Blushing and Gaze Avoidance in Social Anxiety Disorder: A structural neuroanatomical investigation

by

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DECLARATION

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ABSTRACT

Background: Social anxiety disorder (SAD) is a common psychiatric condition characterised by fear and avoidance of social situations. Lifetime prevalence is 5-16% and co-morbidity with other mood and substance abuse disorders is common. Symptoms including cognitive, behavioural and physiological components vary between individuals. Of these, blushing and gaze fear and avoidance are regarded as cardinal symptoms. First line treatment of SAD involves SSRIs and cognitive behavioural therapy, while surgery may also be considered for excessive blushing. Blushing and gaze avoidance are thought to have an evolutionary adaptive advantage, promoting the display of submissive behaviour and appeasement in threatening situations. MRI research has demonstrated differences on functional and structural neuroimaging between patients with SAD and healthy controls (HCs). However, little is known about the neurocircuitry underlying gaze fear and avoidance or increased blushing propensity or how the severity of these traits correlate with the neuroimaging differences found in SAD. In this research, I explored the neuroanatomy of blushing propensity and gaze fear and avoidance in the context of SAD.

Methods: 18 SAD patients and 18 HCs underwent structural MRI scans and self-report scales were administered to assess their symptom severity, blushing propensity and gaze fear and avoidance. Structural data was analysed using voxel-based morphometry (VBM). Regression and contrast analyses were used to correlate blushing propensity and gaze anxiety and avoidance symptoms with brain volumes, controlling for total grey matter volume, age and level of education.

Results: Anxiety, blushing propensity and gaze fear and avoidance symptoms were all significantly higher in SAD patients ($p<0.001$). Brainstem volumes were increased for higher blushing scores[a] ($p<0.01$), while the volumes of left inferior parietal lobe[b] ($p=0.04$) and left occipital cortex[a] ($p<0.01$) were decreased. With increased gaze fear and avoidance, there were associated decreases in the right posterior cingulate cortex[a] ($p<0.01$), right occipital lobe[b] ($p=0.03$) and right fusiform gyrus[a] ($p<0.01$). Increased blushing and gaze symptom severity considered together, was associated with increased brainstem volume[a] ($p<0.01$) and decreased pons/cerebellum[b] ($p=0.001$), right cerebellum[b] ($p=0.009$), left cerebellum[c] ($p<0.001$) and left inferior parietal lobe[a] ($p<0.1$), volumes. Contrast analysis of SAD and HC

brain volumes revealed a greater grey matter volume in HCs in the regions of left occipital cortex ($p<0.01$), left anterior cingulate ($p<0.01$) and right inferior parietal lobe ($p<0.01$) when compared to SAD patients. Increased symptom severity in SAD was significantly associated with higher volumes in the left premotor cortex ($p<0.01$), right hippocampus ($p<0.01$), left orbitofrontal cortex ($p<0.01$) and right superior temporal cortex ($p<0.01$). Possible areas for of interest for volume differences between SAD and HCs include total grey matter volume (d=0.83), left and right anterior cingulate cortex (d=0.68 and d=0.65), and left and right dorsolateral prefrontal cortex (d=0.55 and d=0.54), yet these differences were not significantly different. *([a]uncorrected peak levels [b]uncorrected cluster level, [c]corrected cluster level)*.

Conclusion: Differences in brain volumes pertaining to blushing and gaze fear and avoidance in SAD patients may be a contributing factor or a consequence of these core symptoms, and a potential biomarker for SAD. Future studies could build on this preliminary research with increased sample sizes, and determine the possible effects of reduced symptom severity and treatment options on brain structure and function. Most importantly, an investigation of the genetic underpinnings and functional neural correlates of blushing and gaze avoidance behaviour may enhance our understanding of the complex aetiology of these cardinal SAD symptoms, thereby improving our understanding of SAD as a psychiatric disorder and facilitating better patient care and management.

Key words: social anxiety; social anxiety disorder; social phobia; gaze avoidance; gaze fear; gaze anxiety; blushing; fear of blushing; erythrophobia; blushing treatment; structural MRI; grey matter volume; voxel-based morphometry

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ABBREVIATIONS

The following abbreviations appear in this dissertation:

ACC – anterior cingulate cortex

BPS – blushing propensity scale

CBT – cognitive behavioural therapy

CS – compensatory sweating

CSF – cerebrospinal fluid

DLPFC – dorsolateral prefrontal cortex

DMPFC – dorsomedial prefrontal cortex

DSM – diagnostic and statistical manual of mental disorders

ESB – endoscopic thoracic block

ETS – endoscopic thoracic sympathectomy

fMRI – functional magnetic resonance Imaging

FWE – familywise error

GARS – gaze anxiety rating scale

HC – healthy control

LSAS – Liebowitz social anxiety scale

MNI – Montreal Neurological Institute

MRI – magnetic resonance imaging

MRS – magnetic resonance spectroscopy

PET – positron emission tomography

PRS – percutaneous radiofrequency sympathicolysis

QOL – quality of life

RC – rami communicantes

RDoC – Research Domain Criteria

SAD – social anxiety disorder

SD – standard deviation

SPM – statistical parametric mapping

SSRI – selective serotonin reuptake inhibitor

T1, T2, T3, T4 – first, second, third, fourth thoracic vertebra

VBM – voxel-based morphometry

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INTRODUCTION

Social anxiety disorder (SAD) is a prevalent psychiatric disorder, characterized by fear of social situations. Characteristic symptoms of SAD include blushing and gaze avoidance. The aim of this chapter is to review the literature on social anxiety, with a particular focus on blushing and gaze avoidance. There is growing information from animal studies and imaging research on the psychobiology of social anxiety, and this will be summarized. At the same time, areas that have not yet been adequately explored will be highlighted, with the intention of further exploring them in this dissertation.

Literature Search

Articles for the literature review were obtained by searching the electronic journal databases of PubMed, Science Direct and Google Scholar. Relevant articles found using the search terms "social anxiety disorder" *or* "social phobia", "blushing", "gaze", "MRI", "blushing treatment", and "social emotions" were reviewed. Other relevant articles were found through the references in the articles obtained from the search.

Social Anxiety Disorder: Definition, Classification, and Epidemiology

Social anxiety disorder (SAD), also referred to as Social Phobia (DSM-IV), is one of the six major anxiety disorders listed in the *Diagnostic and Statistical Manual of Mental Disorder* (DSM-V; APA, 2013). The disorder is characterised by "marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others" (DSM-V, p. 202). This fear may be limited to certain domains (e.g. public speaking) or may be generalized across many social situations (Muller, Koen, Seedat & Stein, 2005), usually with the generalised sub-type leading to worse symptoms and greater impairment (Brook & Schmidt, 2008). Everyday situations that are easily negotiated by many (e.g. eating or drinking while being observed by others, having a conversation, and meeting unfamiliar people) have the potential to provoke excessive anxiety in those with SAD, beyond what could be

considered normal shyness (den Boer, 1997). Symptoms consist of affective, cognitive, behavioural and physical components (Muller et al., 2005; Price, 2003). These may include panic responses (even full panic attacks in some cases), extreme situational avoidance, avoidance of eye contact, tension, stuttering, mumbling, nail biting, and a partial or complete range of somatic complaints, such as increased heart rate, sweating, shaking, trembling, and blushing (Albano, 1995; Beidel & Turner, 2007). Self-conscious emotions and cognitive appraisals such as embarrassment, desire to escape, self-criticism, feelings of inadequacy and failure may accompany these experiences (Ollendick & Hirshfeld-Becker, 2002). Those with SAD experience significant impairment of functioning in social, academic and occupational domains (APA, 2013).

After depression and alcohol abuse, this debilitating disorder is reportedly the third most common psychiatric diagnosis (Heimberg, Stein, Hiripi & Kessler, 2000; Schneier, 2006). Lifelong prevalence rates are high, between 5-16% in Western countries (Heimberg et al., 2000; Wittchen, Stein & Kessler, 1999) with a higher preponderance in females (ratio estimated between 1.5:1 and 2.5:1; Judd, 1994; Hidalgo, Barnett & Davidson, 2001; Rapee & Spence, 2004), although clinical samples often have even or reversed gender representation (Muller et al., 2005). The disorder may have its onset in childhood, but more commonly begins during mid-adolescence (Furmark, 2002; Seedat & Stein, 2007; Schneier, Johnson, Hornig, Liebowitz & Weissman, 1992). The course of SAD tends to be lifelong (den Boer, 1997) and patients are more likely to have lower levels of education, remain unemployed, earn less, or remain single (Schneier et al., 1992).

It is common for individuals with SAD to experience co-morbid psychiatric disorders (between 69-81% according to Fehm & Wittchen, 2004), including other anxiety disorders, substance abuse, major depressive disorder, bipolar disorder and dysthymia (den Boer, 1997; Fava et al., 2000; Kessler, Stang, Wittchen, Stein & Walters, 1999; Merikangas & Angst, 1995; Merikangas, Angst, Eaton & Canino, 1996; Merikangas et al., 2007). Of all the anxiety disorders, social anxiety disorder is thought to be the most likely to co-occur with mood disorders, often preceding a

mood disorder diagnosis (Fava et al., 2000; Pini et al., 2006). Patients may also self-medicate with alcohol, which may contribute to explaining co-morbid substance abuse diagnoses.

Diagnosis of SAD

Evidence suggests that this chronic disorder is both under-diagnosed and under-treated due to a combination of delayed presentation (due to avoidance of help-seeking as a result of anxiety or lack of recognition of symptoms as diagnosable and treatable), lack of awareness or diagnostic clarity among primary care professionals, and the presence of co-morbid presentations (Katzelnick & Griest, 2001; Lydiard, 2001). For a diagnosis to be made, the individual must suffer from persistent, marked and irrational fear or anxiety about one or more social situations, and either avoids these situations or suffers them with great anxiety (APA, 2013). Individuals fear that they will exhibit behaviour or symptoms that will lead to negative evaluation. The fear, anxiety or avoidance causes significant distress to the individual, interfering with functioning, and usually persists for at least 6 months. Other psychiatric differentials, medical conditions and drug related causes need to be excluded.

Aetiology of SAD

SAD is a psychiatric disorder encompassing multiple aetiological causes including genetic, hormonal, developmental, and environmental. The interaction between these various aetiological factors is complex, and any one factor is neither necessary nor sufficient to determine the development of the disorder (Ollendick & Hirshfeld-Becker, 2002). The aetiology of SAD with reference to cognitive, affective and genetic components is discussed below, with the neural components discussed later.

Transient, age-related anxiety behaviour is a normal part of human development (Ollendick & Hirshfeld-Becker, 2002). For example, stranger anxiety can be observed in infants as young as 6 months old (Rosenbaum, Biederman, Hirshfeld, Bolduc & Chaloff, 1991). This and other developmental phases of anxiety fade in

most cases. However, a minority may retain social anxiety and the consequent inhibited behaviour as they grow up, which increases the risk of SAD developing in these individuals (Rosenbaum et al., 1991; Ollendick & Hirshfeld-Becker, 2002).

Cognitive behavioural models for the development of SAD suggest that there is an attentional bias and hypervigilance to internal negative cognitions, as well as external stimuli that are perceived to be threatening, leading to increased threat detection (Eysenck, 1992; Clark & Wells, 1995; Rapee & Heimberg, 1997). Individuals with SAD may have difficulty disengaging from perceived threat (Rapee & Heimberg, 1997) or exhibit increased avoidance behaviour (Clark & Wells, 1995). This is thought to play a role in maintaining the fear experienced by those with SAD.

This disorder is partially heritable, occurring more commonly in first degree relatives than in the general population (Merikangas & Angst, 1995; Rosenbaum, Bierderman, Pollock & Hirshfeld, 1994). Environmental factors may also play a role, including exposure to stressors early in life (Gabbard, 1992). Developmental theory suggests that individual temperamental, cognitive and genetic factors may interplay with environmental factors in the development of the disorder (Ollendick & Hirshfeld-Becker, 2002). Such environmental factors include parental psychopathology and over-control, adverse life events, difficult interpersonal relationships, and cultural values (Brook & Schmidt, 2008). These environmental factors interacting with a genetic pre-disposition, may contribute to the development of SAD in an individual.

Adaptive function of blushing and gaze avoidance in social anxiety

Characteristic symptoms of SAD include exaggerated blushing propensity and gaze avoidance, including fear of making eye contact (Edelmann, 1990; Schneier, Rodenbaugh, Blanco, Lewin & Leibowitz, 2011). This is consistent with an evolutionary perspective which highlights the adaptive nature of anxiety, and social anxiety specifically.

In the environment inhabited by early mammals, dangerous situations arose with frequency, particularly in the event of perilous natural events (e.g. lightning strikes and falling objects), being hunted by a predator, being antagonised by conspecfics (Tooby & Cosmides, 1990). Thus, it was necessary for the development of defensive adaptations to escape and avoid such threats in order to survive and reproduce (Öhman & Mineka, 2001). These defensive mechanisms first required sensory perception and motor reflexes, followed by innate defence mechanisms, conditioned responses, and later developments of affective and cognitive states that allow for deliberation and decisions in response to threat (Razran, 1971). Fear, or anxiety, became a central driver of these responses. Anxiety, therefore, is a strong motivator for self-preservation through escape and avoidance of danger or conflict (Epstein, 1972 as cited in Öhman & Mineka, 2001). The anxiety response (fight-or-flight, freezing, aggression etc.) may be much the same across a large variety of situations, because the same type of response may have yielded survival advantage across a variety of situations in the past (Price, 2003). While anxiety has adaptive advantages, excessive is likely to impact negatively on functioning, leading to disordered behaviour and may impede ability to effectively manage situations (Price, 2003).

Individuals with SAD tend to avoid social interaction or display avoidance behaviour during social interactions, possibly due to fear of negative evaluation (APA, 2013; Bögels et al., 2010; Voncken, Rinck, Deckers & Lange, 2012). Individuals suffering from SAD often exhibit submissive behaviours during social encounters (Russell et al., 2011). Such “safety behaviours” are thought to perpetuate and maintain SAD in an individual (Clark, 2001; Hofmann, 2007; Rapee & Heimberg, 1997). These behaviours may be under voluntary control, or may happen on a subconscious, involuntary level. Consciously employed safety behaviours may include remaining silent, concealing physical anxiety symptoms with clothing (Cuming et al, 2009; Voncken et al., 2012). Automatic safety behaviours may include avoidance of eye-contact and maintaining interpersonal distance (Foa and Kozak, 1986). Avoidance behaviours increase with the intensity of a social stressor (Roelofs, Elzinga & Rotteveel, 2005; Roelofs et al., 2009), and this has been corroborated by research on visual avoidance in non-social phobias (Aue, Hoeppli, Piguet, Sterpenich, & Vuilleumier, 2013; Tolin, Lohr, Lee & Sawchuk, 1999).

Blushing

Blushing in SAD may also be regarded as a submissive behaviour that may serve an adaptive function, but may contribute to pathological cognitive and affective patterns in some individuals. Despite featuring as a component of this psychiatric disorder, blushing is generally regarded a universal emotional response (Leary, Britt, Cutlip, & Templeton, 1992). The universality of blushing hints at its evolutionary advantage. Darwin (1892/1904, p. 327) regarded it as the "most peculiar and most human of all expressions".

Facial blushing, caused by cutaneous blood vessel dilatation, is both a salient and rapidly developing response elicited by emotional stimuli (Drott, Claes, & Rex, 2002). This response is mediated by the upper thoracic chain of sympathetic nervous system: the blush region is supplied with beta-adrenoreceptors, resulting in a dilator effect on the basal tone of the vasculature (Drummond, 1997; Mellander, Andersson, Afzelius, & Hellstrand, 1982). The blush region includes the face, forehead, neck, ears and sometimes the upper chest (Gerlach, Wilhelm, Gruber, & Roth, 2001). Blushing is socially produced, and is not to be confused with non-social reddening (flushing), caused by temperature changes, physical exertion or consumption of alcohol (Leary et al., 1992). Blushing may differ between individuals in frequency and intensity (across cultures and ages), and perceptibility (depending on skin darkness; Darwin 1982/1904).

Face-to-face contact involving self-conscious emotions of embarrassment or shame is the predominant cause of blushing (Shields, Mallory, & Simon, 1990). Blushing very rarely occurs when not in the presence of others (Darwin 1982/1904). While blushing is thought to be a hallmark response to embarrassment (Buss, 1980 as cited in Edelmann & Skov, 1993), it is thought that it may also result more generally from social attention (Leary et al., 1992). However, blushing and embarrassment may commonly co-occur, given that embarrassment often results from unwanted social attention (Edelmann & Skov, 1993). Social situations that elicit blushing include threats to an individual's public identity (through the violation of social norms), or undesired social attention from others (through scrutiny or positive attention and

praise). While embarrassment is usually brought about by an external event, it is possible that expressive cues (such as blushing) resulting from internal cognitive processes, may be enough to cause severe embarrassment (Edelmann, 1990; 1991). Thus, individuals, such as those with SAD, who are particularly sensitive to internal cues, may be more prone to blush and suffer from embarrassment. Indeed, chronic blushing is associated with high levels of social anxiety and self-consciousness (Endelman, 1990; 1991) as well as embarrassability (Leary & Meadows, 1991).

Displaying embarrassment or shame may have instrumental value in social interactions, because it indicates that the individual recognises the social transgression that he or she has made and regrets having done so (Keltner & Buswell, 1997). This signal of admittance may effectively diffuse a threatening situation by appeasing the recipient or observer of the social transgression. Such displays in both human and non-human animals involve gaze aversion, smiling, displaying the neck and reducing physical size. This phylogenetic similarity indicates an evolutionary basis for human variants of appeasement. Thus, blushing, as a signal of embarrassment or shame, may function to appease conspecifics (Leary et al., 1992; Keltner, 1995).

Despite its potential adaptive function, individuals often regard blushing as an undesirable response that they seek to prevent or conceal (de Jong & Peters, 2005; Shields et al., 1990). Some individuals experience distress due to blushing to the extent of becoming phobic and seeking treatment (Bögels, 2006; Gerlach et al., 2001), and it has been noted that some patients with SAD develop a fear of blushing and increased blushing propensity (Bögels, 2006; Bögels & Stein, 2009; Bögels et al., 2010; Edelmann, 1990; Gerlach et al., 2001), and it has been included as a "hallmark physical response" of the disorder (APA, 2013, p. 204). It has been argued that fear of blushing should be considered a specific sub-type of this disorder, where erythophobia (fear of blushing) is the primary complaint (Drott, 2004). Erythophobia is characterised by frequent episodes of severe blushing that are easily and instantly elicited, and are often associated with embarrassment and social incapacitation (Drott et al., 2002). Indeed, in research conducted in the Netherlands

(Bögels, 2006) and Japan (Matsunaga, Kiriike, Matsui, Iwasaki & Stein, 2001), over half of individuals with SAD report somatic complaints, such as blushing and sweating, as their largest fear.

While SAD patients with a fear of blushing may subjectively perceive that they blush more readily than others, it is unclear whether they objectively blush more than those without the disorder. There is some evidence that individuals with SAD as well as blushing complaints, exhibit greater physiological blushing (measured by blood flow and cheek temperature compared to SAD individuals without blushing complaints (Voncken & Bögels, 2008). The intensity of the blush depends on the amount of stress experienced in the situation provoking the blush (Mulkens, de Jong, Dobbelaar, & Bögels, 1999).

SAD patients without fear of blushing seem to have a reduced blush response, even compared to controls without SAD. However, these findings are not consistent across other studies, which found that there was no physiological difference in blushing between those who are fearful of blushing and those who are not (Mulkens, de Jong & Bögels, 1997; Mulkens et al., 1999). Instead, these studies found that severity of blushing was a subjective experience in blushing fearful individuals. Thus, it is unclear whether those SAD patients, who report increased blushing propensity or a fear of blushing, have an objectively increased blush response or not.

Gaze avoidance

Like blushing, gaze avoidance is considered to be a significant behavioural component of SAD (Schneier et al., 2011; Weeks, Howell & Goldin, 2013). This is thought to be problematic in SAD, because it impairs social interactions. Non-verbal visual communication is important in social, group-living animals, particularly primates (Emery, 2000). Communication via sustained eye contact is a behaviour readily employed by humans (Gilbert, 2001), and is normally used to facilitate social interactions, convey important emotional information, and moderate how one is perceived by others (Kleinke, 1986; Napieralski, Brooks & Droney, 1995; Öhman, Lundqvist & Esteves, 2001). Perception of, and attention to, faces, particularly the

eye area, is an important component of emotional and verbal communication (Gilbert, 2001; Öhman et al., 2001).

Evolutionary theory further posits that the emotion of fear (discussed earlier as a conserved adaptation) ensures rapid focusing of attention on potential threats, with heavy reliance on attentional gaze (Öhman & Mineka, 2001). Direct gaze may signal attention from a threatening individual (e.g. predator), making gaze detection an evolutionary survival mechanism, often resulting in a fearful or submissive response (Emery, 2000; Gilbert, 2001). Gaze avoidance is a cross-species behaviour that indicates social submission and may have evolved as a defence against conflict (Öhman, 1986). In SAD, this mechanism results in a pattern of vigilance followed by avoidance, with increased attention to threat followed by increased avoidance of the threat.

Research on the phenomenon of gaze avoidance has determined that individuals with SAD exhibit significantly less eye contact when engaging with others than do those without the disorder (Baker & Edelmann, 2002). Studies have used eye-tracking to determine eye contact patterns in individuals with SAD reacting to images of negative and positive faces (Horley, Williams, Gonsalves & Gordon, 2003; 2004; Moukheiber et al., 2010; Wieser, Pauli, Alpers & Muhlberger, 2009). These studies generally found that while most individuals with SAD tended to avoid eye contact more than healthy controls (HCs), increased symptom severity was associated with increased gaze avoidance and decreased fixation on the eye area of faces. Gaze avoidance has been found to be consistent across gender (Moukheiber et al., 2010) and increased for negative emotion (e.g. anger) directed at the observer through direct gaze (Lange et al., 2011; Roelofs et al., 2010). It is postulated that gaze avoidance plays a significant role in sustaining social anxiety disorder, by negatively reinforcing fearful responses (Greist, 1995; Marks & Gelder, 1969 as cited in Moukheiber et al., 2010; Öhman, 1986).

Blushing and gaze in the context of SAD have been explored in the context of evolutionary adaptation, cognitive and affective mechanisms as well as their place in

the pathology of SAD. It seems clear that blushing is physiological response with complex social and psychological components. While the basic physiology of sympathetic stimulation and cutaneous vasodilatation of blushing is well-known, the precise mechanism is poorly understood. Furthermore, the regions of the brain involved in the blush response remain unexplored. Similarly, while gaze behaviour in SAD individuals has been investigated, only a handful of studies have conducted research into the neurobiological underpinnings of this trait.

Neurobiology of SAD, gaze behaviour and blushing

What is known of the neurobiological underpinnings of these cognitive, affective and behavioural components of SAD will now be discussed. There is evidence for alterations in brain structure, functional brain activation, and neurotransmitter systems in patients with SAD. However, less is known about the neurobiology of blushing and brain behaviour.

Neurobiology of SAD

Abnormalities in the basal emotional centres of the brain, detected in functional neuroimaging (fMRI) studies, have been implicated in SAD pathogenesis. Several fMRI studies suggest that individuals with the disorder may possess amygdala hyperactivity and an inability to engage the ventromedial frontal areas implicated in the regulation of emotions (Hattingh, 2011; Phan, Fitzgerald, Nathan & Tancer, 2006; Shin & Liberzon, 2010; Stein, Goldin, Sareen, Zorrilla & Brown, 2002; Straube, Mentzel & Miltner, 2005). The amygdala has been implicated in early, reflexive detection of salient threat stimuli (LeDoux, 1998; Morris, Öhman & Dolan, 1998; Schneier, Kent, Star & Hirsch, 2009), thus increased activity in this region suggests exaggerated threat response. Furthermore, differences in resting state functional connectivity between amygdala and higher cortical structures were found between SAD and HCs (Pannekoek et al., 2013), suggesting altered emotional processing in SAD.

Higher brain centres, as well as those at the interface between the prefrontal cortex and the deeper emotional centres have also been implicated in the disorder. The prefrontal cortex has been implicated in high level cognitive functioning, including social cognition and executive control (Bzdok, Laird, Zilles, Fox & Eickhoff. 2013). Altered emotional and self-referential processing is implicated by alterations in activation of dorsomedial prefrontal cortical (DMPFC) areas (Amir et al., 2005; Blair et al., 2011; Freitas-Ferrari et al., 2010; Goldin, Manber, Hakimi, Canli & Gross, 2009; Lorberbaum et al., 2004; Phan et al., 2006; Stein, Hunter, Rolfe & Oakes, 2002; Straube et al., 2005). Increased ACC response has been found in controls, which implies that they are able to shift attention more readily (Klumpp, Post, Angstadt, Fitzgerald & Phan, 2013). In the case of SAD individuals, it is thought that there is a difficulty disengaging from threat stimuli. Furthermore, it has been suggested that there is an increased effort and adjustment required by higher centres to control more basal structures, such as the amygdala, when individuals with SAD are exposed to potentially threatening social stimuli, as evidenced by heightened activation followed by a habituation effect observed in the amygdala, OFC and thalamus in SAD patients after exposure to emotional stimuli (Sladky et al., 2012).

In addition, it appears that patients with SAD activate regions related to self-referential processing, visual attention and related memory (Dumas et al., 2013). Differences in activation have been found in the fusiform gyrus and inferior temporal cortex (Etkin & Wager, 2007; Gentili et al., 2008). Increased insula activation has been found in individuals with generalised SAD when perceiving emotional faces (Klumpp et al., 2013). Individuals with SAD also tend to have an enhanced visual cortical response to emotional faces (McTeague, Shumen, Wieser, Lang & Keil, 2011). Indeed, the insula is thought to be associated with the experience of emotion, particularly anxiety (Paulus & Stein, 2006). The fusiform gyrus, also known as the fusiform face area, deals specifically with facial processing (Kanwisher, McDermott & Chun, 1997). This may be related to gaze anxiety and avoidance behaviour, which is discussed later.

The most coherent finding among the brain imaging techniques reflect increased activity in limbic and paralimbic regions in SAD. The predominance of evidence implicating the amygdala strengthens the notion that it plays a crucial role in the pathophysiology of SAD. The observation of alterations in pre-frontal regions and the reduced activity observed in striatal and parietal areas show that much remains to be investigated within the complexity of SAD

While research points towards functional alterations in both basal and higher centres, these findings need to be viewed in the light of a recent review of the neuroscientific and electrophysiological studies indicating results obtained vary according to neuroscientific methods and experimental tasks (Schulz, Mothes-Lasch & Straube, 2013). This review concluded that there is a lack of systematic studies with consistent methodology in order to produce reliable findings. Thus, it is prudent to regard the existing findings with care. Furthermore, neurobiological variation found in SAD patients across different studies may also be the result of other variables. Furmark et al. (2009), for example, note that over-activity in the amygdala may be more related to adrenergic genetic polymorphisms rather than directly to SAD. Thus variations in research results may be partly related to methodological differences or to biological variation influenced by other factors.

Referring to meta-analyses of existing neuroimaging studies on the topic by is useful in distilling a coherent picture of neurobiological differences in SAD patients. Etkin & Wager (2007)'s quantitative meta-analysis of eight studies (including fMRI and positron emission tomography, or PET) revealed increased activation in the amygdala and insula in SAD patients. Both of these structures are thought to be involved in negative emotional responses (Phan et al. 2006; Stein, Goldin et al., 2002; Straube et al., 2004; 2005). Freitas-Ferrari et al.'s (2010) systematic review of forty-eight studies (including fMRI, PET, and magnetic resonance spectroscopy, or MRS, methods) found increased activity in the limbic area, paralimbic regions, and amygdala, as well as possible alterations in frontal regions. Hattingh's (2011) likelihood analysis of eleven studies indicated increased activation for SAD patients in the hippocampus, amygdala, insula, dorsal striatum, occipital lobe, and

cerebellum. Hattingh et al. (2013) followed up with a likelihood analysis of seven fMRI studies determined that there was significantly increased activation in the amygdala bilaterally, left medial temporal lobe (including parahippocampus), right anterior cingulate, postcentral gyrus and right globus palidus in individuals with SAD relative to HCs. Taken together, these analyses indicate that combined research findings correspond to neuroanatomical models of fear conditioning and demonstrate the importance of the limbic system in SAD.

Functional activation differences may be underpinned by structural brain volume or cortical thickness differences. Structural investigations of the neurobiology of SAD have demonstrated cortical volume differences associated with the disorder. The findings of research in this area have been variable, suggesting that a range of neurocircuitry is involved in SAD. For instance, some studies have found no volumetric differences in whole brain, thalamus, striatum (Potts, Davidson, Krishnan & Doraiswamy, 1994), amygdala or hippocampus (Syal et al., 2012), while other studies have found either increases or decreases in various regions. Volume decreases in the amygdala (Irle et al, 2010; Hattingh, 2011), hippocampus (Irle et al., 2010, Liao et al., 2011), orbitofrontal, insular (Hattingh, 2011; Syal et al., 2012), parietal, and temporal cortex (Syal et al., 2012; Talati, Pantazatos, Schneier, Weissman & Hirsch, 2013), including the fusiform gyrus (Syal et al. 2012) have been noted in SAD patients. Decreased hippocoampal volume (Irle et al., 2010; Liao et al., 2011), thinning of the postcentral cortex (Syal et al., 2012) and decreases right rostral anterior cingulate cortex thickness (Frick et al., 2013) have been found to be associated with increased symptom severity. In contrast, increased cortical thickness has been associated with SAD in the fusiform and left parahippocampal gyri and the cerebellum (Talati et al., 2013), left inferior temporal cortex (Frick et al., 2013), left insula, right temporal pole, right anterior cingulate, left insula, right dorsolateral prefrontal and parietal cortical areas (Brühl et al., 2013) and medial prefrontal cortex (Liao et al., 2011). These variable findings suggest that while it is likely that there are structural anatomical differences associated with SAD, the disorder may involve a range of complex neurocircuitry.

In addition to grey matter volume differences, white matter tract alterations have been found in individuals with SAD. Currently, it is thought that the white matter tract of the uncinate fasciculus, that connects temporal and frontal brain regions, was found to be reduced bilaterally in SAD patients, suggesting a deficiency in connection between higher centres and basal structures, such as the amygdala (Bauer et al., 2013). Liao et al. (2011) found right medial prefrontal cortex volume and corpus callosum connectivity were increased SAD patients (Liao et al., 2011). They concluded that these enhancements imply a compensatory mechanism employed by those with the disorder. Relatively few studies have been published in this area, however, so evidence is contradictory and limited.

Adding to the developing picture of structural anatomical and functional activation differences, there is evidence of differences at the molecular level. Evidence from the efficacy of SSRIs suggests the role of neurotransmitters, specifically dopaminergic and serotonergic circuits, in the disorder's pathogenesis (Brunello et al., 2000; Stein, Hunter et al., 2002; Stein & Seedat, 2007). Furthermore, evidence from both non-human and human primates suggests altered regulation of the hypothalamic-pituitary-adrenal (HPA) axis. In non-human primates, elevated cortisol levels in response to stress, lead to displays of submissive and avoidant behaviour in social situations (Sapolsky, 1990; Kalin, Larson, Shelton, & Davidson, 1998). Similarly, in humans, increased cortisol response is associated with increased avoidant behaviour, suggesting a hyperactive HPA axis response in SAD (Roelofs et al., 2009).

Neurocircuitry of embarrassment and blushing

Some neurological research has been conducted into the experience of emotions underlying blushing, but the neural correlates of the blush response itself are relatively unknown. As previously mentioned, blushing occurs in response to the self-conscious or moral emotions of embarrassment and shame (Shields et al., 1990)

Various neuroimaging studies on social, self-conscious and moral emotions have revealed certain brain areas correlated with their expression. The amygdala, a brain

region heavily implicated in the conditioning and expression of basic emotions, has been implicated in affective response to one's own moral transgressions, and the experience of social emotions (Moll, de Oliveira-Souza, Eslinger et al., 2002; Berthoz, Grèzes, Armony, Passingham, & Dolan, 2006; Britton et al., 2006). Social emotions have also been found to trigger activation in the superior temporal gyrus, hippocampus and posterior cingulate (Britton et al., 2006), upper midbrain and thalamus (Moll, de Oliveira-Souza, Bramati, & Grafman, 2002; Moll, de Oliveira-Souza, Eslinger et al., 2002). Moral emotions (or prosocial emotions) additionally recruited the orbital and medial prefrontal cortex and superior temporal sulcus (Moll, de Oliveira-Souza, Eslinger et al., 2002; Moll et al., 2007).

Activation patterns for embarrassment, specifically, include the ventrolateral and dorsomedial prefrontal cortex, bilateral hippocampus, right anterior temporal cortex, and visual cortex (Takahashi et al., 2004). The ventrolateral and dorsomedial prefrontal cortex is increasingly active for social transgressions in the presence of an audience, and for all moral transgressions. It has been suggested that these regions process aversive social stimuli in order to facilitate a change in behaviour from the one prompting the aversive reaction to a more beneficial one (Finger, Marsh, Kamel, Mitchell, & Blair, 2006).

Understanding the neural correlates of the emotions that are thought to underlie the blush response may go some way to suggest the higher level processing that may be involved in the blush response. However, no studies of SAD have determined the neural correlates of blushing symptoms in this disorder.

Neurocircuitry of gaze behaviour

Neuroimaging research has determined that eye contact and gaze cues are associated with increased cortical activity in the amygdala (Spezio, Huang, Castelli & Adolphs, 2007; Dumas et al., 2013), ventral striatum (Kampe, Frith, Dolan & Frith, 2001) and superior temporal sulcus (Nummenmaa & Calder, 2009). Pupil dilatation, which is thought to play a role in eye contact interactions, is regulated by autonomic pathways (Yoshitomi, Ito & Inomata, 1985). It is influenced by emotional salience and by

activity in the anterior cingulate cortex and amygdala (Pissiota et al., 2003; Critchley, Tang, Galser, Butterworth & Dolan, 2005). Individuals with amygdala damage also show increased gaze avoidance (Adolphs, Tranel, Damasio & Damasio, 1994; Adolphs et al., 2005), lending further support to the idea that the amygdala plays an important role in gaze behaviour.

Research into the functional neurology of gaze behaviour in individuals with SAD demonstrates that SAD patients and HCs differ in the activation of fusiform, insula, anterior cingulate, prefrontal cortex and amygdala in response to gaze (Schneier et al., 2009). Heightened brain activation has been observed in the fusiform gyrus (or fusiform face area) of SAD patients relative to HCs (Mueller et al., 2009). This increased activation is suggestive of hyper-vigilance in individuals with SAD (Mueller et al., 2009), increased activation in the neurological fear neurocircuitry in response to eye contact (Schneier et al., 2009) and threatening facial expressions (Stein, Goldin et al., 2002). This, together with increased pupil dilatation observed in individuals with SAD as a result of subjective perception of eye contact, suggests increased autonomic arousal and fear in response to eye contact (Honma, 2013). However, only a few studies have looked at these neuroanatomical correlates of gaze fear and avoidance in SAD patients. Thus, research into this little explored area would enhance the understanding of SAD and may inform management of this common disorder.

While a number of studies have explored the functional neurobiology of SAD, there is still work to be done in resolving methodological heterogeneity in order to move towards a more coherent picture of the underpinnings of the disorder. Even less work has been done on the structural neurobiology of the disorder. A smattering of studies has demonstrated some grey and white matter volume differences in individuals with SAD, but these findings have been somewhat contradictory (Brühl et al., 2013).

Treatment of SAD, blushing and gaze avoidance

The chronicity and significant functional impairment experienced by individuals with SAD indicates the necessity for treatment of the disorder as well as possibly

specifically targeting salient symptoms. While a number of treatments are available for the treatment of SAD in general, targeted treatment for the specific symptoms of blushing and gaze avoidance requires attention. The current treatment available for blushing is far from ideal, and research into the treatment of gaze avoidance is still in its infancy. Treatment improvement or expansion of treatment options relies, at least in part, on an improved understanding of the physiological and neurological bases of self-conscious emotions, blushing and gaze avoidance behaviour. Indeed, Cuthbert and Insel (2013), posit that current diagnostic classifications may not adequately reflect the behavioural and neurobiological components of disorders, which impedes true understanding of the aetiology as well as treatment development. Furthermore, the development of more effective treatments may contribute to the understanding of the neurobiology of these.

Treatment of SAD

SAD is best managed with a combination of psychological and pharmacological therapies (den Boer, 1997; Muller et al., 2005). Pharmacotherapies that have been used for SAD include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reverse inhibitors of monoamine oxidase A (RIMAs), benzodiazepines, and beta blockers (den Boer, 1997; Muller et al., 2005).

A systematic review on these therapies demonstrated medication to be more effective than placebo, with SSRIs demonstrated to be the best for first line therapy because of their effectiveness, safety and tolerability and use in the treatment of co-morbidities (Muller et al., 2005). MAOIs and RIMAs are considered for second line therapy, with a worse side-effect profile than SSRIs (Muller et al., 2005; Stein & Ipser, 2000). Such treatment was also effective in reducing co-morbid depression. Results from the review supported short-term therapy with long-term maintenance in those who responded. However, while these therapies may be effective in a broad range of SAD patients, research into the effectiveness of medication for specific phobias, such as fear of public speaking, is limited. Psychological therapy of the disorder usually involves cognitive behaviour therapy (CBT), which consists of

restructuring of maladaptive thinking and exposure to situations that provoke anxiety, and can be administered at any stage of the treatment process (Muller et al., 2005; Stein & Ipser, 2000).

Treatment of blushing

Treatment options available to patients with a fear of blushing include behaviour modification, medication, or surgery (Mulkens, Bögels, de Jong, & Louwers, 2001; Drott et al., 2002; Connor, Davidson, Chung, Yang, & Clary, 2006). Table 1 summarises the literature that exists for the treatment of blushing specifically. While some therapies used to treat SAD generally can have effects on blushing, these studies have not been included. This summary is included here, because while meta-analyses exist for neuroimaging research in SAD (Hattingh et al., 2013), and for the psychological and pharmacological treatment of SAD in general (Muller et al., 2005; Stein & Ipser, 2000), no such current summary exists for the blushing or gaze avoidance treatment literature (a single review by Neumayer in 2005 addressed blushing treatment was only on surgical options and included indications not limited to blushing).

There are several medications that may be used for the treatment of fear of blushing (erythrophobia), although the effects are mostly as a by-product of treating the primary SAD diagnosis. Given the proposed sympathetic mediation of the blush response, beta blockers and anxiolytic drugs, that target symptoms related to the sympathetic nervous system, have been used by some patients (Drott et al., 2002). However, these therapies are ones that are used for the treatment of SAD and not blushing specifically, and the efficacy for blushing remains untested (except in one study discussed below). A number of individuals seeking surgical intervention have previously tried beta-blockers and anxiolytics with limited success (Drott et al., 2002).

There is some evidence of efficacy for SSRIs, suggesting the involvement of serotonergic systems in the blush response. Sertraline, one such SSRI, has been found to reduce fear, avoidance and the physiological symptoms, specifically

blushing (13% reduction) and palpitations (10% reduction), in patients with social anxiety disorder (Connor et al., 2006; Table 1). While the use of SSRIs may be beneficial in mild blushers, the magnitude of this reduction may not be sufficient for severe cases and surgery may be necessary. For example, Drott et al. (2002) found that a number of their patients had unsuccessfully tried SSRIs. Furthermore, the work by Connor et al. (2006) was the first randomised-control trial into the use of pharmacotherapy in the treatment of blushing. More research is needed into the effects of pharmacological management of blushing, before strong conclusions can be drawn.

Some researchers recommend that individuals who suffer from fear of blushing should first attempt to treat the underlying cause of blushing, using psychological therapies before considering the drastic option of surgery (Bracha & Lenze, 2006). One such method, CBT, involves decreasing a patient's anxiety surrounding the blush response (Mulkens et al., 2001). Another method, exposure training, involves guiding the patient through situations that produce anxiety in order to diminish their problematic responses (Scholing & Emmelkamp, 1993). Task concentration is yet another method that attempts to redirect the patient's attention from the bodily symptoms they experience to the social task at hand (Bögels, 2006). There is some evidence to suggest that these therapies result in improvement in fear of blushing. Relaxation techniques can also be tried, but these have been shown to be less effective (Bögels, 2006). However, there are very few studies on the effectiveness of these therapies, so their success with treating blushing specifically is still largely unconfirmed.

In severe cases, patients obtain no relief from either psychotherapy or medication and turn to surgery. This more drastic, yet more effective, treatment is an endoscopic thoracic sympathectomy (ETS) or endoscopic thoracic block (EBS) by clipping, a surgery that interrupts the facial sympathetic innervation of the upper thoracic chain (Drott et al., 2002). The surgery, originally used for hyperhidrosis (excessive sweating), was first proposed for facial blushing in 1985 (Wittmoser, 1985). It is now indicated for hyperhidrosis, facial blushing, digital ischemia or sympathetic dystrophy (Kwong et al., 2005). For facial blushing, surgery or clipping is bilateral

and usually occurs at the level of the second and third thoracic (T2-T3) or third and fourth vertebrae (T3-T4). While the pathophysiological mechanism of blushing is still poorly understood, this surgery has been found to produce a 63-100% reduction in facial blushing among patients (Table 1).

However, side effects of this surgery make it an option reserved only for intractable symptoms. Undesirable side effects, most commonly compensatory sweating, have been reported with a wide range of variability (between 12.5- 88%) of patients (Table 1; Bracha & Lenze, 2006; Chou et al., 2006; Smidvelt & Drott, 2011). These side effects may lead to regret of having had the surgery (Cameron, 2003). ESB may be more advantageous to this end, because of reversibility and reduced complications (Lin et al., 1998; Chou et al., 2006). Also, there is some evidence that performing the surgery at the T3-T4 level causes less compensatory sweating than at T2-T3 (Reisveld, 2006), however the T2 level is most commonly blocked for blushing complaints (Neumayer, 2005). Other surgical risks include the complications associated with all surgery (failure of procedure, haemorrhage and anaesthetic complications), as well as pleural effusion, pneumothorax (air in the pleural space of the lung), haemothorax (blood accumulation in the pleural space), and Horner's syndrome (eye palsy involving drooped eyelid with pupil constriction; Cameron, 2003; Chou et al., 2006; Kwong et al., 2005). The use of a harmonic scalpel (Callejas, 2004) or laser (Black, Taylor, Russel, Ariga & Thomas, 2008) instead of diathermy may prevent some of the more severe complications compared to traditional techniques, however only a few studies have investigated such alternative methods.

Even though surgery has been showing to be highly effective in reducing blushing, the side-effects and risks of this elective procedure make it less than an ideal solution. Furthermore, some experts propose that surgery is the wrong approach to fear of blushing (Dijk & De Jong, 2006; Drummond, 2000). Firstly, the surgical side effects may be worse than the original symptoms in some patients (Drummond, 2000). Secondly, evidence of surgical efficacy is has been largely determined by uncontrolled retrospective studies. Thirdly, as previously discussed, there is evidence

to suggest that those who fear blushing may not actually blush more than non-fearful individuals, and it is rather the fearful preoccupation with blushing that requires treatment (Gerlach et al., 2001; Drummond, 2006). Finally, removal of blushing may affect the communication of social and moral emotions (i.e. shame and embarrassment), thereby affecting social functioning (de Jong, 1999).

Treatment for gaze avoidance

There are several treatment options available for blushing (despite being suboptimal), but treatment available for gaze avoidance is even more limited. So far, there is some evidence for the effects of neuropeptide and neurotransmitter imbalances affecting gaze behaviour in SAD patients (Gamer, Zurowski & Buchel, 2010; Laubuschane et al., 2010; Table 1). Oxytocin is a neuropeptide that plays an important role in regulating social behaviour in humans and other animals. Administration of oxytocin has been found to attenuate amygdala hyperactivity activity and increase gaze behaviour in SAD patients (Gamer et al., 2010; Laubuschane et al., 2010). SAD patients treated with the SSRI paroxetine displaced decreased fear and avoidance of eye contact after 8-12 weeks (Schneier et al., 2011).

Despite the options currently available, there is no ideal treatment for blushing in blushing-fearful individuals, and more efficient pharmacotherapies and psychotherapies should be investigated. Furthermore, treatment research for gaze avoidance still has far to go. Investigating the underpinnings of self-conscious emotions, blushing and gaze avoidance behaviour is an important step towards better treatment options for SAD patients with these specific complaints.

Table 1.

Summary of blushing and gaze avoidance treatment research

Reference	Treatment Type	Total study participants	Participants with gaze/blushing complaints	Follow-up time (months)	Level of surgical intervention	Treatment success and satisfaction	Treatment side effects and complications [a]
Gaze avoidance							
Pharmacological*							
Gamer et al. (2010)	Oxytocin	46	0 (all HCs)	Immediate	-	Increased likelihood of gaze towards eyes, with increase in posterior amygdala as determined by fMRI	-
Labuschagne et al. (2010)	Oxytocin	36	18	45 (min)	-	Normalisation of amygdala activation as determined by fMRI	-
Blushing							
Pharmacological*							
Connor et al. (2006)	Sertraline (SSRI)	346	346	3	-	Efficacy 48%, *behavioural:* 17% reduction in fear, 18% reduction in avoidance, *physiological:* 13% reduction in blushing, 10% reduction in palpitations, 8% reduction in sweating	-
Psychological**							
Scholing & Emmelkamp, (1993)	CBT vs. exposure therapy	35	35 (30 for analysis, 85.7%)	Immediately after treatment then at 3	-	No significant difference between treatments	-
Bögels (2006)	Task ncentration vs. relaxation	65	24	Immediately after treatment then at 3 and 12	-	Task concentration more effective than relaxation	-

Reference	Treatment Type	Total study participants	Participants with gaze/blushing complaints	Follow-up time (months)	Level of surgical intervention	Treatment success, satisfaction, side effects[a]	Treatment side effects and complications
Surgical* **							
Wittmoser (1985)	ETS	70	70 (43 for analysis, 61.4%)	24 (max)	T2 – T3 + RC	Efficacy 95% bilateral, 66% unilateral	No major complications
Yilmaz et al. (1996)	ETS	50	11	66 (max)	Lower T1 –T5	Efficacy 93.3%	*CS* 67%, *Complications*: 1 Horner's syndrome, 1 neuralgia, 1 pneumothorax, 4 winged scapula
Drott et al. (1998)	ETS	244	244 (219 for analysis, 95%)	8 (mean)	Lower T1 –T3	Efficacy VAS 8.7 before vs. 2.2 after (74.7% improvement), Satisfied 85%, Partially satisfied 13%, Dissatisfied 2	%, *CS* 75%. *Complications*: 2 pneumothorax, 1 pulmonary embolus
Rex et al. (1998)	ETS	1152	244	8 (mean)	T2-T3	Efficacy 96%, Satisfied 85%, Partially satisfied, 13%, Dissatisfied 2%	*CS* 59.8%
Drott et al. (2002)	ETS	1314	1314 (831 for analysis, 63%)	29	Lower T1-T3	Efficacy in 95% of patients, VAS 8.8 before vs. 2.5 after (71.6% improvement), Satisfied 85%, Partially satisfied 15%	*CS* 83%
Lardinois (2002)	ETS	37	18	30 (mean)	T2 – T5 + RC	Efficacy 89%, Satisfied 95%, 94.5% QOL improvement	*CS* 44-67%, *Complications*: 1 Cerebral emboli with motor aphasia, 1 pneumothorax, 2 Horner's Syndrome
Rajesh (2002)	ETS	26	3	29 (mean)	T2 –T4	Efficacy 65%	*CS* 77%; *Complications*: 2 Horner's syndrome, 10 pneumothorax, 2 haemothorax, 2 surgical emphysema,1 pleural effusion, 2 chest infections

Reference	Treatment Type	Total study participants	Participants with gaze/blushing complaints	Follow-up time (months)	Level of surgical intervention	Treatment success, satisfaction, side effects[a]	Treatment side effects and complications
Fishel et al. (2003)	ETS (harmonic scalpel)	486	5	42 (max)	T2 –T3	Efficacy 90%	*CS* 19%, no complications
Neumayer et al., (2003)	ESB	184	18	5 (median)	T2	Efficacy 100% , Satisfied 93.7%, Partially satisfied 6.3%	*CS* 12.5%, *Complications*: 1 pneumothorax, 1 partial Horner's syndrome
Callejas et al. (2004)	ETS (diathermy, harmonic scalpel)	100	100	20 (max)	Lower T1-T3		No complications in harmonic scalpel group vs. Complications in diathermy: 1 temporary Horner's syndrome, 3 persistent pain, 9 asymptomatic pneumothorax
Licht et al. (2004)	ETS (diathermy, harmonic scalpel)	158	49	26 (median)	T2	Efficacy 43%, Satisfied 25%, Some effect 17%, No effect 15%	*CS* 81%, *Complications*: 4 Horner's syndrome, 40 pneumothorax (10 symptomatic), 1 pleural empyema
Adair et al. (2005)	ETS	80	59	20	T2 – T3	Efficacy Score 78 before vs. 26 after (66.6% score reduction), Complete resolution 29%, QOL improvement 63%	*CS* 91%, *Complications*: 5 pneumothorax, 2 transient Horner's syndrome, 52 transient chest pain
Neumayer et al. (2005)	ESB	57	27	20.4 (mean)	T2	Efficacy 96.2%, Satisfied 76.9%, Partially satisfied 11.5%, Partially dissatisfied 11.5% Marked improvement 3.8%	*CS* 23.1%, *Complications*: 1 pneumothorax, 1 partial miosis, 3 neuralgia
Kwong et al. (2005)	ETS	202	21	13 (mean)	T2	Efficacy 90%	*CS* 40%, *Complications*: 1 pneumothroax, 1 pleural effusion, 2 Horner's Syndrome, 2 chylothorax

Reference	Treatment Type	Total study participants	Participants with gaze/blushing complaints	Follow-up time (months)	Level of surgical intervention	Treatment success, satisfaction, side effects[a]	Treatment side effects and complications
Chou et al. (2006)	ESB	73	14	28 ± 10.5 (mean)	T2	Efficacy 100%	*CS* 7.1%
Licht et al. (2006)	ETS	180	180 (173 for analysis, 96%)	20 (median)	T2 and T2 – T3	Efficacy 90%, Excellent 55%, satisfied 19%, Some effect 16%, No effect 10%	*CS* 88%, *Complications*: 1 pneumothorax, 1 temporary Horner's syndrome
Black et al. (2008)	ETS with laser	233	8 (6 for analysis, 75%)	6-120 (range)	T2 – T3	Efficacy 83%, Satisfied 66.7%, Partially satisfied 16.7% No improvement 16.7%	*CS* 55%, *Complications*: 1 pulmonary oedema, 2 bleeding, 2 failed procedures
Jeganathan et al. (2008)	ETS	163	24	51 (mean)	T2	Efficacy 84%, Failure 16%, Recurrence 4.7%	*CS* 77%, *Complications*: 6 pneumothorax, 1 chronic wound
Fibla et al. (2009)	ESB	61	16	1 week, then 3 and 12	T2	Efficacy 95%	*CS* 62.2%, *Complications*: 5 pneumothorax (4 asymptomatic)
Franco et al. (2011)	ETS and PRS	58	18	12-14	T2 and C7 – T1	Efficacy 72.5% ETS vs. 15% PRS, higher QOL improvement for ETS	*CS* 40%
Smidvelt & Drott (2011)	ETS	3015	536	14.6	T2 – T3	Efficacy 72.8%, Satisfaction 73.5%	*CS* 80%

Key: CBT= cognitive behavioural therapy, ETS = endoscopic thoracic sympathectomy, ESB = endoscopic thoracic block, PRS = percutaneous radiofrequency sympathicolysis, T1 = thoracic vertebra 1, T2= thoracic vertebra 2, T3= thoracic vertebra 3, T4= thoracic vertebra 4, RC = Rami communicantes, CS = compensatory sweating, QOL = quality of life, *Randomised control trial, **Treatment outcome trial, ***Uncontrolled, retrospective analysis, [a]complications reported for total sample

Summary

SAD is one of the major psychiatric disorders, thought to account for a third of diagnoses. It is characterized by a marked fear of social interaction or scrutiny by others. An individual with the disorder may present with a constellation of physiological and psychological symptoms, of which blushing and gaze avoidance have been demonstrated to be strongly associated (Edelmann, 1990; Gerlach et al., 2001; Baker & Edelmann, 2002; Bögels, 2006; Bögels & Stein, 2009; Bögels, 2011; APA, 2013). The disorder is chronic and severely debilitating in nature and may often occur with other co-morbid conditions, such as mood disorders, other anxiety disorders and substance abuse.

Given its severity and chronicity, treatment is imperative. First line treatment of SAD involves SSRIs, with other options including TCAs, MAOIs, RIMAs, benzodiazapines and beta blockers, together with cognitive behavioural therapy. Treatment for blushing may comprise CBT and other forms of psychotherapy, as well as the medications used in SAD treatment. However, these treatments have limited success on the blush response, and surgery may be required to produce lasting results. There is some evidence for the use of oxytocin and SSRIs in the management of gaze avoidance. However, treatment for these specific components of SAD are far from ideal, given the side-effects of surgery and limited exploration of gaze avoidance treatment options. This may, in part, be related to our limited understanding of the neurobiology of these specific symptoms.

Neurobiological and treatment research has suggested abnormalities in neurotransmitters, as well as functional and structural differences in the deep, emotional centres and higher centres of the brain. Meta-analysis of the available imaging literature indicates increased activation has been demonstrated in the amygdala bilaterally, left medial temporal lobe (including parahippocampus), right anterior cingulate, postcentral gyrus and right globus palidus in individuals with SAD. There is also some evidence for cortical volume and white matter tract differences in SAD patients, implicating a range of neurocircuitry that may be altered

in the disorder. Dopaminergic, serotonergic circuits and the HPA-axis have also been implicated in the pathology of SAD.

Gaze fear and avoidance, and blushing are both potentially adaptive traits that have become maladaptive, salient features of SAD. In their adaptive role, both eye contact and blushing facilitate non-verbal communication, by conveying important emotional information, indicating submissive behaviour or recognition of social transgressions. However, in SAD, these behaviours are disordered to the extent of inhibiting successful social interactions.

While the neurobiology of SAD is partially understood, investigation into the neurobiology of the cardinal symptoms of blushing and gaze avoidance is limited. Individuals with SAD have been shown to have altered brain activation in response to gaze and avoidance behaviour in the areas of the fusiform gyrus, insula, anterior cingulate, amygdala and prefrontal cortex. However, little is known about the structural differences underlying gaze fear and avoidance in SAD. While the pre-frontal cortex, amygdala, temporal, hippocampal, and cingulate regions have been implicated in the processing of self-conscious emotions, including embarrassment, virtually no research has been conducted into the neurological correlates of blushing. Furthermore, while some research has been conducted into how general SAD symptom severity relates to structural brain differences, how the severity of these specific, salient, SAD symptoms correlate with the altered neurocircuitry observed in SAD, remains unexplored.

Furthering an understanding of this has implications for the understanding of SAD neurobiology as a whole and also may influence future treatment of the disorder. Investigations into the structural brain differences associated with these behaviours may shed light into the structural biology of SAD and associated symptoms, further developing the picture of the disorder on a structural neurological level. Having reviewed the literature, I will now propose a study that aims to address some of these questions.

AIMS AND OBJECTIVES

In light of the areas requiring further investigation, the aim of this research project was to study the neuroanatomy of blushing propensity and gaze avoidance in participants with SAD. The objectives of this were to:

1. Determine whether differences exist between participants with SAD and controls on measures of blushing and gaze anxiety and avoidance.
2. Determine whether these differences correlate with brain volume differences in participants with SAD versus controls.

I hypothesised that SAD patients and HCs would differ significantly on measures of blushing and gaze behaviour, given my argument that these are cardinal symptoms of SAD. Furthermore, I hypothesised that these symptoms would be associated with structural brain volume differences associated with these symptoms. Based on the literature of blushing and gaze neurocircuitry, I thought it plausible that these differences may be in regions associated basic, social and moral emotions, autonomic pathways and the amygdala.

METHODS

Participants

Participants were recruited as patients of local psychiatrists and psychologists, community-based advocacy groups via advertisements placed in newspapers and from university campuses. Only participants who were over the age of 18 and were right handed were initially considered. Those who did not give consent, had co-morbid psychiatric or neurological illnesses, were psychotic or unable to adequately comprehend the procedure were excluded. Approximately two-thirds of all participants who were recruited were excluded as a result of co-morbid diagnoses or other exclusion criteria. The remainder were included in the study.

Participants in the SAD group (n = 18) consisted of ten SAD males and eight SAD females, while there were seven males and eleven females in the HC group (n = 18) respectively. SAD patients and HCs were similar in age and education level with no significant differences between them (Table 2). All participants were assessed by a clinical psychologist, who conducted a diagnostic interview with each. Participants included in the SAD group had a primary diagnosis of generalized social anxiety disorder without co-morbid psychiatric diagnoses on Axis I of the DSM-IV (The DSM-V had not yet been released at the time of data collection). The Structured Clinical Interview for DSM-IV was used to determine the presence of co-morbidities (First, Spitzer, Gibbon & Williams, 2012). None of the HCs had psychiatric or neurological diagnoses. All participants were right handed. Ten SAD patients and six HCs responded to follow up questionnaires. Data from these participants will be used in the current study. None of the SAD participants or healthy controls (HCs) were on any psychotropic medications when scanned or when they completed the questionnaires.

Table 2

Descriptive statistics (mean, standard deviation and effect size) and independent sample t-tests for SAD patients and HCs for age and education level (n = 18)

	SAD Mean (SD)	HC Mean (SD)	SAD Range	HC Range	*t*	*p*	*df*
Age	30.5(9.1)	30.7(8.1)	19 – 52	19 - 44	0.06	0.954	21
Education level	7.12 (0.89)*	6.8 (0.92)	6 – 8	6 – 8	-0.89	0.385	19

Key: HC=Healthy Controls, SAD=Social Anxiety Disorder patients, CSF=Cerebrospinal Fluid, SD = standard deviation, Education: 6= grade 11-12, 7= college/technicon, 8= University *Missing data: n=10 for education in SAD group

Materials

Structural MRI

An MRI scanner was used to structurally image the brains of participants. Neuroimaging was performed on a 3T Allegra MRI scanner (Siemens Medical Systems/MAGNETOM, Erlangen, Germany) at Cape Universities Brain Imaging Centre. Images were acquired using the following parameters: spatial resolution 0 1.0×1.0×1.0 mm3; slices 0 160; matrix 0 179×256; TR 0 2,300 ms; TE 0 3.93 ms; TI 0 1,100 ms and flip angle of 12°. The images were whole brain T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) (Brookeman, 1990).

Administered Scales

The scales administered were the Liebowitz Social Anxiety Scale (LSAS; Appendix A), the Blushing Propensity Scale (BPS; Appendix B), and the Gaze Anxiety Rating Scale (GARS; Appendix C). Detail on the scales, including content, scoring and reliability are outlined here.

The Liebowitz Social Anxiety Scale (LSAS; Leibowitz, 1987) was administered to all participants in order to determine the severity of social anxiety in individuals across the SAD and HC groups, as done by Heimberg et al. (2000). The LSAS consists of 48-items, each describing a situation that is potentially anxiety inducing across a range of social and performance situations (Leibowitz, 1987). Participants

rate how fearful or anxious the situation would make them feel on a 4 point scale from “none” to “severe” (24 items) and how often they would avoid the situation on a 4 point scale from “never” to “usually” (24 items). A score less than 50 indicates a clinically insignificant level of social anxiety, between 55-65 indicates a moderate level, between 65-80 indicates a marked level, between 80-95 indicates a severe level, and above 95 indicates a very severe level. This measure has been found to have good internal consistency (Cronbach’s $\alpha = 0.95$) and test-retest reliability in North American samples ($r = 0.83$; Baker, Heinrichs, Kim & Hoffman, 2002).

The Blushing Propensity Scale (BPS; Leary & Meadows, 1991) was used to determine the degree to which participants blush in everyday social situations. The BPS consists of 14 items, each describing a social situation. Participants indicate how often they would feel themselves blush in each situation on a 5-point scale from ‘never’ to ‘always’. This scale has high internal consistency (Cronbach’s $\alpha = 0.92$) and a high test-retest reliability in North American samples ($r = 0.93$; Mulkens et al., 1999). The BPS has been used in a number of previous blushing studies (de Jong & Peters, 2005; Drummond et al., 2007; Mulkens et al., 1999). From an unpublished pilot study (van der Merwe, 2008), high scores on the BPS were found to be correlated with a greater embarrassment and blush response.

The Gaze Anxiety Rating Scale (GARS; Schneier et al., 2011) was used to measure the degree of anxiety and avoidance participants experienced in response to eye contact made across a variety of social situations. Questions consist of 17 items that describe a variety of social situations including speaking to someone perceived to be attractive, being complemented and delivering a speech. Participants were required to rate their level of fear and avoidance to making eye contact in each of the situations within the past week. Similar to the LSAS, there are two scales to each item. Scores for each item for fear and avoidance of eye contact range from 0 (no anxiety/no avoidance) to 3 (a lot of anxiety/avoid a lot). The total score is determined by adding all the items. Avoidance and anxiety subscales are highly correlated ($r=0.90$, $p<0.01$; Langer, Rodebaugh, Menatti, Weeks & Schneier, 2013). The GARS has been found to be a psychometrically valid scale for measuring gaze anxiety and

avoidance consistency (Langer et al., 2013); it is significantly associated with social anxiety severity in both non-patient and social anxiety disorder patients, and has demonstrated good internal consistency (Cronbach's $\alpha = 0.96$ for SAD patients and $\alpha = 0.95$ for non-patients) and test-retest reliability in North American samples ($r = 0.99$, $p < 0.001$; Schneier et al., 2011).

Procedure

Individuals interested in participating in the study were first screened for exclusion criteria. Those who were eligible for inclusion were invited to attend an MRI scanning session at CUBIC. Participants underwent structural, resting state scans on the 3T Allegra scanner (acquisition details below under "materials"). Participants were then invited to complete additional scales after they had completed their scans. Both SAD and HCs were administered the LSAS, BPS and the GARS questionnaires. Thirteen SAD patients and eight HCs returned completed questionnaires. Of these, most completed all questionnaires, while two HCs completed only the LSAS. Multiple attempts to obtain the missing data were made, including email and telephone calls. However, it remained impossible to contact some participants.

This study was conducted in accordance with the guidelines of The Declaration of Helsinki (Brazil, 2013) and the Medical Research Council of South Africa's guidelines (2008) on the ethical conduct of research studies in humans. The study protocol received approval from the Human Research Ethics Committee of University of Cape Town. Participation in this study was voluntary and participants gave written informed consent prior to taking part in the study. All participants were told that all data collected were kept strictly confidential and that the results of the study would be shared without compromising confidentiality. It was made clear to all participants that they were free to refuse to participate, or to withdraw from the study at any point.

MRI Data analysis

After manually reorienting and realigning the cross-hair on the AC-PC plane in all of the nifty converted DICOM T1 images, and initial quality control for signal artefacts, morphological changes were calculated in grey matter by segmenting from white matter and cerebrospinal fluid using the voxel-based morphometry (VBM) unified segmentation approach (Ashburner & Friston, 2005) in Statistical Parametric Mapping (SPM8) (www.fil.ucl.acuk/spm8). Following this segmentation procedure, probability maps of grey matter were "modulated" to account for the effect of spatial normalisation, by multiplying the probability value of each voxel by its relative volume in native space before and after warping. Grey matter images based on probability maps at each voxel were spatially normalised to the Montreal Neurological Institute (MNI) template and then co-registered using the same segmented template. Modulated images were smoothed with an 8 mm 'Full Width Half Maximum [FWHM]' Gaussian kernel, consistent with other recent VBM studies REFS. This smoothing kernel was applied prior to statistical analysis, to reduce signal noise and to correct for image misregistration.

Statistical analysis of MRI and questionnaire data

The data was tested for normality, and t-tests were run to compare the means of the SAD and HC groups for test scores, demographic variables and brain volumes. The full sample (n = 18) was used for brain volume t-test analyses, while smaller sample sizes were used for analyses with scale results and demographic variables, because of missing data. Correlations between the LSAS, BPS and GARS were calculated to determine the strength of association between measures. Effect sizes were calculated using Cohen's d (Thalheimer & Cook, 2002). Post-hoc analyses were used to determine the statistical power of those results with large t-values but were not statistically significant, in order to determine the required sample size to yield significant results.

A contrast analysis in VBM, between SAD and HC was conducted, using age, education level and total matter volume as covariates of no interest. Sex variables were not used because of the small sample size. While these demographic variables

are by no means exhaustive, it was reasoned that these variables are most associated with differences in global brain volume in any given population, and the commonly used covariates used in VBM analyses. Thus, we controlled for these factors in an attempt to isolate the effects of blushing and gaze data on brain volume differences. Further, the LSAS was added as a regressor of interest to examine how anxiety influences the differences in brain volume in the total cohort.

In regression models, we firstly examined the relationship between brain volume data and LSAS scores, with age, education and total brain volumes as covariates of no interest. This was to determine how anxiety is associated with brain volume in the total cohort. Secondly, we examined BPS and GARS in separate regression models to determine the effects of these sub-scores on brain volume in the total sample. In a final model, we examined BPS and GARS together to determine whether they have a different impact on brain volume in the total cohort. Within group analyses could not be done due to the small sample sizes. The results obtained from the regression analyses were corrected using familywise error (FWE). However, uncorrected results as well as uncorrected results are reported here, given the exploratory and preliminary nature of this research.

RESULTS

Test of normality

Normality testing on the data of HCs and SAD patients indicated that most of the data was normally distributed except for the demographic variables of age (AD^2= p=0.011), education (AD^2 = 2.29, p<0.001), and CSF volume (AD^2 = 1.47, p<0.001).

Administered Scale Scores

There were significant differences between SAD patient and HC scores on the LSAS, BPS and GARS scales. SAD patients scored significantly higher on all measures than HCs (Table 3). The effect sizes of these differences were also large (all differences approximately equal to or greater than two standard deviations). There was a significantly strong positive correlation between LSAS scores, blushing propensity scores and gaze total scores across patients (p<0.001; Figures 1-3).

Scores on the LSAS ranged from 51 – 133 for SAD participants and 4 – 25 for HCs (out of a theoretical maximum of 144). All of the SAD patients scored in the significant range for social anxiety (significant score >50), with three participants scoring just above the lower bound of significance (score of 50-55), two had marked social anxiety (score of 65-80), three had a severe level (score of 81-95), and six had a very severe level (score above 95). None of the HCs had a clinically significant score on the LSAS.

BPS Scores ranged from 37 – 70 for SAD participants and 18-45 for HCs (out of a theoretical maximum of 70). GARS total scores ranged from 10-91 (out of a maximum of 102) for SAD participants and 0-16 for HCs. GARS anxiety subscale scores ranged from 8-46 for SAD participants and 0-13 for HC (out of a maximum of 51), while GARS avoidance subscale scores ranged from 1-45 for SAD participants and 0-4 for HCs (out of a maximum of 51).

Table 3

Descriptive statistics (mean, standard deviation and effect size) and independent sample t-tests of SAD patients and health controls for scores on anxiety, blushing and gaze scales (SAD n=16, HC=10)

Scale Scores	SAD Mean (SD)	HC Mean (SD)	*t*	*P*	*df*	Effect size (Cohen's d)
Liebowitz Score (Total)	89(24.8)*	12(7.5)*	-11.07	<0.001	18.11	**3.88**
Blushing Score (Total)	53(9.4)*	27(10)*	-5.41	<0.001	9.20	**2.90**
Gaze (Anxiety)	27(11.8)*	6(4.9)*	-5.82	<0.001	18.87	**2.13**
Gaze (Avoid)	24(13.5)*	2(4.9)*	-6.13	<0.001	15.10	**1.97**
Gaze (Total)	51(24.6)*	8(6.4)*	-6.26	<0.001	17.69	**2.11**

Note: HC = Healthy Controls, SAD = Social Anxiety Disorder patients, SD = standard deviation, *Missing data = *HC:* Liebowitz score total *n* = 8, Blushing score total *n* = 6, gaze anxiety, avoidance and total *n* = 6, *SAD:* Liebowitz score total *n* = 15, Blushing score total *n* = 13*)*.

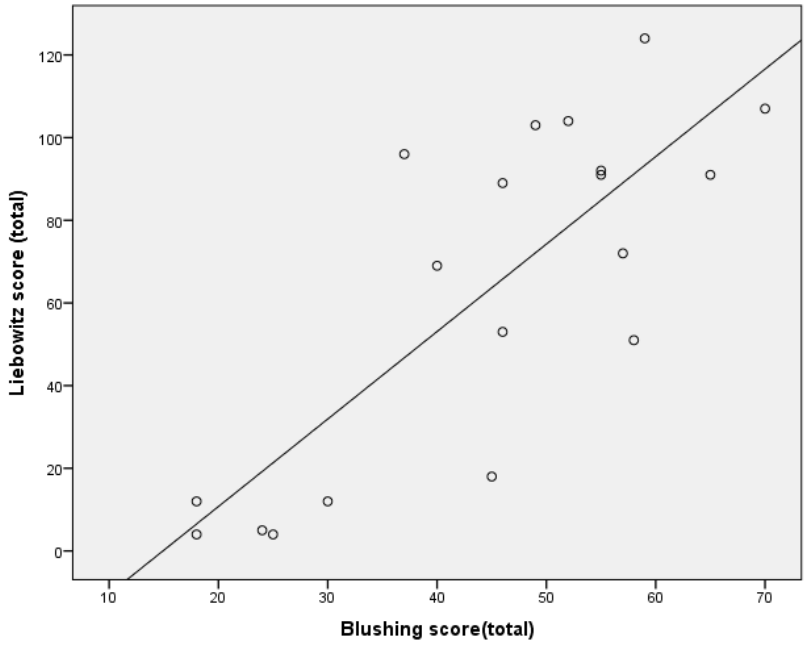

Figure 1. Correlation between social anxiety and blushing propensity (*r*=0.798)

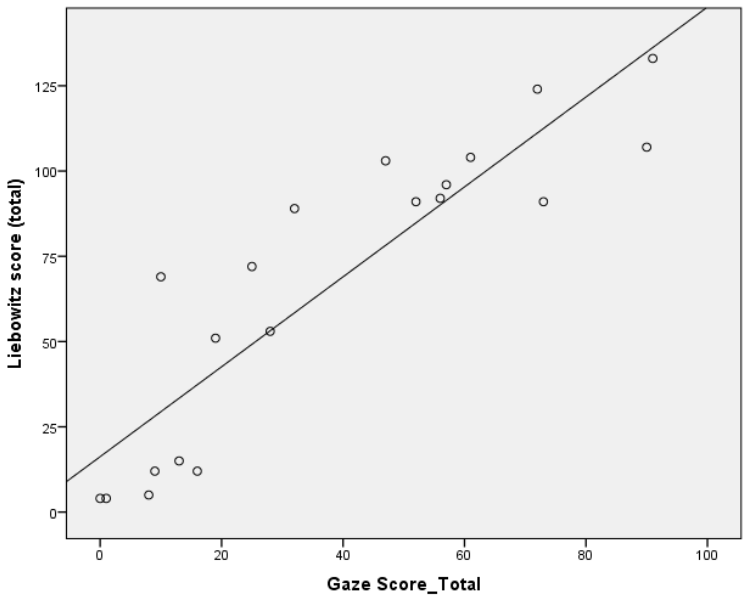

Figure 2. Correlation between social anxiety and gaze total score (r=0.893)

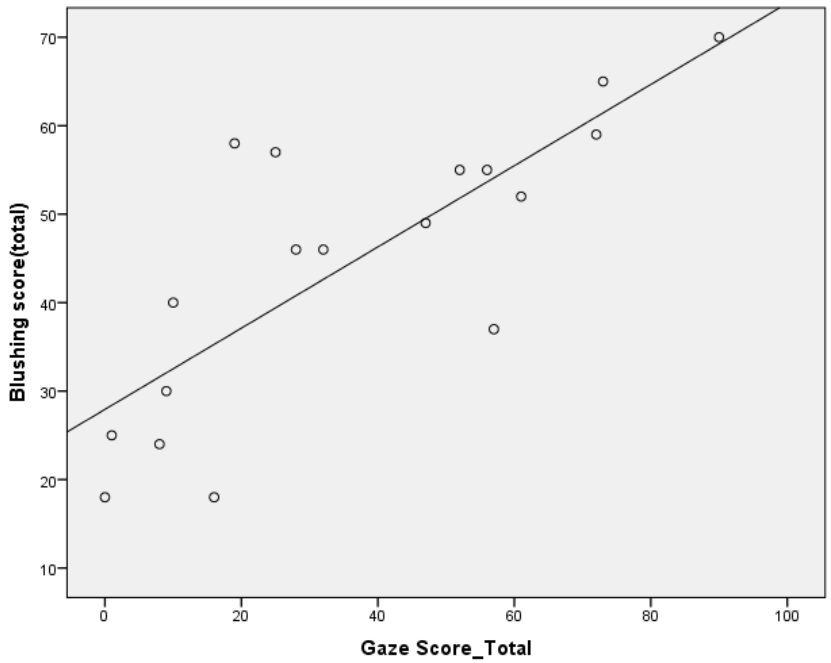

Figure 3. Correlation between blushing propensity and gaze total score (r=0.789)

Structural grey matter differences between participants with Social Anxiety Disorder and healthy controls

T-tests did not yield any significant differences in the mean volumes of any brain regions between SAD patients and HCs for the total sample (Table 4). However, several brain regions had medium to medium to large effect sizes and high *t*-statistics, suggesting that differences in some brain volumes between SAD and HCs may be of interest. SAD patients had less grey matter volume than HCs (46ml mean difference with strong effect; Table 4). Less volume was also found for SAD patients in both left and right anterior cingulate cortex (ACC) volume (0.5ml and 0.4ml mean difference for left and right ACC respectively, with medium effect; Table 4). Similarly, SAD patients had less left and right dorsolateral prefrontal cortex (DPLFC) volume than HCs (0.6ml and 1.0ml mean difference for left and right DLPFC respectively, with medium effect; Table 4). While analysis of brain volumes was conducted on the full sample of 18 SAD and 18 HCs, an alternative analysis using the sample that was subsequently used for the other analyses is included in Appendix D. The difference between the two analyses was negligible so the results from the large analysis are reported here.

Post-hoc analysis (Table 5) for brain volume differences indicates that, given the sample sizes, the statistical power of correctly explaining differences for the medium-sized effects (total grey matter volume, left and right ACC, and left and right DLPFC), the probability of correctly indentifying the difference between the SAD and HC cases is between 19-39%. The minimum sample size required to explain the medium-sized effects to a 95% certainty is 79 for total grey mater volume, 87 and 100 for left and right ACC respectively, and 82 and 86 for left and right DLPFC respectively.

Table 4

Descriptive statistics (mean, standard deviation and effect size) and independent sample t-tests of SAD patients and health controls for brain volumes (n=18)

Scale Scores	SAD Mean (SD)	HC Mean (SD)	*t*	*p*	*df*	Effect size (Cohen's d)
Total brain volumes						
Grey Matter (ml)	703(64)	742(69)	1.73	0.093	34	**0.59**
White Matter (ml)	474(57)	482(54)	0.43	0.669	34	0.15
CSF (ml)	1177(112)	1223(118)	1.21	0.234	34	0.42
Total Intracranial volume (ml)	1700(284)	1801(222)	1.19	0.245	32	0.41
Grey matter volumes						
Left Insula (ml)	7.4(0.7)	7.6(1.0)	0.54	0.592	32	0.19
Right Insula (ml)	7.0(0.6)	7.0(0.9)	0.35	0.730	31	0.12
Left ACC (ml)	6.1(0.7)	6.5(0.8)	1.65	0.108	33	**0.57**
Right ACC (ml)	5.2(0.7)	5.5(0.7)	1.54	0.133	34	**0.53**
Left Hippocampus (ml)	3.9(0.4)	3.9(0.4)	0.23	0.820	33	0.08
Right Hippocampus (ml)	3.7(0.4)	3.7(0.5)	0.05	0.960	33	0.02
Left Amygdala (ml)	1.0(0.1)	1.1(0.1)	0.47	0.644	32	0.16
Right Amygdala (ml)	1.0(0.1)	1.1(0.1)	0.69	0.497	32	0.24
Left DLPFC (ml)	11.3(1.3)	12.2(1.6)	1.70	0.098	33	**0.58**
Right DLPFC (ml)	13.1(1.6)	14.1(2.0)	1.66	0.107	32	**0.57**

Note: HC = Healthy Controls, SAD = Social Anxiety Disorder patients, CSF = Cerebrospinal Fluid, SD = standard deviation, ml = millilitres, ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex.

Table 5

Post-hoc power calculations for brain volume differences between SAD and HC participants (n = 18)

	Post-Hoc Power Calculations	
	Statistical Power*	**Required sample size****
Total brain volumes		
Grey Matter (ml)	**0.39**	**79.39**
White Matter (ml)	0.07	1257.98
CSF (ml)	0.13	346.27
Total Intracranial volume (ml)	0.21	167.53
Grey matter volumes		
Left Insula (ml)	0.08	797.86
Right Insula (ml)	0.06	1930.53
Left ACC (ml)	**0.36**	**86.73**
Right ACC (ml)	**0.32**	**99.54**
Left Hippocampus (ml)	0.06	4452.61
Right Hippocampus (ml)	0.05	92443.09
Left Amygdala (ml)	0.07	1075.85
Right Amygdala (ml)	0.10	497.62
Left DLPFC (ml)	**0.38**	**81.60**
Right DLPFC (ml)	**0.36**	**86.02**

Note: Values in bold indicate those that had medium Cohen's d effect sizes, *Probability of observing Cohen's d given samples size and significance, **Number of samples required for 95% statistical power to give observed Cohen's d

Regression analysis taking the variables of age, education and total matter volume as covariates of no interest, revealed a greater grey matter volume in HCs in the regions of left occipital cortex, left anterior cingulate and right inferior parietal lobe when compared to SAD patients (Table 6; Figures 4-10). In this model, SAD patients did not have any areas that were larger than HCs. However, when LSAS score was taken as the predictor. SAD patients had significantly higher volumes in the left premotor cortex (Brodmann area 8), right hippocampus and left orbitofrontal cortex (Brodmann area 47). Accounting for LSAS score demonstrated a significantly larger volume in right superior temporal cortex (Brodmann area 42), while diminishing the significance of the differences that were found in the first model that only accounted for covariates of age, education and total matter volume.

Table 6

Contrast between SAD patients and healthy controls (HCs) covarying or age, education and total matter volume, with LSAS score as a regressor of interest

Brain regions	MNI Coordinates			Cluster size (voxels)	*z*	*p*
	X	*Y*	*Z*			
SAD > HC						
-----	---	---	---	---		---
HC > SAD						
Left occipital cortex (Brodmann area 18)	-40	-60	-20	63	4.43	<0.01
Left Anterior Cingulate	-2	26	2	37	5.26	<0.01
Right inferior parietal lobe (Brodmann area 7)	40	-20	32	32	3.79	<0.01
SAD > HC (with LSAS score as regressor)						
Left premotor cortex (Brodmann area 8)	-32	16	44	69	4.49	<0.01
Right hippocampus	32	-22	-10	38	3.59	<0.01
Left orbitofrontal cortex (Brodmann area 47)	-20	16	-30	32	3.44	<0.01
HC >SAD (with LSAS score as regressor)						
Right superior temporal cortex (Brodmann area 42)	60	-34	18	25	3.93	<0.01

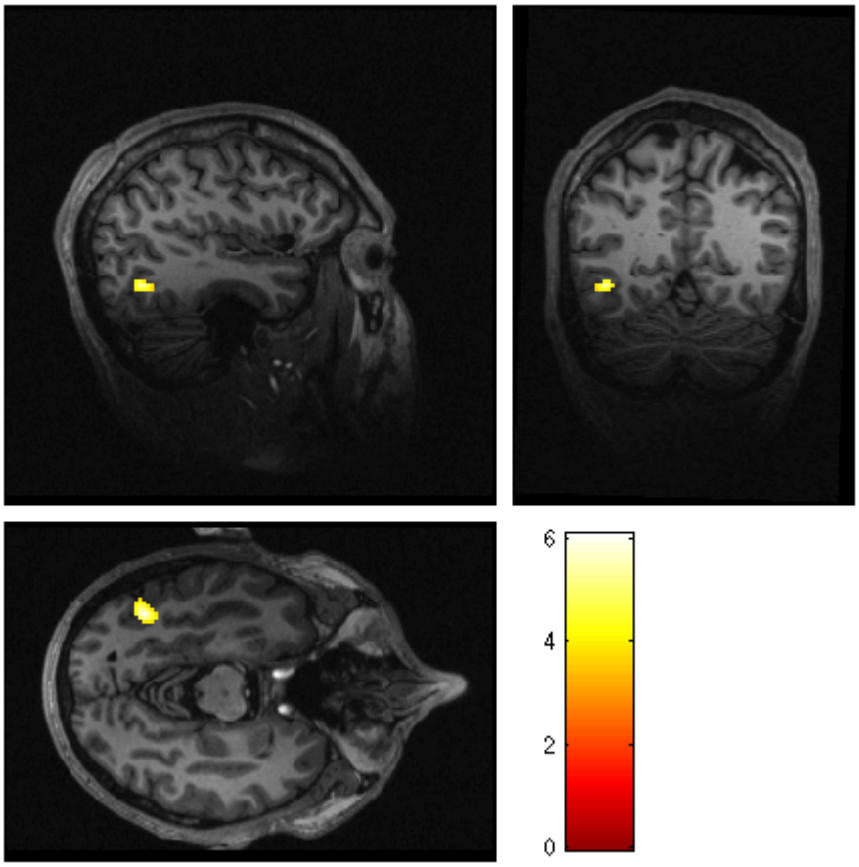

Figure 4. *Contrast analysis between SAD patients and HCs showing greater volume in left occipital cortex for HCs, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

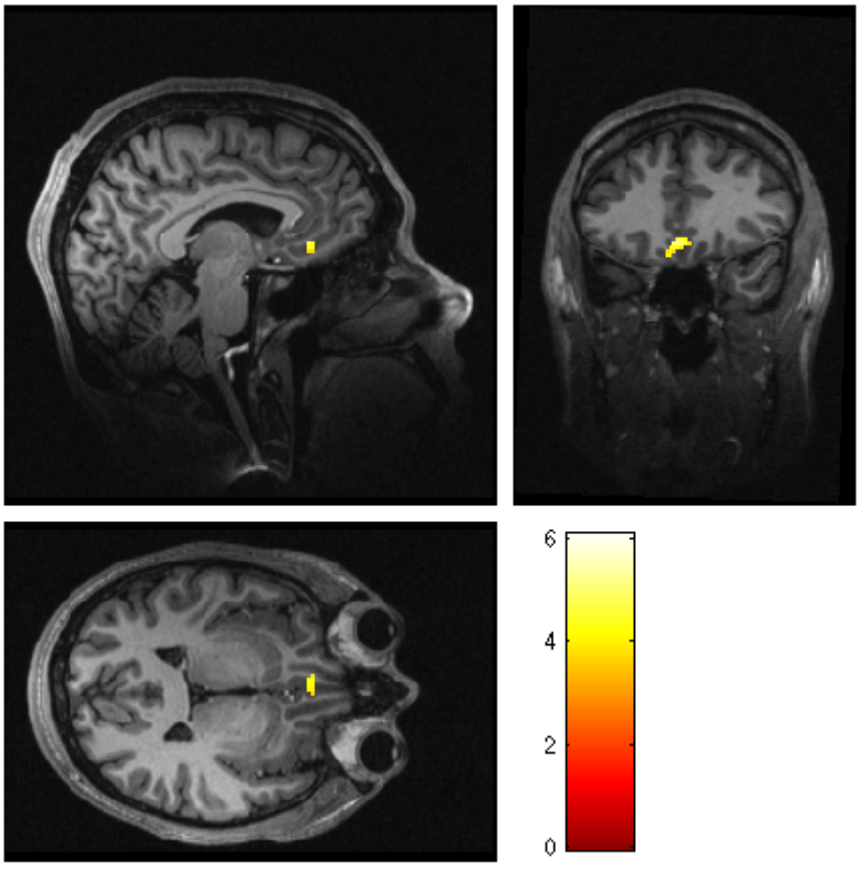

Figure 5. *Contrast analysis between SAD patients and HCs showing greater volume in left anterior cingulate (ACC) for HCs, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

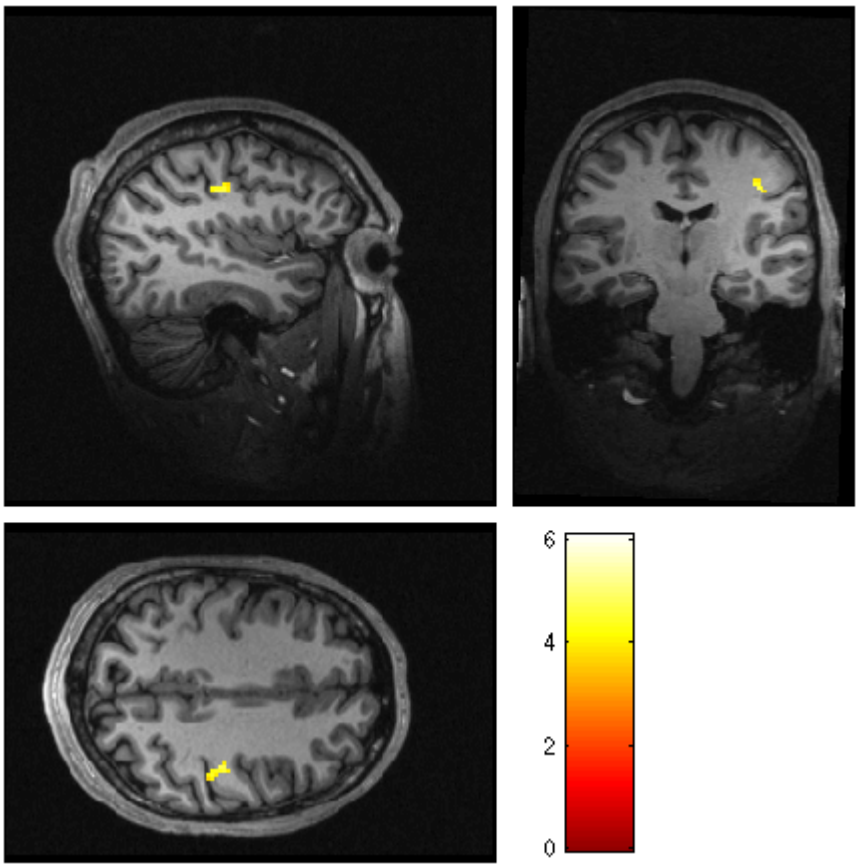

Figure 6. *Contrast analysis between SAD patients and HCs showing greater volume in right inferior parietal lobe for HCs, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

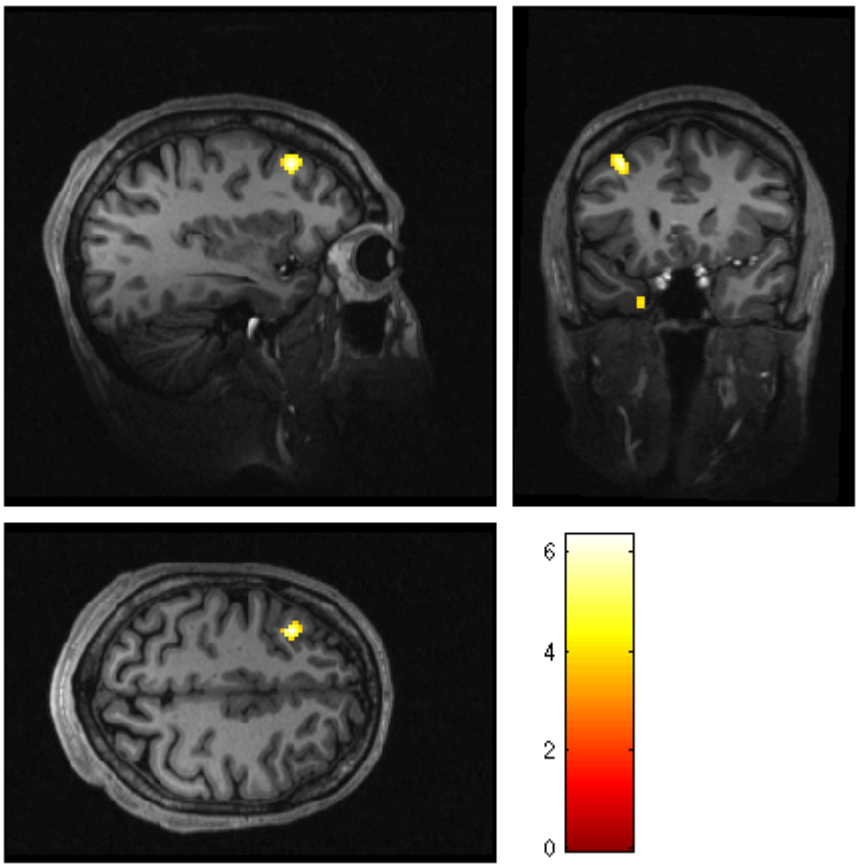

Figure 7. *Contrast analysis between SAD patients and HCs accounting for LSAS score, showing greater volume in left premotor cortex for SAD, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

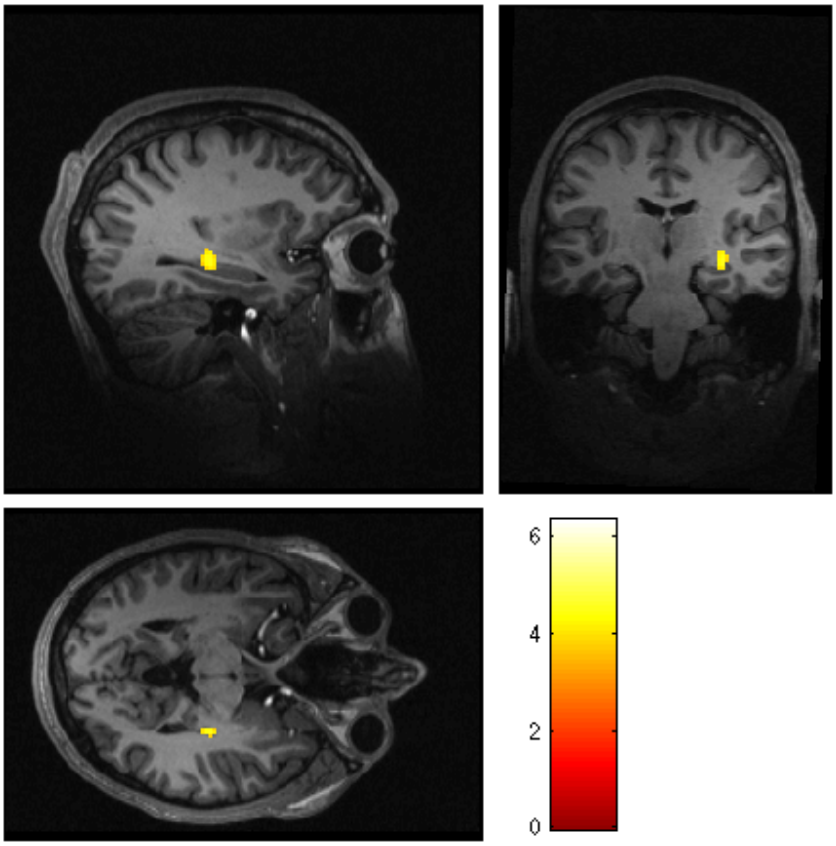

Figure 8. *Contrast analysis between SAD patients and HCs accounting for LSAS score, showing greater volume in right hippocampus for SAD, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

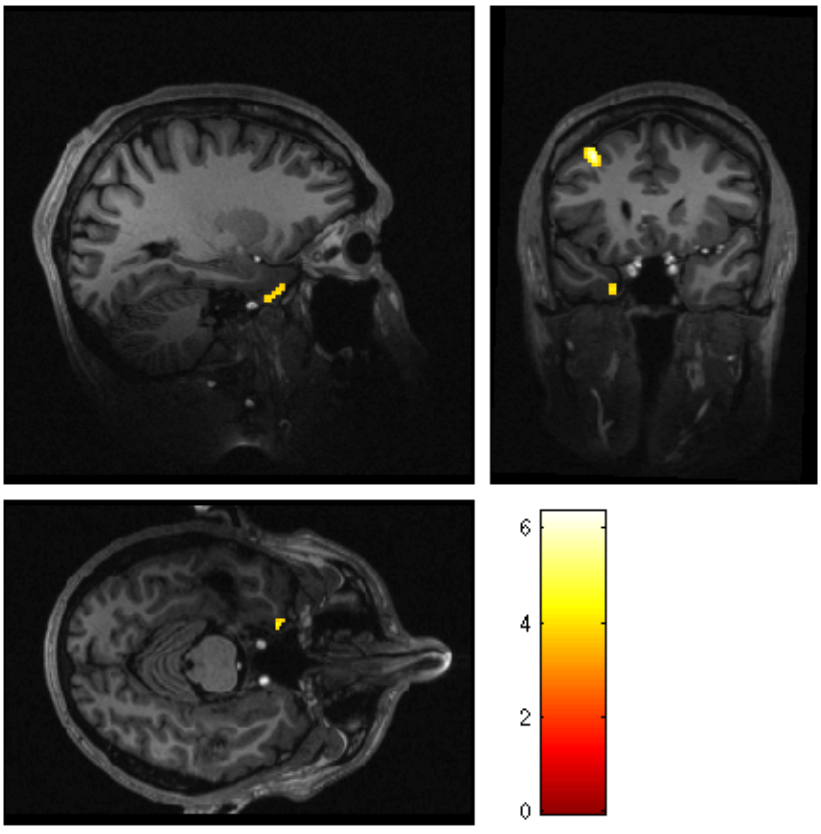

Figure 9. *Contrast analysis between SAD patients and HCs accounting for LSAS score, showing greater volume in left orbitorfrontal cortex (OFC) for SAD, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

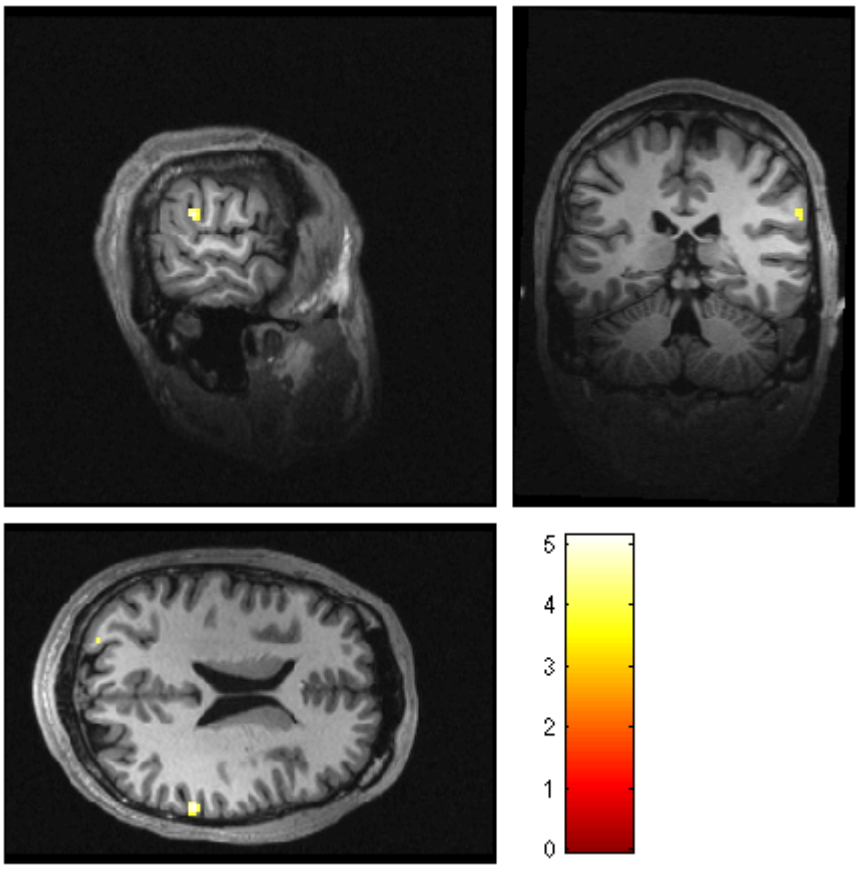

Figure 10. *Contrast analysis between SAD patients and HCs accounting for LSAS score, showing greater volume in right superior temporal cortex for HC, p < 0.01, uncorrected peak value, Note:* colour bar = *F*-score

For regression with age, education and total matter volume as covariates of no interest, the brainstem volumes in SAD patients were increased for higher blushing scores, while the volumes of left inferior parietal lobe (Brodmann area 7) and left occipital cortex (Brodmann area 18) were decreased for higher blushing scores (Table 5; Figures 11-13). The volume of left inferior parietal lobe was significant at the cluster level.

Again, running the regression with age, education level and total matter volume as covariates of no interest, with total gaze fear and avoidance score as the variable of interest, it was found that no brain regions were increased in SAD patients. However, there were decreases in matter volume of SAD patients when compared to HCs as gaze scores increased for right posterior cingulate cortex (Brodmann area 31) and right occipital lobe (Brodmann area 19) and right fusiform gyrus (Brodmann area 20) (Table 7; Figures 14-16). The right occipital lobe size decrease was significant at the cluster level.

Using both blushing scores and total gaze fear and avoidance scores as variables of interest (once again controlling for age, education level and total matter volume), it was found that as blushing and gaze scores increased, the brainstem volume was, again, significantly larger (Table 7; Figure 17). In contrast, the pons/cerebellum (significant at the cluster uncorrected level), left inferior parietal lobe, right cerebellum (significant at the cluster uncorrected level) and left cerebellum volumes decreased with increased scores in both score measures (Table 7; Figures 18-19). Bilaterally increasing cerebellar volume was also observed for an interaction between increased blushing severity and decreased gaze symptom severity (cluster level FWE corrected value; Table 7; Figure 20).

Table 7

Regression analyses in blushing and gaze scores in relation to brain volume in SAD patients (corrected for age, education and total matter volume)

Brain regions	MNI Coordinates			Cluster size (voxels)	*z*	*P*
	X	*y*	*Z*			
Positive regression with Blushing Total score						
Brainstem	0	-12	-38	31	3.58	<0.01
Positive regression with Gaze Total score						
---	---	---		---		---
Negative regression with Blushing Total score						
Left inferior parietal lobe (Brodmann area 7)	-32	-60	42	43	4.27	0.04*
Left occipital cortex (Brodmann area 18)	-12	90	12	34	3.53	<0.01
Negative regression with Gaze Total score						
Right posterior cingulate cortex (Brodmann area 31)	14	-58	24	35	3.74	<0.01
Right occipital lobe (Brodmann area 19)	48	-82	2	61	3.74	0.03*
Right fusiform gyrus (Brodmann area 20)	40	-8	-28	31	3.59	<0.01
Positive regression Blushing + Gaze total						
Brainstem	-2	-12	-38	31	4.01	<0.01
Negative regression Blushing + Gaze total						
Pons/cerebellum	2	-44	-60	115	4.01	0.001*
Left inferior parietal lobe	-30	-62	42	30	3.24	<0.01
Right cerebellum	12	-70	-52	66	3.46	0.009*
Left cerebellum	-14	-90	-26	30	3.22	<0.01
Interaction (Increased blushing, decreased gaze)						
Left cerebellum	-14	-70	-56	827	4.14	<0.001**
Right cerebellum	8	-36	-50	346	3.84	<0.001**

*Cluster level uncorrected p value, **Cluster level FWE corrected p value

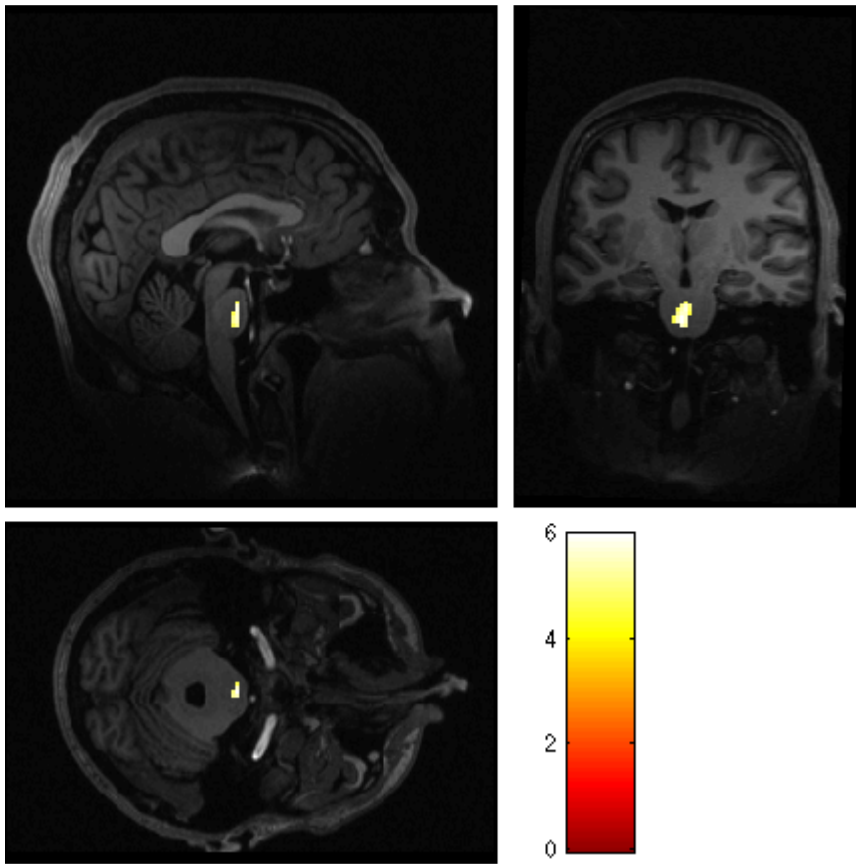

Figure 11. *Positive regression showing increased brainstem volume with increased blushing severity, p < 0.01, uncorrected peak value, Note:* colour bar = *t*-score

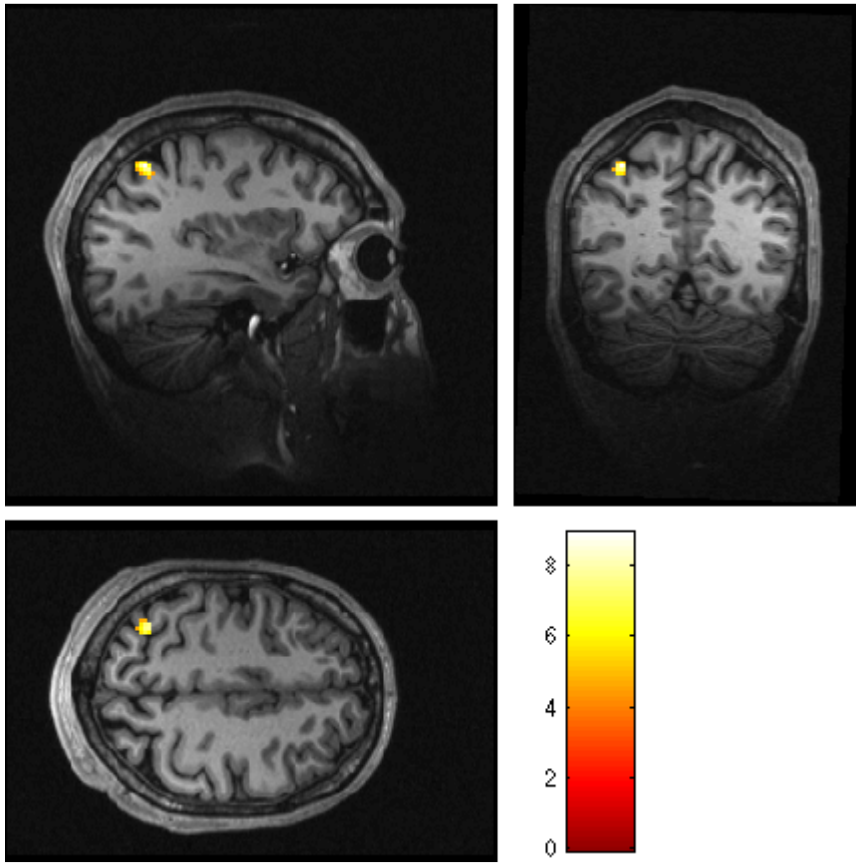

Figure 12. *Negative regression showing decreased left inferior parietal lobe volume with increased blushing severity, p = 0.04, cluster level uncorrected value, Note:* colour bar = *t*-score

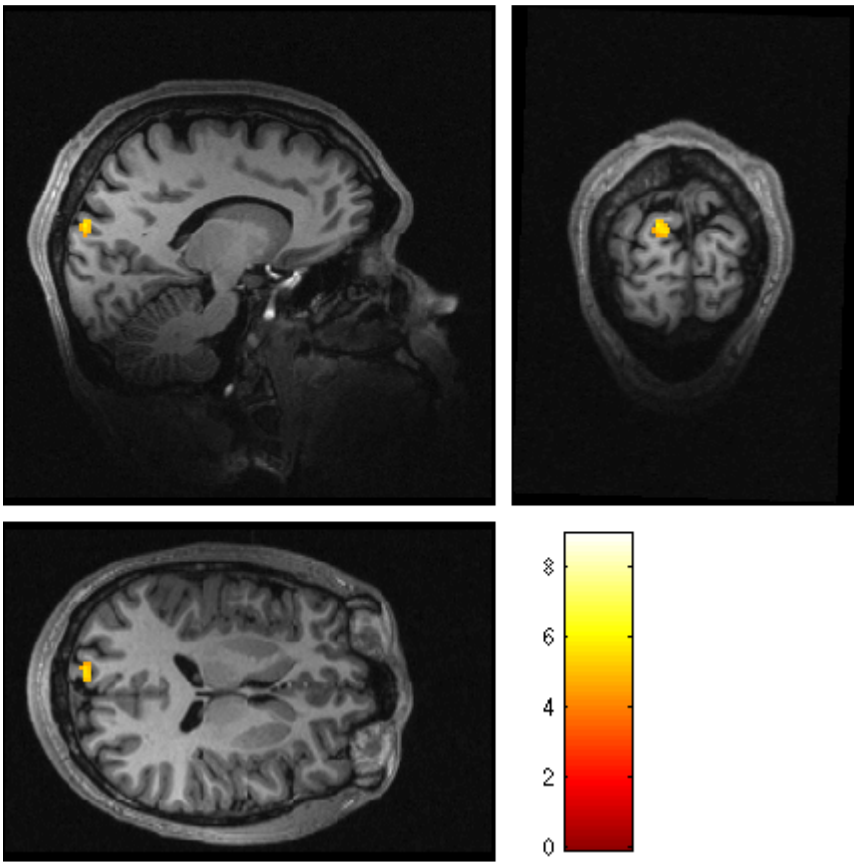

Figure 13. *Negative regression showing decreased left occipital cortex volume with increased blushing severity, p < 0.01, uncorrected peak level value, Note:* colour bar = *t*-score

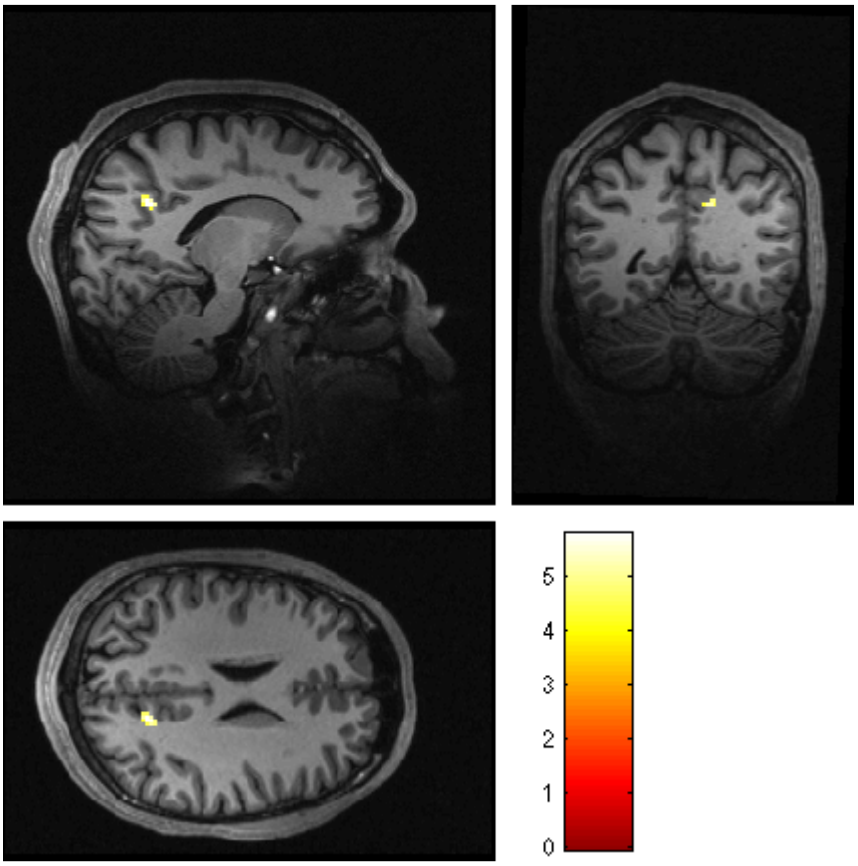

Figure 14. *Negative regression showing decreased right posterior cingulate cortex (PCC) volume with increased gaze symptom severity, p < 0.01, uncorrected peak level value, Note:* colour bar = *t*-score

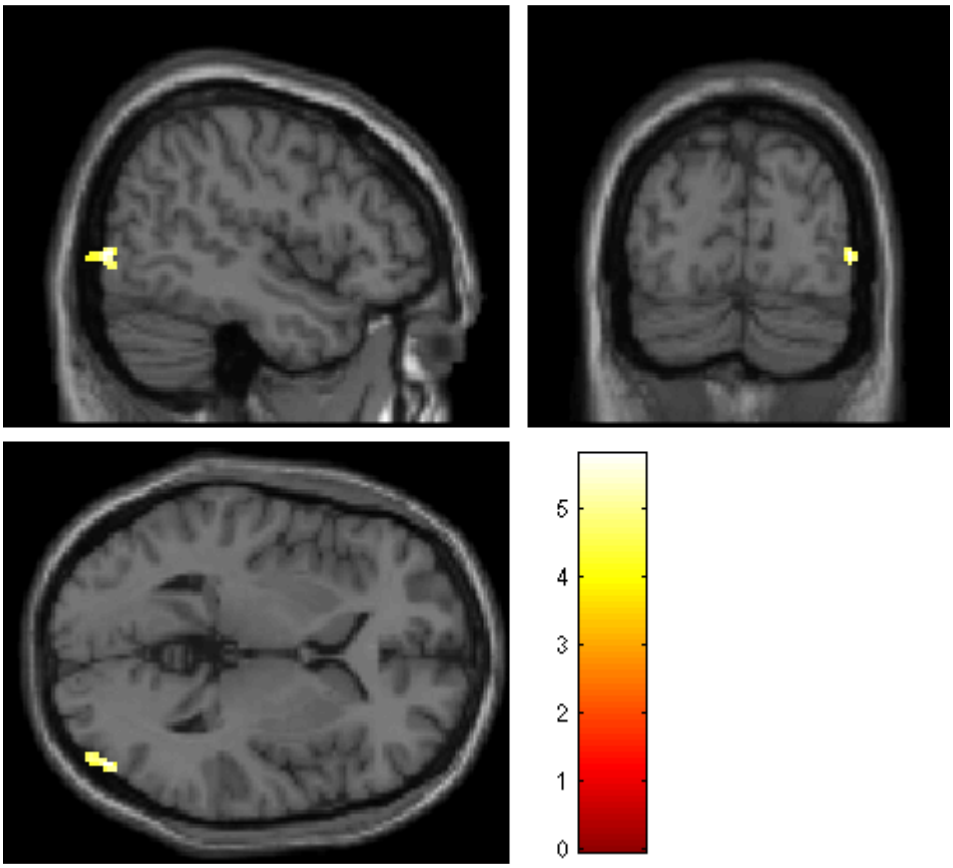

Figure 15. *Negative regression showing decreased right occipital lobe volume with increased gaze symptom severity, p < 0.03, cluster level uncorrected value, Note:* colour bar = *t*-score

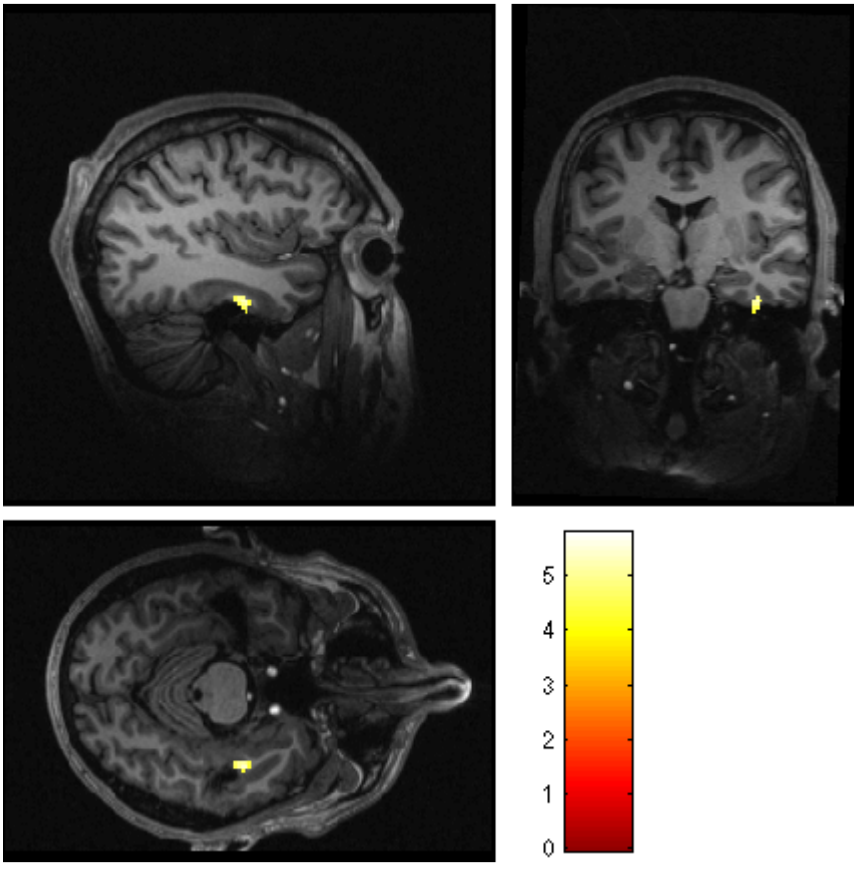

Figure 16. *Negative regression showing decreased right fusiform gyrus volume with increased gaze symptom severity, p < 0.01, uncorrected peak level value, Note:* colour bar = *t*-score

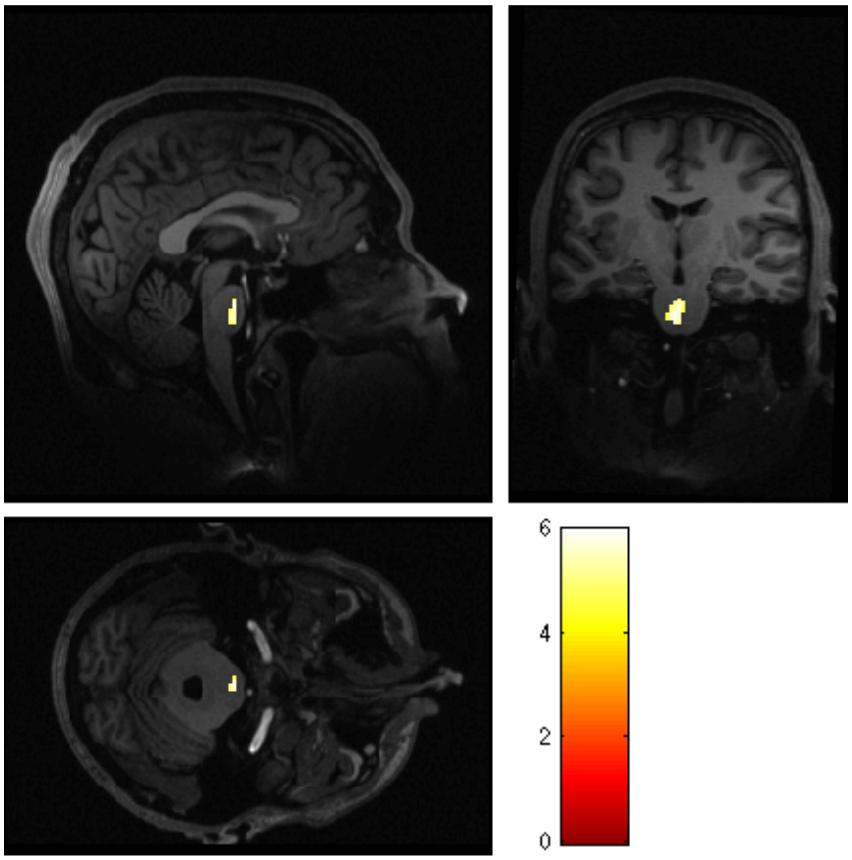

Figure 17. *Positive regression showing increased brainstem volume with increased blushing and gaze symptom severity*

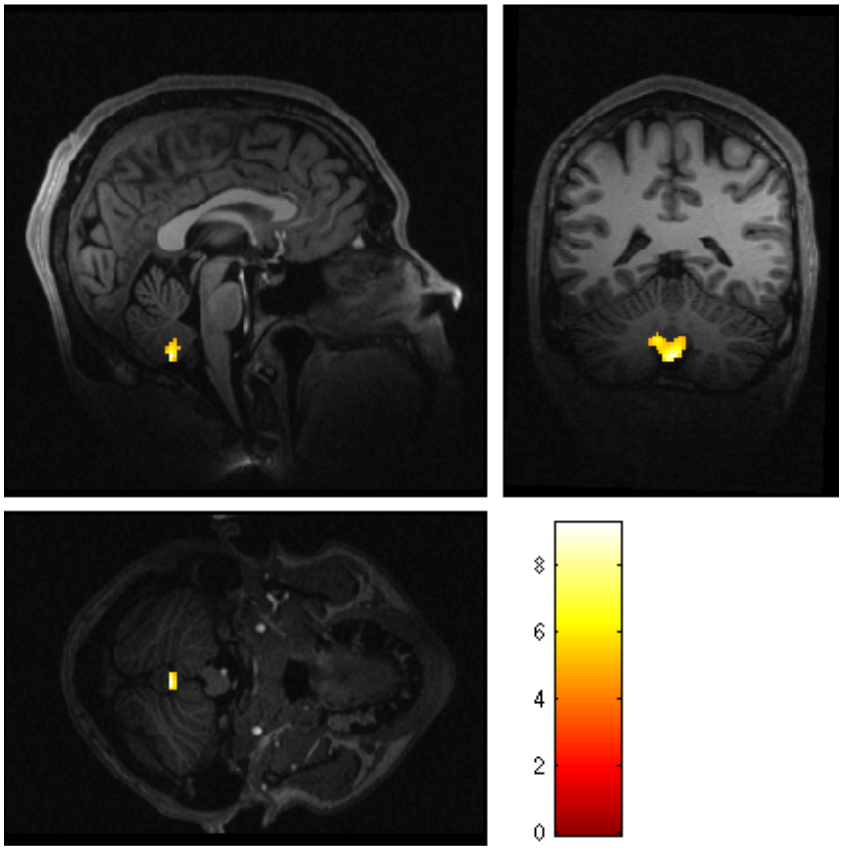

Figure 18. *Negative regression showing decreased cerebellum volume bilaterally with increased blushing and gaze symptom severity: right cerebellum p = 0.009, cluster level uncorrected value; left cerebellum p < 0.01, uncorrected peak level value; Pons/cerebellum result (not shown), p=0.001, cluster level uncorrected value, Note:* colour bar = *t*-score

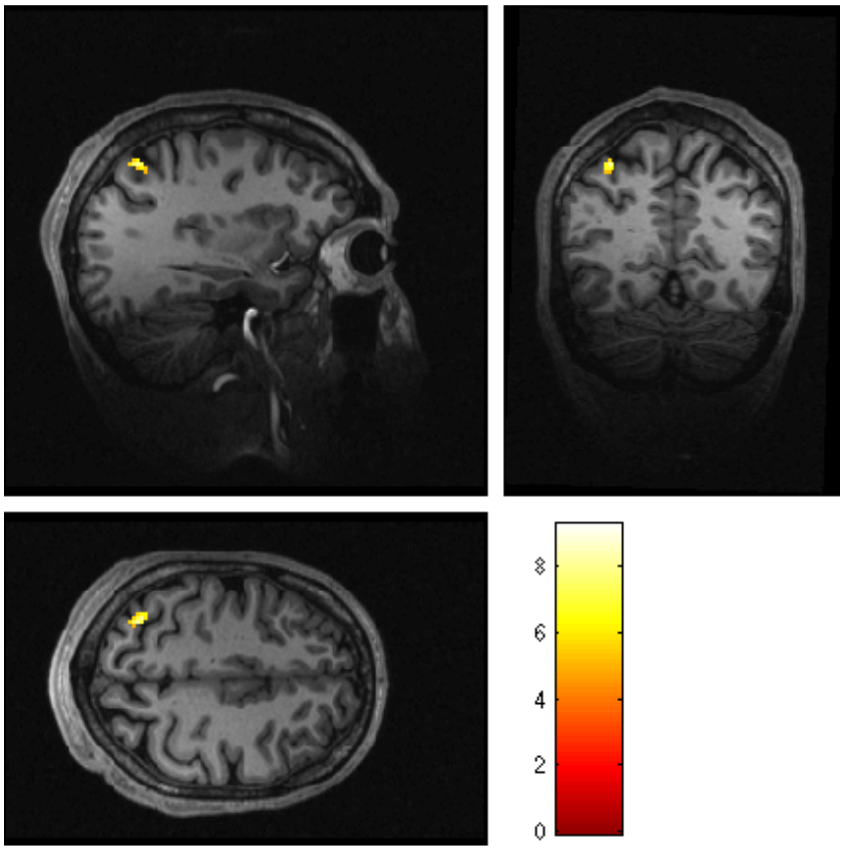

Figure 19. *Negative regression showing decreased left inferior parietal lobe volume with increased blushing and gaze symptom severity, p < 0.01, uncorrected peak level value, Note:* colour bar = *t*-score

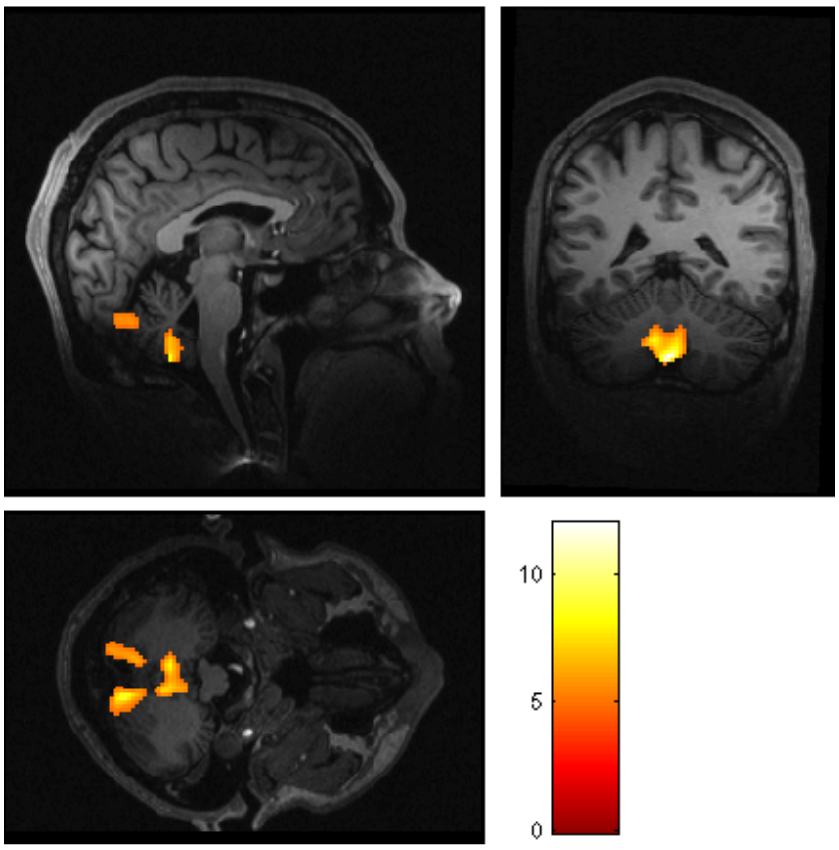

Figure 20. *Interaction showing increased cerebellar volume bilaterally with increased blushing and decreased gaze symptom severity, p < 0.001, cluster level FWE corrected value, Note:* colour bar = *t*-score

DISCUSSION

The aim of this research was to study the neuroanatomy of the blushing and gaze avoidance in patients with SAD. The objectives were firstly to determine if there were differences between individuals with SAD and HCs regarding their blushing propensity and gaze avoidance behaviour and fear of gaze; and secondly to determine whether these differences correlated with structural brain differences in the brains of participants with SAD relative to controls. At the same time, looking at the structural brain differences between SAD and HCs may support or add to the developing picture of research on the topic of SAD neurobiology. I will now discuss the findings pertaining to these objectives in light of the current understanding and research in the field.

Objective 1: Blushing propensity and gaze fear and avoidance symptoms in SAD

Significant differences were found between the SAD and HC groups for all symptom scales (including the LSAS, BPS and Gaze). Importantly, this indicates that the SAD group had significantly increased levels of social anxiety symptoms (as measured by the LSAS) when compared to the HCs. This corroborates the clinical diagnosis that determined the grouping of participants into patient and control groups. Thus, the SAD group had symptoms representative of their psychiatric diagnosis, as determined by valid and reliable measures (Leary & Meadows, 1991; Leibowitz, 1987; Schneier et al., 2011). This indicates that the SAD group and HCs were clinically distinct from each other, and thus a comparison of differences related to these clinical symptoms could be justified.

The scores on various scales used to determine symptom severity, specifically including the symptoms of interest (blushing and gaze fear and avoidance), correlated strongly with each other. This suggests that both blushing and gaze fear and avoidance symptoms tend to co-occur, and that increasing prominence of both symptoms in an individual correlates with symptom severity of SAD, as measured by the LSAS. Furthermore, significant differences were found between SAD patients and HCs for both blushing propensity and gaze fear and avoidance (as measured by the BPS and Gaze respectively). These findings are congruent with the current

understanding that both blushing (Bögels, 2006; Bögels & Stein, 2009; Bögels et al., 2010; Drott, 2004; Edelmann, 1990; Gerlach et al., 2001) and gaze fear and avoidance (Schneier et al., 2011; Weeks et al., 2013) are considered to be cardinal symptoms of SAD. Furthermore it suggests that the two symptoms tend to occur together as part of the symptomatology of the disorder.

However, while these symptoms are thought to be important in SAD, the heterogeneity of symptom presentation in this disorder means that the presence of these symptoms may be less prominent or absent in some patients. It has been proposed that two or three subtypes of SAD exist, with different levels of physiological arousability, behavioural and cognitive responses (Öst, Jerremalm & Johannson, 1981; Turner & Beidel, 1985). Öst et al (1980) identified physiological, cognitive and behavioural responders. Turner & Beidel (1985) determined that while SAD patients generally all have highly negative cognition, they may either have low or high physiological arousability. Thus, it is important to acknowledge that these symptoms may be hallmarks in only a subset of SAD patients.

Despite this heterogeneity in symptom presentation, the findings of the current research, together with those of previous research, suggest that these symptoms should be given adequate attention when treating individuals with SAD. This is because these symptoms may play a large role in both the manifestation of the disorder in certain individuals, and in the debilitating effects that the disorder has on daily functioning. Fostering a greater understanding of the underpinning neurobiology of these symptoms may assist with the optimal treatment options and recommendations for these specific complaints as well as for the disorder as a whole. This is in line with the idea of Research Domain Criteria (RDoC), in which a more comprehensive understanding of psychiatric disorders is developed by investigating the genetic, neuroscientific and cognitive components that comprise these (Cuthbert & Insel, 2013). In this instance, furthering the understanding of the underpinnings of blushing and gaze fear and avoidance symptoms of SAD may assist in this endeavour.

Objective 2: Structural neurological differences in relation to blushing propensity and gaze fear and avoidance

Structural differences between SAD patients and HCs

Before undertaking a detailed analysis of how blushing and gaze symptoms correlate with structural brain volume differences in the context of SAD, it is necessary to explore what the data set contains regarding structural brain volume differences between SAD patients and HCs generally. Direct comparison of grey matter volumes of SAD patients and HCs to each other (before taking demographic variables into account), demonstrated medium to large effect sizes, yet no statistically significant differences for the sample size, for total grey matter volume, left and right ACC, left and right DLPFC and right amygdala. The medium to high effect sizes of these brain region differences suggest that while these results are not statistically significant at the 95% confidence level, that they are still of interest. The post-hoc power calculations indicate that while the difference between the groups cannot be asserted to the desired statistical certainty, there appears to be signal within the noisy data. Higher sample sizes would be required for increased certainty regarding these differences. However, in light of the magnitude of the effect sizes, it is useful consider these brain regions as areas of interest, and these will now be discussed as areas of possible difference between HCs and SAD patients.

A medium effect size was observed for volume differences between the total grey matter volume of HCs and SAD patients, with SAD patients having less volume. This is in line with previous research that has found decreased volumes in various brain regions in SAD patients (Hattingh, 2011; Irle et al., 2010; Liao et al., 2011; Syal et al., 2012), contributing to overall grey matter decreases. This is in contrast to other studies have found increased cortical thickness, with no deceases in SAD patients (Brühl et al., 2013; Frick et al., 2013; Talati et al., 2013). Furthermore, fMRI research (Etkin & Wager, 2007; Freitas-Ferrari et al., 2010; Hattingh et al., 2013) suggests increased activation in SAD patients, which intuitively seems to contradict these findings of volume decreases. These inconsistencies will be discussed later in this section.

Decreased volume in the left and right ACC (with medium effect size) found in this analysis is congruent with the findings of Klumpp et al. (2013) and Frick et al. (2013), who found increased ACC response in HCs and a correlation of decreases in this area with symptom severity respectively. The ACC has been implicated in regulatory processes of emotional regulation (Goldin et al., 2009), specifically attention, emotional expression and cognitive appraisal (Etkin, Egner & Kalisch, 2011). Decreased ACC volume suggests that SAD patients may experience altered emotional regulation and cognitive processing of social situations. Furthermore, this region has been implicated in altered activation in gaze behaviour and the fear circuitry of SAD (Schneier et al., 2009). Activation of the ACC has been found in the phenomenon of pupil dilatation and, by extension, eye contact (Pissiota et al., 2003; Critchley et al., 2005), which may explain lower volumes in this brain region of SAD patients, who display gaze avoidance behaviour.

A number of studies have found functional activation differences in the prefrontal cortex of patients with SAD (Stein, Goldin et al., 2002; Amir et al., 2005; Lorberbaum et al., 2004; Straube et al., 2005, Phan et al., 2006; Goldin et al., 2009; Freitas-Ferrari et al., 2010; Blair et al., 2011). The finding of decreased left and right dorsolateral prefrontal cortical (DLPFC) volume is thus in line with such findings. While some researchers, such as Brühl et al. (2013), found increases in this brain region rather than decreases, finding differences in this region in either direction points to altered neural functioning in the prefrontal cortex in SAD.

A medium effect size was observed for differences in the left and right DLPFC of HCs and SAD patients, with SAD patients having less volume. Decreased frontal lobe volume or thickness has been implicated in problematic emotional regulation (Etkin et al., 2011; Liao et al., 2011; Syal et al., 2012). The DLPFC has been implicated emotional, executive and attentional regulation, along with the ACC and parietal lobe (Diekhof, Geier, Falkai & Gruber, 2011; Etkin, Prater, Schatzberg, Menon & Greicius, 2009; Herwig et al., 2007; Kalisch, 2009; Oschner, Bunge, Gross & Gabrieli, 2002; Ochsner, Silvers, & Buhle, 2012). It has also been implicated in the experiences of moral transgressions and social transgressions in front of an audience

(Finger et al., 2006). Studies that have found increased volumes in this area (e.g. Brühl et al., 2013), suggest that this is due to hyperactive neural circuitry when processing emotional stimuli and as well as dysregulation in attentional networks (Sylvester et al., 2012). Studies have found reduced structural connections in the DLPFC (Baur et al., 2011, 2013; Phan et al., 2009), as well as disturbed connectivity (Hahn et al., 2011; Liao et al., 2011; Prater et al., 2013). These findings may explain some of the altered affective and cognitive processing in SAD patients. Furthermore, the DLPFC is part of the frontal cortex, which is closely connected to the orbitofrontal cortex, thalamus and hippocampus (Stein et al., 2000), in which differences in SAD patients have been found. This possibly suggests altered functional networks in the pathogenesis of the disorder.

Again, a medium effect was observed for higher right amygdala volume in HCs when compared to SAD patients. Structural and functional amygdala changes have been previously found in the context of SAD (Etkin & Wager, 2007; Freitas-Ferrari et al., 2010; Hattingh, 2011; Hattingh et al., 2013; Irle et al., 2010; Phan et al., 2006; Stein, Goldin et al., 2002; Straube et al., 2005; Syal et al., 2012). The amygdala is thought to be form part of the brain's emotional circuitry, and is particularly involved in fear conditioning (LeDoux, 1998; Morris et al., 1998; Schneier, Kent, Star & Hirsch, 2007). Studies investigating gaze have also found differences in the amygdala in relation to altered gaze behaviour (Dumas et al., 2013; Spezio et al., 2007). Furthermore, studies investigating the neural circuitry of social emotions have also found alterations in amygdala activation (Berthoz et al. 2006; Britton et al., 2006; Eslinger et al., 2002; Moll, de Oliveira-Souza, Bramati et al., 2002; Moll, de Oliveira-Souza). The amygdala is clearly an integral part of emotion and fear circuitry, which are thought to be central to SAD pathology. Thus, it is not surprising that a moderate effect was demonstrated in the current research for differences between SAD and HCs in the amygdala.

Once age, education and total grey matter variables were taken into account in a regression analysis, statistically significant greater volumes in the left occipital cortex, left ACC and right inferior parietal lobe were found in HCs compared to SAD

patients (uncorrected peak values). However, the possible differences observed originally in the amygdala, right ACC and DLPFC bilaterally did not surface once variables of non-interest were included in the model. This suggests that those differences could be explained by differences in total grey matter volume, and even possibly to the demographic differences of age and education. Decreases in the right inferior parietal cortex are in line with the findings of Syal et al. (2012) and Talati et al. (2013). The parietal cortex has been implicated in empathic social behaviour (Carr, Iacoboni, Dubeau, Mazziotta & Lenzi, 2003; Rizzolatti & Craighero, 2004) and is decreased in socially debilitating disorders, such as autism spectrum disorder (Hadjikhani, Joseph, Snyder & Tager-Flusberg, 2006). Decreases in the left occipital cortex may be explained by the role of this area in the experience of embarrassment (Takahashi et al., 2004). It has been suggested that the occipital cortex undergoes increased activation to stimuli that are rich in emotional content, or that demand increased attention (Phan, Wagner, Taylor & Liberzon, 2002; Takahashi et al., 2004). It is thought that the cortex modulates sensory processes that involve the amygdala (Emery & Amaral, 2000). Decreases in this region may suggest decreased efficacy of this processing capacity. However, the results obtained when correcting for age, education and total grey matter should be interpreted with caution, given that they are significant at the peak and not cluster level.

Structural differences predicted by symptom severity, blushing propensity and gaze avoidance

Major Findings

While differences in brain volumes between SAD patients and HCs are of value, the focus of this research is on how brain volume differences correlate with cardinal symptoms of the disorder, specifically blushing and gaze fear and avoidance. Severity of blushing and gaze fear and avoidance were found to be associated with brain volume differences in the cerebellum, left inferior parietal lobe and right occipital lobe at the cluster level. While further differences were found in other regions, these were singificant only at the uncorrected peak level, and should not be given as much credence.

Taking both gaze and blushing symptoms (which are strongly collinear) into account, decreases in cerebellar volume were observed (significant at the uncorrected cluster level) with increased severity of both symptoms. Differences in cerebellar volume were also observed for an interaction between blushing and gaze symptoms, with increases in blushing severity and decreases in gaze fear and avoidance severity (significant at the corrected cluster level). This is in direct contrast to findings of increased cerebellar cortical thickness in SAD patients (Talati et al., 2013). However, it does implicate alterations in cerebellar functioning in SAD, despite the direction of the changes being contradictory. The cerebellum is thought to be involved in the control and coordination of motor activity (Brooks & Thach, 1981). However, it is now also thought that the cerebellum projects to non-motor areas of the cerebrum forming cerebral-cerebellar neural circuits, including the prefrontal, and parietal cortex (Strick, Dum & Fiez, 2009). The cerebellum may play a role in memory, attention, executive control, language, and learning (Strick et al., 2009). Thus, the possible differences found in the DLPFC and parietal lobe when directly comparing SAD and HC brain volumes in the current research may be related to these changes in the cerebellum. Furthermore, decreases in cerebellar volume and in the areas that comprise these circuits, may lead to deficits in these higher functions.

Related to the observed volume decrease in the cerebellum, a decrease in pons volume was also suggested in this model (significant at the uncorrected cluster level). The pons serves as a major relay centre for information passing between the spinal cord and the cerebellum and cerebrum, as well as playing some role in balance, auditory processing and vision (Zillmer, Spiers & Culbertson, 2008). The cerebellar subdivisions project to midbrain areas of medulla and pons, which are responsible for regulation of autonomic responses. Such autonomic responses are raised in individuals with SAD (Baldacara, Borgio, Lacerda & Jackowski, 2008). Thus, abnormalities in the cerebellum may make individuals vulnerable to autonomic hyperactivity and thus anxiety.

Increased severity of blushing was also associated with decreased volumes in the left inferior parietal lobe (cluster level uncorrected value). This decrease was also

predicted by the increases in blushing and gaze symptoms together (uncorrected peak value). The parietal lobe has been implicated in anxiety and it is thought to play a role in the hypervigilance that is present in anxious states (Davidson, 1998; Davidson, Abercrombie, Nitschke & Putnam, 1999). This may be why Syal et al. (2012) and Talati et al. (2013) found alterations in this region between SAD and HCs. Decreases in this region in association with increased blushing severity indicate a possible relationship between alterations in the parietal lobe and blushing propensity, as a specific symptom. That increases in gaze symptom severity alone did not predict this structural difference, suggests that blushing is more likely to be responsible for the observed changes. It is possible that the blush response may be interconnected with hypervigilance, and may be involved in a positive feedback mechanism with anxiety, in that anxiety triggers blushing, which triggers anxiety and so forth.

Increased blushing severity was also associated with decreased volumes in left occipital cortex (uncorrected peak level) of SAD patients compared to controls. A similar finding was found for increased gaze symptom severity, but in the right occipital lobe (uncorrected cluster level). The occipital cortex has been implicated in the experience and evaluation of social transgressions, which may point to alterations in the emotional experience and cognitive processing of social stimuli in SAD patients compared to HCs. Altered activation of visual attention areas (Dumas et al., 2013) and enhanced visual cortical responses (McTeague et al., 2011) have been observed in SAD, which is in line with the current findings. As previously discussed, decreases in the occipital cortex volume was demonstrated earlier in the current research when SAD and HCs were compared, accounting for symptom severity overall, but before taking the specific symptoms of blushing and gaze into account. The emergence of the occipital cortex in multiple models reinforces the hypothesis that this structure is important in mediating SAD and its characteristic symptoms. The significance of the right occipital lobe differences at the cluster level indicates the strength of this finding.

Minor findings

While the associations found between blushing and gaze symptoms and the cerebellum, left inferior pareital love and right occipital lobe were the most robust, additional differences were found by the regression models and contrasts. However, these differences were not significant at the cluster level, and are therefore discussed here bearing that in mind. Of particular interest in these minor findings is the suggestion that increases in blushing severity were associated with increases in brainstem volume, because of the likely relationship between blushing and autonomic processes originating from the brainstem.

Increased severity of blushing was associated with increased volumes in the brainstem (uncorrected peak value). Increased brainstem volume was also found for increased blushing and gaze fear and avoidance symptoms together (uncorrected peak value), further reinforcing the importance of the brainstem in blushing, and possibly in the symptoms as a cluster. However, brainstem volume changes were not predicted by increases in gaze symptom severity, suggesting that blushing propensity is most likely a major contributor to differences observed in this brain region.

The brainstem plays a role in the autonomic processing, and while it has not yet been confirmed by MRI research, it is likely that the physiological elicitation of blushing may involve the brainstem vasomotor centres, in addition to central control centres, and peripheral dilatation mechanisms (Wilkins, 1983). An increase in the volume of this area in individuals with high blushing scores lends support to the idea that individuals suffering from SAD and blushing complaints may physically blush more than HCs, as found by Voncken and Bögels (2008), rather than just subjectively perceiving increased blushing or being more aware of their blushing, as suggested by some researchers in the field (Mulkens et al., 1997; Mulkens et al., 1999).

Increases in gaze symptom severity predicted decreases in the volume of the right posterior cingulate cortex (PCC; uncorrected peak level) and right fusiform gyrus (uncorrected peak level) of SAD patients. Decreases in the fusiform gyrus of SAD patients were also found by Syal et al. (2012) and the fusiform gyrus has been implicated in altered gaze behaviour in SAD patients (Mueller et al., 2009; Fusar-Poli

et al., 2009), except that increased activation in this region was found. Contrastingly, increased thickness in the fusiform gyrus has been found by Talati et al. (2013), while altered regulation of this region has been found in SAD patients (Etkin & Wager, 2007; Gentili et al., 2008). The fusiform gyrus is part of the parahippocampal cortex and has been found to be involved in processing facial expression and facial recognition (Straube, Kolassa, Glauer, Mentzel & Miltner, 2004; Fairhall & Ishai, 2007; Gentili et al., 2008). Decreases in this region may indicate less facial expression processing during social situations in SAD patients than in HCs. It is plausible that this may be because increased gaze avoidance reduces the amount of time that an individual focuses on facial cues. Altered activation in the PCC has been implicated in the experience of social emotions, social capacity and the ability to self-reflect and make inferences about others (Britton et al., 2006; Johnson et al., 2002; Ochsner et al., 2002).

When taking overall symptom severity (as measured by the LSAS) as a predictor, larger volumes were observed in SAD patients in several cortical areas, namely the left premotor cortex, right hippocampus, and left orbitofrontal cortex (uncorrected peak values). Decreased volumes were found in the right superior temporal cortex (uncorrected peak values). These findings are consistent with research that found decreases in the volume of (Syal et al., 2012; Talati et al., 2013) and altered activation in (Etkin & Wager, 2007; Gentili et al., 2008; Hattingh et al., 2013) the temporal cortex, as well as increases in the hippocampal area (Hattingh, 2011).

These regions have been implicated in social and emotional processing (Carr et al., 2003; Syal et al., 2012). The hippocampus has been specifically implicated in retrieval of socially relevant memories (Strange, Fletcher, Henson, Friston, & Dolan, 1999). The temporal lobes are thought to be involved in emotional and social processing, as demonstrated from animal temporal lobe lesion experiments showing decreased social signalling (Franzen & Myers, 1973), facial processing problems (Snowden et al., 2003; Snowden, Thompson & Neary, 2004), perception of emotional faces (Fusar-Poli et al., 2009), and dementia resulting in social dysfunction (Thompson, Patterson & Hodges, 2003) when the temporal lobes were ablated. Thus,

decreases in the temporal cortex in SAD patients may explain problems in processing social emotional stimuli. The temporal lobe is integrally connected to the amygdala and the orbitofrontal cortex, which are both involved in emotional processing (Carr et al., 2003), and the right temporal cortex has been shown to be closely involved with social memory and emotion (Olson, Plotzker & Ezzyat, 2007). Thus, increased symptom severity has implications for increasingly problematic social and emotional cognition, and that this increasing severity may be structurally reflected in the brain.

Summary

In the current research, the results that were significant at the corrected cluster level, followed by those that were significant at the uncorrected cluster level, should be regarded as more reliable than the uncorrected results. While uncorrected peak level results were discussed here, it is acknowledged that this was done for interest, given the exploratory nature of this research. Such results should not be regarded as robust findings, but rather as areas that have potential as areas of interest in future research. Thus, decreases in the cerebellum in relation to increased blushing propensity and gaze fear and avoidance together, decreases in the inferior parietal lobe with increased blushing, and decreases in the right occipital lobe with increased gaze anxiety and avoidance, should be regarded as the overarching picture from this analysis of specific SAD symptoms in relation to structural brain differences. However, while brainstem differences were significantly associated with blushing only at the uncorrected peak level, this may be an important region of future interest, given its likely role in autonomic processes. These differences lend further support to the notion that the aberrant affective and cognitive processing of SAD may be partly determined by altered brain structure.

Further considerations

The regions where neuroanatomical differences were found in the current research have been implicated in emotional processing circuitry. Social and emotional neurological processing is thought to involve the frontal, temporal, pre-motor, motor cortices as well as the limbic system (including the hippocampus and amygdala) of humans (Shin et al., 2010). Interestingly, no significant structural differences were

found in the amygdala or insula of SAD patients in any of the current analyses (apart from the medium effect size yet not significant difference observed in the right amygdala). This is contrary to the significant differences found by a number of researchers in the context of SAD (Stein, Goldin et al., 2002; Straube et al., 2005; Phan et al., 2006; Etkin & Wager, 2007; Freitas-Ferrari et al., 2010; Irle et al., 2010; Hattingh, 2011; Syal et al., 2012; Hattingh et al., 2013) and gaze pathology (Spezio et al., 2007; Dumas et al., 2013). However, the findings of the current research are in line with the findings of Syal et al., (2012), who also found no changes in the amygdala. Given that increased effort may be required by higher centres to control more basal structures when exposed to emotional stimuli (Sladky et al., 2012), the structural changes may be more evident in the higher centres. Syal et al. (2012) also note that the other regions in which they found differences (many similar to those found in the current research), are strongly interconnected with the amygdala, suggesting that such networks could underlie social threat processing networks. However, this is speculative, and highlights the need for further research into the role of the amygdala in relation to SAD symptom severity.

The reasons for contrary findings between several studies, including the current research, regarding the direction of brain volume changes (i.e. some studies finding increases where others find decreases), may be multiple. Firstly, research into the neurobiology of SAD has made use of a variety of methods, including functional and structural imaging. Even between structural imaging studies, methods have been heterogeneous including cortical thickness reconstruction (e.g. Freesurfer analyses, as done by Brühl et al., 2013 and Hattingh, 2011) and volume calculations (e.g. manual tracings and VBM as done by Fusar-Poli et al., 2009). This problem within the field makes it difficult to compare the current study, which used VBM methodology, to other studies that used different methods. Secondly, the relationship between cortical thickness and function is unclear. In general, decreased volume is thought to be related to reduced function, while increased thickness is thought to related to increased utilisation (Brühl et al., 2013). Cortical volume increases observed in SAD patients suggest compensatory increases resulting from increased efforts to regulate aberrant emotional processing. However, nothing more than correlation between structure and function can be assumed. It is thought that cortical thickness is

determined by neuronal density, neuronal numbers, neuron size, glial cell number and size, myelination, vasculature, related to motor or intellectual exercise (Frick et al., 2013). Furthermore, this between-study variability regarding brain regions implicated in SAD suggests that a number of neural circuits may be implicated in SAD pathology. Any number of these factors may be responsible for structural differences observed between individuals.

Limitations

Limitations of this research include a small sample size, missing data, the use of self-report measures, between-group differences in average education level, not including other possible variables of non-interest in regression analyses, uncorrected peak level results, and not directly eliciting blushing and gaze avoidance in participants to determine real-time neural correlates.

The small sample size (n = 18) limits the relevance of these findings to the wider population, and also reduces the strength of the findings. However, this sample size is generally considered acceptable when compared to other research in the field. This was not different from many neuroimaging studies, which have similarly low samples sizes (e.g. Adams et al., 2012; Blair et al., 2011; Liao et al., 2011; Schneier et al., 2011). These low numbers are most likely due to the difficulty in sourcing patients and the labour intensity of the scanning procedure. However, in the current research, the missing data for several participants further reduced the sample size to less than hoped, so that it was less than in many of the neuroimaging studies (although some, such as Schneier et al., 2009, had similarly low numbers). All possible effort was made to obtain the missing data from participants, the data was not forthcoming. This affected both the results obtained as well as the analyses that were run. This sample size affected the regressions that were run, because it was impossible to run within group analyses due to low numbers. Instead, both SAD and HCs were included in a between group analyses. However, this research is preliminary and exploratory, so that results obtained here can be used to inform research that may follow in the future.

Ideally, all the participants would each have completed the full set of LSAS, BPS and Gaze scales and data would not have been missing. However, participants' response and extent of participation was entirely voluntary so not everyone who participated in the scans decided to complete the tests, despite a number of concerted attempts to obtain this information. All data collected were included, leading to uneven group size for some measures, rather than omitting participants with incomplete data. This prevented reducing the sample size too greatly, allowing for some analyses to have a greater number of data points. This may, in part, be why some results with medium to large effect sizes and large *t* values were not significant. Furthermore, only some results were significant at the cluster level, making the strength of the findings with uncorrected peak values limited. The findings that were significant at the uncorrected and corrected cluster level are to be considered to be stronger than the uncorrected peak values.

Using self-report measures for determining the severity of the symptoms of interest (blushing and gaze fear and avoidance) is limiting in that data may be subject to social desirability bias, response set, recall bias and flaws of subjectivity and introspection (Rosenthal & Rosnow, 2008). Using alternative measures such as physiological recording of blush and sympathetic response (e.g. Voncken & Bögels, 2008) and eye-tracking (e.g. Horley et al., 2003; 2004; Moukheiber et al., 2010; Weister et al., 2009) would more objectively determine the degree of severity of these symptoms, however these would be time-consuming and costly to produce, and would also require the construction of simulated scenarios that would elicit these behaviours. These may be subject to the limitations associated with creating artificial scenarios. Furthermore, the self-report measures used in this research have been shown to be both reliable and valid for determining these symptoms in individuals (Baker et al., 2002; Langer et al., 2013; Leary & Meadows, 1991; Leibowitz, 1987; Mulkens et al., 1999; Schneier et al., 2011).

Regarding variables of non-interest, it can be argued that there are other factors that may have bearing on brain structure, such as sex of participants, should have been included in the analysis. However, it was thought that age, education and total matter

volume would be adequate for the purposes of this study, because the sample size was not large enough to include sex. These factors are the most commonly associated with global brain volume variance in any population. Thus, we wanted to isolate this variance, so that the remaining variances in brain volume observed could be more strongly associated with blushing, gaze and anxiety scores. This would not have been possible to do with more variables given the limited sample size. Thus, this shortcoming should be kept in mind for future analyses.

As noted earlier, a number of the regression and contrast model findings were not significant at the cluster level and were observed, instead, at the uncorrected peak level. Thus, these particular results cannot be given same weight as the results that were significant at the cluster (corrected or uncorrected) level.

This study was a structural MRI protocol that looked at how differences in SAD and HC brain areas could be predicted by high blushing and gaze scores. Like many MRI studies, the resulting differences are correlations and causation (in either direction) cannot be determined. Furthermore, a functional MRI study designed to elicit blushing and gaze fear and avoidance would go further to determine the brain areas associated with these symptoms in both HCs and SAD patients. However, a structural study can serve as an initial phase of a functional study, providing results that can contribute to hypotheses or determine research focus of a future functional study. It is important to understand both structural and functional biology when investigating a neurobiological disorder of this kind.

Recommendations for Future Research

Further research on this topic could include repeating the analysis with a larger and more complete data set. Meeting minimum sample size requirements as indicated by post-hoc power analyses would help to establish whether areas of interest indicated by medium to large effect sizes are in fact signals rather than noise. A larger sample size will allow for within group regression analyses to be run. It may also be worth exploring the possible effects of reduced symptom severity and treatment options on brain structure and function. Given the exploratory nature of this research, the brain

regions that emerged in the analysis as areas of difference between SAD patients and HCs could be used to generate hypotheses for future research, guiding focus on particular areas of interest. Furthermore, while the symptoms of blushing propensity and gaze fear and avoidance have a strong relationship with SAD, it may be worth investigating other symptoms considered to be associated with SAD, including other physical symptoms (such as panic, stuttering, sweating and trembling), as well as other behavioural and cognitive symptoms.

More research into structural and functional neurobiology of SAD, especially with a focus on cardinal symptoms in patients, is needed. The research into blushing and gaze is very limited, and even more so when considered in the context of SAD. It remains a challenge to image directly elicited behaviour in an MRI scanner. A protocol for the direct elicitation of blushing that is compatible with the scanner has been developed by van der Merwe (2008), and was piloted with HCs in 2010 (unpublished work), but data from the use of this protocol has yet to be successfully obtained. Using this protocol for both HCs and SAD patient would shed light on the neural correlates of blushing and the differences between normal and pathological blushing. As far as I am aware, a protocol for the direct elicitation of gaze avoidance has not yet been established. However, by developing and using a functional MRI protocol that could directly image gaze avoidance, this could be used in a similar way to further understanding of the functional neural circuitry involved in gaze behaviour, and how SAD patients and HCs differ from each other. This could complement and build on the structural findings of this research. Genetic studies of both blushing and gaze may also be worth exploring, given the multifactorial nature of these symptoms and of SAD. The current study serves as a foundation for such research.

Conclusion

In the current research, I found that increased blushing and increased gaze fear and avoidance are highly associated with a diagnosis of SAD, while also being associated with structural neuroanatomical differences in individuals with the disorder. It was

also found that these symptoms correlated highly with general symptom severity, and with each other, suggesting that they are both a prominent component of SAD pathology, and may likely to occur together. This is consistent with previous research that has linked blushing and gaze avoidance behaviour closely to SAD, as well as research that neurobiological factors are likely to play an important role in the aetiology of SAD.

Regarding structural neurobiological underpinnings of SAD, my findings suggest that there are significant volume differences between SAD and HCs in the regions of the left occipital cortex, left anterior cingulate and right inferior parietal lobe for SAD in general (lesser volumes in SAD patients), as well as differences in the left premotor cortex, left orbitofrontal cortex (both increased in SAD), and right superior temporal cortex (decreased in SAD) with increasing symptom severity. Medium effects were observed for differences in the ACC and DPLFC and amygdala between SAD patients and HCs, as well as total grey matter volume (strong effect) but these were not significant.

Furthermore, my findings indicate that the symptoms of blushing propensity and gaze avoidance behaviour (including anxiety about gaze), are correlated with structural neuroanatomical differences. Increased blushing propensity corresponds to increases in the brainstem, and decreases in the inferior parietal lobe and left occipital cortex. Increases in gaze symptom severity corresponded to decreases in the posterior cingulated cortex, occipital lobe and fusiform gyrus. Blushing and gaze together were found to relate to increased volumes in the brainstem, and decreases in the pons/cerebellum, parietal lobe.

Taking these results together, SAD patients and HCs were found to have significantly different brain structure in the areas associated with emotional regulation and cognitive appraisal. With increasing symptom severity SAD patients had increased brain volume in areas responsible for social emotional processing, possibly related to hypervigilance and altered social cognition. Decreases in the temporal lobe for SAD patients may explain problems processing social stimuli. Brainstem increases with

increased blushing propensity is suggestive of increased sympathetic activation and enhanced blush response, while decreases in the parietal and occipital lobes suggest alterations in the evaluation of social transgressions and emotional processing. Decreases in the cingulate cortex, occipital lobe and fusiform gyrus with increased aze fear and avoidance severity suggest changes in social emotion processing and capacity for reflection.

However, out of all these results, those significant at the cluster level were decreases in the left inferior parietal lobe with increased blushing symptom severity, decreases in the right occipital cortex with increased gaze symptoms severity, decreases in the pons/cerebellum and right cerebellum with collinear increases in blushing and gaze severity (significant at the uncorrected cluster level), and in the cerebellum bilaterally for increased blushing and decreased gaze severity (significant at the corrected FWE cluster level). Thus, these results should be regarded as being more robust than the others. These regions imply alterations in higher functions that are modulated by the cerebellum, altered emotional and cognitive processing of social stimuli, and hypervigilance (which has implications for anxiety). These regions can be considered areas of interest for studies that further explore these symptoms in relation to SAD.

Currently, gold standard treatment available for pathological blushing involves drastic surgery that is prone to side-effects, and research into the treatment for gaze avoidance is still in its infancy. While treatment for SAD as a disorder is well established, and may have some effect on the specific symptoms of blushing and gaze avoidance, more targeted treatments would be desirable in individuals with these as primary complaints. Furthermore, pharmacotherapy of blushing has been shown to be transiently successful at best. Thus, developing a sound understanding of the neurobiology of blushing and gaze behaviour in relation to SAD, in accordance with RDoC, may assist in developing targeted treatment and improve patient management.

In conclusion, differences in brain volumes pertaining to blushing and gaze avoidance behaviour in SAD patients may be a contributing factor or a consequence of these core symptoms, and a potential biomarker for SAD. Future studies could build on

this preliminary research with increased sample sizes, and determine the possible effects of reduced symptom severity and treatment options on brain structure and function. Most importantly, an investigation of the genetic underpinnings and functional neural correlates of blushing and gaze avoidance behaviour may enhance our understanding of the complex aetiology of these cardinal SAD symptoms, thereby improving our understanding of SAD as a psychiatric disorder and facilitating better patient care and management.

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APPENDIX A

LIEBOWITZ SOCIAL ANXIETY SCALE

Name:_____Date:_____

Indicate how often you feel fearful or anxious in each of the following situations and how often you avoid each of them using the scales below. Circle the most appropriate answer.

Fear or Anxiety:	Avoidance
0 = None	0 = Never (0%)
1 = Mild	1 = Occasionally (1-33%)
2= Moderate	2 = Often (33-67%)
3=Severe	3 = Usually (67-100%)

1. **Telephoning in public**

Fear or Anxiety				
0	1	2	3	
	None	Mild	Moderate	Severe
Avoidance	0	1	2	3
	Never	Occasionally	Often	Usually

2. **Participating in small groups**

Fear or Anxiety	0	1	2	3
	None	Mild	Moderate	Severe
Avoidance	0	1	2	3
	Never	Occasionally	Often	Usually

3. **Acting, performing or giving a talk in front of an audience.**

Fear or Anxiety	0	1	2	3
	None	Mild	Moderate	Severe
Avoidance	0	1	2	3
	Never	Occasionally	Often	Usually

4. **Eating in public places**

Fear or Anxiety	0	1	2	3
	None	Mild	Moderate	Severe
Avoidance	0	1	2	3
	Never	Occasionally	Often	Usually

5. **Drinking with others in public places.**

Fear or Anxiety	0	1	2	3
	None	Mild	Moderate	Severe
Avoidance	0	1	2	3
	Never	Occasionally	Often	Usually

6. Talking to people in authority.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

7. Going to a party

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

8. Working while being observed.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

9. Writing while being observed.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

10. Calling someone you don't know very well.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

11. Talking with people you don't know very well.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

12. Meeting strangers.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

13. Urination in a public bathroom.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

14. Entering a room when others are already seated.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

15. Being the centre of attention.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

16. Speaking up at a meeting.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

17. Taking a test.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

18. Expressing a disagreement or disapproval to people you don't know very well.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

19. Looking at people you don't know very well in the eyes.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

20. Giving a report to a group.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

21. Trying to pick up someone.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

22. Returning goods to a store.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

23. Giving a party.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

24. Resisting a high pressure salesperson.

Fear or Anxiety	0 None	1 Mild	2 Moderate	3 Severe
Avoidance	0 Never	1 Occasionally	2 Often	3 Usually

APPENDIX B

BLUSHING PROPENSITY SCALE

Name:_____ Date:_____

Indicate how often you feel yourself blush in each of the following situations using the scale below. Circle the most appropriate answer.

1 = I **NEVER** feel myself blush in this situation.
2 = I **RARELY** feel myself blush in this situation.
3 = I **OCCASIONALLY** feel myself blush in this situation.
4 = I **OFTEN** feel myself blush in this situation.
5 = I **ALWAYS** feel myself blush in this situation.

1. When a teacher calls on me in class

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

2. When talking to someone about a personal topic

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

3. When I'm embarrassed

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

4. When I'm introduced to someone I don't know

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

5. When I've been caught doing something improper or shameful

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

6. When I'm the center of attention

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

7. When a group of people sings "Happy Birthday" to me

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

8. When I'm around someone I want to impress

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

9. When talking to a teacher or boss

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

10. When speaking in front of a group of people

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

11. When someone looks me right in the eye

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

12. When someone pays me a compliment

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

13. When I've looked stupid or incompetent in front of others

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

14. When I'm talking to a member of the other sex

1	2	3	4	5
Never	Rarely	Occasionally	Often	Always

APPENDIX C

GAZE ANXIETY RATING SCALE

The following questions ask if you feel anxiety making eye contact and avoid eye contact in various situations. Base your ratings on the way you have felt and behaved in the past week. If you have not been in the situation recently, please you imagine your expected anxiety and avoidance of eye contact in the situation.

Note: Do not rate anxiety related to just being in the situation. Rate anxiety and avoidance of making eye contact while in the situation.

	ANXIETY MAKING EYE CONTACT 0 No anxiety 1 A little anxiety 2 Moderate anxiety clinic 3 A lot of anxiety	AVOIDANCE OF EYE CONTACT 0 No avoidance 1 Avoid a little 2 Avoid moderately 3 Avoid a lot
1. Giving a speech	_____	_____
2. Speaking to a group of people at a party	_____	_____
3. Speaking up at a meeting	_____	_____
4. Speaking in a discussion with a few people	_____	_____
5. Dealing with a cashier when buying something	_____	_____
6. Being introduced	_____	_____
7. Greeting an acquaintance passing by on the street	_____	_____
8. Speaking with someone you don't know well	_____	_____
9. Speaking to someone you find attractive	_____	_____
10. Inviting someone you don't know well on a date or other social activity.	_____	_____
11. Feeling close to someone you love	_____	_____
12. Discussing the quality of your work with a boss or a teacher.	_____	_____
13. Having a routine talk with a close family member	_____	_____
14. Listening while a person speaks to you, in general	_____	_____

15. Speaking while a person listens to you, in general	_____		_____	
16. Expressing a disagreement	_____		_____	
17. Receiving a compliment	_____		_____	
TOTAL SCORE (Sum of items 1-17):	_____	+	_____ =	_____
				Grand Total

Descriptive Items

Please rate the additional items on the following scale:

0 Not at all
1 A little
2 Moderately
3 A lot

18. ___ I avoid eye contact because it make me anxious
19. ___ I avoid eye contact only because it interferes with my concentration (not due to anxiety)
20. ___ I feel self-conscious when I make eye contact.
21. ___ I am concerned that I stare too much into others' eyes.
22. ___ I have difficulty deciding how much eye contact is best.
23. ___ Making eye contact is important for my social and work relationships

(If you have no anxiety about eye contact, check here ____ and skip items below.)
Complete the following items if you have some anxiety about eye contact or avoidance of eye contact

APPENDIX D

Analysis of brain volume differences with SAD *n*= 16 and HC *n*=10

Table 6

Descriptive statistics (mean, standard deviation and effect size) and independent sample t-tests of SAD patients and health controls for brain volumes (SAD n=16, HC=10

Scale Scores	**SAD Mean (SD)**	**HC Mean (SD)**	***t***	***p***	***df***	**Effect size (Cohen's d)**
Total brain volumes						
Grey Matter (ml)	714(60)	760(56)	2.01	0.058	20	**0.83**
White Matter (ml)	483(54)	502(52)	0.90	0.376	20	0.38
CSF (ml)	557(199)	594(185)	0.48	0.637	20	0.20
Total Intracranial volume (ml)	1754(251)	1856 (183)	1.20	0.242	23	0.47
Grey matter volumes						
Left Insula (ml)	7.5(0.7)	7.7 (0.9)	0.664	0.516	16	0.30
Right Insula (ml)	7.0(0.6)	7.2(0.9)	0.44	0.668	15	0.20
Left ACC (ml)	6.2(0.7)	6.7(0.9)	1.51	0.150	15	**0.68**
Right ACC (ml)	5.3(0.6)	5.7(0.8)	1.43	0.172	15	**0.65**
Left Hippocampus (ml)	4(0.4)	4.1(0.4)	0.55	0.592	17	0.24
Right Hippocampus (ml)	3.7(0.4)	3.8(0.4)	0.40	0.690	20	0.17
Left Amygdala (ml)	1.06(0.11)	1.10(0.13)	0.88	0.391	17	0.38
Right Amygdala (ml)	1.05(0.12)	1.11(0.14)	1.22	0.241	16	**0.54**
Left DLPFC (ml)	11.5(1.3)	12.1(1.1)	1.37	0.185	22	**0.61**
Right DLPFC (ml)	13.3(1.5)	14.3(1.8)	1.4	0.180	16	**0.60**