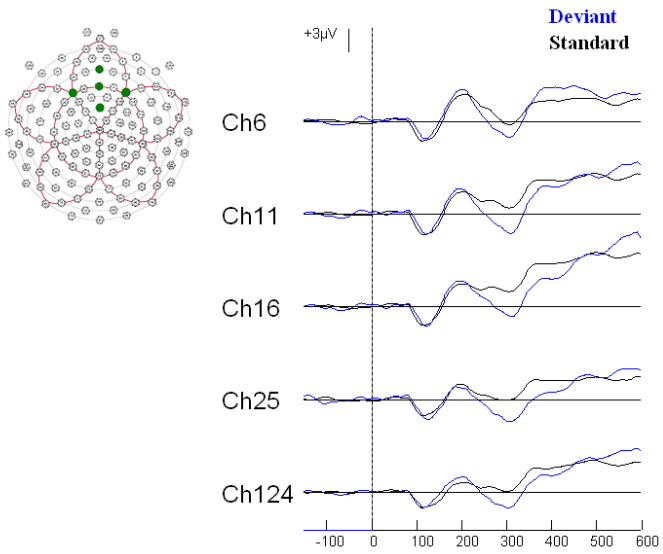


Figure 3.4: Grand averaged ERP waveforms for the anterior sensors. Stimulus-locked activity is depicted for the sensors highlighted in green.

Correlational Analyses There were no significant correlations between SPIN/BDI and early posterior negativity (rs > 0.05 and < 0.27, ps > 0.16), N2 (rs > -0.07 and < 0.30, ps > 0.10), or P3b/late positive complex (rs > -0.22 and < -0.10, ps > 0.20) amplitudes.

3.4 Discussion

This study examined whether the brains of high and low socially anxious individuals are differentially sensitive to the contextual novelty of stimuli, independently of socio-emotional content. Contrary to initial hypotheses, the electrocortical response to simple contextual novelty was observed in all participants and did not appear to be modulated by the degree of social anxiety. Collapsing across the high and low socially anxious groups, the entire sample showed enhanced reactivity to novel geometric shapes,

both in an early period (the N2 response component) and at a later stage (the P3b/late positive complex) of processing. Furthermore, the most robust responses were observed for stimuli that were task relevant (the oddball targets), consistent with previous evidence that components of the orienting response are elicited, most robustly, by those stimuli that are being actively attended (Sokolov, 1963). These findings suggest that stimuli that have low probability and are also significant in a given experimental context, recruit a widely distributed brain circuit that centers on several cortico-limbic regions, including the amygdala (Ranganath & Rainer, 2003). However, since responses to novelty appear to be highly conserved across evolution (Campbell, Wood, & McBride, 1997; Knight & Nakada, 1998), they may represent an "upstream" cognitive process that is relatively unaffected by individual differences in social anxiety.

Implications for Social Anxiety An emerging ERP literature demonstrates that temperamentally shy infants (Marshall, Reeb, & Fox, 2009) and children (Kagan & Snidman, 2004) are more reactive to contextual novelty than their non-shy counterparts. By adolescence, although there were no absolute group differences, brain responses to novelty were related to clinical outcomes among adolescents who were temperamentally shy children (Reeb-Sutherland et al., 2009). There are several reasons that could explain the discrepancy between the earlier findings and those presented here. For one, all of the aforementioned studies were longitudinal in design, and consisted of following a well-defined and characterized group of individuals with a particular temperamental profile from infancy onwards. As previously mentioned, social anxiety in adulthood may be the outcome of multiple pathways, and the socially anxious participants in the present study

presumably constituted a more heterogeneous sample than the carefully selected samples employed in longitudinal work. Second, the previous studies (Kagan & Snidman, 2004; Marshall, Reeb, & Fox, 2009; Reeb-Sutherland et al., 2009) employed auditory oddball paradigms and it is possible that the novelty-related differences could be modality specific. Finally, none of the previous oddball studies examined adult participants. It is highly possible that by adulthood, the high socially anxious individuals have developed adequate regulatory and coping mechanisms such that their attentional allocation is not attracted by simple (i.e., non-social) forms of sensory novelty to a greater extent when compared with non-anxious individuals.

Nevertheless, it appears that socially anxious adults do differ from their non-anxious counterparts when novelty occurs within the domain of social signals. The previous chapter provided preliminary evidence that social anxiety is positively related with enhanced sensory-perceptual responses when a facial expression changes from a non-threatening to a threatening one (i.e., threatening faces that are contextually novel). In a related manner, several fMRI studies have demonstrated a link between anxiety and greater (or more sustained) amygdala responses to novel (never seen before) neutral faces (Beaton et al., 2008; Blackford et al., 2009, 2010; Schwartz et al., 2003).

Taken together, these considerations can be used to devise a theoretical model of stimulus novelty (see also Bradley, 2009) that has relevance to the study of social anxiety. As illustrated in Figure 3.5, a broad distinction can be made between non-social and social domains of novelty.

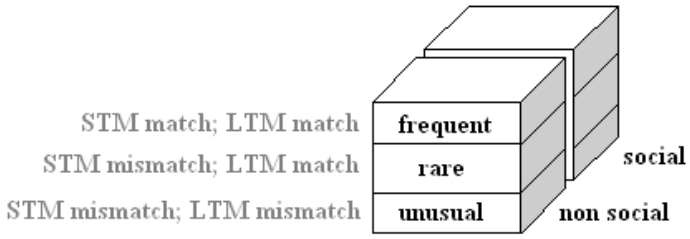


Figure 3.5: A theoretical model of stimulus novelty and information processing.

The social domain of novelty processing appears to be particularly relevant for the study of social anxiety, although the non-social domain could be important at earlier developmental windows (infancy and childhood) and/or for other anxiety disorders (e.g., PTSD, panic disorder). Within each respective domain of sensory signals, a similar cognitive mechanism is postulated to determine the relative degree of novelty (see Bradley, 2009). All incoming stimuli are subject to a dual-comparator mechanism that scans for consistency with currently active templates in short-term memory and more latent templates stored in long-term memory. The frequent stimulus corresponds to one that contains both a short- and long-term match (the standard stimulus in the oddball paradigm). Novelty is enhanced when there is no match with items in a short-term memory store, although there are, at least partially matching, long-term memory representations (the target stimulus in the oddball paradigm). Items that have no short-term match, but do correspond to long-term memory representations can be classified as contextually novel (e.g., a rare threatening face inserted in a repetitive train of neutral faces). Such stimuli are unexpected in a given context but they are not unfamiliar in principle – for example, participants have familiarity with threatening faces, even if such expressions have a low probability of occurrence in most daily social interactions. The

most unusual items are those that have no match in short or long-term memory stores and are thereby categorically novel. Although categorically novel stimuli are extremely difficult to study in adult human populations[24], researchers have investigated responses to such stimuli in non-human primates (Bradley, 2009). It remains to be determined whether social anxiety affects the processing of categorically novel non-social and social stimuli. At present, it appears that contextually novel social threatening stimuli contain the affective potency that is requisite to reveal differences between high and low socially anxious adults.

Limitations The present study had several limitations. A chief limitation concerns the ERP technique itself, which as noted earlier, is not capable of detecting event-related electrical fluctuations originating directly from amygdalar nuclei. It remains possible that high and low socially anxious individuals differ in the degree to which they process non-social contextual novelty, but that these differences occur in brain regions that do not contribute to generation of ERP signals although they might detectable using other neuroimaging methods (e.g., fMRI). Second, there was no evidence that the distractor P3a, a brain electric response that is sometimes observed in relation to deviant items in a three-stimulus oddball (Polich, 2007), was evoked in the current experiment. The distractor P3a response is regarded as an elusive ERP component that can be difficult to replicate in novelty experiments (Linden, 2005). The multi-coloured three-dimensional shapes that were used as deviant distractors in the present study simply may not have been adequately novel to produce a strong P3a

[24] Several studies have shown that the human amygdala is sensitive to unusual images (e.g., surrealist paintings) that could putatively be called categorically novel (Blackford et al., 2010a; Hamann et al., 2002).

signature. Finally, a limitation of this chapter, as well as Chapter 2, is that they do not provide behavioural evidence of processing biases in socially anxious individuals. Although the ERP technique can serve as a useful index of covert attentional processes, it remains important to establish that high and low socially anxious individuals differ on simple behavioural indices of attention (e.g., reaction times) that also reflect decision making mechanisms.

Conclusions On the basis of the data reviewed here, it appears that social anxiety does not influence the processing of contextual novelty when the latter occurs in the non-social domain (e.g., simple geometric shapes). Instead, it appears that the processing of simple contextually novel stimuli is enhanced across all individuals, regardless of their social anxiety levels. A potential reason for this finding is that detecting discrepancy in one's sensory environment is an adaptive response that is relatively unaffected by individual differences in anxiety.

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Chapter 4

Abstract

Although anxiety disorders and anxious personality traits are associated with biased attention for threat-related stimuli, considerable controversy persists regarding the existence (and nature) of threat-related biases among socially anxious individuals in particular. One possible contribution to this controversy may be linked to the failure of previous studies to consider how variations in the temporal (e.g., exposure duration) and energetic (e.g., emotional intensity) dimensions of affective stimulus delivery interact with anxiety-related individual differences to predict biased attention. Accordingly, we examined reaction times to a dot-probe task, using faces (threatening, friendly) that varied in affective intensity (mild, moderate, strong) and presentation rate (100, 500, 1250 ms) in a nonclinical sample of young adults selected for high and low social anxiety. The high socially anxious group showed vigilance towards threatening faces as well as emotionally ambiguous faces more generally. However, the anxiety-related bias was restricted to the early aspects of information processing (100 ms). By 1250 ms, there was only a non-specific motor slowing associated with threatening faces in the high socially anxious group. These results provide evidence that socially anxious adults show biases to threatening faces as early as 100 ms. Findings also suggest the importance of considering both the chronometric and energetic variations in affective stimuli when examining anxiety-related differences in information processing.

4.1 Introduction

Disturbances in attention for emotional information figure prominently in most etiological theories of anxiety disorders (see Cisler & Koster, 2010; Yiend, 2010, for recent reviews). While there is an obvious adaptive advantage to possessing an attentional system tuned to signals of danger (e.g., Öhman & Wiens, 2004), a wealth of evidence indicates that anxious individuals display hypervigilance and/or delayed disengagement from threat when compared to healthy controls (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007). To date, the strongest evidence for threat-related attention biases derives from studies of patients with generalized anxiety disorder, specific phobias, and high levels of trait anxiety in the normative range.

Considerable controversy persists regarding the existence (and nature) of threat-related biases among socially anxious individuals (Bögels & Mansell, 2004; Yiend, 2010). Social anxiety involves excessive fears and worry surrounding interpersonal interactions, especially those with potential for scrutiny and evaluation. Several influential models of information processing in social anxiety have been proposed (see Heinrichs & Hofmann, 2001, for a review). According to some models (Clark, 1999; Clark & McManus, 2002), social anxiety involves active avoidance of external threat cues combined with an allocation of cognitive resources towards the processing of distressing internal information (e.g., distorted self-representations, visceral sensations). This model makes the prediction that people high in social anxiety will avert attention away from signals in the external environment, including potentially threatening cues

(e.g., threatening faces). By contrast, other models (Rapee & Heimberg, 1997) suggest that socially anxious individuals are perpetually scanning their environment for subtle signs of negative evaluation. A plausible prediction from this model is that social anxiety is associated with selective orienting towards threat-related cues.

Experimental Studies of Selective Attention in Social Anxiety The existing evidence concerning threat-related biases in social anxiety is largely contradictory (Bögels & Mansell, 2004; Yiend, 2010). The majority of research examining threat-related processing biases in social anxiety and phobia has relied on the emotional Stroop test where selective attention toward stimuli is inferred on the basis of colour naming latencies. Several (e.g., Becker, Rinck, Margraf, & Roth, 2001; Hope, Rapee, Heimberg, & Dombeck, 1990; Spector, Pecknold, & Libman, 2003), but not all (Amir, McNally, Riemann, Burns, Lorenz, & Mullen, 1996), studies have reported slower reaction times to socially threatening stimuli among individuals high in social anxiety, suggesting that attention is drawn towards threat-related cues. However, results from the emotional Stroop task are difficult to interpret directly in terms of vigilance or avoidance, as colour naming latencies confound multiple cognitive processes (Bar-Haim et al., 2007) and do not provide a "process pure" measure of attention (Yiend, 2010).

Detection paradigms (e.g., visual search tasks) provide more robust measures of hypervigilance to threat. However, there have been an equal number of positive (Gilboa-Schechtman, Foa & Amir, 1999; Perowne & Mansell, 2002; Veljaca & Rapee, 1998) and null (Esteves, 1999; Pozo, Carver, Wellens, & Scheier, 1991; Rinck, Becker,

Kellerrmann, & Roth, 2003; Winton, Clark & Edelmann, 1995) findings with respect to attention biases among socially anxious populations using these tasks.

Visual dot-probe experiments offer a promising avenue to the study of emotion-attention interactions (Bar-Haim et al., 2007; Yiend, 2010) and have been extended to genetic (Perez-Edgar et al., 2010), neuroimaging (Pourtois & Vuilleumier, 2006), computational (Frewen, Dozois, Joanisse, & Neufeld, 2008) and non-human primate (Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009) research paradigms. The dot-probe task involves the simultaneous presentation of two stimuli – affectively valenced and non-valenced – at spatially distinct locations (e.g., left and right of a fixation cross). Immediately following stimulus offset, a neutral probe is shown in one of the two spatial positions with equal (50%) probability of replacing the affective or non-affective stimulus. Emotional biases in spatial attention can be inferred when reaction times are faster for probes occurring in the location previously occupied by the affective stimulus compared to probes occurring in the opposite location, since attention facilitates perceptuo-motor responding. Since the dot probe design does not confound the target stimulus (the probe) with emotional valence, it is considered a "process pure" behavioural index of attention (Yiend, 2010). An additional strength of the dot probe paradigm is that affective and non-affective expressions of faces are presented on the screen simultaneously. This latter feature is an important consideration since classical cognitive models (e.g., Desimone & Duncan, 1995), as well as clinical ones (e.g., Mathews & Mackintosh, 1998) stipulate stimulus competition as being necessary in order to observe biases in *selective* attention.

Efforts to extend the dot-probe task to socially anxious populations have yielded inconsistent results. Studies using verbal stimuli have found either selective attention towards social threat words (Amir, Elias, Klumpp, & Przeworski, 2003), non-specific vigilance for negative *and* positive emotional words (Asmundson & Stein, 1994) or absence of all affectively biased processing (Horenstein & Segui, 1997; Mansell, Ehlers, Clark, & Chen, 2002). Similarly, studies using pictorial (facial) stimuli have noted either vigilance towards threatening faces (Mogg & Bradley, 2002; Mogg, Philippot, & Bradley, 2004), avoidance of emotional faces in general (Chen, Ehlers, Clark, & Mansell, 2002; Mansell, Clark, Ehlers, & Chen, 1999; Mansell, Clark & Ehlers, 2003) or no emotion-related attentional bias at all (Bradley et al., 1997) in socially anxious individuals.

The diversity of findings is at least partially explained by methodological differences across studies, with respect to type of task, nature of stimuli (verbal versus pictorial) as well as their exposure duration and experimental context[25]. For example, within the scope of the dot-probe paradigm, vigilance towards social threat seems more likely when the stimuli are presented at rapid durations, while avoidance appears more common at longer exposures (Bögels & Mansell, 2004).

Stimulus Exposure Duration and Intensity Recent meta-analyses clearly demonstrate that biased processing in anxious individuals varies across different stimulus exposure durations (e.g., Bar-Haim et al., 2007; Frewen et al., 2008). Each stimulus

[25] Avoidance of threat cues may occur following acute activation of the fear system (e.g., Helfinstein, White, Bar-Haim, & Fox, 2008), while vigilance appears more common when participants are tested during 'baseline' conditions.

duration provides a unique 'snapshot' of spatial attention, allowing investigators to track both automatic and strategic aspects of information processing[26] (Yiend, 2010). Although 500 ms durations constitute a standard in the dot-probe literature, anxious individuals consistently exhibit threat-related attention biases at more rapid exposures, including those that preclude conscious awareness (Fox, 2002; Mogg & Bradley, 1999, 2002). Indeed, effect sizes for anxious-control comparisons are more robust in studies employing subliminal compared to supraliminal cue exposures (Bar-Haim et al., 2007). By contrast, an attentive bias for threatening stimuli appears to dissipate at longer durations (< 1000 ms), suggesting that the threat detection system in anxious individuals operates during the early, implicit stages of processing and reflects the output of a phasically operating system (Frewen et al., 2008). Neuroimaging results (Monk et al., 2006, 2008) provide a putative neural basis for such effects by demonstrating different degrees of amygdala involvement during rapid versus prolonged threat exposure[27].

Unfortunately, there have been relatively few studies that have systematically examined threat biases in socially anxious individuals at different exposure durations. One of these (Mogg et al., 2004) used a facial dot-probe task presented at 500 and 1250 ms durations among patients with social phobia and non-anxious controls. The authors found vigilance for threatening faces only at the 500 ms exposure in the anxious group. In another dot-probe study, socially phobic individuals showed threat-related attention

[26] There are some differences between attention and psychopathology researchers with respect to which durations are presumed to index these two types of information processing stages; these differences may reflect the varying degrees of complexity in the types of stimuli used in cognitive and affective studies (e.g., simple shapes versus facial expressions of emotion) (Yiend, 2010).

[27] Clinically anxious adolescents exhibit selective attention towards threat cues that correlates positively with amygdala activation at rapid durations; at longer durations, the adolescents show avoidance of threat that is inversely related to the degree of ventrolateral PFC involvement.

bias in the 175 ms but not during a longer 600 ms condition (Stevens, Rist, & Gerlach, 2009). A third study (Mansell et al., 2003) was a modified dot-probe experiment that varied the onset of probes (150 or 500 ms) relative to fixed latency pictures of faces or objects. The sample consisted of high and low socially anxious adults and involved a threat induction procedure. The authors noted a trend for avoidance of emotional faces in the < 500 ms condition. However, given the considerable methodological deviations of that study from previous dot-probe experiments, results of the latter experiment are difficult to integrate with the extant literature.

In addition to stimulus duration, another factor that can influence the magnitude and direction of attention biases involves the affective intensity of stimuli. Multiple theoretical models converge on the suggestion that individual differences in anxiety reflect variable settings of a relatively automatic threat evaluative system (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998; Yiend, 2010), such that anxious individuals generate stronger activations for an average or moderate-level of threat intensity. These models predict that the effects of anxiety on processing are most prominent for ambiguous stimuli – anxious individuals are more likely to interpret such items as threatening and exhibit vigilance towards them. In laboratory protocols, the threat value of stimuli can be operationalized by systematically altering salient physical features – for example, by the use of computer-generated morphs of emotional expressions. Indeed, a recent study by Wilson and MacLeod (2003) employed such an approach to show that high trait anxious individuals exhibit significantly greater vigilance towards moderately threatening faces when compared to low anxious controls. Interestingly, the authors did

not find support for the suggestion that highly anxious individuals oriented more towards stimuli of mild or strong intensity (but see Mogg, Garner, & Bradley, 2007). However, to our knowledge, there are no dot probe studies that have adopted such an approach in the study of social anxiety specifically[28].

In sum, selective attention biases to threat appear to be modulated by distinct exposure durations and stimulus intensities (in addition to individual differences in anxiety). In a recent review of the literature, Yiend (2010) concluded that future dot-probe studies should systematically manipulate both of these experimental variables to provide a complete picture of anxiety-related processing biases.

The Current Study The main purpose of the present study was to further investigate selective attention biases to social threat cues in a sample of high and low socially anxious young adults in an attempt to clarify and extend previous findings. In order to foster comparison with the extant literature, this study used a well-validated dot-probe methodology. Unlike the study described in Chapter 2, this experiment used behavioural measures in the context of an experiment that included the simultaneous presentation of affective and neutral stimuli. Exposure durations of the faces were varied in order to index relatively early (100 ms), mid-latency (500 ms) and late (1250 ms) aspects of attentional processing. Furthermore, computer generated morphs of emotional facial expressions (threatening, friendly) were used to model differences in affective intensity, ranging from mild (25% morph from neutral), moderate (50%) to strong

[28]An event-related potential study by Kolassa and colleagues (2009) failed to find evidence that socially anxious individuals were faster than low anxious controls to identify graded morphs of angry schematic faces. However, there is some evidence that high socially anxious individuals require less information (i.e., exhibit a lowered threshold) in order to interpret faces as negative in valence (Coles, Heimberg, & Schofield, 2008). Neither of these studies employed the dot-probe paradigm.

(100%) gradations. The goal of the study was to provide a more comprehensive characterization of selective attention biases in social anxiety by separately manipulating temporal and energetic aspects of affective stimulus delivery.

The main hypothesis was that socially anxious individuals, compared to their low anxious peers, would show vigilance towards threatening faces at the relatively early (~100 ms exposure) and mid-latency (~500 ms exposure) stages of information processing consistent with existing theoretical models (Rapee & Heimberg, 1997) and previous experiments (Mogg & Bradley, 2002; Mogg et al., 2004). Avoidant or attenuated responses to social threat were expected at the longer (1250 ms) durations. Furthermore, high, compared to low, socially anxious individuals were expected to show significantly enhanced orienting to moderately threatening faces in particular, similar to previous findings among individuals high in trait anxiety (Wilson & MacLeod, 2003). No between-group differences were predicted for selective attention biases toward friendly facial expressions.

4.2 Method

Participant recruitment procedures and self-report measures were identical to those described in Chapter 2.

Experimental Procedures and Stimuli All participants were tested at the Child Emotion Laboratory at McMaster University. Each participant was given a consent form to sign and briefed about the procedures of the experiment. The dot-probe task was completed in a dimly lit, sound attenuated room. Participants sat ~ 100cm away from the monitor (75 Hz vertical refresh rate) with both hands positioned on the PST Serial

Response Box (Psychology Software Tools, Inc.) situated on the table in front of them. Participants were encouraged to take short (two minute breaks) in between the blocks and were monitored for compliance via a closed circuit television in an adjoining room.

The face stimuli were photographs of two female (Models 3 and 10) and two male (Models 24 and 25) models depicting threatening, friendly and neutral facial expressions drawn from the NimStim set (Tottenham et al., 2009). The procedures for morph production are described more fully elsewhere (Gao & Maurer, 2009). Briefly, the variable intensities were created by morphing a neutral face with the threatening and friendly expressions of the same model adjusted to 25% (mild), 50% (moderate) and 100% (strong) increments (see Figure 4.1, for an example). Morphs were created using MorphX software (http://www.norkross.com), following established procedures (Calder, Young, Perrett, & Etcoff, 1996) based on 160 points manually positioned on the anatomical landmarks of each face.

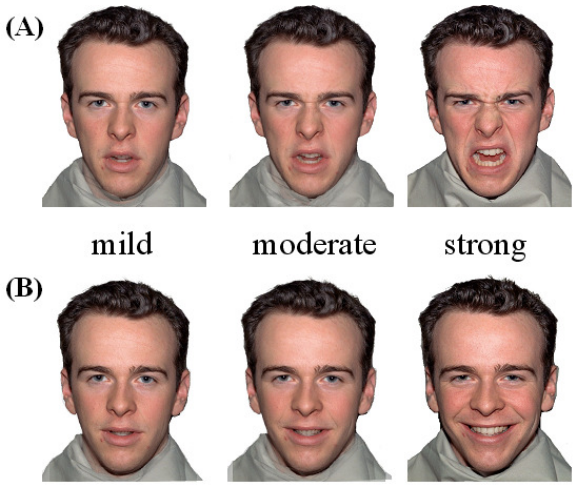

Figure 4.1: An example of the different affective intensities for (A) angry and (B) happy faces, in a single male model.

All of the photographs were matched for luminance and contrast using Photoshop (Version 10.0). Each face photograph was presented in full RGB color with a 234 x 300 pixel resolution.

Dot-Probe Task Each trial of the dot-probe task involved the following event sequence: (i) presentation of a central fixation cross for 500 ms, (ii) simultaneous presentation of two faces from the same model (threatening-neutral, friendly-neutral or neutral-neutral) side-by-side for variable durations (100, 500 or 1250 ms) and variable affective intensities (mild, moderate strong; see Figure 4.1), (iii) probe (asterisk) presentation in the left or right visual field. Participants indicated probe location (left/right) using a custom labeled response pad. Both speed and accuracy were emphasized. Trials were initiated by participant response or, if no response was recorded within 1500 ms of probe presentation, the next trial was automatically initiated.

Following a practice block of 15 trials, there were 3 experimental blocks of 156 trials each. In total, there were 24 presentations of threatening-neutral and friendly-neutral pairings for each exposure duration and at each level of affective intensity. Additionally, there were 12 neutral-neutral trials in total for every exposure duration. The faces were presented within a white rectangular area superimposed on a silver background. The precise order of stimulus exposure durations and intensities was randomized differently for every participant within each block. All of the trials were balanced to have the emotional stimuli and targets appear with equal probability in the left and right visual fields. Likewise, the probability (50%) of congruent (probe in same position as emotional face) and incongruent (probe in same position as neutral face) trials

was balanced throughout the experiment. The experiment was programmed and controlled using E-Prime (Version 1.2) software.

Data Analyses and Exclusion The data analyses focused on mean reaction times (RTs) from correct trials. Incorrect responses, as well as RTs less than 100 ms or longer than 1000 ms, were discarded. Reaction time data from two participants (1 high and 1 low socially anxious) were excluded due to failure to follow task instructions: participants were observed over closed circuit television to close their eyes and doze off at several points during the task (later confirmed by self-report). Three additional participants (2 high and 1 low socially anxious) were excluded for the following reasons: (i) inability to concentrate due to self-reported sleep deprivation and uncontrollable noise disturbance in testing room, (ii) recent substance use (marijuana) and (iii) repeated answering of a cell phone during the experiment. A total of 17 high and 16 low socially anxious participants were included in final data analyses following the exclusions.

Inspection of Q-Q plots indicated that mean RTs (in ms) were approximately normally distributed. The initial omnibus ANOVA revealed a significant four-way interaction of Group (2: High/Low Socially Anxious) x Congruence (2: Congruent/Incongruent) x Emotion (2: Threatening, Friendly) x Exposure Duration (3: 100/500/1250 ms), [$F(2, 30) = 4.84$, $p = 0.015$, $\eta^2 = 0.25$]. Separate mixed-model analyses of variance (ANOVAs) were conducted for each of the three exposure durations, using Group as the between-subject factor and Congruence, Probe Location, Emotion and Intensity as the within-subject factors. Significant interactions that involved the Congruence term were further decomposed by computing attention bias indices according

to the following formula: Attention Bias Index = Mean Incongruent RT – Mean Congruent RT. Accordingly, a positive attention bias index denotes vigilance and a negative index denotes avoidance of a stimulus. Dimensional analyses focused on partial correlations (controlling for BDI depression) between the SPIN scores and total attention bias scores for threatening and friendly faces. Correlations were examined separately for each of the three exposure durations.

4.3 Results

Demographic and Clinical Characteristics There was no difference in age ($p >$ 0.28) or sex composition ($p > 0.57$) between the high and low socially anxious groups. The SPIN scores showed high test-rest reliability from pre-screening to the laboratory visit ($r = 0.93$, $p < 0.001$). One-way ANOVAs confirmed that the high socially anxious group exhibited greater SPIN scores than the low anxious group, both at pre-screening and at the time of the laboratory visit several months later (ps < 0.001, η^2s > 0.85), confirming the intended groupings. The high socially anxious group ($M = 16.06$, $SD =$ 10.08) also reported significantly more BDI symptoms than the low socially anxious group ($M = 6.07$, $SD = 5.89$) at the time of the laboratory visit ($p = 0.002$, $\eta^2 = 0.28$).

Selective Attention RT Data

100 ms There was a main effect of Location [$F(1, 31) = 11.68$, $p = 0.002$, $\eta^2 =$ 0.27] with participants responding faster when probes occurred in the right ($M = 392.76$, $SEM = 10.57$), compared to the left ($M = 404.83$ ms, $SEM = 10.70$) visual field. There were also significant Group x Congruence x Emotion [$F(1, 31) = 5.73$, $p = 0.02$, $\eta^2 =$ 0.16] and Group x Congruence x Intensity [$F(2, 30) = 4.36$, $p = 0.02$, $\eta^2 = 0.23$]

interactions. There were no other significant main or interaction effects, although there was a Location x Emotion trend [$F(1, 31) = 3.64$, $p = 0.07$].

To clarify the first interaction, separate one-way ANOVAs were performed on attention bias index scores for threatening-neutral and friendly-neutral face pairs. There was a significant main effect of Group for the threatening-neutral [$F(1, 31) = 4.63$, $p = 0.04$, $\eta^2 = 0.13$], but not the friendly-neutral pairs ($p > 0.13$). As illustrated in Figure 4.2, high socially anxious adults showed greater vigilance towards threatening faces compared to low socially anxious adults. Within-group contrasts of the bias scores against zero (no bias) confirmed that the high socially anxious group showed selective attention toward threatening faces [$t(16) = 2.43$, $p = 0.03$], but no preferential processing of friendly faces ($p > 0.58$). The low socially anxious participants did not show significant attention biases for either of the emotional faces ($ps > 0.12$).

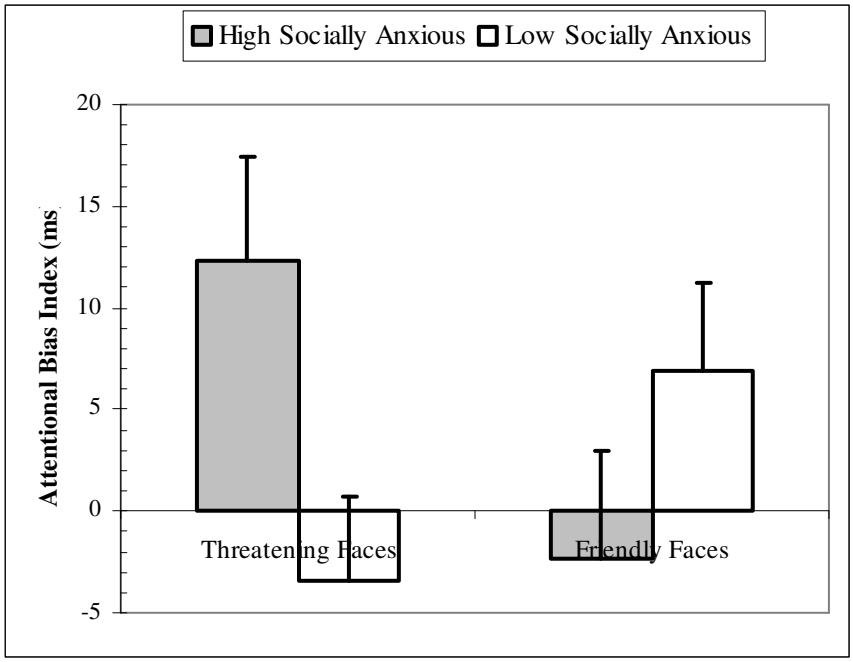

Figure 4.2: The 100 ms attentional bias index shown separately for angry and happy faces (collapsing across intensities) in the high and low socially anxious groups. A positive attention bias index denotes vigilance and a negative index denotes stimulus avoidance. Bars denote S.E.M.

To break down the second interaction, attention bias scores were collapsed across threatening-neutral and friendly-neutral pairs for each morph intensity and entered as dependent variables into three separate one-way ANOVAs. There was a significant main effect of Group for the moderate intensity only [$F(1, 31) = 8.08$, $p = 0.01$, $\eta^2 = 0.21$] (other ps > 0.38). Table 4.1 illustrates that high socially anxious participants showed more vigilance toward moderately intense faces compared to low socially anxious individuals, regardless of emotion[29]. Within-group contrasts against zero indicated a significant attention bias for emotional faces with moderate intensity in the high socially anxious group ($p = 0.02$), while this effect was missing in the low socially anxious sample ($p > 0.19$).

[29] However, a closer inspection of the means within the high socially anxious group revealed that this effect was driven primarily by the large attention bias for the moderately angry faces ($M = 23.29$ ms, $SEM = 9.25$), compared to a somewhat negligible advantage for the moderately happy faces ($M = 2.15$ ms, $SEM = 5.91$).

Table 4.1: Attention bias score means (S.E.M.) for the 100 ms exposure collapsed across emotions

Intensity	High Anxious	Low Anxious
Mild	-4.12 (4.59)	3.13 (6.93)
Moderate	12.72 (4.83)[a]	-5.78 (4.32)[a]
Strong	6.50 (5.31)	7.91 (4.56)

Note: Positive scores indicate attentional vigilance, negative scores indicate attentional avoidance. Means with the same superscript are significantly different between groups ($p < 0.05$).

In order to ensure that the social anxiety group effects were not confounded by concurrent depression and dysphoria, we conducted control analyses, in which we regressed the attention bias scores on BDI symptoms at the first step and on group (1 = high, 2 = low) at the second step. Being high versus low in social anxiety continued to predict the total threatening attention bias score ($\beta = -0.51$, $p = 0.02$) and attentional bias for faces with moderate emotional intensity ($\beta = -0.51$, $p = 0.02$), while BDI scores failed to account for a significant degree of variance (ps > 0.11). The addition of group membership improved the predictive utility of both models (ΔR^2s $= 0.19$, ps < 0.02).

500 ms There were no significant main or interaction effects at this exposure duration, only trends for Location ($p = 0.09$) and Emotion x Intensity ($p = 0.08$).

1250 ms There was a main effect of Location [$F(1, 31) = 9.69$, $p = 0.004$] with participants responding faster to probes occurring in the right ($M = 375.91$ ms, $SEM = 10.12$) versus left ($M = 385.97$ ms, $SEM = 11.93$) visual field. Additionally, there was a Group x Emotion interaction [$F(1, 31) = 4.35$, $p = 0.05$, $\eta^2 = 0.23$]. This interaction

reflected the finding that high socially anxious participants responded slightly slower (p = 0.05) on threatening-neutral compared with friendly-neutral trials (M threatening-neutral = 378.07 ms, SEM = 15.22 vs. M friendly-neutral = 372.39 ms, SEM = 14.33) regardless of probe location (i.e., congruent or incongruent). No such effect was observed among low socially anxious participants (p = 0.41).

Correlational Analyses There was a positive association between social anxiety (total SPIN scores) and attention bias for threatening faces presented at 100 ms durations, controlling for BDI symptoms (partial r = 0.38, $p < 0.05$). There was no significant association between SPIN scores and attention bias for friendly faces at 100 ms exposures (p = 0.2). Follow-up analyses showed a positive relation between attention bias for threatening faces and the fear (partial r = 0.37, $p < 0.05$) and physiological arousal (partial r = 0.44, $p < 0.02$) SPIN subscales, with BDI scores partialled out. There was no relation ($p > 0.13$) between threat-related attention bias scores and the avoidance subscale. There were no other significant correlations between the self-report and attention measures.

Selective Attention Accuracy Data

Accuracy was examined in addition to the RT data reported above. There were no main or interaction effects involving Group at 100 (ps > 0.24) or 500 (ps > 0.18) ms exposure durations. However, there was a significant Group x Emotion x Intensity interaction ($p < 0.02$, $\eta^2 = 0.24$), in the 1250 ms condition. Separate analyses for each valence indicated a significant Group x Intensity interaction for friendly (p = 0.01, η^2 = 0.28), but not threatening ($p > 0.67$) faces. There were no significant between group

differences (ps ≥ 0.10) in accuracy on trials that included friendly faces of any degree of intensity. However, within the low socially anxious group there was a significant main effect of Intensity that fit a linear model [$F(1, 15) = 15.25$, $p = 0.001$, $\eta^2 = 0.50$] on trials that included a friendly face. Trials that included a friendly face of mild intensity were associated with the least accuracy ($M = 95.1\%$), in comparison to faces of moderate ($M = 97.7\%$) and strong ($M = 98\%$) intensity. By contrast, there was no effect of Intensity on response accuracy among high socially anxious individuals ($p > 0.74$).

4.4 Discussion

Separate manipulations of the temporal and energetic dimensions of affective stimulus delivery in a dot probe task were used in order to delineate the dynamic patterns of biased attentional processing associated with subsyndromal social anxiety. There were several findings that deserve to be highlighted. First, collapsing across morph gradations, the high socially anxious group exhibited increased attentional processing of threatening faces. Second, when examining responses to the different intensities of emotional expressions, the high socially anxious group showed increased attentional processing of emotional faces that were moderate in intensity (i.e., morphed by 50% from neutral). Importantly, these patterns of biased attention emerged only when the faces were presented rapidly (100 ms) and were relatively specific to social anxiety, since removing the effects of concomitant depression did not diminish the effects. Finally, at the longest exposure duration (1250 ms), the high socially anxious group showed a general motor

slowing on trials that included a threatening-neutral face pair versus those that included a friendly-neutral pair.

Increased attentional processing of threatening faces by the high socially anxious group is consistent with one influential cognitive-behavioral model of social phobia (Rapee & Heimberg, 1997). Specifically, if as the model predicts, individuals high in social anxiety are constantly scanning their environment for cues of others' negative evaluation, then threatening facial expressions, which signal social transgression and disapproval, should dominate over neutral expressions in competition for limited attentional resources. The dimensional analyses indicated that threat vigilance was related to the fearfulness (e.g., being afraid of speaking with strangers) and physiological arousal (e.g., distress associated with sweating in front of others) aspects of social anxiety, rather than avoidance oriented behaviours. Our findings further suggest that social anxiety-related biases operate at early stages of information processing, implicating relatively automatic aspects of cognition. This pattern is consistent with the ERP results from Chapter 2 and previous studies that have demonstrated stronger effects of anxiety on dot-probe experiments with rapid presentation of affective stimuli[30] (Bar-Haim et al., 2007). Recently, investigators have developed neural network connectionist models of the affective dot-probe task, incorporating physiologically realistic time-varying responses of amygdala nodes (Frewen, Dozois, Joanisse, & Neufeld, 2008).

[30]However, it should be noted that ~100 ms exposures are supraliminal and not below the threshold of conscious detection. There is reason to hypothesize that subliminal presentations might have enhanced the between-group differences.

Importantly, simulation results from this computational model also generate threat-related biases that are larger for more rapid exposures.

It is not clear why there was an absence of threat-related attention biases at the longer exposure durations. The 500 ms exposure, in particular, is considered as the 'standard' duration in dot probe studies of anxiety so that the lack of significant findings here is somewhat surprising. One previous study (Mogg, Philippot, & Bradley, 2004) that included patients diagnosed with social phobia found evidence of vigilance toward threatening faces, when these were presented at 500 ms, but not at the 1250 ms duration. In an analogue study, high socially anxious participants showed vigilance for threatening faces that were backward masked (Mogg & Bradley, 2002). Unfortunately, the latter experiment did not include multiple exposure durations. It is possible that when social anxiety is severe enough to warrant clinical diagnosis, biases in attention for social threat are evident at exposures that allow enough time for multiple eye movements. However, a recent study by Stevens and colleagues (2009) found evidence for vigilance to threat during rapid (175 ms) but not longer (600 ms) exposures in a clinically diagnosed socially phobic sample. It is also possible that the dot-probe task itself serves as a more sensitive index of attentional processing when images are presented at rapid speeds (see Staugaard, 2010).

Another possibility is that following initial biases in attention for signals of social disapproval, socially anxious individuals shift their attention primarily towards internal threat cues (e.g., heart palpitations, perspiration) as they establish increasingly negative self-representations. Indeed, this internal focus of attention is predicted by some of the

existing cognitive models of social anxiety (Clark, 1999; Clark & McManus, 2002). The findings here would suggest that such an internal focus occurs only after an initial scan for external threat cues, however, future studies need to specifically test this possibility. There are practical implications for such experiments since the proposed attention bias modification treatments appear to target late, rather than early, stages of threat processing (Koster, Baert, Bockstaele, De Raedt, 2010). If the hypothesis above is valid, it may suggest that tailoring attention bias modification treatments for social anxiety to focus on internal cue processing may have greater anxiolytic impact than training attention for external threats.

It should also be noted that there was no evidence from the present study that high socially anxious participants exhibited active avoidance of threatening faces at late stages of information processing, as would be predicted by some popular vigilance-avoidance cognitive models. Our null findings in this regard appear consistent with a prior dot probe study of social phobics (Mogg & Bradley, 2004) that likewise failed to find evidence for late avoidance. To date, support for vigilance-avoidance processing in anxiety has tended to derive primarily from eye tracking (Brunet, Heisz, Mondloch, Shore, & Schmidt, 2009; Rohner, 2002) and electrocortical (Jetha, Zheng, Schmidt, & Segalowitz, 2011; but see, Wieser, McTeague & Keil, 2010) data.

With regard to affective intensity, our initial hypotheses were only partially supported. High socially anxious individuals showed increased attentional processing of expressions that were moderate in intensity, but this effect manifested regardless of the emotion (i.e., there was no significant triple interaction between group, intensity and

emotion). However, it should be noted that a post-hoc inspection of the means within the high socially anxious group revealed that the effect was explained mostly by increased vigilance for the moderately threatening faces. Emotional faces with a moderate degree of morphing were the most ambiguous of all gradations as they included equal (50%) portions of neutral and affective features. According to recent formulations (e.g., Pessoa, 2010), ambiguous stimuli are particularly effective at mobilizing brain circuits for affective attention. In previous work, socially anxious participants have been shown to exhibit a strong bias for interpreting ambiguous social information in a more threatening or negative context than low socially anxious individuals (Constans, Penn, Ihen, & Hope, 1999; Kanai, Sasagawa, Chen, Shimada, & Sakano, 2010; Moser, Hajcak, Huppert, Foa, & Simons, 2008). It is possible that socially anxious individuals exhibit a lowered threshold for assigning threat value to social signals (Coles, Heimberg, & Schofield, 2008). Unfortunately, the present experiment did not measure individuals' ratings of emotional arousal in response to the face stimuli.

Although unexpected, the general reaction time slowing observed on trials that included an threatening-neutral face pair (at 1250 ms) in the high, but not the low, socially anxious group may be interpreted in light of extensive evidence that the perception of threat elicits a slight motor inhibition in anxiety, resulting from a transient interruption of ongoing activity (e.g., Mogg, Holmes, Garner, & Bradley, 2008). Since this motor slowing effect was observed regardless of trial type (i.e., congruent or incongruent probe location), it suggests that high socially anxious participants were more sensitive to the threat content of faces, regardless of whether the threatening faces were

being actively attended. However, it should be mentioned that another interpretion of the RT slowing could be offered in the context of greater cognitive resources being invested among high socially anxious individuals in the inhibition of threat-related information.

Finally, the behavioural performance of the low socially anxious group within the 1250 ms condition was greater on trials that included friendly faces of stronger intensity. Since dot probe studies typically focus solely on reaction time differences and do not examine accuracy rates, it is difficult to interpret the accuracy-related effects observed at the 1250 ms exposure. However, these findings may suggest that low socially anxious participants exhibit optimal attention for faces with high 'friendliness' during strategic stages of cognitive processing.

Limitations and Future Directions The present study had several limitations that should be addressed in future work. First, participant ratings of hostility for the different morph gradations were not collected, thereby missing an opportunity to determine whether high socially anxious individuals really do assign a greater negative value to ambiguous faces. Second, in the absence an anxiety control group (e.g., spider fearful individuals) the relative specificity of the processing biases uncovered in the high socially anxious group remains to be determined. The specificity issue is an important one since threat-related biases may be the functional outcome of hyperexcitability of a generic fear system that is shared across multiple anxiety disorders[31]. Additionally,

[31] An interesting question concerns the degree to which vigilance for angry faces may manifest as a function of hyperreactivity in a generalized fear system, not necessarily one that is dedicated solely to social fears (see also, Mansell et al., 1999). Indeed, in the present sample there was a significant association between a self-report index of a generic behavioral inhibition system (BIS; Carver & White, 1994) and attention bias for angry faces presented at 100 ms ($r = 0.41$, $p = 0.02$), but not the other

future work should consider using critical facial expressions other than angry ones (e.g., disgust, contempt). Finally, future work should consider taking advantage of recent technological innovations (e.g., virtual reality simulations of large audiences) to embed research in more ecologically valid settings that may generalize to real world phenomena better than idealized laboratory paradigms that rely on simple stimulus/response measures.

Conclusions Similar to other anxiety disorders and anxious personality traits, individuals who are high in socially anxiety appear to exhibit vigilance for social threat signals as well as emotionally ambiguous faces more generally. These biases in selective attention seem to operate relatively early in the processing stream and tend to dissipate during later, more strategic stages. An important contribution of this chapter is that, unlike Chapter 2, it provides evidence for a behavioural (and not just a covert, physiological) difference between the high and low socially anxious groups during the processing of threat-related signals.

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durations. The behavioral inhibition system is presumed to respond to cues of punishment (including, but not limited to, social cues) and to be grounded in septo-hippocampal and amygdala brain circuits.

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Chapter 5

Abstract

Coupling between electroencephalographic (EEG) δ and β oscillations is enhanced among anxious individuals and healthy individuals during anticipatory anxiety. EEG coupling patterns associated with psychotherapy have not yet been quantified in socially anxious individuals. We used a double- baseline, repeated measures design in which 25 adults with a principal DSM-IV diagnosis of social anxiety disorder completed 12 weekly sessions of standardized group cognitive behavioral therapy and four electrophysiological and clinical assessments: two at pretreatment, one at midtreatment, and one at posttreatment. Treatment was associated with reductions in symptom severity across multiple measures and informants, as well as reductions in δ/β coupling magnitude at rest and during speech anticipation. Moreover, the clinical group exhibited greater coupling at pretreatment than low socially anxious post-hoc controls. The EEG cross-frequency profiles in the clinical group normalized by posttreatment. Our findings provide evidence of concomitant improvement in neural and behavioral functioning among socially anxious adults in response to psychotherapy.

5.1 Introduction

Studies examining the neural correlates of psychological treatment are far outnumbered by analogous studies on pharmacological interventions despite evidence that cognitive behavioural therapy (CBT) and medications have equal clinical efficacy for the acute treatment of anxiety (Otto, Behar, Smits, & Hofmann, 2009), with CBT being

more cost effective over the long term (Heuzenroeder et al., 2004). A promising line of research involves tracking brain activity before and after the delivery of evidence-based psychological treatments that are standardized and proven to reduce symptoms. One example of such a treatment is CBT, a highly structured and collaborative form of psychotherapy that helps patients identify and modify their maladaptive, interactive patterns of thoughts and behaviors underlying emotional dysfunction (Barlow, 2008).

The majority of current research on brain changes in response to psychotherapy consists of nuclear and magnetic imaging studies, involving activation comparisons pre and posttreatment[32] (Porto, Oliveira, Mari, Volchan, Figueira, & Ventura, 2009; Roffman, Marci, Glick, Dougherty, & Rauch, 2005). Rather than regionally isolated alterations, psychotherapeutic interventions seem to produce changes in the dynamic interactions between multiple cortical and subcortical brain regions. For example, psychotherapy for obsessive-compulsive disorder reduces correlated activity in cortico-striatal-thalamic circuits (Baxter et al., 1992; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996), while depression treatment affects the balance of fronto-limbic activity (Goldapple et al., 2004).

By comparison to fMRI and PET scans, studies quantifying treatment-related electrophysiological changes are rare (for exceptions, see Leutgeb, Schafer, & Schienle, 2009; Oathes et al., 2008; Rabe, Zoellner, Beauducel, Maercker, & Karl, 2008). Brain electrical measures (EEG) reveal the oscillatory characteristics of neuronal mass activity,

[32]Studies have differed considerably in design, including the type of therapy, the extent to which comparisons were primarily within or between-group (employing wait-list or healthy control groups) and the nature of the neural signals recorded.

and unlike blood-oxygenation levels (Attwell & Iadecola, 2002), they provide a direct index of synchronous dendritic potentials in real time. Accordingly, the EEG may be uniquely suited to examining the brain's interactive dynamics that are assumed to accompany successful clinical treatments.

The macroscopic brain oscillations revealed by EEG measures cover a broad frequency spectrum, ranging from slow (SW; δ, θ) to fast wave (FW; β, γ) activities. It has been suggested that the frequency of oscillations reflects recirculation time in neuronal pathway loops (Bressler & Tognoli, 2006), such that SW oscillations integrate neural processes spanning large distances, while FW electrical signatures relate to synchronization of topographically restricted regions (von Stein & Sarnthein, 2000). Several independent lines of evidence from human and animal studies support the suggestion that subcortical structures play a stronger role in SW oscillatory generation, while FW rhythms are chiefly mediated by resonant cortico-cortical connections (for reviews, see Knyazev, 2007; Uhlhaas & Singer, 2006).

First, electrophysiological recordings from anesthetized and freely moving non-human animals show that δ oscillations are generated by cell bodies in the ventral tegmental area (Grace, 1995), ventral pallidum (Lavin & Grace, 1996), and the nucleus accumbens (Leung & Yim, 1993). Oscillations of approximately 7 Hz have been observed following limbic system stimulation[33] (Gray, 1991). Second, although it is impossible to non-invasively record electrical activity from deep neural structures in humans, source localization studies of scalp EEG provide evidence that δ generators lie

[33]In human studies, such oscillations are positively related to cerebral metabolism in the anterior cingulate cortex (Pizzagalli, Oakes, & Davidson, 2003).

in deeper layers of the cortex than β generators (Hjorth & Rodin, 1988; Michel, Lehmann, & Henggeler, 1992; Michel, Henggeler, & Brandeis, 1993; Tsuno, Shigeta, Hyoki, Kinoshita, Ushijima, Faber et al., 2002). Moreover, regions that have been identified as putative cortical sources of delta activity (e.g., medial frontal cortex) show extensive reciprocal connectivity with various midbrain and limbic structures (Alper, Günther, & Prichep, 1998; Alper, John, Brodie, Günther, Daruwala, & Prichep, 2006). Finally, comparative EEG analyses indicate a progressive shift in peak power across phylogeny: reptilian brains oscillate mostly in the δ frequency range (Gonzáles, Gamundi, Rial, Nicolau, De Vera, & Pereda, 1999), while θ constitutes the dominant rhythm in lower mammals (Sainsbury, 1985). By contrast, human brains, equipped with a large neocortex, display peak EEG power in the 10 Hz α-range (Başar & Güntekin, 2006). The neural origins of β and γ rhythms are not clear, but they most likely reflect the electrical properties of intracortical connections and resonant activities in thalamo-cortical and cortico-cortical circuits (Gómez, Marco-Pallares, & Grau, 2006; Steriade, 2005).

Since EEG frequency bands appear to represent the arousal of distinct neuronal systems, interactions among them are possible. Recently, it has been demonstrated that SW and FW oscillations exhibit coupling in spectral power and/or phase or some combination of domains (e.g., phase-to-power coupling; see Jensen & Colgin, 2007). Cross-frequency coupling may represent a neural code for integrating activity across different neuroanatomical levels (Friston, 1997). A sustained increase in coherence between SW and FW power has been implicated in multiple neuropsychiatric conditions

(Llinás & Steriade, 2006; Llinás, Ribary, Jeanmonod, Kronberg, Mitra, 1999). Some researchers (e.g., Schutter, Leitner, Kenemans, & van Honk, 2006) have suggested that δ/β power coupling might be an EEG correlate of cortico-subcortical communication, where greater positive coupling reflects increased cortical-subcortical interaction[34]. It has previously been shown that δ/β power correlations are enhanced in anxiogenic situations (Knyazev, Schutter, & van Honk, 2006; Miskovic, Ashbaugh, Santesso, McCabe, Antony, & Schmidt, 2010) relative to resting periods. Moreover, δ/β coupling is also significantly elevated at rest in behaviorally inhibited adults (van Peer, Roelofs, & Spinhoven, 2008) and and high amounts of positively correlated δ/β activity predict selective attention to socially threatening images (Putman, 2011). Recently, it has also been shown that patients with obsessive-compulsive disorder exhibit atypical δ/β power correlations as well, potentially related to cortico-striatal dysfunction (Velikova, Locatelli, Insacco, Smeraldi, Comi, & Leocani, 2010).

On a neuroendocrine basis, two classes of steroid hormones – cortisol and testosterone – that prepare organisms for behavioral avoidance (Rosen & Schulkin, 1998) and approach (Hermans, Putman, Baas, Koppeschaar, & van Honk, 2006), respectively, affect EEG δ/β coupling in opposite ways. Coupling is increased by high concentrations of natural (Schutter & van Honk, 2005) and synthetic cortisol (van Peer, Roelofs, & Spinhoven, 2008). By contrast, the anxiolytic hormone testosterone is associated with δ/β decoupling, whether administered in its synthetic form (Schutter & van Honk, 2004)

[34]It should be noted that in all of the δ/β coupling studies reported in the present study, 'coupling' is quantified across participants, rather than separately within each individual. Likewise, the cross-frequency coupling highlighted here is distinct from cross-regional (e.g., frontal to occipital) coupling. Recent evidence (Knyazev, 2011) suggests that within-subject patterns of δ/β coupling during acute anxiety are highly similar to results reported across participants.

or present at high physiological concentrations (Miskovic & Schmidt, 2009). A testosterone induced decoupling of prefrontal and subcortical regions has also been observed in a recent fMRI study (van Wingen, Mattern, Verkes, Buitelaar, & Fernandez, 2010). It is interesting to note that non-human animal work suggests that cortisol and testosterone exhibit largely antagonistic actions at several corticolimbic centres (Viau, 2002), which suggests that the EEG findings may be sensitive to two distinct motivational states.

Social anxiety, its treatment and EEG cross-frequency coupling To date, no studies appear to have examined treatment-related EEG changes in social anxiety disorder (SAD), despite evidence from controlled clinical trials that CBT is effective in the treatment of this condition (Antony & Rowa, 2008; Moscovitch, Antony, & Swinson, 2009; Smits & Hofmann, 2009). Knowing more about the biological and cognitive (Moscovitch et al., under review) correlates associated with treatment outcome represents an important research area since SAD is currently one of the most under-treated anxiety disorders (Cuthbert, 2002).

Previous work from our group has shown that the anticipation of public speaking produced significant increases of prefrontal δ/β coupling in a subclinical sample of high socially anxious adults (Miskovic et al., 2010). An experimental design that involves the anticipation of public speech is particularly well-suited for studying social anxiety since one of the hallmarks of anxiety is the anticipation of and worry surrounding impending threats, real or imagined (Barlow, 2008). Here, we were interested in extending our previous EEG findings from a subclinical to a clinical sample. More specifically, we

wanted to examine whether psychotherapeutic treatment of SAD leads to concomitant δ/β coupling decreases. Discovering a reliable neural correlate of treatment, and moreover one that can be obtained non-invasively, may potentially provide novel insights into the psychophysiology of social anxiety as well as carry significant practical implications.

Regional EEG was measured at rest and prior to an anticipated public speech in a sample of 25 adults diagnosed with SAD (generalized subtype)[35]. Continuous brain electrical activity was recorded at four separate visits (two pretreatment, one midtreatment and one posttreatment) in a double-baseline repeated measures design where participants served as their own controls. Treatment consisted of 12 standardized group CBT sessions. Additionally, the EEG profiles of the treatment group at pre- and posttreatment were compared with a subclinical sample of high and low socially anxious adults that we have previously studied (Miskovic et al., 2010). The subclinical sample served as a post-hoc control group.

We hypothesized that measures of cross-frequency coupling, which may index aspects of cortico-subcortical dynamics that are not immediately available in functional neuroimaging[36](Schutter et al., 2006), would be sensitive to treatment-related reductions in clinical symptomatology. On the basis of prior studies, reductions in δ/β coupling were expected to occur primarily in electrodes overlying the prefrontal cortex. In terms of comparisons with the post-hoc control groups, patterns of δ/β coupling in the clinically diagnosed SAD participants were expected to be similar to the high anxious group at the

[35]Generalized subtype indicates that anxiety is prevalent in most social situations, rather than being restricted to very specific contexts.
[36]Cross-frequency coupling patterns observed in oscillatory measures are not likely to produce a hemodynamic response that is detectable in fMRI environments (Cohen, 2011).

pretreatment assessment and analogous to the low socially anxious group by posttreatment.

5.2 Method

Participants Thirty-three outpatients from a large anxiety treatment clinic at an urban hospital in Hamilton, Ontario participated in this study. All participants received a principal SAD (generalized subtype) diagnosis as determined by trained clinicians on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders—4th edition (SCID-IV; First et al., 2001). Because of attrition, the final sample size was 25 (12 females, 13 males; see Figure 5.1). Clinical severity ratings (CSRs) were assigned on a 0 to 8 scale, with CSRs of 4 and above representing an increasing level of clinically significant interference and distress associated with the principal diagnosis. The CSRs for SAD diagnoses assigned in the study sample ranged from 4 to 7 (M = 5.54, SD = 0.90). All participants were of Caucasian ethnicity, right-handed and ranged in age from 19 to 73 years (M = 35.9 yrs, SD = 15.18).

Figure 5.1 summarizes study design details. Participants were requested to maintain stable medication type and dosage throughout the study. Seven patients reported changes either in medication type or dosage throughout the study's course.

Exclusion criteria included current mania, psychosis, significant suicidality, and/or organic brain disorders. We also excluded individuals with current substance abuse/dependence if these patients: (a) could not agree to refrain from use prior to and during treatment and experimental protocols; and (b) were deemed by the clinical team to

be unsuitable for group CBT targeting SAD and required initial substance use treatment. Additionally, we excluded participants who self-reported consuming β-blockers within 3 days of the EEG testing and alcohol, marijuana or antihistamines within 12 hours of EEG testing (see Figure 5.2 for additional clinical information about the sample).

Figure 5.1: Flowchart of study design and sample attritition.

Post-Hoc Controls For a post-hoc control group, we used a nonclinical sample of high (n = 24) and low (n = 25) socially anxious adults who were selected from among 330 young adults on the Social Phobia Inventory (SPIN; Connor et al., 2000). The selected sample participated in an experimental protocol involving a resting and speech

anticipation condition comparable to the one used with the clinical sample (see Miskovic et al., 2010, for overview of sample demographics).

Clinical Treatment Procedures All of the participants completed 12 weekly, 2-hour sessions of group CBT for SAD at the Anxiety Treatment and Research Centre, in St. Joseph's Healthcare, Hamilton, Ontario. The structure for the group CBT sessions was based on a standardized protocol (Antony & Swinson 2009; Heimberg & Becker, 2002). Core components of group CBT included psychoeducation, cognitive restructuring, in-session and between-session exposure exercises and social skills training. Group CBT sessions were administered by two to three qualified therapists with seven to nine patients per group. Sessions were administered in consecutive weeks, with a 1-week break between the 6th and 7th sessions to allow for midtreatment assessments.

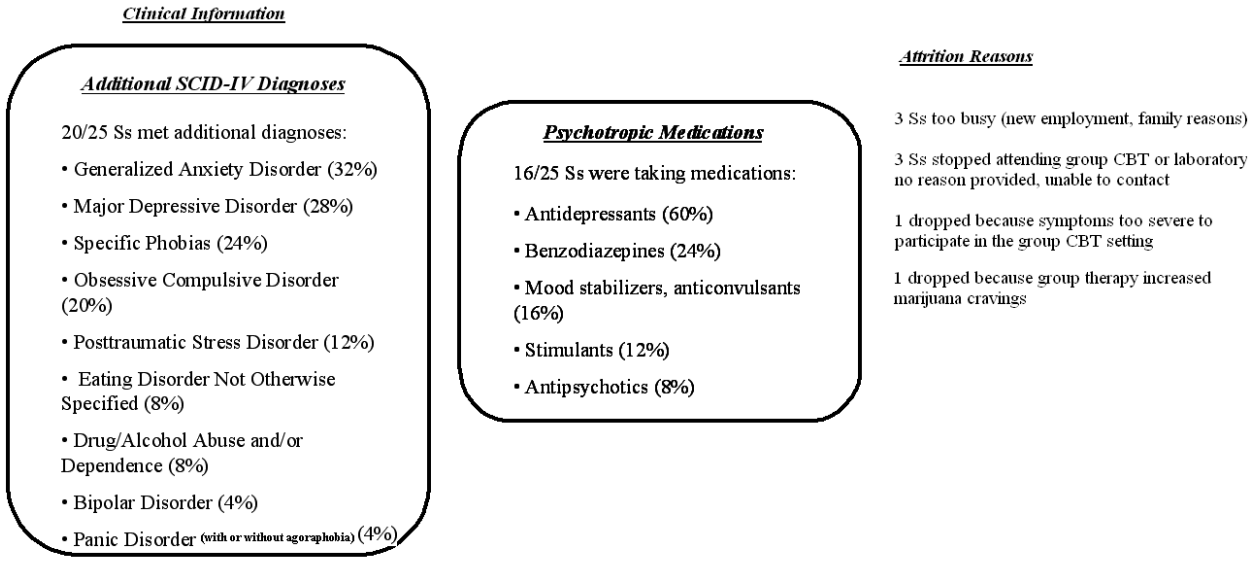

Figure 5.2: Additional clinical information about the study sample.

Experimental Procedures EEG testing prior to a standardized speech task was administered in the laboratory twice at pretreatment, once at midtreatment, and once at posttreatment. Upon arrival to the laboratory, procedures were explained to participants and written informed consent was obtained for the psychophysiological portion of the study. A different set of speech topics were generated for each of the four EEG laboratory assessments, but otherwise procedures remained identical. Following EEG application, participants were given several minutes to acclimate to the testing environment. Participants' EEG measures were then collected continuously during 6 minutes of rest, consisting of alternating three 1-minute eyes open and eyes closed epochs. Following the resting recording, participants completed a measure of state anxiety.

Participants were then given 3 minutes to prepare an impromptu speech in front of two female observers and a video camera. EEG was recorded during this anticipatory (eyes open) period. At the end of the anticipation period, participants completed state anxiety measures for the second time. Participants were next provided with a set of three predetermined speech topics on controversial issues (e.g., capital punishment, same-sex marriage, funding of religious schools) and performed the public speaking task on any one or more of these topics for a maximum of 3 minutes. Each participant's posttreatment assessment was scheduled to occur within a window of approximately 2 weeks following the final (12^{th}) group CBT session. All laboratory procedures were conducted under the supervision of trained research staff and approved by the University of Waterloo and Hamilton Health Sciences Ethics Committees.

Clinical and Self-Report Measures We administered several measures to track treatment efficacy and obtain measures of state anxiety during the EEG visits. Independent, trained clinicians blind to the study purpose and participants' treatment status, as well as one of the group therapists, rated each participants' illness severity on the *Clinical Global Impression Scale* (CGI; Guy, 1976), at both pre- and posttreatment. Previous work has established CGI validity in evaluating treatment efficacy for SAD (Zaider et al., 2003). In addition, participants completed the following self-report scales (1) the *Illness Intrusiveness Ratings Scale* (IIRS; Devins, 1994), a 13-item questionnaire measuring the extent to which an illness, its treatment or both interfere with daily life, (2) the *SPIN* (Connor et al., 2000), a 17-item inventory measuring symptoms of social fear, avoidance and arousal, (3) the *Liebowitz Social Anxiety Scale* (LSAS-SR; Baker et al., 2002), a 24-item measure that assesses fear and avoidance in a broad range of social interactions, and (4) the *Beck Depression Inventory - 2nd edition* (BDI-II; Beck, Steer & Brown, 1996). Participants' state anxiety during the speech at each EEG visit was measured using the *Subjective Units of Distress Scale* (SUDS), from 0 (no anxiety) to 100 (highest possible level of anxiety), both before and following the speech anticipation[37].

EEG Data Collection and Data Reduction Regional EEG was recorded using a lycra stretch cap (Electro-Cap International, Eaton, OH). Electrodes were positioned according to the International 10/20 Electrode System. The experimenter used the blunt

[37]To ensure that the speech anticipation task was experienced as stressful, we ran four separate repeated measures ANOVAs on SUDS scores. There was a main effect of condition across all four laboratory visits (resting, speech anticipation; $ps < 0.001$). Overall, participants provided higher SUDS ratings (i.e., reported more anxiety) during the speech anticipation condition than during the resting condition.

end of a cotton swab in combination with an abrasive gel to gently abrade each site. An electrolyte gel was applied to each site to act as a conductor. Electrode impedances were all below 10kΩ and within 500Ω between homologous sites.

EEG was recorded from 8 locations: left and right midfrontal (F3, F4), central (C3, C4), parietal (P3, P4) and occipital (O1, O2) regions. Electrodes were referenced to the central vertex (Cz) during recording. The channels were amplified using SA Instrumentation Bioamplifiers and bandpass filtered between 1 and 100 Hz. Each channel was digitized on-line at a sampling rate of 512 Hz.

EEG data were visually scored for artifact due to eyeblinks, eye movements, and other movements using software developed by James Long Company (EEG Analysis Program, Caroga Lake, NY). Artifact contaminated portions of the EEG were manually identified and excluded from analysis. All artifact-free data were analyzed using a discrete Fourier transform (DFT), with Hanning window of 1 s width, with a 50% overlap. Spectral power (μV^2) was derived from the DFT output in the δ (1 to 4 Hz) and β (14 to 20 Hz) frequency bands and natural log (*ln*) transformed to reduce skewness of the spectral power values (as recommended in Pivik, Broughton, Coppola, Davidson, Fox, & Nuwer, 1993). Visual inspection of Q-Q plots and results from Kolmogrov-Smirnov tests confirmed that the spectral data were normally distributed following the *ln* transformation. The eyes closed and eyes open epochs from the resting period were combined into a common EEG resting condition. The EEG data were screened for outliers (+/- 3 SDs), and individual data points were excluded accordingly, per electrode

site and per frequency band. One participant had missing speech anticipation EEG data at the posttreatment assessment due to a hard disk error resulting in a lost computer file.

5.3 Results

Treatment Efficacy We conducted separate repeated measures ANOVAs, using Time (2: Pre- and Posttreatment) as the within-subjects factor, on both the clinician rated (CGI illness severity) and patient rated (IIRS, SPIN, LSAS, and BDI) measures. As expected, there was a main effect of Time (ps < 0.02) across all of the dependent variables, as assessed by clinicians and patients (see Table 5.1).

Table 5.1: Mean ratings for multiple symptom severity measures.

(A) Clinician Rated

Scale	Pretreatment	Posttreatment	p-val.	partial η^2
CGI Illness Severity (Independent Clinician)	5.00 (0.17)	4.29 (0.26)	< 0.001	0.47
CGI Illness Severity (Group Therapist)	5.28 (0.17)	3.76 (0.23)	< 0.001	0.64

(B) Patient Rated

IIRS Total	59.48 (2.70)	51.33 (4.12)	0.017	0.25
SPIN Total	46.92 (2.50)	31.83 (3.21)	< 0.001	0.59
LSAS-SR Total	97.42 (4.65)	67.13 (6.56)	< 0.001	0.54
BDI-II Total	23.96 (1.89)	17.42 (2.37)	0.003	0.33

Note: Standard errors are given in parentheses. BDI-II = second edition of the Beck Depression Inventory (Beck, Steer, & Brown, 1996); CGI = Clinical Global Impression (Guy, 1976); IIRS = Illness Intrusiveness Ratings Scale (Devins, 1994); LSAS-SR = self-report version of the Liebowitz Social Anxiety Scale (Baker, Heinrichs, Kim, & Hofmann, 2002); SPIN = Social Phobia Inventory (Connor et al., 2000).

EEG Cross-Frequency Coupling Findings To study the effects of group CBT on brain electrical activity, we computed a set of Pearson correlation coefficients[38] (ρ) between *ln* δ and *ln* β band power separately for each electrode at each laboratory assessment and for each experimental condition. Curve estimation tests showed that the EEG spectral power data fit a linear model [$F(1,23)=28.81$, $p < 0.001$]. We used Fisher's *r*-to-*Z* transformation in order to normalize the distribution of correlation coefficients and then performed a Steiger test for dependent comparisons (Steiger, 1980). Since preliminary analyses indicated no significant differences in δ/β coupling magnitude between the two pre-treatment visits (*p*s > 0.13), these were averaged into a common pretreatment measure in order to reduce the number of comparisons. In addition to the electrode sites overlying the prefrontal cortex (F3 and F4), we performed exploratory analyses incorporating the central, parietal and occipital leads (see Figure 5.3). Two-tailed *p*-values were used for all comparisons.

Resting There was a significant decrease in delta-beta coupling from pre- to midtreatment, both in the left ($Z = 2.64$, $p = 0.008$) and right ($Z = 2.12$, $p = 0.03$) midfrontal electrodes. The pre to posttreatment comparison likewise revealed a significant reduction in δ/β coupling bilaterally (F3: $Z = 2.74$, $p = 0.006$; F4: $Z = 2.65$, $p = 0.008$). By contrast, there was no difference in coupling from mid to posttreatment in either of the frontal electrodes (*p*s > 0.66).

[38] Since the data were normally distributed and since previous studies in the literature have employed identical statistical procedures (e.g., van Peer et al., 2008; Putman, 2011), Pearson correlation coefficients were appropriate for the present purposes.

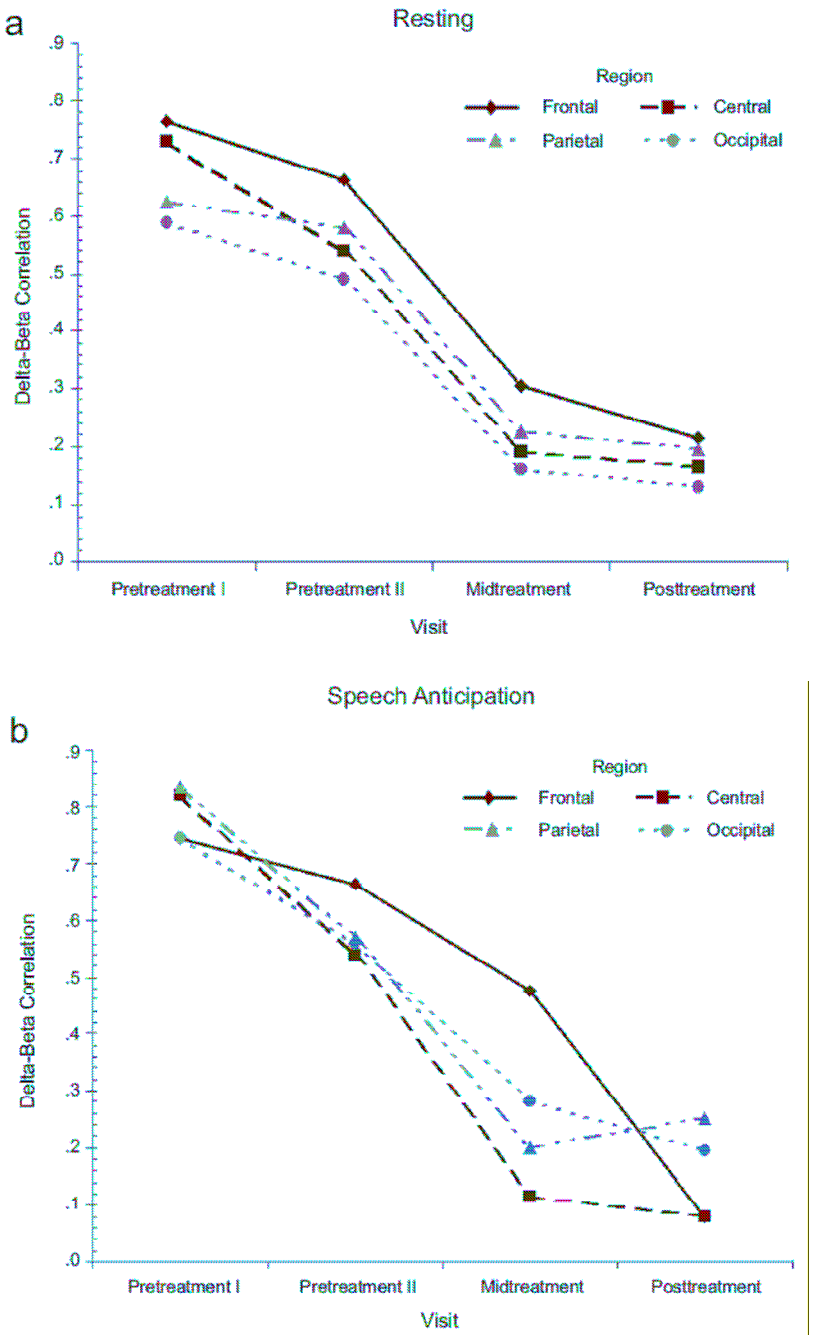

Figure 5.3: Strength of δ/β correlations (*r*) collapsed across left and right cerebral hemispheres.

Extended analyses indicated that reductions in δ/β coupling from pre to midtreatment also reached significance (ps < 0.03) at other electrode locations (C4, P4, and O2). Likewise, the pre to posttreatment comparison revealed reductions (ps < 0.03), covering all of the regions in the left hemisphere (C3, P3, and O1). There were no differences in coupling from mid to posttreatment (ps > 0.33). Although the findings lacked regional specificity, the strongest differences were generally located in electrodes overlying the frontocentral cortex as illustrated in Figure 5.4.

Speech Anticipation There was no decrease in frontal δ/β coupling from pre- to midtreatment (p's > 0.10). As expected, the complete set of 12 weekly sessions of group CBT led to a decrease in prefrontal δ/β coupling (F3: $Z = 3.35$, $p = 0.001$; F4: $Z = 3.04$, $p = 0.002$). There were no significant changes in frontal oscillatory coupling from mid to posttreatment.

Extended analyses showed that the coupling changes were not specific to the frontal region. δ/β coupling was reduced from pre to midtreatment in all of the central, parietal and occipital electrodes (ps < 0.02), except for O2. Similarly, coupling was reduced (ps < 0.04) at all of the recording sites from pre to posttreatment. There were no differences from mid to posttreatment (ps > 0.25). Overall, Figures 5.4 shows that statistically, the strongest treatment-related differences emerged for electrodes covering the fronto-central cortex.

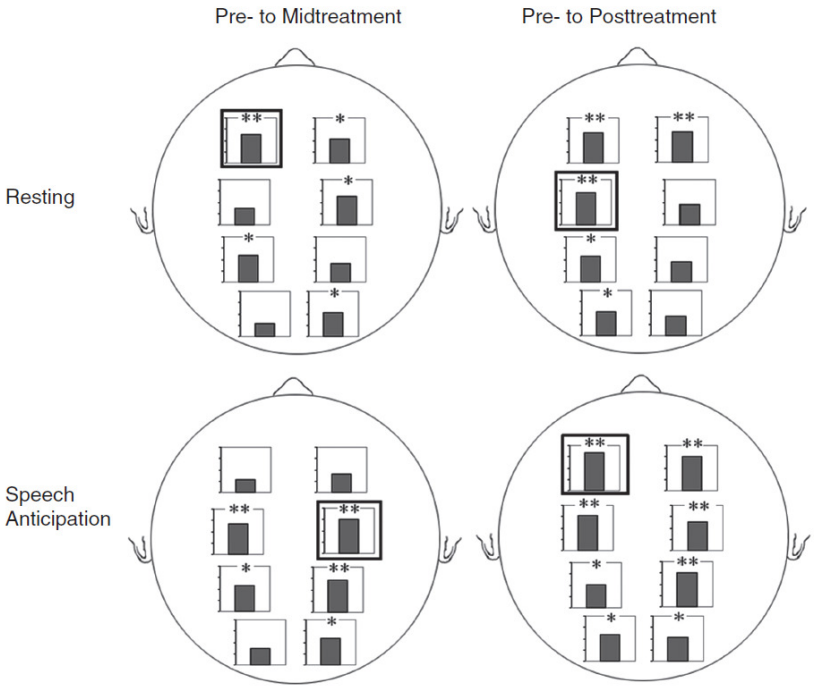

Figure 5.4: Electrode-specific Steiger-test values for dependent comparisons of δ/β spectral correlations between pretreatment and midtreatment and between pretreatment and posttreatment. Each panel shows test values (y-axis from 0 to 4) for comparisons conducted at eight different electrodes during resting or speech-anticipation conditions. The results are depicted in the following order within each panel (top to bottom): left and right midfrontal (F3, F4), central (C3, C4), parietal (P3, P4), and occipital (O1, O2) regions. Significant reductions in correlated δ/β spectral power are indicated by asterisks (*$p < .05$, **$p < .01$). Bold outlines indicate the electrode location with the largest Steiger-test value within each comparison and experimental condition.

Medication Confounds Importantly, the results reported above remained significant following exclusion of seven patients who did not remain stable on medication type/dosage over the course of the study[39].

Effects of Sex Given the apparent sensitivity of δ/β coupling to variations in circulating steroid hormones (cortisol and testosterone), we wanted to explore potential sex differences. Table 5.2 summarizes anticipatory δ/β coupling for electrodes covering the fronto-central cortex, separately for males and females across the pre, mid and posttreatment EEG assessments. Confining analyses the posttreatment period, females and males did not significantly differ in the amount of δ/β coupling.

Table 5.2: Anticipatory EEG δ/β correlation strengths shown separately for the two sexes

		F3	F4	C3	C4
Pretreatment					
	Females	.87**	.78**	.76**	.79**
	Males	.71**	.77**	.70**	.72**
Midtreatment					
	Females	.21	-.18	-.19	.14
	Males	.62*	.64*	.28	.09

[39] We also performed planned analyses restricted to the midfrontal electrodes for the small subset of patients ($n = 8$) who were medication free. There was a trend ($p < 0.07$) for reduced right midfrontal (F4) δ/β coupling from pre to posttreatment, in the speech anticipation condition only. There were no other significant or trend level effects for the resting condition or the left midfrontal (F3) site. However, the psychotherapy pure subgroup reported significantly less severe social anxiety on the SPIN and lower clinician rated illness severity ratings ($p < 0.06$) even at pretreatment, indicating that this was overall a less clinically impaired sample.

Posttreatment					
	Females	.53	.12	.23	.61*
	Males	.01	.25	-.20	-.05

Note: * $p < 0.05$; ** $p < 0.01$. The *df* for females was 10 and 11 for males. The *df* at C3 and C4 leads was 10 for males at midtreatment and 9 for females at posttreatment. Some *df* variance occurred due to removal of individual outlier values.

Post-Hoc Control Comparisons Post-hoc control comparisons were confined to the midfrontal electrodes (F3 and F4) as our previous study (Miskovic et al., 2010) indicated significant δ/β coupling solely for these sites in a speech anticipation task. The scatter plots of the comparisons are illustrated in Figure 5.5.

Pretreatment versus High and Low Socially Anxious The clinical group at pretreatment had greater ($p < 0.01$) δ/β coupling in the right midfrontal electrode during speech anticipation than the low socially anxious group. There were no other significant between-group comparisons.

Posttreatment versus High and Low Socially Anxious There was a trend ($p = 0.06$) for the clinical group at posttreatment to exhibit diminished δ/β coupling relative to the high socially anxious group in the right midfrontal electrode. By posttreatment, the clinical and low socially anxious groups did not differ in δ/β coupling magnitude (p's > 0.37).

EEG Band Power Findings To test for treatment-related changes in single frequency band power, we ran separate repeated measures ANOVAs for δ and β frequency bands, using Region (Frontal, Central, Parietal, Occipital), Hemisphere (Left, Right), Condition

(Resting, Speech Anticipation) and Time (3: Pre-, Mid-, Post-Treatment) as within-subject factors.

In contrast to the coupling patterns, analyses revealed no main or interaction effects involving Time for δ (*p*s > 0.11) or β (*p*s > 0.23) spectral power. Main or interaction effects involving other independent variables are not reported as they do not directly inform treatment-related hypotheses.

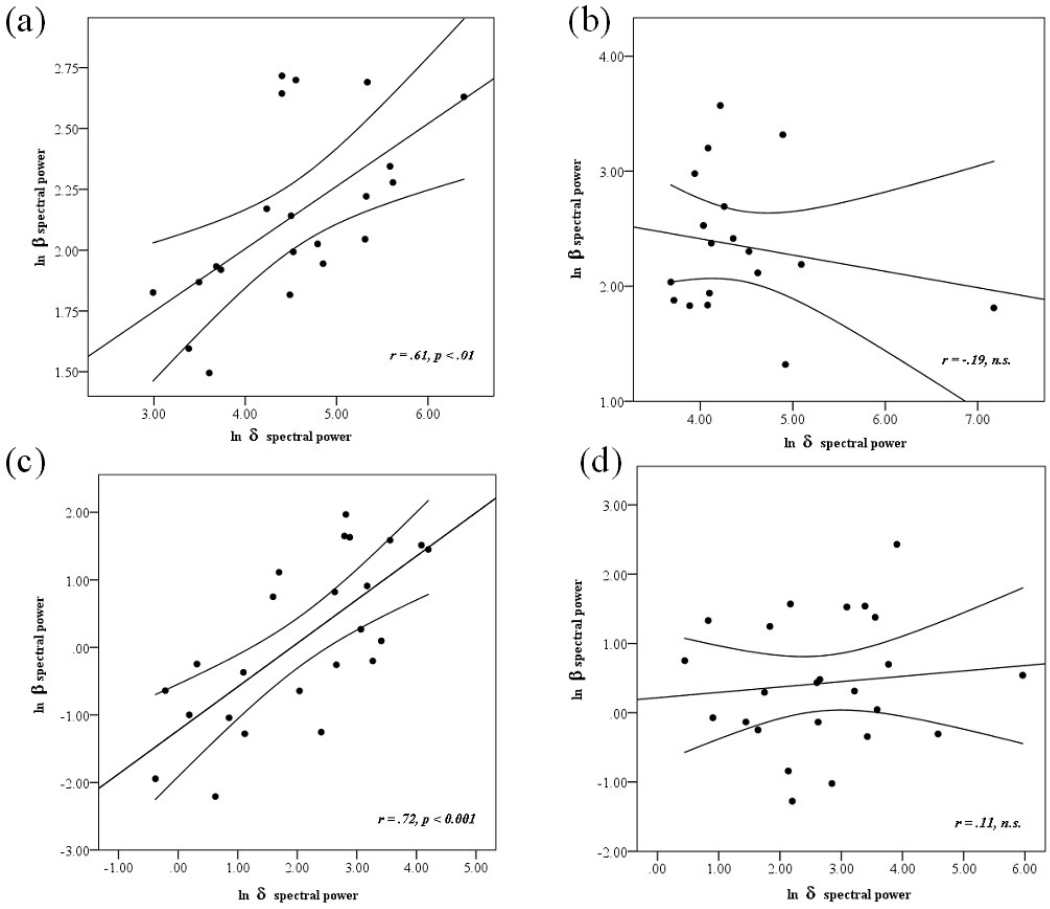

Figure 5.5: Scatterplots of anticipatory EEG δ/β spectral power at the F4 electrode shown for (a) high (non-clinical) and (b) low socially anxious groups, and for (c) SAD patients pre- and (d) posttreatment. Curved lines represent the mean 95% confidence interval.

5.4 Discussion

Our findings indicate that effective group CBT for SAD was associated with changes in brain rhythmic activity, pointing to a potential neural correlate of psychotherapy. Reductions in δ/β EEG coupling were observed during both resting and speech anticipation conditions and were detectable by the midtreatment assessment, although the strongest differences emerged for the pre- to posttreatment comparisons. Interestingly, the clinical group showed increased δ/β coupling in the right midfrontal electrode when compared to a post-hoc control group of low socially anxious participants. However, there were no significant differences in coupling between the two groups when the clinical group was assessed at posttreatment, suggesting that brain electrical activity was normalized in patients following therapy completion. This is the first study to demonstrate EEG changes following treatment for social anxiety.

Reductions in δ/β coupling following treatment for SAD appear to reflect a brain spectral profile associated with diminished anxiety, in agreement with therapists' and patients' perceptions of improvement. Since there were no independent changes in δ and β spectral power, CBT may have specifically altered the degree of temporally coherent SW-FW energy distribution. These results provide further evidence that analyses focused on cross-frequency interactions provide increased sensitivity and have implications for the study of emotion. Previous work suggests that correlated activity in δ and β frequency bands may be an EEG index of cortico-subcortical interactions (Schutter et al., 2006; Velikova et al., 2010). A plausible argument is that the decreased information transfer (reflected in low δ/β coupling) is associated with less threat-related information

being transmitted from limbic centres to the neocortical mantle[40] (e.g., van Honk & Schutter, 2007; van Honk, Harmon-Jones, Morgan, & Schutter, 2010). Although this interpretation remains highly speculative, it provides a heuristic framework that is generally convergent with previous metabolic imaging findings, suggesting that psychotherapy for mood and anxiety disorders is associated with changes in the parallel distributed activity of cortico-subcortical systems rather than regionally isolated changes (Baxter et al., 1992; Goldapple et al., 2004; Schwartz et al., 1996). A previous PET study of social phobics undergoing CBT or receiving antidepressants found that both treatments produced reductions of limbic excitability (Furmark et al., 2002).

It is also worth emphasizing that significant EEG changes were evident by the midtreatment assessment since previous neuroimaging investigations of brain changes during psychotherapy have relied on pre versus posttreatment comparisons only (Roffman et al., 2005). Demonstrating changes in brain physiology by midtreatment may carry interesting implications for the clinical concept of "sudden gains", where considerable symptom improvements occur in the initial portions of therapy (Hofmann, Schulz, Meuret, Moscovitch, & Suvak, 2006).

Previous studies have been inconsistent in regards to whether an explicit affective challenge is required (Knyazev et al., 2005, 2006; Miskovic et al., 2010) for eliciting increased δ/β coupling or whether such patterns are also obvious in resting baseline recordings (Miskovic, et al., 2011; van Peer et al., 2008). It is possible that these

[40]This latter hypothesis has been supported, most recently, by a study demonstrating a direct link between high positive δ/β coupling and selective attention to threat (Putman, 2011).

inconsistencies reflect differing levels of pre-existing anxiety that subsequently influences the degree to which 'baseline' conditions (which involve slightly intrusive psychophysiological set-up procedures) are experienced as anxiety provoking. Accordingly, participants who are more anxious to begin with are likely to find the baseline condition itself sufficiently stressful to exhibit increased δ/β coupling even at rest. For example, contrary to the high levels of baseline δ/β coupling evident in the clinical group used in the present study, we have previously reported no significant δ/β coupling at rest in a subclinical group of high socially anxious adults (Miskovic, et al., 2010). Comparison of the SPIN scores between these two samples indicates that the clinical group (at pre-treatment) employed in the present study indeed exhibited significantly greater social anxiety than the subclinical group (Miskovic et al., 2010). Similarly, clinically meaningful levels of anxiety in the present sample may explain why we found differences in δ/β coupling across multiple electrodes in both hemispheres, rather than differences that are specific to the frontal sites as previously reported (e.g., Miskovic & Schmidt, 2009; Miskovic et al., 2010; Miskovic et al., 2011; van Peer et al., 2008). However, we note that the largest treatment-related statistical comparison differences were evident in electrodes overlying the fronto-central cortex.

It is somewhat surprising that we found no between group differences when examining the anticipatory EEGs of female and male patients at posttreatment, given previous evidence that δ/β coupling is sensitive to hormonal variations that are likely to be sex-dependent (e.g., higher testosterone levels in males). Females and males also differ in the structure (e.g., Gur, Gunning-Dixon, Bilker, & Gur, 2002) and function (e.g.,

Hall, Witelson, Szechtman, & Nahmias, 2004) of certain brain regions (e.g., the orbitofrontal cortex) that are characterized as forming components of the limbic system, with an important role in affective processes. Although it is difficult or impossible to infer detailed structural knowledge on the basis of scalp-recorded EEG potentials, it is nonetheless possible to discover sex differences in regional EEG activation patterns under some experimental contexts. Future studies should more carefully examine under what circumstances sex may moderate the relations between δ/β interactions and anxiety, using electrode arrays with increased spatial sampling.

It is important to acknowledge that ocular movements generate slow wave artifacts that spill over into the δ frequency range (e.g., Hagemann & Naumann, 2001), potentially complicating experimental inferences that are based on this band. However, we believe that there are at least two reasons arguing against a non-neurogenic origin for the differences reported in the present study. First, we note that our significant results extended over much of the scalp, rather than being confined to electrodes neighbouring the eyes which are most susceptible to ocular artifacts. Second, it is important to remember that the effects reported here were specific to the degree of correlated δ/β activity and were not present when examining absolute δ spectral power.

Limitations The present study had several limitations that preclude causal generalizations. A major limitation is the lack of a waitlist control group and/or a healthy control group that was assessed at multiple time points. Previous randomized control studies have clearly established that CBT for SAD is associated with clinical improvements that are not observed among waitlist controls (Ponniah & Hollon, 2008),

and ethical review boards at treatment institutions have begun to discourage investigators from delaying treatment to patients in need by assigning them to waitlist control conditions. Thus, rather than waitlist controls, we utilized a double-baseline approach that involved two pretreatment visits, in addition to post-hoc comparisons of our clinical group with two distinct nonclinical groups of high and low socially anxious adults. Notably, there were no significant differences in coupling strength between the two pretreatment visits, arguing against an interpretation of nonspecific reductions in coupling strength or "habituation" effects. Moreover, EEG differences between the clinical group and post-hoc controls were consistent with the notion that treatment-related changes in coupling reflected a measure of neural activity that was normalized by intervention. However, in order to attribute the changes in oscillatory coupling strength specifically to treatment, future studies need to examine the long-term stability of EEG spectral profiles in SAD adults not undergoing psychotherapy.

A second limitation is that, for some participants, psychotherapeutic and medication treatments were combined. Rather than exclude these treatment-seeking patients from the study, participants were asked to remain stable on their medication type and dosage throughout the study. Importantly, the EEG coupling results remained significant after excluding individuals who self-reported changes in medication regimen. In the future, it may be instructive to move from quantification of treatment-related brain changes to randomized controlled trials testing the active ingredients of psychotherapy that are necessary and sufficient for mediating changes in brain function. Such

knowledge would assist in designing more effective forms of psychological treatment for specific disorders.

Conclusions Overall, the present study suggests that are predictable changes in gross neuronal activity that accompany completion of CBT for SAD and that these physiological changes parallel clinical improvements. There is both theoretical and practical value to discovering neural correlates associated with clinical symptom reduction. Theoretically, these findings are informative with regard to the sorts of distributed patterns of brain activity that may underlie the presentation of social anxiety as well as their capacity for environmental modification. At a practical level, identifying neural correlates of psychotherapy may suggest possible treatment markers and/or have inherent value as a treatment tool in itself, through the development of neurofeedback techniques.

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Chapter 6

General Conclusions

Epidemiological surveys indicate that social anxiety disorder is the second most common DMS-IV anxiety disorder and among the most prevalent of all psychiatric illnesses (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005). The clinical manifestations of social anxiety likely represent the extreme ends of a fear continuum and reflect cascading effects stemming from dysregulation of complex neural systems that mediate social interactions in humans and their close primate relatives (Hermans & van Honk, 2006; Öhman, 1986, 2009). In its severe forms, social anxiety constitutes a disabling disorder that also functions as a risk factor for other psychiatric impairments (Weiller, Bisserbe, Boyer, Lepine, & LeCrubier, 1996) and a predictor of poorer prognosis when co-morbid with chronic illnesses such as schizophrenia (Goldberg & Schmidt, 2001; Pallanti, Quercioli, & Hollander, 2004). An increased understanding of the pathophysiological mechanisms underlying social anxiety is imperative for future developments in diagnosis and treatment (Charney, 2004). By extension, knowing more about the biological correlates of social anxiety treatment also represents an important area of research that has been scarcely investigated, despite its clinical implications.

Although the last two decades have witnessed considerable progress in our knowledge about the psychobiology of social anxiety and shyness (see Pérez-Edgar &

Fox, 2005; Schmidt & Schulkin, 1999; Shin & Liberzon, 2010, for reviews), there are still many remaining questions that need to be answered. The set of studies collected here represented an effort to address some of the existing knowledge gaps by an integration of neural, cognitive, behavioural and self-report measures. A brief summary of the findings along with their theoretical and clinical implications is sketched out below and promising future directions are explored.

6.1 Chapters 2 to 4

The empirical ERP studies described in Chapters 2 and 3 attempted to characterize the time course of processing biases in subsyndromal social anxiety during separate tasks that measured sensitivity to contextual novelty, embedded in either socio-affective or affectively neutral contexts. High socially anxious participants showed enhanced sensory-perceptual responses when detecting novel threatening faces, but did not differ from low socially anxious adults during subsequent, post-perceptual stages. Moreover, social anxiety did not seem to influence neural correlates of orienting towards novelty in affectively neutral contexts. Chapter 4 described reaction time data gathered from a modified version of the dot-probe task that examined the effects of chronometric and energetic variations in affective stimuli on attentional performance. The behavioural findings from Chapter 4 suggest that heightened sensitivity to social threat among high socially anxious individuals may be due to the increased activation of a phasically operating system. Convergent evidence from Chapters 2 and 4 implicates early

perceptual (rather than later, strategic) biases for threatening images in social anxiety[41]. Additionally, the results indicated that the relations between social anxiety and processing biases were at least partially independent of effects attributable to general dysphoric symptoms.

Theoretical Implications Theoretical models of affective information processing, whether derived from studies of normative or clinical populations, and regardless of reliance on behavioural or physiological data, have all postulated the existence of multiple processing stages (Beck & Clark, 1997; Öhman, 1986; Robinson, 1998; Schupp et al., 2006). A common distinction that is made by all of the theoretical models is the one drawn between early-perceptual and late-conceptual levels of processing. The initial stage involves a largely automatic and involuntary detection of threat, while subsequent stages of processing involve elaborative and strategic analysis of the threatening stimulus. Electrocortical and behavioural findings from Chapters 2 and 4 implicate early perceptual (rather than later, more strategically controlled) biases for threatening images in social anxiety. Although modest in nature, these results appear to agree with a recent literature review of threat processing in social anxiety, which concluded that biases are largely confined to the initial stages of information processing and may not persist over time (Staugaard, 2010). It may be possible that the poor persistence of processing biases in some experimental tasks is explained by the artificial nature of still photographs depicting emotional expressions and that strategic biases are

[41]Strategic differences in threat responding between high and low socially anxious individuals may emerge on tasks designed to place emphasis on actively regulating emotional reactivity to negative affective material (e.g., cognitive reappraisal tasks; Hajcak & Nieuwenhuis, 2006).

engaged when socially anxious individuals are in the midst of real social interactions. Nevertheless, the experimental results do suggest that dysregulated attention for threat in anxious individuals onsets relatively early in the processing stream.

The appearance of early threat-related biases seems to be a plausible functional outcome of hyperactive amygdala circuits though caution is warranted in drawing such a conclusion in the absence of concurrent functional neuroimaging data. Indirect support for amygdala involvement in the perceptual processing biases reported in Chapter 2 comes from extant models linking feedback projections from the amygdala to the extrastriate visual cortex in the generation of the early posterior negativity (Lee et al., 2009; Sato et al., 2001). Chapter 2 reviewed the anatomical and physiological evidence that is consistent with the amygdala-based interpretation of the ERP data. Likewise, computational modeling efforts (Frewen, Dozois, Joanisse, & Neufeld, 2008) suggest that exposure-dependent variation in the magnitude of threat-related biases (larger during rapid presentation speeds) on the dot-probe task could be explained by the phasic response properties of the amygdala.

Emery and Amaral (2000) advanced a model of amygdala function in primate social cognition that provides an opportunity to formulate a biologically based framework for understanding human social anxiety (Amaral, 2002). According to this neuroethological model, the basal nucleus of the amygdala evaluates the affective significance of stimuli in virtue of the multiple connections that it receives from face-sensitive areas of the extrastriate cortex and neurons in the orbitofrontal cortex that embody implicit knowledge about social hierarchy structures. Importantly, the basal

nucleus sends return projections to extrastriate regions as well as to the orbitofrontal cortex and is thereby able to bias neural activity of these regions[42]. Under the hypothesis that basal nuclei circuits are hyperexcitable in social anxiety, return projections should enhance the sensory-perceptual representations of socially threatening stimuli in extrastriate visual cortex and bias frontally mediated cognitive processes toward threat vigilance. Results suggesting that the threat-related biases appear early, and dissipate after some time, may indicate that social anxiety is largely explained by enhanced *bottom-up* reactivity and that more executively-controlled, *top-down* processes are able to dampen initial biases, at least under standard laboratory experiments where the threat associated with stimuli is presumably low. It is possible that variability in the severity of social anxiety may reflect individual differences in the effectiveness of top-down control over largely involuntary biases.

In the future, additional research will be needed to increase our understanding of the precise neural dynamics that instantiate threat processing in ways that move beyond highlighting the independent contributions of single brain regions. In particular, the application of measures such as functional connectivity in fMRI datasets and event-related coherence in electrocortical recordings holds the potential to advance more sophisticated, neuroscience-based models of affective information processing[43]. In the future, there will also be a need to include other anxious groups (e.g., spider phobics) for

[42]Projections from the basal to the central nuclei are involved in initiating the cascade of peripheral and behavioural consequences of defense activation.

[43]Knowing about how information processing functions develop in time (and how anxiety perturbs this temporal coding), may turn out to be more informative in the long run than the localization of processing operations in space (e.g., Cohen, 2011).

comparison with socially anxious individuals and to begin using stimuli that are more ecologically valid than still photographs of human faces (Staugaard, 2010).

Clinical Implications Identifying the precise stages at which anxiety begins to influence the attentional processing of threat bears directly on issues of clinical etiology and treatment (Mobini & Grant, 2007). Clinically oriented investigators have differed in the extent to which they have placed theoretical emphasis on pervasive biases in threat-related processing (e.g., Beck & Clark, 1997) versus biases that are restricted to specific (early/automatic) processing stages (e.g., McNally, 1995). Although automaticity is relatively well defined within certain experimental areas, such as skill mastery and expertise[44], in the domain of socio-affective processing it primarily indicates the involuntary nature of perceptual biases for emotional materials (McNally, 1995). If biases for threat in social anxiety are relatively automatic in the latter sense, then this may explain the clinical observation that the fears in SAD are often recognized to be irrational by the patients themselves (American Psychiatric Association, 2000). More importantly, verbally mediated interventions, such as cognitive restructuring, aimed at targeting strategically controlled processing, may be less efficacious in modifying early, automatic biases when compared to techniques like exposure (Mobini & Grant, 2007). Therefore, research that helps clarify which stages of threat processing are affected in anxiety also suggests potential modifications to treatment protocols and may help to explain why cognitive behavioural treatments for SAD that incorporate exposure training are more effective than those that do not (Taylor, 1996).

[44]Automaticity here is defined as those cognitive operations that are capacity-free (effortless) and occurring unconsciously.

Basic research on attention biases in anxiety also raises the possibility of using bias modification as a form of treatment, either as stand-alone or (more likely) as a supplement to cognitive behavioural therapy and/or psychotropic medication. Experimental paradigms like the dot-probe can be adapted to train attention either toward or away from threat, by systematic manipulations of the contingency between the threat stimulus and the probe. Attention bias modification involves implicit learning, and it presumably targets subcortically situated processes by eliciting response repetition over hundreds of trials (Hakamata et al., 2010). Attentional training on the dot-probe has causal consequences on subsequent self-assessments of mood and anxiety (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). More recently, attentional retraining procedures have been also demonstrated to modulate neural indices of sensory processing, such that learning to orient away from a stimulus results in reduced ERP components (Eldar & Bar-Haim, 2011). To date, several studies have shown that attentional retraining focused around teaching SAD patients to shift attention away from critical and towards neutral faces in the dot-probe, resulted in significant clinical improvements on multiple outcome measures (Amir et al., 2009; Schmidt, Richey, Buckner, & Timpano, 2009) and reduced anxiety in response to a public speaking challenge (Klumpp & Amir, 2010). A recent-meta analysis documents moderate, but reliable, effects of attentional bias modification on the reduction of anxious symptoms (Hakamata et al., 2010). More research is required to determine whether attention bias training is capable of altering the early (versus the later, more controlled) stages of

information processing, especially since the initial responses are considered to be important in clinical anxiety (Koster, Baert, Bockstaele, & De Raedt, 2010).

6.2 Chapter 5

Social anxiety disorder is one of the most under-treated anxiety disorders (Cuthbert, 2002), so that understanding more about the biological changes in response to clinical interventions represents a pressing research question. The study described in Chapter 5 was one of only two existing ones (see also Furmark et al., 2002) to describe neural changes in response to cognitive behavioural therapy for SAD and the first one to do so using an EEG-based measure. Patients diagnosed with SAD showed significant reductions in the amount of cross-frequency δ/β coupling from pre to posttreatment, in parallel with self-report and clinician derived indices of symptom improvement. The findings from Chapter 5 suggest a potential neural correlate of successful, standardized treatment for social anxiety.

Theoretical Implications The majority of previous EEG work on emotion and psychopathology has relied on quantifying regional spectral power in single frequency bands (typically, alpha), without considering interactions between neural oscillations of different frequencies. However, evidence derived from scalp and intracranial EEG recordings has shown that low frequency oscillations (e.g., δ) exhibit dynamic interactions with topographically restricted high frequency oscillations (e.g., β) across multiple domains (Jensen & Colgin, 2007). High correlations between δ and β power were suggested to indicate increased cortico-limbic synchronization (Schutter, Leitner, Kenemans, & van Honk, 2006) and were found, by independent investigators, to be

differentially responsive to synthetic and natural concentrations of cortisol and testosterone (Schutter & van Honk, 2004, 2005; van Peer, Roelofs, & Spinhoven, 2008). Treatment related reductions in δ/β coupling, reported in Chapter 5, are complimented by other evidence that state manipulations of social anxiety (Miskovic, Ashbaugh, Santesso, McCabe, Antony, & Schmidt, 2010) and uncertainty (Knyazev, Schutter, & van Honk, 2006) increase δ/β correlations[45]. Taken together, these studies suggest that a cross-frequency analysis of the EEG spectrum is a promising approach to studying the neural correlates of anxiety and that such metrics can advance traditional EEG work based on analyses of single frequency bands. Since measures of power coupling are considered to be less sensitive than other parameters of cross-frequency interactions, future work in this area may focus on quantifying coupling between the phase of low frequency and the power of high frequency oscillations in addition to phase/phase coupling (Canolty & Knight, 2010). Indeed, a recent study indicates the presence of the entrainment of beta spectral power to delta phase during periods of acute state anxiety (Knyazev, 2011). In conclusion, quantitative EEG data can provide convergent and novel evidence of treatment-related brain changes that compliments nuclear and magnetic forms of neuroimaging, especially since cross-frequency coupling may not be associated with hemodynamic responses recorded using fMRI protocols (Cohen, 2011).

Clinical Implications If correlated δ/β EEG activity does indeed reflect functional synchronization between cortico-subcortical circuits, then the findings from Chapter 5 provide additional evidence that interactions among multiple brain systems are

[45]High positively correlated δ/β power also appears to relate to attentional vigilance for social threat (Putman, 2011).

involved in the maintenance and treatment of social anxiety. The latter suggestion is consistent with an older body of research on other anxiety disorders (e.g., OCD) where treatment leads to a decoupling of pathologically correlated cortico-striatal-thalamic activity (e.g., Baxter et al., 1992). In the future, it will be interesting to compare groups undergoing different treatment modalities (e.g., psychotherapy-pure vs. medication-pure) to discover common or distinct patterns of brain change at posttreatment.

Identifying the neural correlates of therapeutic intervention may also help to guide clinical decision-making and treatment in the future in several ways. First, controlled study designs could be implemented to test what specific ingredients of cognitive behavioural therapy (e.g., exposure training) lead to the most robust EEG changes at follow-up. Second, EEG parameters shown to be sensitive to clinical treatment could have some utility as non-invasive pretherapeutic markers that might predict patients' response to different forms of treatment. To some extent, the goal of discovering neural measures that can predict treatment success has already been achieved in research on depression and OCD (Roffman, Marci, Glick, Dougherty, & Rauch, 2005). Finally, patterns of δ/β EEG coupling may be useful as early indicators of risk for the development of pathological social anxiety. A pilot study from our research team (Miskovic, Campbell, Santesso, Van Ameringen, Mancini, & Schmidt, 2011) provides preliminary evidence that biological children of socially phobic parents shown significantly increased resting δ/β coupling when compared to the biological children of healthy parents. Importantly, earlier epidemiological research has shown that children of socially phobic parents are at significantly elevated risk for the development of

psychiatric impairment, especially social anxiety disorder (Mancini, Van Ameringen, Szatmari, Fugere, & Boyle, 1996).

6.3 Integrating Basic and Clinical Research: Future Prospects

Biases in attention and perception likely interact with threat-related biases in other information processing functions such as learning (Britton, Lissek, Grillon, Norcross, & Pine, 2011). A promising future avenue for extending basic research into the clinical domain involves the use of fear learning paradigms. Basic research using preclinical models (see LeDoux, 1996), and functional neuroimaging in humans (Büchel & Dolan, 2000) has described the neurocircuitry that is involved in classical fear conditioning. In turn, aversive conditioning processes have long been recognized as contributing to the onset and maintenance of social anxiety disorder (Mineka & Zinbarg, 1995). According to some estimates (McCabe, Antony, Summerfeldt, Liss, & Swinson, 2003), up to 92% of adult patients with social anxiety disorder report having experienced a history of aversive social experiences that preceded clinical onset. Indeed, it is possible that an individual's history of aversive social conditioning processes shapes an initial presdisposition towards general fearfulness (the product of hyperexcitable limbic circuits) into a specific phobia of social situations rather than an animal phobia or panic disorder, for example.

Psychophysiological studies examining conditioning processes in social anxiety disorder have been scarce. Socially anxious patients do not appear to condition to a greater extent than their non-anxious counterparts when using noxious odors (Hermann, Ziegler, Birbaumer & Flor, 2002; Schneider et al., 1999) or painful tactile stimulation (Veit et al., 2002) as unconditioned stimuli. However, recent evidence employing

socially relevant unconditioned stimuli demonstrates that patients with SAD demonstrate augmented conditioning to neutral faces when these stimuli are paired with harsh facial expressions and critical insults (Lissek et al., 2008). Experimental designs that make use of disorder-relevant materials could therefore yield novel insights in the future.

Another interesting research question that can be addressed using fear-conditioning experiments concerns the potential existence of sensitive periods in the acquisition of social fears. Human fears follow a developmental schedule that is largely consistent across different cultures (Boyer & Bergstrom, 2011) and probably reflects biogenetic constraints on the maturation of threat-responsive systems (Todd, Evans, Morris, Lewis, & Taylor, 2011). Social fears become more prominent during the late childhood/early adolescent period (Öhman, 1986), while the median age of SAD onset in large epidemiological surveys appears to be around 13 years (Kessler et al., 2005). It seems reasonable to hypothesize that prepared or augmented learning of social fears would occur during the late childhood period. Experiences that lead to the repeated consolidation of socially threatening information, perhaps combined with a tendency to ruminate on socially aversive experiences from the past, could induce long-term synaptic changes in the associated neurocircuitry, eventually culminating in social phobia (Pine et al., 2009). However, the existence (and nature) of sensitive periods for the learning of social fears has yet to be demonstrated in psychophysiological paradigms. A recent study (Lau et al., 2011) has provided evidence that adolescents, compared to adults, discriminate less effectively between conditioned threat and safety signals and over-recruit amygdalar circuits during learning. These findings raise the intriguing possibility

that there might be similar developmental differences in social forms of fear conditioning.

One of the most exciting new directions opened by the integration of basic and clinical research is the possibility of discovering novel therapeutics for social anxiety. One example is provided by emerging research programs focused on attention bias modification for the amelioration of pathological anxiety (Hakamata et al., 2010). A second example involves the use of $_{D}$-Cycloserine dosing to augment the benefits of exposure therapy for social anxiety disorder (Hofmann et al., 2006). Rationale for the use of $_{D}$-Cycloserine in the treatment of human social anxiety was originally based on results from animal studies showing that this molecule functions as an agonist at NMDA glutamate receptors and bolsters extinction learning. Although still preliminary, EEG findings demonstrating high δ/β coupling in anxiety could indicate a treatment target that might be sensitive to biofeedback manipulations. While this suggestion may seem highly speculative at first, others (Allen, Harmon-Jones, & Cavender, 2001) have shown that standardized and repetitive biofeedback training can change individual EEG activation patterns in ways that are reflected in both self-report and behavioural measures of mood. Instructing participants to generate oscillatory shifts in particular frequency bands has also been demonstrated to improve cognitive performance on certain tasks (e.g., Zoefel, Huster, & Herrmann, 2010). Biofeedback manipulations of correlated EEG activity (and potentially, the resulting impact on emotional state) would help in advancing the field from correlative to causative evidence.

Despite its wide prevalence and psychiatric impact, neuroscience research on social anxiety and its treatment remains scarce when compared to conditions such as depression, schizophrenia and OCD. Like many of the other anxiety disorders, social phobia seems to represent the outcome of hyperexcitable limbic circuits involving the amygdala. Additional work is required to understand how a common biological vulnerability becomes expressed in different ways (e.g., as a fear of other people versus a fear of spiders), perhaps through the contribution of attentional and learning mechanisms.

Basic research that measures biological and behavioural responses during states of rest and during performance on cognitive and affective activation experiments has and will continue to advance our understanding about the pathophysiological mechanisms underlying social anxiety. In parallel, preclinical models of stress and anxiety have the potential to continue making considerable contributions to neuroscience-based models of social anxiety. As always, a key challenge for the future will lie in translating findings from the laboratory to the clinic.

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Appendix A: Social Phobia Inventory (SPIN)

Please check how much the following problems have bothered you during the past week. Mark only one box for each problem, and be sure to answer all items.

	Not at all	A little bit	Somewhat	Very much	Extremely
1. I am afraid of people in authority	☐	☐	☐	☐	☐
2. I am bothered by blushing in front of people	☐	☐	☐	☐	☐
3. Parties and social events scare me	☐	☐	☐	☐	☐
4. I avoid talking to people I don't know	☐	☐	☐	☐	☐
5. Being criticized scares me a lot	☐	☐	☐	☐	☐
6. Fear of embarrassment caused me to avoid doing things or speaking to people	☐	☐	☐	☐	☐
7. Sweating in front of people causes me distress	☐	☐	☐	☐	☐
8. I avoid going to parties	☐	☐	☐	☐	☐
9. I avoid activities in which I am the centre of attention	☐	☐	☐	☐	☐
10. Talking to strangers scares me	☐	☐	☐	☐	☐
11. I avoid having to give speeches	☐	☐	☐	☐	☐
12. I would do anything to avoid being criticized	☐	☐	☐	☐	☐
13. Heart palpitations bother me when I am around people	☐	☐	☐	☐	☐
14. I am afraid of doing things when people might be watching	☐	☐	☐	☐	☐
15. Being embarrassed or looking stupid are among my worst fears	☐	☐	☐	☐	☐
16. I avoid speaking to anyone in authority	☐	☐	☐	☐	☐

17. Trembling or shaking in front of others is distressing to me	□	□	□	□	□

Appendix B: Beck Depression Inventory (BDI)

This questionnaire consists of 21 groups of statements. After reaching each group of statements carefully, circle the number next to the one statement in each group which best describes the way you have been feeling the past week, including today. If several statements within a group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1)	0	I don't feel sad
	1	I feel sad
	2	I am sad all the time and I can't snap out of it
	3	I am so sad or unhappy that I can't stand it
2)	0	I am not particularly discouraged about the future
	1	I feel discouraged about the future
	2	I feel I have nothing to look forward to
	3	I feel that the future is hopeless and that things cannot improve
3)	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2	As I look back on my life, all I can see is a lot of failures
	3	I feel I am a complete failure as a person
4)	0	I get as much satisfaction out of things as I used to
	1	I don't enjoy things the way I used to
	2	I don't get real satisfaction out of anything anymore
	3	I am dissatisfied or bored with everything
5)	0	I don't feel particularly guilty
	1	I feel guilty a good part of the time
	2	I feel quite guilty most of the time
	3	I feel guilty all of the time
6)	0	I don't feel I am being punished
	1	I feel I may be punished
	2	I expect to be punished
	3	I feel I am being punished
7)	0	I don't feel disappointed in myself
	1	I am disappointed in myself
	2	I am disgusted with myself
	3	I hate myself
8)	0	I don't feel I am any worse than anybody else

	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9)	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself but I would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10)	0	I don't cry any more than usual
	1	I cry more now than I used to
	2	I cry all the time now
	3	I used to be able to cry, but now I can't cry even though I want to
11)	0	I am no more irritated now than I ever am
	1	I get annoyed or irritated more easily than I used to
	2	I feel irritated all the time now
	3	I don't get irritated at all by the things that used to irritate me
12)	0	I have not lost interest in other people
	1	I am less interested in other people than I used to be
	2	I have lost most of my interest in other people
	3	I have lost all of my interest in other people
13)	0	I make decision about as well as I ever could
	1	I put off making decisions more than I used to
	2	I have greater difficulty in making decisions than before
	3	I can't make decisions at all anymore
14)	0	I don't feel I look any worse than I used to
	1	I am worried that I am looking old or unattractive
	2	I feel that there are permanent changes in my appearance that make me look unattractive
	3	I believe that I look ugly
15)	0	I can work about as well as before
	1	It takes an extra effort to get started at doing something
	2	I have to push myself very hard to do anything
	3	I can't do any work at all
16)	0	I can sleep as well as usual
	1	I don't sleep as well as I used to
	2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
	3	I wake up several hours earlier than I used to and cannot get back to sleep

17) 0 I don't get more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything
3 I am too tired to do anything

18) 0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all anymore

19) 0 I haven't lost much weight, if any, lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds

I am purposely trying to lose weight by eating less. Yes ___ No ___

20) 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation
2 I am very worried about physical problems and it's hard to think of much else
3 I am so worried about my physical problems that I cannot think about anything else

21) 0 I have not noticed any recent change in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely