Chapter 12

Neuroendocrinology and Neuroimaging Studies of Social Anxiety Disorder

K. Luan Phan[1,2] and Heide Klumpp[1]

[1]*Department of Psychiatry, University of Illinois, Chicago, IL;* [2]*Mental Health Service Line, Jesse Brown VA Medical Center, Chicago, IL*

INTRODUCTION

Social anxiety disorder (SAD), otherwise known as social phobia (SP), is a common anxiety disorder characterized by an intense, irrational and persistent fear of being scrutinized or negatively evaluated by others (American Psychiatric Association, 2013). Feared social or performance situations typically provoke an anxious reaction ranging from diffuse apprehension to situational panic. When faced with social scrutiny, individuals with SAD respond with signs of hyper-arousal (e.g., blushing, increased heart rate, shaking, sweating). Situations that evoke anxiety and fear are often avoided, for fear of embarrassment in the context of perceived threat and/or criticism. Broadly, it has also been proposed that individuals with social anxiety have difficulty in the way that social and emotion-laden information cues are processed (Clark & McManus, 2002) and/or regulated (Sung et al., 2012).

Given the response to social threat in SAD, several broad complementary theories exist about the neuropathophysiology of social phobia. Firstly, the brain and body's neuroendocrine system, which is activated when a person comes under threat, may be dysregulated. Secondly, the amygdala and associated paralimbic brain regions, which govern fear perception, memory, responding, and learning, may be hyper-sensitive to information that convey the *potential* for threat or may be hyper-reactive during threat-relevant situations (e.g., public scrutiny). Thirdly, the frontal and associative cortices involved in cognition and executive functions may exhibit deficient functioning when incoming social signals require complex interpretation and/or when negative feedback requires reappraisal or other forms of emotion regulation (e.g., attentional control).

Collectively, these theories are based on the theory that SAD involves aberrant social cognitive affective functioning. For example, patients with SAD are

Social Anxiety. DOI: 10.1016/B978-0-12-394427-6.00012-1

hypervigilant for social signals that convey threat or criticism such as "harsh' (e.g., angry, afraid, contemptuous, disgusted) faces (Bögels & Mansell, 2004) and tend to *mis*interpret ambiguous interpersonal situations as threatening (Amir, Beard, & Przeworski, 2005; Hirsch & Clark, 2004; Stopa & Clark, 2000; Yoon & Zinbarg, 2008). If these social cognitive affective processes are abnormal in SAD, then examining the stress-related neuroendocrine and structure-function of relevant brain areas may further our knowledge about the underlying biological mechanisms that cause and/or maintain the symptoms and behaviors of patients with the disorder.

In the past two decades, substantial advances have been made in the neurobiology of stress and of fear from animal, lesion, and human studies. By extension, these advances have been translated into clinical investigations of patients with SAD. In this chapter, we provide a qualitative review and synthesis of the extant literature on the neuroendocrinology and neuroanatomy of social anxiety disorder.

NEUROENDOCRINOLOGY OF SOCIAL ANXIETY DISORDER

The neuroendocrine response to stress involves the activation of the hypothalamic–pituitary–adrenal (HPA) axis represented by a cascade of interactive neuroactive hormones, starting with the peptide corticotropin-releasing hormone (CRH) from the hypothalamus to stimulate release of adrenocorticotropin hormone (ACTH) from the pituitary gland, which in turn evokes adrenal release of glucocorticoids such as cortisol (Brown, Koob, & Rivier, 1991). Cortisol is an extensively used stress marker, as it modulates mental and physical states associated with stress (Khan, King, Abelson, & Liberzon, 2009). Normal HPA activity is associated with circadian rhythm and therefore fluctuates with relatively elevated levels in the early morning and low levels in the evening. Another measure of HPA function is the dexamethasone suppression test (DST), which involves the administration of a synthetic glucocorticoid that suppresses plasma adrenocorticotropic hormone and cortisol concentrations. Behavioral challenges (e.g., "psychological stressor" such as public speaking) permit investigation of endogenous cortisol levels in response to stress. Additionally, the administration of exogenous glucocorticoids (e.g., cortisone), which is metabolized into endogenous cortisol or pharmacologic panicogens (e.g., pentagastrin) allows for the manipulation of stress hormones.

Atypical neuroendocrine response and its connection to SAD are evident early in life. For example, among risk factors for the development of SAD by adolescence are high levels of behavioral inhibition and elevated cortisol levels in early childhood (Essex et al., 2010). An association between elevated cortisol and temperament has also been shown in children of socially phobic mothers, such that behaviorally inhibited children display elevated afternoon cortisol levels in general and when confronted with a naturalistic stressor (i.e., first week of school), elevated night-time cortisol levels (Russ et al., 2012). Whereas early

disruptions in HPA activity appear to factor into the development of social anxiety, it is less clear how these disruptions are presented in adulthood. In a cohort of anxious adults, elevated awakening cortisol response was observed though it was not specific to social phobia (Vreeburg et al., 2010). Lack of specificity to SAD has also been demonstrated in older adults (average 74.7 ± 5.3 years), wherein clinical anxiety was associated with *lower* cortisol awakening response, suggesting chronic anxiety may reduce HPA activity (Hek et al., 2013). Moreover, a number of studies have failed to find evidence of abnormal HPA activity in terms of circadian cortisol levels (Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001; Potts, Davidson, Krishnan, Doraiswamy, & Ritchie, 1991; Uhde, Tancer, Gelernter, & Vittone, 1994; van Veen et al., 2008). Regarding the DST, a few studies report an absence of HPA-axis over/underactivity from DST challenge in social phobia patients (Uhde et al., 1994; Vreeburg et al., 2010). However, one DST study (van Veen et al., 2008) reported that SAD patients had normal levels of cortisol but higher diurnal and post-dexamethasone alpha-amylase (sAA) levels, a putative index of autonomic nervous system (ANS) stimulation, suggesting a relative increased activity of the ANS as compared to the HPA axis, in line with the observed hyperarousal in SAD.

Unlike basal state, cortisol reactivity to psychological stressors that often provoke anxiety may better reflect HPA axis dysregulation in SAD and reflect the real-life social situations feared and avoided by patients, although the findings have been mixed. Early studies show that speech task stressors do not precipitate a larger cortisol response in SAD participants than controls (Furlan et al., 2001), while cognitive tasks (i.e., subtraction and digit span) in front of an audience did (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002). More recently, reactivity to a public speaking challenge (Trier Social Stress Test, TSST) has been associated with exaggerated cortisol responses, which correlated with social avoidance behavior in SAD (Roelofs et al., 2009). These patterns may be evident in children (van West, Claes, Sulon, & Deboutte, 2008), though others have observed enhanced pre-stress (e.g., anticipatory anxiety) cortisol but not during the stressor itself (Martel et al., 1999). Individual differences in comorbid psychopathology across SAD may contribute to variability in stress-induced responses. For example, a history of childhood abuse (Elzinga, Spinhoven, Berretty, de Jong, & Roelofs, 2010) and depression (Young, Abelson, & Cameron, 2004) may contribute to increased cortisol reactivity to a TSST challenge in individuals with SAD (but see Yoon & Joormann, 2012).

In summary, much further study is needed to draw definitive conclusions regarding the specificity of neuroendocrine dysregulation in SAD and their relation to subjective anxiety and avoidance behaviors (Roelofs et al., 2009; Yoon & Joormann, 2012). Future studies might also further elucidate the role of neuroendocrine function in SAD through the use of pharmacologic manipulations to mimic the stress response with agents like the panicogenic CCK-tetrapeptide (CCK-4) (Katzman, Koszycki, & Bradwejn, 2004) or exogenous cortisone in

the absence or presence of social stress (Soravia et al., 2006), or how cortisol impacts cognitive and cognitive-emotional function and dysfunction in SAD (Erickson, Drevets, & Schulkin, 2003).

NEUROANATOMY OF SOCIAL ANXIETY DISORDER

Brain Imaging Approaches

Human brain imaging provides a unique opportunity to examine the neural substrates in SAD *in vivo*, by providing data on structural and/or morphometric changes, functional neuroanatomy, neurochemistry, and brain receptor systems with techniques such as computed tomography (CT), structural magnetic resonance imaging (sMRI), diffusion tensor imaging (DTI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional MRI (fMRI).

The "neuroanatomy" of social phobia is often inferred by the comparison between individuals with SAD and those who are psychiatrically healthy, using extant models of emotional, cognitive, and social brain function (Lieberman, 2007; Miller & Cohen, 2001; Ochsner & Gross, 2005; Phan, Wager, Taylor, & Liberzon, 2002), which may differ between patients and healthy controls at the level of structure, function, or neurochemistry. For example, affective/emotion neuroscience has implicated limbic (amygdala) and paralimbic (insula, orbitofrontal cortex [OFC], medial prefrontal cortex [MPFC], rostral anterior cingulate cortex [rACC], retrospenial cortex including the posterior cingulate cortex (PCC) and adjacent precuneus) brain regions in emotional or affective processing in humans, including the generation and control of emotional (i.e., anxiety) states and emotional memory and threat processing (Barrett, Mesquita, Ochsner, & Gross, 2007; R. J. Davidson, 2002; Maddock, 1999; Paulus & Stein, 2006; Phan, Wager, Taylor, & Liberzon, 2002). In parallel, cognitive neuroscience links the frontal cortex including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and dorsal portions of the ACC (dACC) with executive function, attention, and cognitive control of behavior (Miller & Cohen, 2001). Social neuroscience (Lieberman, 2007) integrates self with the appraisal of signals from the social environment and highlights the role of the MPFC, amygdala, and superior temporal sulcus in governing these functions (Ochsner, 2004).

Below, we organized our qualitative review of the literature in terms of various types of neuroimaging methodologies: (1) structural brain imaging studies (CT, MRI); (2) functional "activation" studies which probe areas engaged in relation to a particular affective, cognitive, and/or social task (rCBF PET, fMRI); (3) functional imaging studies of the resting state, disassociated from task demands (GMR PET, fMRI); and (4) neurochemical (MRS) and neuroreceptor (receptor PET) imaging studies. We focus on regions commonly highlighted across studies and that have been implicated in affective, cognitive,

and/or social function. If data are available, we discuss these findings in the context of effects of treatment and/or psychopharmacology on brain structure and function.

Structural Brain Imaging

Early structural imaging studies did not show brain volume differences between SAD subjects and controls (Potts, Davidson, Krishnan, & Doraiswamy, 1994). However, recent studies have observed reduced amygdala and/or hippocampal volume or gray matter density in adults (Irle et al., 2010) and adolescents with SAD (Mueller et al., 2013) as well as in cortical areas such as bilateral VLPFC and precuneus in clinically anxious children (Milham et al., 2005). Further evidence of structural disturbances extending beyond limbic areas comes from a multi-modal imaging study in SAD adults (VBM, DTI, and resting state fMRI) which suggest a reduced volume in the parahippocampal/hippocampal gyrus and the posterior inferior temporal gyrus, yet increased volume in the MPFC is linked in part to broad, diffuse aberrant patterns of regional and region-region connectivity amongst several areas, including the middle temporal gyrus and inferior occipital gyrus (IOG) (Liao et al., 2011).

However, reductions in amygdala or hippocampal volume in SAD have not always been observed (Syal et al., 2012; van Tol & van der Wee, 2010), and as noted above, accumulating data point to abnormalities beyond limbic regions. For example, male patients with SAD (relative to controls) show cortical thickness in face processing areas (e.g., lingual and fusiform gyrus) and a negative relationship between symptom severity and rostral ACC thickness (Frick et al., 2013). Reduced rostral ACC as well as reduced posterior cingulate volume has also been observed in SAD as well as other anxiety disorders and depression, but are uncorrelated to illness severity (van Tol & van der Wee, 2010). On the other hand, cortical thinning in SAD has been demonstrated in temporal areas (e.g., temporal pole, insular cortex) in addition to areas involved in cognitive-affective functions (e.g., DLPFC and medial OFC) and face perception (e.g., fusiform gyrus) (Syal et al., 2012) with further evidence of reduced volume in temporal pole and inferior prefrontal/OFC in SAD, relative to controls (Talati, Pantazatos, Schneier, Weissman, & Hirsch, 2013). Future studies are needed to examine the effect of the treatment on these volume and gray matter density alterations (Cassimjee et al., 2010).

DTI examines microstructural white matter (WM) connectivity, using measures of an axonal organization such as fractional anisotropy (FA). Of particular interest is the uncinate fasciculus (UF), the main WM tract linking the amygdala and orbitofrontal cortex (Ghashghaei, Hilgetag, & Barbas, 2007), which has been shown to have less FA in SAD patients (relative to controls) (Phan et al., 2009). In addition to lower FA in the UF, reduced FA has also been implicated in broader tracts (e.g., inferior fronto-occipital fasciculus, superior longitudinal fasciculus) (Baur et al., 2011, 2013). Together these findings suggest

that structural alterations in SAD can be localized to specific gray and white matter. Interpretations of these structural findings can be further informed by findings obtained in functional brain imaging studies reviewed below.

Functional Brain Imaging: Task-related "Activation" Studies

Emotional Face Processing

Facial expressions are potent non-verbal cues that facilitate social communication and motivate approach or avoid behaviors (Ekman, 2003), and serve as ecologically valid probes of social anxiety symptoms. In particular, a reliable circuitry is engaged in processing the social information decoded from faces, including the amygdala, fusiform gyrus (fusiform face area [FFA]), inferior frontal gyrus (IFG)/OFC, and superior temporal sulcus (STS) (Adolphs, 1999, 2002). In an fMRI study of patients with SAD engaged in the processing of emotional faces, Stein and colleagues were among the first to demonstrate that the amygdala exhibits greater activation to "harsh" (angry, fearful, and contemptuous) faces that convey negative feedback, than those that connote acceptance/approval (happy). In addition, the authors also observed greater BOLD response in dorsal MPFC, IFG, uncus and parahippocampal gyrus (pHG) (Stein, Goldin, Sareen, Zorrilla, & Brown, 2002). Since Stein et al. (2002), studies examining response to faces in SAD has grown considerably, including the replication and extension that amygdala reactivity to "harsh" (angry, fearful, disgust) versus happy faces is exaggerated in patients with SAD (relative to controls) and correlated with symptom severity (Phan, Fitzgerald, Nathan, & Tancer, 2006). This pattern is evident even at moderate levels of "harsh" expression intensity (50–60% of full), suggesting individuals with SAD have enhanced perceptual acuity for social threat (Klumpp, Angstadt, Nathan, & Phan, 2010). However, it should be noted findings of hyper-reactivity in SAD may be contingent on what is construed as "baseline", for example, when contrasting angry, fearful, sad, happy and neutral faces against scrambled faces, SAD and healthy control groups exhibit equivalent amygdala reactivity (Demenescu et al., 2011).

That said, other studies have revealed neural patterns in SAD that may be specific to certain facial expressions. For example, Blair and colleagues (Blair, Shaywitz, et al., 2008) observed that SAD subjects exhibited greater amygdala and frontal polar/MPFC reactivity to fearful, but not angry, faces (versus neutral faces) than controls and, similarly, Labuschagne et al. (2010) reported exaggerated amygdala reactivity in gSAD (versus controls) to fearful, but not angry or happy expressions. On the other hand, Evans et al. (Evans, Wright, et al., 2008) demonstrated greater response to schematic angry (versus neutral) faces in the amygdala, superior frontal cortex, and ACC, and to angry (versus happy) faces in the lingual gyrus, fusiform gyrus, precentral gyrus, insula, PCC, middle frontal gyrus, and middle temporal gyrus. Straube and co-authors (Straube, Mentzel, & Miltner, 2005) reported amygdala hyper-reactivity in SAD (relative to controls) to angry *and* happy faces and greater insula activation in response

to angry faces, but not to neutral or happy faces (Straube et al., 2005). Likewise, increased amygdala and insula reactivity (along with other regions, e.g., fusiform gyrus) has been observed to angry faces (versus neutral faces) in SAD with results impacted by condition (e.g., explicit, implicit processing; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004). Evidence processing level affecting findings is a reminder that methodological differences among studies need to be taken into consideration before drawing firm conclusions in addition to individual differences that impact brain activity. For example, Furmark et al. (2009) did not find group effects in the amygdala response for angry (versus neutral) faces but did observe a genetic influence on amygdala reactivity in SAD. The amygdala comprises serotonergic fibers (Bauman & Amaral, 2005), and in healthy volunteers (Hariri, Drabant, & Weinberger, 2006) and SAD subjects (Furmark et al., 2004), carriers of the short (s) allele of the serotonin transporter gene-linked polymorphic region (5-HTTLPR) display amygdala hyper-reactivity to negative stimuli relative to individuals who are homozygous for the long (l) allele. Though SAD and control subjects exhibited comparable amygdala response to angry faces, it was greater among SAD subjects with 5-HT-related high-response alleles relative to those with low-response alleles. A similar pattern was observed in healthy controls, though the effect of genotype was less than that observed in patients, indicating that the genetic variation in serotonergic function may have greater impact in individuals with SAD. The relationship between serotonin modulation and amygdala reactivity is further evinced by the observation pre-treatment exaggerated amygdala activity to fearful (versus happy) and attenuated vmPFC response to angry (versus happy) faces in SAD (relative to controls) significantly changed after 12 weeks of treatment with the serotonin reuptake inhibitor (SSRI) sertraline, such that amygdala and vmPFC activity did not differ from controls posttreatment (Phan et al., 2013). Furthermore, regression analysis between symptom severity and brain activation change revealed that decreases in social anxiety primarily corresponded with decreases in visual and parietal cortical areas to angry and fearful faces, and with increases in superior temporal gyrus to angry faces and increases in postcentral and mid-cingulate gyrus to fearful faces. However, changes in activation were not significantly related to social anxiety symptom improvement.

There have been relatively fewer studies of children and adolescents with SAD, though there is some evidence that this pattern of amygdala hyper-reactivity to negative faces exists in younger participants. Firstly, adolescents with anxiety (SAD and/or generalized anxiety disorder [GAD]) exhibit greater amygdala reactivity to fearful (than happy) faces (Beesdo et al., 2009). Subsequently, Blair et al. (Blair, Geraci, Korelitz, et al., 2011) observed that SAD adolescents and adults (relative to matched controls) showed exaggerated amygdala and rostral ACC response to fearful faces as well as rostral ACC hyper-reactivity to angry expressions; symptom severity positively corresponded with ACC activity to fearful and angry faces in adults; whereas no correlations emerged for amygdala activity in adults or adolescents (Blair, Geraci, Korelitz, et al., 2011),

suggesting the relationship between illness and threat-related brain response may occur outside amygdala.

While other investigations have not found exaggerated amygdala responsivity to faces in SAD, they have observed hyper-reactivity in areas implicated in mind-body interactions (insula), face processing (e.g., middle frontal gyrus), and cognitive-affective functions (e.g., mPFC). For example, SAD subjects have been shown to exhibit greater activation to disgust (versus neutral) faces than controls in rACC, dACC, caudate, insula, lingual gyrus, pHG, STG, and middle frontal gyrus (Amir, Klumpp, et al., 2005). Also, in a "looming faces task" wherein angry and contemptuous faces appear to move closer to the viewer, SAD subjects (relative to controls) showed exaggerated activity in various fronto-temporal regions (e.g., medial frontal gyrus, middle temporal gyrus/inferior frontal gyrus (Ziv, Goldin, Jazaieri, Hahn, & Gross, 2013)). Additionally, symptom severity correlated with insula reactivity in SAD subjects, although no group differences emerged for insula (Ziv, Goldin, Jazaieri, Hahn, & Gross, 2013). Individual differences along subclinical—clinical social anxiety have also been shown to positively correspond to insula and lateral PFC activity for angry faces (versus shapes) but not for other expressions (fear, sad, happy, neutral) (Carré et al., 2013). Evidence of treatment-related reduction in insula has also been observed after 12 weeks of cognitive-behavioral therapy (CBT) (Klumpp, Fitzgerald, & Phan, 2013). Specifically, SAD patients (relative to controls) exhibited pre-treatment hyper-reactivity to angry (versus happy) faces in insula, OFC, superior medial frontal gyrus, STG, and hippocampus, which significantly decreased after completing CBT. However, pre- to post-CBT brain changes in limbic/paralimbic areas to fearful (versus happy) faces did not correlate with changes in symptom severity, whereas higher level visual areas (i.e., middle temporal and angular gyri) as well as prefrontal regions (e.g., ACC, OFC) did (Klumpp, Fitzgerald, & Phan, 2013). These findings are consistent with a recent study that showed pretreatment response to angry (versus neutral) faces in occipital and ventral temporal regions and to a lesser extent prefrontal areas (dorso- and ventro-lateral PFC) predicted CBT success (Doehrmann et al., 2012).

Despite some inconsistencies, most studies have shown that exaggerated amygdala reactivity to these harsh/negative faces in SAD though hyper-reactivity may not be limited to faces that directly express threat. Given SAD is associated with negative bias for "neutral" and/or ambiguous social signals (Amir, Beard, & Przeworski, 2005), patients may have acquired an aversive response to "neutral" faces. Consistent with this view, amygdala reactivity appears to be enhanced during fear conditioning in SAD patients, particularly when presented with a "neutral" face previously paired with an aversive event (e.g., aversive odor) (Birbaumer et al., 1998; Schneider et al., 1999; Veit et al., 2002). Interestingly, Birbaumer et al. (1998) reported that the SAD group exhibited this hyperactive amygdala response to neutral faces even *prior* to aversive conditioning and continued to exhibit amygdala hyper-reactivity during the "habituation"

phase (Veit et al., 2002). Moreover, Cooney et al. (Cooney, Atlas, Joormann, Eugène, & Gotlib, 2006) showed that SAD participants had greater amygdala reactivity to neutral faces during an appraisal task, and were more likely to assign a negative valence to these faces (although not significantly more so than controls) (Cooney et al., 2006).

Complementary facial cues such as the direction of eye gaze may also convey a sense of "threat" from an otherwise neutral face or elicit self-consciousness in SAD given fears of eye contact in this population (Schneier, Rodebaugh, Blanco, Lewin, & Liebowitz, 2011). In support, patients with SAD (versus controls) have shown greater amygdala activation to neutral faces when eye gaze was directed at them, as opposed to away from them, along with greater reactivity in the insula, associated frontal regions (rACC, MPFC), and fusiform gyrus (Schneier, Kent, Star, & Hirsch, 2009). In the context of an SSRI (i.e., paroxetine) treatment study, SAD patients (relative to healthy controls) demonstrated greater pre-treatment reactivity to neutral expressions of direct (versus averted) gaze in inferior parietal lobule, supramarginal gyrus, posterior cingulate, and middle occipital cortex but not in amygdala response (Schneier, Pomplun, Sy, & Hirsch, 2011). After eight weeks of treatment, patients showed reductions in insula, middle temporal gyrus, occipital cortex, posterior cingulate cortex, and precuneus. Changes in activation correlated with reductions in symptom severity in areas involved in "top down" regulation (ACC, MPFC, IFG; Etkin et al., 2011; Miller & Cohen, 2001; Ochsner, 2004) and self-referential processing (e.g., posterior cingulate cortex, precuneus; Vogt and Laureys, 2005; Paulus and Stein, 2006). Findings indicate treatment "normalized" a distributed network implicated in perceived scrutiny in the context of direct eye gaze in SAD (Schneier, Pomplun, et al., 2011), similar to that observed in relation to the processing of threat faces (Phan et al., 2013).

Beyond "threat", studies have also demonstrated enhanced amygdala reactivity in SAD subjects (relative to controls) to emotionally-valenced expressions that include happy faces (Hahn et al., 2011; Yoon, Fitzgerald, Angstadt, McCarron, & Phan, 2007) as well as amygdala hyper-reactivity to only happy faces in SAD (Evans, Wright, et al., 2008; Straube et al., 2005). Straube et al. demonstrated that social phobics (relative to controls) had greater amygdala reactivity to happy (but not neutral) faces (Straube et al., 2005). Evans and colleagues also showed that SAD patients had greater amygdala responses to happy (relative to neutral) schematic faces than control subjects (Evans, Wright, et al., 2008). One explanation for these findings is that the amygdala, which does appear to activate happy faces in healthy volunteers (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Yang, Menon, Reid, Gotlib, & Reiss, 2003), may show greater reactivity in phobic participants because it is responding to the arousal dimension of affective stimuli rather than their valence (i.e., negative versus positive) (Liberzon, Phan, Decker, & Taylor, 2003; Phan et al., 2003).

Alternatively, individuals with SAD have rated happy faces as less approachable than controls, with social anxiety severity corresponding to lower

approachability ratings, indicating explicit, subjective social interpretation biases to overtly presented positive feedback in SAD (Campbell et al., 2009). Complementary research has suggested that happy faces may be interpreted as reflecting mockery or misrepresented as another form of threat signal (e.g., social dominance, higher social expectations, disingenuous expression) (Alden & Taylor, 2004; Coles & Heimberg, 2005; Yoon & Zinbarg, 2008).

Emerging findings suggest that functional connectivity between amygdala and/or insula and other brain areas is altered in SAD, indicating that aberrant activity in a particular region might be due to anomalous interactions among regions. For example, in a study that focused on circuitry involved in face perception, SAD patients who exhibit greater amygdala reactivity to emotionally-valenced faces (versus scrambled images) than controls, also showed stronger negative coupling between amygdala to the superior temporal cortex, inferior parietal, anterior middle prefrontal, and postcentral cortex, whereas controls exhibited a greater negative coupling to paracentral sensorimotor cortex (Danti et al., 2010). SAD patients have also been shown to exhibit decreased amygdala-dlPFC and decreased amygdala-ACC connectivity when viewing threatening faces compared to controls (Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013); although reduced amygdala-ACC coupling in SAD (versus controls) was also evident at "rest" (i.e., not engaged in a task) suggesting both phasic and tonic alterations in connectivity, whether threat signals were present or not (Prater et al., 2013). In another study, despite a lack of differential amygdala response to emotional faces and its connectivity to other brain regions between SAD and controls, symptom severity across patients positively correlated with amygdala-rostral ACC and amygdala-dorsal mPFC connectivity to fearful (versus neutral) faces (Demenescu et al., 2013).

While the predominant focus has been on amygdala-related connectivity, there is evidence that exaggerated insula response to threat faces in SAD has also been shown to co-occur with reduced dorsal ACC connectivity (versus controls) (Klumpp, Angstadt, & Phan, 2012). Collectively these studies show that when amygdala or insula over-reacts to social signals in SAD, it does not do so in anatomical isolation but in concert with interactions with prefrontal and visual processing areas.

Beyond those noted above, future studies are needed to delineate whether responses in the amygdala, insula, prefrontal and sensory cortices to emotional faces can serve as biomarkers of treatment mechanisms and/or of treatment predictors, both to clinical response and non-response. Thus far, emerging findings suggest that treatment-related brain changes are localized to different areas to those that predict treatment response. Moreover, these observed neural markers appear to involve a distributed network that taps into self-referential and emotion regulation functions but not necessarily "core" emotion (e.g., faces) processing regions (e.g., amygdala). Lastly, brain responses to emotional faces may not be a sensitive measure of treatment-related brain changes. Therefore,

additional probes of brain function are needed to test if they may serve as better indices of treatment mechanisms and predictors.

Emotion Regulation

There is increasing evidence that limbic-frontal interactions are critical during emotion processing, particularly when the explicit or implicit regulation of negative emotional states is required (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Ochsner & Gross, 2005; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008; Gyurak, Gross, & Etkin, 2011). Goldin and colleagues, whose chapter provides a broader discussion of emotion regulation in SAD, were among the first to extend these emotion regulation "activation" paradigms into SAD. In a study that deployed a well-validated emotion regulation technique (e.g., reappraisal) (Gross, 1999) to reduce negative affect evoked by "harsh" faces and negative non-social images (Goldin, Manber, Hakimi, Canli, & Gross, 2009). Unlike controls, SAD patients failed to engage DLPFC, dACC, and PCC (and dorsal parietal, fusiform, superior temporal gyrus) when reappraising harsh faces. These findings represent the first evidence of dysfunctional frontal cortical function during the cognitive regulation of negative social cues in SAD. Similarly, when using a variation on "reappraisal", SAD subjects have reduced activity in DLPFC, ACC, amygdala and insula as well as in bilateral parietotemporal regions when compared to those not using this strategy (Annette Beatrix Brühl et al., 2013).

Subsequently, Blair and colleagues evaluated both explicit regulation (reappraisal) and implicit regulation (attentional control) in patients with SAD, generalized anxiety disorder (GAD), and healthy controls, and showed that healthy controls exhibited greater activity in ACC and parietal regions during both cognitive reappraisal and top-down attentional control, unlike SAD and GAD subjects (Blair et al., 2012). Additionally, less ACC response has been shown in SAD (compared to controls) when asked to look away from distracting emotional faces (Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013), further supporting evidence of prefrontal, particularly ACC, deficiency during implicit regulation.

As an alternative regulation method, mindfulness-based strategies (i.e., non-judgmental, present-focused awareness), which promote focused attention, have also been evaluated in SAD by Goldin and colleagues (Goldin & Gross, 2010; Goldin, Ziv, Jazaieri, & Gross, 2012; Goldin, Ziv, Jazaieri, Hahn, & Gross, 2013). In the context of a mindfulness-based stress reduction (MBSR) protocol (Kabat-Zinn & Hanh, 1990), there was enhanced activation during breath-focused attention (versus react), at post- (versus pre-) MBSR in SAD subjects in parahippocampal gyrus and regions associated with attention (inferior and superior parietal lobule, cuneus, precuneus, middle occipital gyrus) (Goldin & Gross, 2010). Subsequently, Goldin et al. showed that pre-to-post MBSR revealed *increased* activity to negative self-views (versus baseline), elicited by a self-referential encoding task (SERT) in ventromedial, ventrolateral,

dlPFC, PCC/precuneus, inferior parietal lobule, and posterior superior temporal gyrus with increases in similar regions (e.g., dorsomedial, ventrolateral, and anterior dorsolateral PFC) for positive self (versus baseline). Additionally, evidence of a relationship between increased dmPFC activity to negative self-view and decreased pre-to-post MBSR disability illustrate the effects MBSR has on higher-order functions (Goldin et al., 2012). Interestingly, when an MBSR-related strategy to "observe" (e.g., non-judgmental monitoring) versus "react" was examined, more posterior brain areas were exhibited in the context of pre-to-post MBSR change, specifically decreases in posterior superior temporal gyrus, lingual gyrus but increases in parietal attention-related regions (e.g., anterior inferior parietal lobe (IPL), posterior IPL, and superior parietal lobule), suggesting that the mindfulness strategy reduced distress to social anxiety scenarios by increasing activity in attention-related parietal cortical areas (Goldin et al., 2013).

In summary, dysfunctional frontal cortical function has been observed in SAD when attempting to apply cognitive-linguistic strategies to reduce negative reactivity. However, MBSR strategies, which engage frontal and attention functions may increase emotion regulation capacity in SAD. However, with the exception of a couple of studies (Blair et al., 2012; Klumpp et al., 2013), there has been little attempt to understand the neural substrates of non-volitional, implicit emotion (Etkin et al., 2011) regulation in SAD. Furthermore, evidence that SAD subjects exhibit amygdala and OFC reactivity during the first couple of seconds of exposure to emotionally-valenced expressions relative to controls (Sladky et al., 2012), suggests implicit regulation may be involved and thus requires further investigation.

Symptom Provocation

In an early PET study, Tillfors and colleagues found that during public versus private speaking, which represents a laboratory induction of social evaluative threat and scrutiny, there was enhanced blood flow to the amygdala and reduced flow to orbitofrontal, temporal, parietal and secondary visual and insular cortices in the social phobics compared to the comparison subjects (Tillfors et al., 2001). In line with elevated reactivity to provocation, cerebral blood flow in the ACC, caudate head, and MPFC extending into the DLPFC has been shown to correlate with high-frequency heart rate variability during public speaking in SAD (Åhs, Sollers III, Furmark, Fredrikson, & Thayer, 2009). Moreover, anticipatory anxiety to public speaking has been associated with increased rCBF to the left amygdaloid-hippocampal region, which was accompanied by enhanced cerebral blood flow in the right DLPFC, and left inferior temporal cortex (Tillfors, Furmark, Marteinsdottir, & Fredrikson, 2002), subsequently replicated by an fMRI study which also showed greater subcortical, limbic, and paralimbic activity (pons, striatum, uncus/anterior parahippocampus, insula, temporal pole), and less frontal cortical activity (dorsal ACC, MPFC, DLPFC), suggesting that in the context of anticipation-related anxiety, less frontal activity is engaged for cognitive processing in social phobics, or alternatively, less frontal engagement occurs during greater limbic reactivity (Lorberbaum et al., 2004).

Anticipatory anxiety has also been compared to "recovery" from stress. Here, SAD patients (with or without depression) relative to depressed only and healthy controls, displayed increased activity in the occipital cortex and middle temporal gyrus when asked to prepare a speech, and decreased insula and postcentral gyrus activity when informed there would be no speech; findings of enhanced activity in visual areas when anxiety was evoked followed by reduced activity was interpreted as a vigilance-avoidance pattern of response (Waugh, Hamilton, Chen, Joormann, & Gotlib, 2012).

Regarding treatment-related amygdala effects, Furmark and colleagues have shown that SSRI (citalopram) and group CBT treatment "responders" exhibit a decreased rCBF-response to public speaking in the amygdala, unlike wait-list control subjects and non-responders. Moreover, the degree of amygdala attenuation was associated with clinical improvement when these subjects were re-assessed a year later (Furmark et al., 2002). Responders also exhibited rCBF decreases in the right IFG, DLPFC, and ACC, and in a between-group comparison rCBF decreased more in responders than non-responders in the right DLPFC and ACC. In a subsequent randomized double-blind placebo-controlled study by the authors involving the NK1 antagonist GR205171 and citalopram, the authors demonstrated that symptom improvement was accompanied by reduced rCBF response to public speaking in the amygdala and nearby parahippocampal-hippocampal regions (Furmark et al., 2005). Interestingly, decreased rCBF response to public speaking in the amygdala has also been shown in placebo responders, but only in SAD patients with a particular genetic profile (i.e., homozygous for the l allele of the 5-HTTLPR and the G allele of the TPH2 G-703T polymorphism), indicating symptom improvement after eight weeks of receiving a placebo was mediated by a genetic effect on stress-induced amygdala activity (Furmark et al., 2008). This group also showed a pre-to-post reduction in basomedial/basolateral and ventrolateral amygdala rCBF in responders (regardless of treatment [SSRI or placebo] modality) compared to non-responders (Faria et al., 2012). These findings suggest that pharmacological or psychological properties (e.g., expectation of symptom reduction) modulate common brain regions associated with recovery (Faria et al., 2012).

It should be noted that not all studies of public performance have observed amygdala hyper-reactivity in SAD. Using PET, Kilts and colleagues examined rCBF during script-guided mental imagery of an anxiogenic social situation and a confrontational mental arithmetic task before and after treatment with nefazodone (Kilts et al., 2006). In SAD, subjects exhibited increased activity in the left postcentral gyrus and lenticulate, and the right inferior frontal and middle temporal gyri to the social imagery task, and activation of the MPFC, DLPFC, cerebellum, thalamus, insula, and ventral striatum to the arithmetic task. Interestingly, both tasks were associated with relative *decreases* in activity in the right amygdala and the hippocampus. The authors also observed greater activity in the precentral gyrus, insula, midbrain/hypothalamus, and middle frontal and anterior cingulate gyrus prior to treatment, and greater activity in the left

middle occipital and bilateral lingual gyri, postcentral gyrus, gyrus rectus, and hippocampus after treatment. The authors suggest that the distributed neural activity is consistent with cognitive models of SAD during these tasks, and adaptive decreases in amygdala activity in response to the provocation of social anxiety.

Based on the notion that individuals with SAD tend to focus on themselves (e.g., attend to interoceptive cues, negative thoughts (Clark & McManus, 2002; Clark & Wells, 1995)), van Ameringen et al. diverted from traditional speech paradigms and instructed participants to watch a videotape of either (1) a socially competent stranger giving a talk (baseline condition) or (2) themselves giving a talk in the presence of three confederates (exposure condition) (Van Ameringen et al., 2004). Compared to baseline, there was a significant decrease in rCBF in the right lingual gyrus and the right medial frontal gyrus during the exposure condition, which the authors suggest reflects the possibility that individuals with SAD were diverting their attention away from the anxiety-provoking stimuli (i.e., video clips of themselves giving an impromptu speech). A variation of "self-focused" versus "other-focused" related attention was conducted by Pujol et al. (2013), wherein subjects watched a videotape of themselves (as if viewed from an observer's perspective) performing a verbal task, or watched a demographically-matched unknown subject (baseline condition). While the self-recognition condition elicited activation in emotion-processing areas (e.g., amygdala, insula) in all subjects, the SAD (relative to control) group showed enhanced activity in primary visual cortex, yet reduced responses in regions involved in higher-level cognitive functions (e.g., medial frontal gyrus, anterior cingulate cortex, and dlPFC). Self-focused attention in SAD has also been associated with increased activity in primary visual cortex and cerebellum (relative to controls) as well as increased visual cortical-related connectivity to several regions (e.g., ACC, thalamus, basal ganglia, cerebellum, cuneus) (Giménez et al., 2012). Like the anticipation or act of public speaking, mere focus towards self during performance can elicit a broad alteration in the brain circuit in SAD that may serve to promote heightened awareness of fears and anxiety reactivity (Clark & Wells, 1995).

Along the lines of self-focused attention, individuals with SAD monitor their behavior and may suppress emotions in an effort to guard against potential embarrassment or rejection (Spokas, Luterek, & Heimberg, 2009). Vocal affect is useful in evaluating this type of regulation strategy as vocal expression can be intentionally altered (Cowie & Cornelius, 2003; Scherer, 1989). Accordingly, Laukka et al. (Laukka, Åhs, Furmark, & Fredrikson, 2011) examined associations between rCBF and vocally-related nervousness outside of linguistic content during a speech task in SAD. Controlling for self-reported anxiety, results included negative correlations between rCBF and vocal affect in IFG, ACC, superior frontal gyrus, precuneus, and hippocampus. Furthermore, IFG response, which negatively correlated with expressed nervousness, was functionally coupled with limbic regions (e.g., amygdala, hippocampus) and ACC.

Findings implicate IFG in the monitoring and regulation of vocal expression in SAD, potentially to avoid expressing emotion (Laukka et al., 2011). Aberrant IFG activity in SAD has also been shown during a cognitively stressful task. Specifically, in Koric et al. (Koric et al., 2012) subjects performed a demanding verbal executive task in which a number was delivered randomly, and subjects were asked to state the number out loud and then add up the last two numbers presented. Once this sum was provided by the subject, a new number was given, which needed to be added to the one heard previously. When contrasted against a less demanding task (i.e., a number delivered every three seconds), SAD subjects showed greater activity in IFG and superior frontal gyrus than controls. Together, IFG, limbic, and prefrontal disturbances in SAD may reflect efforts to modulate a prepotent response. However, due to the absence of a normal control group in certain studies, it is not clear whether the deactivation is an abnormal response specific to social anxiety psychopathology.

In summary, there is some evidence of increased limbic reactivity and reduced cortical activation in response to the anxiety-provoking stress of public speaking and/or attention directed towards self. Additionally, some evidence of reduced frontal cortical activation during such anxious events has been proposed to reflect dysregulated control of attention or impaired cognitive function while regulation of stress is needed. This pattern deactivation of cortical areas relevant to emotional appraisal and regulation could indicate possible deficits in cognitive evaluative or self-regulatory processes in SAD under social stress.

Social Interactions

Little information about the psychological processes of appraisal and interpretation of our social environment can be ascertained by examining brain response to static face photographs. The underlying cause of the exaggerated social fear response is unknown, but could partly be due to deficits in social cognition which manifest as a tendency towards inaccurate and distorted interpretations of the beliefs and intentions of others during interpersonal interactions (Hirsch & Clark, 2004). However, the use of static face stimuli in elucidating social cognitive deficits in SAD is likely to be limited, since they primarily engage *perception* of emotional signals and do not reflect real world social interactions that are inherently dynamic and interactive. To address this critical gap in knowledge, Guyer and colleagues developed an fMRI paradigm to examine fear-circuitry dysfunction in the context of anticipated social evaluation, which may result in the misperception of threat from peers to determine whether photographs of negatively evaluated smiling peers viewed during anticipated social evaluation engage the amygdala in adolescents with and without social anxiety (Guyer et al., 2008). Here, the participants classified photos of same-age peers on whether they would like, or not like, to engage in a social interaction. The authors demonstrated that socially anxious adolescents had a greater (than non-anxious controls) amygdala, ACC, and the middle frontal gyrus' response when anticipating interactions and evaluations previously classified as undesirable

to interact with. Given the nature of the paradigm, the authors were able to examine functional amygdala-frontal connectivity and observed a positive correlation between the right amygdala seed and left VLPFC while appraising low- vs high-desirability peers (observed only in patients during appraisal of low-desirability peer) and that lower self-esteem and higher anxiety severity were associated with the pattern of positive connectivity. In contrast, participants who viewed photographs of social situations (e.g., reception, restaurant) which comprised one to seven individuals or none (control condition) and were asked to imagine themselves in the situation, did not show amygdala or prefrontal disturbances even though SAD subjects rated both conditions as more anxiety-evoking than controls (Nakao et al., 2011). Rather, the SAD group exhibited less activity in the PCC, precuneus, and cerebellum than controls, interpreted as evidence that negative views of self in social contexts involve self-focused attention (Nakao et al., 2011).

Along the lines of heightened sensitivity to perceived threat and fears of social disapproval, individuals may have difficulty making accurate context-dependent assumptions about others' behaviors, as evidenced by non-imaging studies that show negative interpretive bias in SAD (Amir, Foa, & Coles, 1998; Hirsch & Clark, 2004; Stopa & Clark, 2000). With this background, Blair et al. (2010) investigated self-referential processing by asking participants to read stories about social events that result in intentional (e.g., disliking and spitting out food) or unintentional (e.g., choking and coughing up food) behaviors (e.g., transgressions), or a neutral event (e.g., swallowing food). SAD subjects rated unintentional actions as more embarrassing than controls and showed greater ventral MPFC activity, a region implicated in self-referential processing (Northoff et al., 2006) to unintentional versus intentional or neutral events; SAD (relative to controls) also exhibited greater MPFC, amygdala/parahippocampal gyrus, and insula response across transgressions. Consistent with the notion MPFC mediates inflated fears of social disapproval in SAD, Blair et al. (Blair, Geraci, Otero, et al., 2011) observed greater ventral MPFC activity in SAD subjects to second-person points of view (i.e., "You're …"), relative to first-person viewpoints (i.e., "I'm …"), whereas healthy controls exhibited the opposite pattern. Across conditions, the SAD group showed greater activity in dorsal MPFC and dorsal areas of lateral middle frontal cortex extending into MPFC. For negative (e.g., "You're ugly") and positive (e.g., "You're beautiful") versus neutral (e.g., "human") comments, the SAD group also revealed greater activity in MPFC and lateral middle frontal cortex, compared to the controls. Along with evidence of a positive relationship between the MPFC response to negative (versus neutral) statements and symptom severity, findings underscore the role the aberrant MPFC plays in self-referential disturbances (Blair, Geraci, Otero, et al., 2011).

In an effort to evaluate negative reactivity in SAD across a spectrum of social situations, Ziv et al. (2013) employed a "looming faces" task whereby "harsh" faces appear to be moving closer to the observer; a social "criticism

task" involving videotaped actors displaying criticism or praise; and a "negative belief task" consisting of social anxiety situations produced by subjects and contrasted with an experimenter-derived neutral situation. Although SAD subjects rated each task as more negative than controls, group effects emerged for frontal and temporal regions as opposed to amygdala activation, which was elicited in all tasks to a similar extent in SAD and control groups. For example, in the presence of harsh faces, SAD subjects showed increased activity (versus controls) in medial frontal and superior medial frontal gyri, middle frontal and temporal gyri, and the superior temporal gyrus. Increased middle temporal gyrus activity in SAD was also observed during "criticism" relative to controls in addition to greater activity in the lingual gyrus and parahippocampus. Yet, for the negative beliefs task, controls displayed increased activity in middle frontal and superior temporal gyri (relative to SAD) with no evidence of heightened activity in patients. Findings indicate certain neural disturbances in SAD and may depend on the context of a social-emotional event (Ziv et al., 2013).

To better understand social cognition deficiencies in SAD, other studies have employed simulated "interactive" social tasks (e.g., the trust game) in which participants engage in an economic exchange with fictitious partners who vary in the likelihood of reciprocity (e.g., sharing invested money) and probe the ability of participants to predict another player's actions-based reputation built over time ("mentalizing") (Sripada et al., 2009). Interactions with a human (versus computer) partner elicited less activity (than controls) in the MPFC, IFG, cuneus, postcentral and middle occipital gyrus, and more activity in the supplementary motor area, middle frontal gyrus, and supramarginal gyrus. These alterations in activation, particularly that in the MPFC, a region increasingly implicated by social neuroscience as part of the brain's social-cognitive network, and particularly critical to mentalizing and forming impressions about others (Frith & Frith, 2003; Gallagher & Frith, 2003; Mitchell, Banaji, & Macrae, 2005), may partly explain tendencies of patients with SAD to form distorted impressions about how others judge them and about more general social events (Stopa & Clark, 2000). The authors have also recently shown that SAD subjects engage ventral striatum, a region known for its response to rewards (see below), regardless of the reputation their partners had for reciprocity; moreover, symptom severity in SAD correlated with reduced vSTR activity to cooperative partners (Sripada, Angstadt, Liberzon, McCabe, & Phan, 2013). This pattern differs from that previously observed in healthy controls, where vSTR "reward" activation was specific to only partners who earned a reputation for reciprocity/cooperation (Phan, Sripada, Angstadt, & McCabe, 2010).

Although the studies in this section are beginning to shift fMRI paradigms towards closer approximations of "real-world" social exchanges, future studies are much needed to refine these formats to reflect the dynamic interactions between SAD patients and individuals they encounter in social settings.

Non-Social Negative and Positive Emotional Processing

A few studies have implicated limbic and paralimbic frontal dysfunction using non-face/non-social stimuli. In a novel design, Blair and colleagues exposed SAD subjects to negative (e.g., "You're ugly") comments, and showed enhanced amygdala and MPFC response in patients to such comments (but not to neutral or positive comments), particularly when those comments were referring to themselves (rather than other people) (Blair, Geraci, et al., 2008). Given that MPFC regions are involved in representations of the self (Schmitz & Johnson, 2006; Van Overwalle, 2009), it might be suggested that this enhanced response, along with amygdala activation, reflects a negative self-image particularly when faced with self-critical comments. Interestingly, examination of amygdala-frontal connectivity showed that the strength of amygdala-MPFC connectivity was significantly greater for the SAD group, relative to the HC group, to negative comments about the self but not to other comment categories.

Another important aspect of interpretation of social situations is appropriate comprehension of emotional prosody. To determine whether neural impairment underlies emotional prosody in SAD, participants performed an emotion identification task and a gender identification task during fMRI (Quadflieg, Mohr, Mentzel, Miltner, & Straube, 2008). For the former task, participants identified the emotion conveyed by the utterance and for the latter task, the gender of speaker was determined. All participants showed activation in the amygdala, insula, striatum and frontotemporal regions in response to angry, relative to neutral, prosody. However, compared to controls, SAD exhibited greater activation in the OFC across task condition, indicating altered comprehension of emotional prosody in SAD. In prior studies of healthy subjects, the OFC has been previously implicated in processing and regulating responses to angry faces and anger (Blair, Morris, Frith, Perrett, & Dolan, 1999; Coccaro, McCloskey, Fitzgerald, & Phan, 2007; Dougherty et al., 1999). Greater OFC activity, along with amygdala hyper-reactivity, has also been observed in SAD (compared to controls) to implicitly presented phobic-related words (Schmidt et. al., 2010). Though groups showed a similar brain response to explicit phobic words, insula activity positively correlated with symptom severity in SAD. Therefore, OFC, amygdala, and insula activity in SAD was modulated by the level of processing a threat signal (Schmidt, Mohr, Miltner, & Straube, 2010). In van Tol et al. (2012) encoding and recognition of emotionally-valenced words was evaluated in patients with SAD, panic disorder, generalized anxiety disorder, major depression disorder (MDD), concurrent MDD and anxiety (CDA), and healthy controls. No SAD specific results were evident. Instead, MDD and CDA groups showed increased amygdala, insula, and IFG activity to negative words, compared to anxious patients and controls. For positive words, MDD and anxious patients exhibited hypoactive hippocampal activity, relative to controls. No correlations between illness severity and activation to negative or positive

words were noted. Furthermore, recognition of positive or negative words yielded no general or anxiety-specific findings.

Two studies involve emotionally evocative, negatively valenced images that have some social content but are not exclusively "face" only photographs. In one, SAD patients showed an enhanced amygdala and insula response to non-social, negative emotional (aversive, disgust and fear-inducing) images and the extent of amygdala activation was associated with social anxiety severity (Shah, Klumpp, Angstadt, Nathan, & Phan, 2009). Amygdala hyper-reactivity in SAD (relative to controls) to negative (versus neutral) images and a relationship with symptom severity (i.e., social phobia score) was also observed by Brühl et al. (2011) suggesting a broader implication of amygdala hyper-reactivity in the pathophysiology of SAD.

Other studies have examined the neural correlates of positively-valenced stimuli. For example, adolescents who were characterized as behaviorally inhibited (a vulnerability trait for subsequent development of SAD), relative to noninhibited adolescents, showed enhanced activation in the ventral striatum when they believed their selection of an action would influence the likelihood of reward, but not when actions were predetermined to result in reward or randomly resulted in reward (Guyer et al., 2006). By extension, Guyer et al. (2012) showed increased striatal activity to monetary incentives of increasing magnitude in adolescents with social phobia, relative to generalized anxiety disorder or healthy comparison groups. In a departure from monetary-only reward paradigms, Richey et al. (2012) used an incentive delay task comprising a social award (i.e., neutral faces) as well as money and observed neural response to reward type distinguished SAD subjects from individuals with autism spectrum disorders (ASD). Namely, in anticipation of a monetary reward, SAD and healthy control subjects showed greater nucleus accumbens (NAc) activation compared to ASD subjects; yet, in anticipation of social rewards, both SAD and ASD subjects exhibited less NAc activation than controls. Interestingly, no differences appeared between groups for monetary or social reward outcomes, although within the SAD group there was less vmPFC activity to outcomes of face reward relative to monetary reward. Results indicate aberrant reward-related activity in SAD was modulated by reward type (i.e., social cues) whereas reward-related disturbances in ASD are more widespread. Striatum functional alterations such as these, including those that involve the trust game noted above (Sripada et al., 2013), should be taken in the context of a prior study that showed that SAD patients had significantly reduced neural activation related to implicit learning, compared with healthy comparison subjects in the caudate head, insula, and inferior parietal lobe during serial reaction time task (i.e., implicit learning) (Sareen et al., 2007).

Together these studies suggest that brain dysfunction outside of the typical "threat"/fear-related areas of the brain (e.g., amygdala) in SAD, which can be elicited by non-social general emotionally evocative stimuli, are both negatively and positively valenced.

Functional Brain Imaging: "Resting State" Studies

Investigation of neural processes in SAD when participants are at rest—namely, not engaged in emotion or cognitive tasks, permit the examination of potential anomalies that may be masked during activation paradigms. It has been proposed that the brain has an organized, baseline default mode of function which represents its intrinsic state (Raichle et al., 2001). This explanation arose from the consistent observation that activity decreases in functional neuroimaging data when the control state was that of passive visual fixation or with eyes closed and resting, or when the brain was actively engaged by a cognitive task (Raichle & Snyder, 2007). Areas that constitute this default mode network (MPFC, PCC, precuneus) can be modulated by different factors such as the emotional state, cognitive load of the task and psychopathology, including anxiety and, as noted above, play a pivotal role in social cognition.

In one of the first "resting state" studies, Stein and Leslie (Stein & Leslie, 1996) showed that SAD patients did not differ from controls on basal metabolic cerebral perfusion using SPECT and technetium-99m-hexamethylpropylenamineoxime (^{99m}Tc-HMPAO) (Stein & Leslie, 1996); however, it should be noted that the authors used an *a priori* region of interest (ROI) analysis based on brain regions previously observed to be abnormal in obsessive-compulsive disorders. In a subsequent SPECT resting-perfusion scan in adult SAD subjects, Warwick and colleagues (Warwick, Carey, Jordaan, Dupont, & Stein, 2008) showed increased resting perfusion in the frontal cortex and right cerebellum, and decreased perfusion in the pons, left cerebellum, and right precuneus in SAD. Moreover, social anxiety severity correlated positively with left frontal cortex resting perfusion, and negatively with right fusiform and right lingual perfusion.

In a previous (^{99m}Tc-HMPAO) SPECT study, Warwick and colleagues (Warwick et al., 2006) measured resting perfusion before and after eight weeks of treatment with either citalopram or the reversible inhibitor of monoamine oxidase (MAOI) moclobemide, and showed that SAD patients in both treatment groups had a decrease in rCBF in the insula post therapy, corresponding with symptom improvement. There was a significant relationship between the magnitude of deactivation and change in symptom severity. Additionally, subjects receiving citalopram had decreased superior cingulate rCBF after therapy, compared to those receiving moclobemide.

To examine the effects of pharmacotherapy on resting perfusion in SAD, patients with a number of anxiety disorders including SAD were SPECT scanned before and after eight weeks of pharmacotherapy with the SSRI, citalopram (Carey et al., 2004). Citalopram treatment resulted in significant deactivation in the superior and anterior cingulate, thalamus, and hippocampus. The authors observed that deactivation within the precentral, mid-frontal, inferior frontal, prefrontal and precuneus was more marked in treatment responders, however, no pattern of baseline activation distinguished responders from non-responders

to subsequent pharmacotherapy. Using a similar approach but with [^{8}F] fluorodeoxyglucose (FDG) PET, Evans examined resting state and treatment effects on regional cerebral metabolic rate of glucose uptake (rCMRglu) before and after treatment with tiagabine, a gamma-aminobutyric acid (GABA) reuptake inhibitor, in SAD patients (Evans, Simon, et al., 2008). Compared to the controls, individuals with SAD demonstrated less pretreatment rCMRglu within the ACC and ventral MPFC at baseline. Following tiagabine treatment, ventral MPFC rCMRglu increased significantly in the patient group, and treatment response was inversely correlated with pretreatment resting metabolism in this region. Using fMRI, Gentili and colleagues (Gentili et al., 2009) examined task-induced deactivations within the default network by examining "activity" in these areas during a conventional face processing task in patients with SAD. The authors report that although both groups exhibit the typical pattern of deactivation observed in MPFC, ACC and PCC, the SAD group (relative to controls) showed a lower deactivation in the precuneus and posterior cingulate regions (PCC, precuneus) during task conditions. Given the role of the PCun/PCC in self-state perception and attribution and, more generally in social cognition, the authors speculated that its impairment in SAD might be relevant in the development of worrying about other's evaluation/judgment and self-focused attention.

Subsequently, Ding et al. (2011) investigated interregional connectivity throughout the brain during resting state; areas of interest were thus parsed into medial temporal (e.g., amygdala, hippocampal), frontal (e.g., ACC, IFG), occipital (e.g., fusiform, cuneus), subcortical (e.g., thalamus, caudate), parietal-(pre)motor (e.g., posterior cingulate, inferior parietal gyrus), and temporal (e.g., insula, middle temporal gyrus) areas. Compared to controls, SAD subjects showed weaker (decreased) positive connectivity between medial prefrontal and inferior frontal cortex as well as weaker negative connectivity between medial prefrontal cortex and calcarine fissure, superior occipital cortex, and cuneus. Moreover, correlations revealed various attenuated negative connections positively related to symptom severity which predominantly involved median prefrontal cortex.

Using resting-state templates derived from previous studies (Mantini, Corbetta, Perrucci, Romani, & Del Gratta, 2009; Mantini, Perrucci, Gratta, Romani, & Corbetta, 2007), Liao et al. (Liao, Qiu, et al., 2010) evaluated functional connectivity in networks, specifically dorsal attention (DAN), central executive (CEN), default mode (DMN), core (CN), self-referential (SRN), somato-motor (SMN), visual (VN), and auditory (AN) networks and showed decreased connectivity in SAD compared to controls in SMN and VN. On the contrary, SAD subjects demonstrated increased coupling in SRN and for other networks, there was evidence of increased and decreased connectivity in DAN, CEN, DMN, and CN. Several networks were also implicated in symptom severity in that LSAS positively correlated with prefrontal regions in DAN, DMN, and CN, yet negatively correlated with the superior parietal gyrus in DAN, superior frontal gyrus in CEN, and inferior occipital gyrus in VN. Using regional homogeneity (ReHo) to examine local fluctuations in BOLD signals during rest, SAD

(relative to controls) exhibited decreased ReHo in the mPFC, dlPFC, inferior parietal gyrus, ACC, fusiform and angular gyri. Increased coherence was observed in SAD in the middle occipital gyrus and putamen. Additionally, symptom severity negatively correlated with the mPFC, dlPFC and putamen but positively with the middle occipital, cuneus, and inferior parietal gyrus (Qiu et al., 2011).

Liao et al. (Liao, Chen, et al., 2010) evaluated *effective* connectivity during rest, which captures the directionality of connectivity patterns. Using bilateral amygdala as "seed" regions, SAD subjects (relative to controls) showed increased left amygdala-related connectivity to the middle frontal cortex, temporal cortex, somato-motor and visual cortex, and cerebellum but decreased connectivity to the medial superior frontal, middle temporal, and postcentral gyri. Increased right amygdala-based connectivity in SAD (relative to controls) was evident in regions that included the mOFC, temporal, occipital, and limbic/paralimbic cortex with decreased connectivity to the superior frontal gyrus, hippocampus, and regions in the parietal lobe and cerebellum. Furthermore, symptom severity (LSAS) related to avoidance behaviors positively correlated with increased amygdala-mOFC effects and negatively to amygdala-inferior temporal gyri influences. Subsequently, Hahn et al. (2011) showed SAD (versus controls) had reduced left amygdala-related connectivity to mOFC and PCun/PCC and enhanced right-amygdala related medial occipital/angular gyrus coupling during resting state. Moreover, SAD subjects showed less mOFC-based connectivity to the ACC (relative to controls). Conversely, Pannekoek et al. (2013) did not observe group effects for PCun/PCC but did report that SAD (compared to controls) exhibited enhanced negative amygdala connectivity with the middle temporal gyrus, supramarginal gyrus and lateral occipital cortex along with evidence of increased dACC coupling with precuneus and lateral occipital cortex in SAD; no correlations were found between functional connectivity strength and anxiety severity (Pannekoek et al., 2013).

Improved technology (with greater signal-to-noise acquisition allowing for greater resolution) has permitted the interrogation of intrinsic functional connectivity with discrete subcortical regions involved in emotion processing. For example, Anteraper et al. (in press) used striatum (caudate and putamen), globus pallidus, thalamus, centromedial amygdala (which activation predicts striatal activity; Roy et al., 2009), and periaqueductal gray as seed regions and showed increased functional connectivity in SAD (relative to healthy controls) with no observations of greater connectivity in controls (versus SAD). More specifically, for the caudate seed, SAD (versus controls) revealed frontotemporal hyper-connectivity (e.g., medial frontal gyrus/superior frontal gyrus, orbital gyrus, ACC, inferior temporal gyrus) and symptom severity positively correlated with ACC linked to caudate. Regarding putamen, hyper-connectivity in SAD (versus controls) was evident for frontoparietal regions consistent with executive control and affective networks (e.g., supramarginal gyrus, rectal gyrus, pre-motor cortex, ACC). Thalamus-related findings also comprised a dysregulated frontoparietal network (e.g., hyper-connectivity in superior parietal,

anterior prefrontal regions). Centromedial amygdala-based increased connectivity included supplementary motor area, inferior temporal gyrus, secondary visual cortex, angular gyrus, and cingulate gyrus. Though findings for the periaqueductal gray seed region was limited to within the SAD group, hyper-connectivity involved parts of the default mode network (i.e., precuneus). These findings indicate that subcortical regions involved in emotion processing and "motor readiness" are functionally hyper-connected in SAD.

Together, studies have detected abnormalities in amygdala-related pathways and along diffuse large-scale networks that mediate emotion and executive functions. As noted above, amygdala connectivity to ACC has also been shown to be reduced at rest in SAD (versus controls) (Prater et al., 2013). Taken together, there are therefore inconsistencies in this literature in relation to both areas and direction of dysconnectivity. Nevertheless, the paper by Anteraper and colleagues demonstrated that hyper-connectivity occurs across a broad set of intrinsic functional connectivity networks (with a number of seeds [striatum (caudate and putamen)], globus pallidus, thalamus, periaqueductal gray, and amygdala) in SAD and suggest that this underlying neural organization, that may contribute to aberrant task-based activations observed in SAD, are implicated in emotion processing, cognitive control, visual attention, self-referential processing, and/or social cognitive functions. Further research is needed to replicate and better understand these observed patterns.

Functional Brain Imaging: Pharmacological Challenge

Selective-serotonin reuptake-inhibitors are an evidence-based treatment for SAD (Stein & Stein, 2008). However, a large proportion of patients remain symptomatic after an initial trial (Koen & Stein, 2011). Medications that more precisely target brain mechanisms that underlie SAD have the potential to expand on current treatments. For example, cannabidiol (CBD) has anxiolytic properties (Zuardi, Cosme, Graeff, & Guimarães, 1993; Zuardi, Crippa, Hallak, Moreira, & Guimarães, 2006) and has been shown to reduce self-reported anxiety in SAD subjects (relative to placebo), without feelings of sedation, when confronted with the challenge of a SPECT procedure (Crippa et al., 2011). CBD-related changes (versus placebo) at rest revealed decreased activity in an area comprising parahippocampal gyrus and hippocampus, yet increased activity in posterior cingulate gyrus, which together suggests that CBD reduced anxiety in SAD by modulating limbic, paralimbic, and sensory cortical activity (Crippa et al., 2011). Oxytocin (OXY), a neuropeptide that increases trust and willingness to take on social risks (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), is another potential therapeutic agent, given the evidence that it normalizes aberrant activity to negative faces in SAD. Specifically, Labuschagne et al. (2010) showed exaggerated amygdala activity to fearful faces in SAD subjects (relative to controls) decreased after OXY treatment (compared to placebo) with no evidence of drug-related effects on mood. Subsequently,

Labuschagne et al. (2011) observed that heightened reactivity to sad faces in SAD subjects (compared to controls) in mPFC, extending to ACC, also decreased after OXY treatment, such that activation was similar to that of controls; again, no drug-related impact on mood emerged. Consequently, these discoveries suggest CBD and OXY may have clinical utility. Emerging studies testing other compounds and their effects on brain (dys)function in SAD are underway.

Neurochemical and Neuroreceptor Brain Imaging

Dopamine System

Striatal and basal ganglia (caudate and putamen) regions are rich in dopamine receptors, and the dopamine (DA) system has been hypothesized to be abnormal in SAD (Stein, Westenberg, & Liebowitz, 2002). Given that dopamine levels are reduced in timid mice, striatal DA receptor binding is reduced in subordinate monkeys, social phobia is associated with Parkinson's disease, and that dopaminergic agents are particularly efficacious in SAD (reviewed in Stein et al., 2002). It has been shown more recently that exogenous dopamine receptor modulation (by pramipexole and sulpiride) can induce increased anxiety during anxiogenic challenges (verbal tasks and autobiographical scripts) in untreated individuals with SAD; effects were partially maintained even in remission after SSRI treatment (Hood et al., 2010). Thus, there is reason to suspect that SAD patients would exhibit a deficient and/or altered dopamine system. In support of this hypothesis, a SPECT study using [^{123}I]β-CIT, a specific ligand for the dopamine transporter, found a decrease in striatal dopamine reuptake sites among individuals with SAD compared to healthy volunteers (Tiihonen et al., 1997). However, another [^{123}I]β-CIT SPECT study showed that SAD patients exhibited higher (compared to controls) striatal ^{123}I-b-CIT binding ratios, suggesting an *increased* number of dopamine reuptake sites. In a different study, Schneier reported that reduced D_2 receptor binding in the striatum was found in individuals with SAD (compared to controls) (Schneier, 2000), suggesting dopaminergic hypofunction in the striatum. In addition, the level of social anxiety in the SAD group was negatively correlated, although non-significantly, with D_2-binding potential. In support, a subsequent study showed that striatal post-synaptic D_2 receptor binding has been associated with severity of SAD (unpublished data; see review [Li, Chokka, & Tibbo, 2001]).

A couple of studies have evaluated dopaminergic effects in SAD before and after treatment. In a PET study that comprised cognitive behavioral therapy (Cervenka et al., 2012), SAD patients exhibited negative correlations between change in anxiety severity (LSAS fear subscale) and change in D_2 receptor binding potential in medial prefrontal cortex and hippocampus, although no relationships were noted for behavioral avoidance (LSAS avoidance subscale). Furthermore, treatment responders demonstrated an increase in binding potential in mPFC while non-responders showed a decrease. A similar pattern was observed in the hippocampus, though at a trend level (Cervenka et al., 2012).

Using SPECT, Warwick et al. (Warwick et al., 2012) found increased dopamine transporter binding after escitalopram in caudate and putamen; however, no correlations were found between the change in symptom severity (LSAS) and the change in binding for striatum. Nevertheless, within the group, findings indicate the SSRI exerted its therapeutic effects in SAD by increasing striatal dopaminergic activity.

Collectively, these findings are supported by complementary studies that show that D_2 receptor density is positively correlated with the detachment scale of the Karolinska Scales of Personality (KSP), which taps into social avoidance (Farde, Gustavsson, & Jönsson, 1997). Similarly, dopamine transporter binding in the putamen correlated negatively with detachment scores on the KSP in a different PET study (Laakso, 2000). As noted above, an MRI study measuring brain volumes found greater age-related reductions in putamen volumes in individuals with SAD (compared with controls), though there were no significant differences between the two groups in total cerebral, caudate, putamen and thalamic volumes (Potts et al., 1994).

However, it should be noted that despite demonstrations of abnormal D_2 receptor binding and evidence of normalization after treatment, some studies have not observed dopaminergic abnormalities in SAD (Bell et al., 2013; Schneier, Abi-Dargham, et al., 2009; Tancer et al., 1994).

In summary, these studies suggest equivocal evidence of dopaminergic dysfunction in SAD. It has been proposed that SAD is associated with reduced extracellular dopamine, increased density of the dopamine transporter, or a combination of both mechanisms (van der Wee et al., 2008). Furthermore, Bell et al. suggest that decreased binding potentials reflect *increased* levels of free dopamine in the vicinity of D_2 receptors, altered affinity of D_2 receptors for dopamine, or some combination of these factors (Bell, Malizia, & Nutt, 1999). Lastly, differences in imaging methods or characteristics of samples or sample size may contribute to the lack of replication across studies (Schneier, Abi-Dargham, et al., 2009). Further studies are needed to clarify the role of the dopamine system.

Serotonin System

Besides dopamine, serotonin (5-HT) is also implicated in SAD (see review by Stein et al., 2002), particularly because SSRI treatments are efficacious for SAD (Schneier, 2006; Stein & Stein, 2008), and because of the role of serotonin in social dominance and affiliation (Knutson et al., 1998). Moreover, SSRIs have been shown to attenuate amygdala reactivity to fearful and other negative faces (Arce, Simmons, Lovero, Stein, & Paulus, 2008; Harmer, Mackay, Reid, Cowen, & Goodwin, 2006). In support, SSRIs have also been shown to attenuate amygdala hyper-reactivity in SAD in the context of a public speaking task (Furmark et al., 2002) and in response to fearful faces (Phan et al., 2013), which expand on an early study (Miner et al., 1995) wherein brain concentrations of fluoxetine, using fluorine ^{19}F-MRS, were measured following an open trial

of the SSRI fluoxetine, and showed treatment responders had higher, albeit non-significant, fluoxetine/norfluoxetine concentrations than non-responders.

Interestingly, allelic variation in a gene that codes the 5-HT transporter (SERT) functionality influenced the extent of amygdala reactivity during a public speaking task in SAD individuals (Furmark et al., 2004). Further supporting the role serotonin played in SAD during stress, it has been observed that SSRI-remitted, SAD patients reported increased anxiety during a behavioral challenge (e.g., fearful autobiographic script) after tryptophan depletion (TD) relative to a control, non-TD day (Argyropoulos et al., 2004), suggesting that tryptophan depletion reverses the therapeutic effect of SSRIs in SAD. There is therefore reason to expect serotonin abnormalities in SAD.

To investigate the effects of the SSRI paroxetine on the occupancy of the serotonin reuptake transporter, Kent et al. studied patients with SAD with [^{11}C] (+)-McN 5652 PET after three to six months of treatment (Kent et al., 2002). All five patients were considered to have significantly improved, and occupancy of the serotonin reuptake transporter was high and in the regions of the highest known serotonin transporter density (i.e., midbrain, thalamus, striatum, hippocampus, amygdala, and cingulate), suggesting that paroxetine at therapeutic doses achieves very high occupancy levels of the SERT.

In a study of the serotonin receptor system, Lanzenberger et al. evaluated 5-HT$_{1A}$ binding potential in the ACC, OFC, insula, amygdala, and hippocampus. Results showed that the greatest decrease in 5-HT$_{1A}$ binding in SAD (compared to controls) was in the amygdala, though significantly lower 5-HT$_{1A}$ binding potential was also evident in the ACC, insula, and dorsal raphe nuclei (Lanzenberger et al., 2007). By extension, reduced cortisol plasma levels in SAD (relative to controls) has been shown to negatively correlate with 5-HT$_{1A}$ binding potential in SAD in the amygdala, hippocampus, and retrosplenial cortex suggesting abnormal 5-HT$_{1A}$ binding is subserved by dysregulated HPA axis (Lanzenberger et al., 2010).

On the other hand, a SPECT study by van der Wee et al. demonstrated SAD patients (relative to controls) had significantly higher [^{123}I]β-CIT binding ratios, specific for the 5-HT transporter (5-HTT) in the thalamus without correlation to severity of SAD symptoms (van der Wee et al., 2008). Further serotonergic findings include a PET study using the [^{11}C]-5-hydroxy-L-tryptophan tracer, which showed a lower uptake of the tracer, mainly in the temporal lobe in SAD patients (compared to controls) (Marteinsdottir et al., 2001).

In conclusion, there is support for attenuated serotonin neurotransmission in cortical and subcortical regions in SAD, though results have been inconsistent. Van der Wee et al. (2008) hypothesized that their finding of higher 5-HTT binding potential is the result of increased densities of 5-HTT in SAD patients due to a "higher homeostatic tone of the serotonergic system (with concomitant lower densities of 5-HT receptors)" (van der Wee et al., 2008). Additionally, the attenuated accumulation of the immediate precursor of serotonin (i.e., 5-HTP) in the temporal lobe might indicate regionally specific serotonin synthesis

suppressions in SAD (Marteinsdottir et al., 2001). However, other studies are needed to further delineate 5-HT receptor subtypes involved in SAD and to elucidate neurotransmission mechanisms.

Other neurotransmitter – neurochemical systems

In addition to possible differences in dopaminergic and serotonergic functions, differences in levels of other neuroactive metabolites have been found in patients with SAD. In an early ^{1}H-MRS study (Davidson et al., 1993), Davidson et al. reported that SAD patients (versus controls) had a decrease in choline and creatine signal-to-noise ratios in the subcortical, thalamic and caudate areas. An ^{1}H-MRS study at high-field (4 Tesla) similarly showed that subjects with SAD had a significantly decreased choline/creatine ratio in the ACC (Phan et al., 2005). However, Tupler had previously observed that patients with SAD had higher choline/creatine levels in cortical gray matter (Tupler et al., 1997). Of particular note, in that study the severity of social anxiety symptoms were correlated with decreased choline/creatine ratios in subcortical gray matter.

The results are somewhat inconsistent regarding N-acetylaspartate (NAA), a putative marker of neuronal viability/density. Some spectroscopic studies have reported increased absolute NAA and/or NAA/creatine concentrations in the frontal cortex of anxious subjects without psychopathology (Grachev & Apkarian, 2000a, 2000b), and in the ACC of subjects with SAD (Phan et al., 2005). Consistently there was a significant positive correlation between severity of social anxiety symptoms and NAA/creatine ratios in cortical gray matter (Tupler et al., 1997). Another study using a similar approach, however, found lowered NAA signal-to-noise ratios in cortical and subcortical regions among individuals with SAD (Davidson et al., 1993). In addition, *myo*-inositol/creatine ratios have been found to be significantly increased in subcortical gray matter and in white matter in the SAD group (Tupler et al., 1997).

Using high-field ^{1}H-MRS, Phan and colleagues reported that subjects with SAD had a significantly higher glutamate/creatine ratio in the perigenual ACC than the normal controls, but no differences were found in glutamate/creatine ratio in the occipital cortex, a control region (Phan et al., 2005). Furthermore, the authors observed that SAD symptom severity was positively correlated with glutamate/creatine ratio in the anterior cingulate cortex, but not in the occipital cortex. In support, increased glutamatergic transmission and/or excessive glutamate release within the limbic system might be involved in anxiety (Cortese & Phan, 2005; Walker & Davis, 2002). Sustained levels of anxiety might increase excitatory neurotransmitter release (localized to limbic/paralimbic regions) and lead to a subsequent neuronal reorganization and an increase in the number of axons and synaptic connections, reflected by increased levels of NAA (Grachev & Apkarian, 2000a, 2000b). Studies thus far indicate that metabolite differences in SAD, if any, concentrate more in gray matter than in white matter. Even with some inconsistencies, it is difficult to derive definitive conclusions from the existing MRS studies because most results are based on the patterns

of ratios rather than from absolute values. It is thus, for example, difficult to conclude that SAD is associated with increased glutamate levels per se, because lower levels of creatine in SAD subjects could lead to similar findings. Given the inconsistent results, however, more studies are needed to confirm a putative link between NAA, glutamate and pathological anxiety, including SAD. More studies and advances in MRS methodology are therefore needed, not only to resolve inconsistencies between previous findings, but also to obtain absolute quantification of these relevant metabolites.

INTEGRATING NEUROENDOCRINE AND NEUROANATOMICAL STUDIES

In this chapter, we reviewed the neuroendocrinology and neuroanatomy of SAD in separate sections. However, systematic integration of findings and approaches across these two lines of biological inquiry is critical to a comprehensive understanding of the neurobiology of SAD. Evidence of neuroendocrine dysregulation in SAD, particularly in response to stress, indicate potential neural abnormality in regions associated with the HPA axis. However, few studies have attempted to link HPA axis measures of stress responsivity and brain "activation" measures related to stress (fear perception, symptom provocation, etc.). In one such study, Åhs and colleagues investigated the association between regional cerebral blood flow (rCBF) and cortisol reactivity during a speech task in SAD (Åhs et al., 2006) and reported no evidence of an increase in cortisol level from baseline to speech despite an increase in subjective anxiety. Nevertheless, a positive covariation between rCBF in the hypothalamus and salivary cortisol was found during the stress task. In addition, cortisol and rCBF was shown to covary negatively in an area encompassing the MPFC and premotor/motor cortices.

These studies suggest the potential utility in combining methodological approaches and integrating neuroendocrine stress systems and neural circuits that mediate stress response and social threat. Interestingly, there is emerging evidence that HPA axis reactivity may be related to the limbic-paralimbic response to emotional and stress-related processing (King & Liberzon, 2009; King et al., 2009; Liberzon et al., 2007).

GENERAL CONCLUSIONS

Neurobiological investigations of SAD, a disorder of abnormal fear and avoidance of social and performance situations, show evidence of neuroendocrine dysregulation in response to stress; however, the pattern of cortisol reactivity has been inconsistent. Moreover, anomalous reactivity may be limited to a subset of individuals with SAD and may reflect individual variability in the stress response. The finding that early aversive experiences (e.g., childhood abuse) contribute to cortisol reactivity in SAD and the possibility that individual

differences in coping style (e.g., repressors) may affect cortisol levels suggest more study in the area of individual differences in HPA axis reactivity and their relation to social anxiety is warranted.

Although gross structural deficits are not evident in SAD, a growing number of functional neuroimaging (PET, fMRI) show abnormalities in discrete brain regions involved in affective, cognitive and social functioning. Most consistent is hyperactive amygdala reactivity to signals of social threat and during the anticipation and act of public speaking. There is also evidence of enhanced insula and ACC activation to social threat and symptom provocation studies in SAD though few studies have focused on these areas. Taken together, hyperactivation in "bottom-up" limbic/paralimbic regions (involved in threat perception, fear responding, anxious states, etc.) and hypo-reactivity of top down frontal cortical regions involved in explicit (cognitive reappraisal) and implicit (attentional control) emotion regulation may contribute to excessive fear and avoidance behaviors in SAD and manifest in information-processing biases and misinterpretation of social information. Frontal function requires further clarification in future studies, as current methodological differences across tasks/paradigms may contribute to the disparity in observations. Most relevant appears to be the relationship of cortical and subcortical regions as pertaining to post-event processing, emotion regulation and "real-life" social interactions. Although there is a suggestion that structural connectivity between amygdala and frontal cortex is altered in SAD, little is known about the *effective* connectivity (the direct and dynamic influence of one region over another) which can provide causal inferences in interpreting the brain function data in the context of social phobic cognitions and behaviors.

FUTURE DIRECTIONS

Given the rapid emergence of novel techniques and discoveries from basic animal and human neuroscience, our field is posed to study domains previously unexplored. Although some evidence exists for the amelioration of neuroendocrine, neuroanatomic and neurochemical abnormalities, the majority of studies have focused on pharmacotherapy. Given that cognitive therapy has been shown to reduce cortisol levels in generally anxious patients (Tafet, Feder, Abulafia, & Roffman, 2005), and that cognitive strategies can reduce both cortisol and ACTH responses to anxiogenic pharmacological challenges (Abelson, Khan, Liberzon, Erickson, & Young, 2008; Abelson, Liberzon, Young, & Khan, 2005), more studies coupling cognitive therapy and/or attentional training with neuroendocrine and neuroimaging studies would facilitate a biological mechanism to explain the symptoms and behavior of SAD patients.

The emerging field of functional genomics, together with neuroimaging (Hariri et al., 2006; Hariri, 2009) ("imaging genetics"), avails the opportunity to explore the relationships between genes, brain, and behavior and is important to discover molecular underpinnings of vulnerability to disease—see

Chapters 13–14. For example, we know that behavioral inhibition observed at infancy is a risk factor for the development of social phobia later in life and is associated with amygdala hyper-reactivity to social cues (Schwartz, Wright, Shin, Kagan, & Rauch, 2003), longitudinal neuroimaging designs coupled with genetic analyses could elucidate predictive biological markers to identify those at high risk to develop SAD for early, preventive interventions.

As we refine our brain models of SAD, it is critical to exploit these mechanisms to improve our understanding of how treatment works, and for whom they work, and when (e.g., sequencing treatments). As such, coupling clinical trials (from treatment development to efficacy studies) will allow us to identify brain markers that predict therapeutic success and failures. Firstly, this may avail the development of new treatments aimed at neuromodulation of discrete brain areas or circuits. Secondly, valid and reliable brain markers can guide patients towards the most optimal treatment strategies on a personalized basis.

Much more progress is urgently needed in integrating across imaging modalities, so that we can link functional neuroanatomical findings with underlying neurochemical (and molecular) mechanisms. Moreover, there is increasing awareness for the importance of interactions among brain regions (as circuits and networks); advances in signal processing and improvements in temporal and spatial resolution will also expedite a more complete understanding of normal brain function. The PET and fMRI approach to study brain function have limited temporal resolution and capacity to reflect actual neuronal events. However, measures with improved temporal resolution of cortical brain activity (which can be localized to more subcortical structures) such as those obtained from electroencephalography (EEG) and similar techniques that measure event-related potentials (ERP) (Kanai, Nittono, Kubo, Sasaki-Aoki, & Iwanaga, 2012; McTeague, Shumen, Wieser, Lang, & Keil, 2011; Moser, Hajcak, Huppert, Foa, & Simons, 2008; Mueller et al., 2009; Rossignol et al., 2012; Schmitz, Scheel, Rigon, Gross, & Blechert, 2012) can complement and be conducted simultaneously with fMRI. More sophisticated integration is needed to fully take advantage of the information derived from multi-modal measures.

Lastly, social anxiety disorder can be conceptualized using unitary constructs such as "social fear"—that may encompass shyness, introversion, behavioral inhibition, avoidant personality, social phobia/social anxiety disorder—but is distinct from other anxiety disorders with its unique theme of concern. However, processes and related neuroanatomical and neurochemical bases (e.g., threat perception and amygdala and serotonin/cortisol; emotion regulation and prefrontal cortex and dopamine) can be considered as dimensional constructs that are likely shared across anxiety disorders. Future work using state-of-the-science neuroscience methods is needed to ascertain the developmental course of social phobia, including longitudinal studies of children and adults and examination of genetic variation and phenotypic variation in the development and

maintenance of the disorder. From there, we will be able to have a comprehensive and precise brain model about the endocrinologic and anatomical bases of social anxiety disorder.

REFERENCES

Abelson, J. L., Khan, S., Liberzon, I., Erickson, T. M., & Young, E. A. (2008). Effects of perceived control and cognitive coping on endocrine stress responses to pharmacological activation. *Biological Psychiatry*, *64*(8), 701–707.

Abelson, J. L., Liberzon, I., Young, E. A., & Khan, S. (2005). Cognitive modulation of the endocrine stress response to a pharmacological challenge in normal and panic disorder subjects. *Archives of General Psychiatry*, *62*(6), 668–675.

Adolphs, R. (1999). Social cognition and the human brain. *Trends in Cognitive Sciences*, *3*(12), 469–479.

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology*, *12*(2), 169–177.

Åhs, F., Furmark, T., Michelgård, Å., Långström, B., Appel, L., Wolf, O. T., et al. (2006). Hypothalamic blood flow correlates positively with stress-induced cortisol levels in subjects with social anxiety disorder. *Psychosomatic Medicine*, *68*(6), 859–862.

Åhs, F., Sollers, J. J., III, Furmark, T., Fredrikson, M., & Thayer, J. F. (2009). High-frequency heart rate variability and cortico-striatal activity in men and women with social phobia. *NeuroImage*, *47*(3), 815–820.

Alden, L. E., & Taylor, C. T. (2004). Interpersonal processes in social phobia. *Clinical Psychology Review*, *24*(7), 857–882.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, fifth edition: DSM-V*. Washington, D.C: American Psychiatric Association.

Amir, N., Beard, C., & Przeworski, A. (2005). Resolving ambiguity: The effect of experience on interpretation of ambiguous events in generalized social phobia. *Journal of Abnormal Psychology*, *114*(3), 402–408.

Amir, N., Foa, E. B., & Coles, M. E. (1998). Automatic activation and strategic avoidance of threat-relevant information in social phobia. *Journal of Abnormal Psychology*, *107*(2), 285–290.

Amir, N., Klumpp, H., Elias, J., Bedwell, J. S., Yanasak, N., & Miller, L. S. (2005). Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. *Biological Psychiatry*, *57*(9), 975–981.

Anteraper, S.A., Triantafyllou, C., Sawyer, A.T., Hofmann, S.G., Gabrieli, J.D., & Whitfield-Gabrieli, S. (in press). Hyper-connectivity of subcortical resting state networks in social anxiety disorder. *Brain Connectivity.*

Arce, E., Simmons, A. N., Lovero, K. L., Stein, M. B., & Paulus, M. P. (2008). Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology*, *196*(4), 661–672.

Argyropoulos, S. V., Hood, S. D., Adrover, M., Bell, C. J., Rich, A. S., Nash, J. R., et al. (2004). Tryptophan depletion reverses the therapeutic effect of selective serotonin reuptake inhibitors in social anxiety disorder. *Biological Psychiatry*, *56*(7), 503–509.

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala–frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*(4), 303–312.

Barrett, L. F., Mesquita, B., Ochsner, K. N., & Gross, J. J. (2007). The experience of emotion. *Annual Review of Psychology*, *58*, 373–403.

Bauman, M. D., & Amaral, D. G. (2005). The distribution of serotonergic fibers in the macaque monkey amygdala: An immunohistochemical study using antisera to 5-hydroxytryptamine. *Neuroscience*, *136*(1), 193–203.

Baur, V., Brühl, A. B., Herwig, U., Eberle, T., Rufer, M., Delsignore, A., et al. (2013). Evidence of frontotemporal structural hypoconnectivity in social anxiety disorder: A quantitative fiber tractography study. *Human Brain Mapping*, *34*, 437–446.

Baur, V., Hänggi, J., Rufer, M., Delsignore, A., Jäncke, L., Herwig, U., & Brühl, A. B. (2011). White matter alterations in social anxiety disorder. *Journal of Psychiatric Research*, *45*, 1366–1372.

Beesdo, K., Lau, J. Y. F., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., et al. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry*, *66*(3), 275–285.

Bell, C., Bhikha, S., Colhoun, H., Carter, F., Frampton, C., & Porter, R. (2013). The response to sulpiride in social anxiety disorder: D2 receptor function. *Journal of Psychopharmacology*, *27*, 146–151.

Bell, C. J., Malizia, A. L., & Nutt, D. J. (1999). The neurobiology of social phobia. *European Archives of Psychiatry and Clinical Neuroscience*, *249*(1), S11–S18.

Birbaumer, N., Grodd, W., Diedrich, O., Klose, U., Erb, M., Lotze, M., et al. (1998). fMRI reveals amygdala activation to human faces in social phobics. *Neuroreport*, *9*(6), 1223–1226.

Blair, K. S., Geraci, M., Devido, J., McCaffrey, D., Chen, G., Vythilingam, M., et al. (2008a). Neural response to self- and other referential praise and criticism in generalized social phobia. *Archives of General Psychiatry*, *65*(10), 1176–1184.

Blair, K. S., Geraci, M., Hollon, N., Otero, M., Devido, J., Majestic, C., et al. (2010). Social norm processing in adult social phobia: Atypically increased ventromedial frontal cortex responsiveness to unintentional (embarrassing) transgressions. *The American Journal of Psychiatry*, *167*(12), 1526–1532.

Blair, K. S., Geraci, M., Korelitz, K., Otero, M., Towbin, K., Ernst, M., et al. (2011a). The pathology of social phobia is independent of developmental changes in face processing. *The American Journal of Psychiatry*, *168*(11), 1202–1209.

Blair, K. S., Geraci, M., Otero, M., Majestic, C., Odenheimer, S., Jacobs, M., et al. (2011b). Atypical modulation of medial prefrontal cortex to self-referential comments in generalized social phobia. *Psychiatry Research*, *193*(1), 38–45.

Blair, K. S., Geraci, M., Smith, B. W., Hollon, N., Devido, J., Otero, M., et al. (2012). Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. *Biological Psychiatry*, *72*, 476–482.

Blair, K. S., Shaywitz, J., Smith, B. W., Rhodes, R., Geraci, M., Jones, M., et al. (2008b). Response to emotional expressions in generalized social phobia and generalized anxiety disorder: Evidence for separate disorders. *The American Journal of Psychiatry*, *165*(9), 1193–1202.

Blair, R. J. R., Morris, J. S., Frith, C. D., Perrett, D. I., & Dolan, R. J. (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain*, *122*(5), 883–893.

Bögels, S. M., & Mansell, W. (2004). Attention processes in the maintenance and treatment of social phobia: Hypervigilance, avoidance and self-focused attention. *Clinical Psychology Review*, *24*(7), 827–856.

Brown, M. R., Koob, G. F., & Rivier, C. (1991). *Stress: Neurobiology and neuroendocrinology*. New York: Dekker.

Brühl, A. B., Rufer, M., Delsignore, A., Kaffenberger, T., Jäncke, L., & Herwig, U. (2011). Neural correlates of altered general emotion processing in social anxiety disorder. *Brain Research*, *1378*, 72–83.

Brühl, Herwig, Delsignore, Jancke, Rufer (2013). General emotion processing in social anxiety disorder: neural issues of cognitive control. *Psychiatry Research: Neuroimaging*, 108–115.

Campbell, D. W., Sareen, J., Stein, M. B., Kravetsky, L. B., Paulus, M. P., Hassard, S. T., & Reiss, J. P. (2009). Happy but not so approachable: The social judgments of individuals with generalized social phobia. *Depression and Anxiety*, *26*(5), 419–424.

Carey, P. D., Warwick, J., Niehaus, D. J. H., van der Linden, G., van Heerden, B. B., Harvey, B. H., et al. (2004). Single photon emission computed tomography (SPECT) of anxiety disorders before and after treatment with citalopram. *BMC Psychiatry*, *4*, 30.

Carré, A., Gierski, F., Lemogne, C., Tran, E., Raucher-Chéné, D., Béra-Potelle, C., et al. (2013). Linear association between social anxiety symptoms and neural activations to angry faces: From subclinical to clinical levels. *Social Cognitive and Affective Neuroscience*.

Cassimjee, N., Fouche, J. -P., Burnett, M., Lochner, C., Warwick, J., Dupont, P., et al. (2010). Changes in regional brain volumes in social anxiety disorder following 12 weeks of treatment with escitalopram. *Metabolic Brain Disease*, *25*(4), 369–374.

Cervenka, S., Hedman, E., Ikoma, Y., Djurfeldt, D. R., Rück, C., Halldin, C., & Lindefors, N. (2012). Changes in dopamine D2-receptor binding are associated to symptom reduction after psychotherapy in social anxiety disorder. *Translational Psychiatry*, *2*, e120.

Clark, D. M., & McManus, F. (2002). Information processing in social phobia. *Biological Psychiatry*, *51*(1), 92–100.

Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. In R. G. Heimberg, M. R. Liebowitz, D. A. Hope, & F. R. Schneier (Eds.), *Social phobia: Diagnosis, assessment, and treatment* (pp. 69–93). New York: Guilford Press.

Coccaro, E. F., McCloskey, M. S., Fitzgerald, D. A., & Phan, K. L. (2007). Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biological Psychiatry*, *62*(2), 168–178.

Coles, M. E., & Heimberg, R. G. (2005). Recognition bias for critical faces in social phobia: a replication and extension. *Behaviour Research and Therapy*, *43*(1), 109–120.

Condren, R. M., O'Neill, A., Ryan, M. C. M., Barrett, P., & Thakore, J. H. (2002). HPA axis response to a psychological stressor in generalised social phobia. *Psychoneuroendocrinology*, *27*(6), 693–703.

Cooney, R. E., Atlas, L. Y., Joormann, J., Eugène, F., & Gotlib, I. H. (2006). Amygdala activation in the processing of neutral faces in social anxiety disorder: Is neutral really neutral? *Psychiatry Research: Neuroimaging*, *148*(1), 55–59.

Cortese, B. M., & Phan, K. L. (2005). The role of glutamate in anxiety and related disorders. *CNS Spectrums*, *10*(10), 820–830.

Cowie, R., & Cornelius, R. R. (2003). Describing the emotional states that are expressed in speech. *Speech Communication*, *40*(1–2), 5–32.

Crippa, J. A. S., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L., Martin-Santos, R., et al. (2011). Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *Journal of Psychopharmacology*, *25*(1), 121–130.

Danti, S., Ricciardi, E., Gentili, C., Gobbini, M. I., Pietrini, P., & Guazzelli, M. (2010). Is social phobia a "mis-communication" disorder? Brain functional connectivity during face perception differs between patients with social phobia and healthy control subjects. *Frontiers in Systems Neuroscience*, *4*, 1–11.

Davidson, J. R., Krishnan, K. R., Charles, H. C., Boyko, O., Potts, N. L., Ford, S. M., & Patterson, L. (1993). Magnetic resonance spectroscopy in social phobia: Preliminary findings. *The Journal of Clinical Psychiatry*, *54*(Suppl), 19–25.

Davidson, R. J. (2002). Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biological Psychiatry*, *51*(1), 68–80.

Demenescu, L. R., Kortekaas, R., Cremers, H. R., Renken, R. J., van Tol, M. J., van der Wee, N. J. A., et al. (2013). Amygdala activation and its functional connectivity during perception of emotional faces in social phobia and panic disorder. *Journal of Psychiatric Research*, *47*(8), 1024–1031.

Demenescu, L. R., Renken, R., Kortekaas, R., van Tol, M. -J., Marsman, J. B. C., van Buchem, M. A., et al. (2011). Neural correlates of perception of emotional facial expressions in out-patients with mild-to-moderate depression and anxiety: A multicenter fMRI study. *Psychological Medicine*, *41*(11), 2253–2264.

Ding, J., Chen, H., Qiu, C., Liao, W., Warwick, J. M., Duan, X., et al. (2011). Disrupted functional connectivity in social anxiety disorder: A resting-state fMRI study. *Magnetic Resonance Imaging*, *29*(5), 701–711.

Doehrmann, O., Ghosh, S. S., Polli, F. E., Reynolds, G. O., Horn, F., Keshavan, A., et al. (2012). Predicting treatment response in social anxiety disorder from functional magnetic resonance imaging. *Archives of General Psychiatry*, 1–11.

Dougherty, D. D., Shin, L. M., Alpert, N. M., Pitman, R. K., Orr, S. P., Lasko, M., et al. (1999). Anger in healthy men: A PET study using script-driven imagery. *Biological Psychiatry*, *46*(4), 466–472.

Ekman, P. (2003). *Emotions revealed: Recognizing faces and feelings to improve communication and emotional life*. New York: Times Books/Henry Holt and Co.

Elzinga, B. M., Spinhoven, P., Berretty, E. D., de Jong, P., & Roelofs, K. (2010). The role of childhood abuse in HPA-axis reactivity in social anxiety disorder: A pilot study. *Biological Psychology*, *83*(1), 1–6.

Erickson, K., Drevets, W., & Schulkin, J. (2003). Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neuroscience & Biobehavioral Reviews*, *27*(3), 233–246.

Essex, M. J., Klein, M. H., Slattery, M. J., Goldsmith, H. H., & Kalin, N. H. (2010). Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. *The American Journal of Psychiatry*, *167*(1), 40–46.

Etkin, E., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93.

Evans, K. C., Simon, N. M., Dougherty, D. D., Hoge, E. A., Worthington, J. J., Chow, C., et al. (2008a). A PET Study of tiagabine treatment implicates ventral medial prefrontal cortex in generalized social anxiety disorder. *Neuropsychopharmacology*, *34*(2), 390–398.

Evans, K. C., Wright, C. I., Wedig, M. M., Gold, A. L., Pollack, M. H., & Rauch, S. L. (2008b). A functional MRI study of amygdala responses to angry schematic faces in social anxiety disorder. *Depression and Anxiety*, *25*(6), 496–505.

Farde, L., Gustavsson, J. P., & Jönsson, E. (1997). D2 dopamine receptors and personality traits. *Nature*, *385*(6617), 590.

Faria, V., Appel, L., Åhs, F., Linnman, C., Pissiota, A., Frans, Ö., et al. (2012). Amygdala subregions tied to SSRI and placebo response in patients with social anxiety disorder. *Neuropsychopharmacology*, *37*(10), 2222–2232.

Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., Nathan, P. J., & Phan, K. L. (2006). Beyond threat: Amygdala reactivity across multiple expressions of facial affect. *NeuroImage*, *30*(4), 1441–1448.

Frick, A., Howner, K., Fischer, H., Eskildsen, S. F., Kristiansson, M., & Furmark, T. (2013). Cortical thickness alterations in social anxiety disorder. *Neuroscience Letters*, *536*, 52–55.

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *358*(1431), 459–473.

Furlan, P. M., DeMartinis, N., Schweizer, E., Rickels, K., & Lucki, I. (2001). Abnormal salivary cortisol levels in social phobic patients in response to acute psychological but not physical stress. *Biological Psychiatry*, *50*(4), 254–259.

Furmark, T., Appel, L., Henningsson, S., Åhs, F., Faria, V., Linnman, C., et al. (2008). A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety. *The Journal of Neuroscience*, *28*(49), 13066–13074.

Furmark, T., Appel, L., Michelgård, Å., Wahlstedt, K., Åhs, F., Zancan, S., et al. (2005). Cerebral blood flow changes after treatment of social phobia with the neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biological Psychiatry*, *58*(2), 132–142.

Furmark, T., Henningsson, S., Appel, L., Åhs, F., Linnman, C., Pissiota, A., et al. (2009). Genotype over-diagnosis in amygdala responsiveness: affective processing in social anxiety disorder. *Journal of Psychiatry & Neuroscience: JPN*, *34*(1), 30–40.

Furmark, T., Tillfors, M., Garpenstrand, H., Marteinsdottir, I., Långström, B., Oreland, L., & Fredrikson, M. (2004). Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. *Neuroscience Letters*, *362*(3), 189–192.

Furmark, T., Tillfors, M., Marteinsdottir, I., Fischer, H., Pissiota, A., Långström, B., & Fredrikson, M. (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Archives of General Psychiatry*, *59*(5), 425–433.

Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of "theory of mind". *Trends in Cognitive Sciences*, *7*(2), 77–83.

Gentili, C., Ricciardi, E., Gobbini, M. I., Santarelli, M. F., Haxby, J. V., Pietrini, P., & Guazzelli, M. (2009). Beyond amygdala: Default mode network activity differs between patients with social phobia and healthy controls. *Brain Research Bulletin*, *79*(6), 409–413.

Ghashghaei, H. T., Hilgetag, C. C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage*, *34*(3), 905–923.

Giménez, M., Pujol, J., Ortiz, H., Soriano-Mas, C., López-Solà, M., Farré, M., et al. (2012). Altered brain functional connectivity in relation to perception of scrutiny in social anxiety disorder. *Psychiatry Research: Neuroimaging*, *202*(3), 214–223.

Goldin, P., & Gross, J. J. (2010). Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. *Emotion*, *10*(1), 83–91.

Goldin, P., Manber, T., Hakimi, S., Canli, T., & Gross, J. J. (2009). Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. *Archives of General Psychiatry*, *66*(2), 170–180.

Goldin, P., Ziv, M., Jazaieri, H., & Gross, J. J. (2012). Randomized controlled trial of mindfulness-based stress reduction versus aerobic exercise: Effects on the self-referential brain network in social anxiety disorder. *Frontiers in Human Neuroscience*, *6*.

Goldin, P., Ziv, M., Jazaieri, H., Hahn, K., & Gross, J. J. (2013). MBSR vs aerobic exercise in social anxiety: fMRI of emotion regulation of negative self-beliefs. *Social Cognitive and Affective Neuroscience*, *8*(1), 65–72.

Grachev, I. D., & Apkarian, A. V. (2000a). Anxiety in healthy humans is associated with orbital frontal chemistry. *Molecular Psychiatry*, *5*(5), 482–488.

Grachev, I. D., & Apkarian, A. V. (2000b). Chemical mapping of anxiety in the brain of healthy humans: An in vivo 1H-MRS study on the effects of sex, age, and brain region. *Human Brain Mapping*, *11*(4), 261–272.

Gross, J. J. (1999). Emotion regulation: Past, present, future. *Cognition & Emotion*, *13*(5), 551–573.

Guyer, A. E., Choate, V. R., Detloff, A., Benson, B., Nelson, E. E., Perez-Edgar, K., et al. (2012). Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. *The American Journal of Psychiatry*, *169*(2), 205–212.

Guyer, A. E., Lau, J. Y. F., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., et al. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Archives of General Psychiatry*, *65*(11), 1303–1312.

Guyer, A. E., Nelson, E. E., Perez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., et al. (2006). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *The Journal of Neuroscience*, *26*(24), 6399–6405.

Gyurak, A., Gross, J. J., & Etkin, A. (2011). Explicit and implicit emotion regulation: A dual-process framework. *Cognition & Emotion*, *25*(3), 400–412.

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., et al. (2011). Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *NeuroImage*, *56*(3), 881–889.

Hariri, A. R. (2009). The neurobiology of individual differences in complex behavioral traits. *Annual Review of Neuroscience*, *32*, 225–247.

Hariri, A. R., Drabant, E. M., & Weinberger, D. R. (2006). Imaging genetics: perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. *Biological Psychiatry*, *59*(10), 888–897.

Harmer, C. J., Mackay, C. E., Reid, C. B., Cowen, P. J., & Goodwin, G. M. (2006). Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biological Psychiatry*, *59*(9), 816–820.

Hek, K., Direk, N., Newson, R. S., Hofman, A., Hoogendijk, W. J. G., Mulder, C. L., & Tiemeier, H. (2013). Anxiety disorders and salivary cortisol levels in older adults: A population-based study. *Psychoneuroendocrinology*, *38*(2), 300–305.

Hirsch, C. R., & Clark, D. M. (2004). Information-processing bias in social phobia. *Clinical Psychology Review*, *24*(7), 799–825.

Hood, S. D., Potokar, J. P., Davies, S. J. C., Hince, D. A., Morris, K., Seddon, K. M., et al. (2010). Dopaminergic challenges in social anxiety disorder: evidence for dopamine D3 desensitisation following successful treatment with serotonergic antidepressants. *Journal of Psychopharmacology*, *24*(5), 709–716.

Irle, E., Ruhleder, M., Lange, C., Seidler-Brandler, U., Salzer, S., Dechent, P., et al. (2010). Reduced amygdalar and hippocampal size in adults with generalized social phobia. *Journal of Psychiatry & Neuroscience: JPN*, *35*(2), 126–131.

Kabat-Zinn, J., & Hanh, T. N. (1990). *Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness* (Reprint edition). New York: Delta.

Kanai, Y., Nittono, H., Kubo, K., Sasaki-Aoki, S., & Iwanaga, M. (2012). Early somatosensory event-related potentials reveal attentional bias for internal stimuli in social anxiety. *Biological Psychology*, *89*(3), 591–597.

Katzman, M. A., Koszycki, D., & Bradwejn, J. (2004). Effects of CCK-tetrapeptide in patients with social phobia and obsessive–compulsive disorder. *Depression and Anxiety*, *20*(2), 51–58.

Kent, J. M., Coplan, J. D., Lombardo, I., Hwang, D. -R., Huang, Y., Mawlawi, O., et al. (2002). Occupancy of brain serotonin transporters during treatment with paroxetine in patients with social phobia: a positron emission tomography study with [11C]McN 5652. *Psychopharmacology*, *164*(4), 341–348.

Khan, S., King, A. P., Abelson, J. L., & Liberzon, I. (2009). Neuroendocrinology of anxiety disorders. In M. Anthony, & M. B. Stein (Eds.), *Oxford handbook of anxiety and related disorders* (pp. 111–122). New York: Oxford University Press.

Kilts, C. D., Kelsey, J. E., Knight, B., Ely, T. D., Bowman, F. D., Gross, R. E., et al. (2006). The neural correlates of social anxiety disorder and response to pharmacotherapy. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *31*(10), 2243–2253.

King, A. P., Abelson, J. L., Britton, J. C., Phan, K. L., Taylor, S. F., & Liberzon, I. (2009). Medial prefrontal cortex and right insula activity predict plasma ACTH response to trauma recall. *NeuroImage*, *47*(3), 872–880.

King, A. P., & Liberzon, I. (2009). Assessing the neuroendocrine stress response in the functional neuroimaging context. *NeuroImage*, *47*(3), 1116–1124.

Klumpp, H., Angstadt, M., Nathan, P. J., & Phan, K. L. (2010). Amygdala reactivity to faces at varying intensities of threat in generalized social phobia: An event-related functional MRI study. *Psychiatry Research: Neuroimaging*, *183*(2), 167–169.

Klumpp, H., Angstadt, M., & Phan, K. L. (2012). Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biological Psychology*, *89*(1), 273–276.

Klumpp, H., Fitzgerald, D. A., & Phan, K. L. (2013). Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *45*, 83–91.

Klumpp, H., Post, D., Angstadt, M., Fitzgerald, D. A., & Phan, K. L. (2013). Anterior cingulate cortex and insula response during indirect and direct processing of emotional faces in generalized social anxiety disorder. *Biology of Mood & Anxiety Disorders*, *3*(1), 7.

Knutson, B., Wolkowitz, O. M., Cole, S. W., Chan, T., Moore, E. A., Johnson, R. C., & Reus, V. I. (1998). Selective alteration of personality and social behavior by serotonergic intervention. *The American Journal of Psychiatry*, *155*(3), 373–379.

Koen, N., & Stein, D. J. (2011). Pharmacotherapy of anxiety disorders: A critical review. *Dialogues in Clinical Neuroscience*, *13*(4), 423–437.

Koric, L., Volle, E., Seassau, M., Bernard, F. A., Mancini, J., Dubois, B., et al. (2012). How cognitive performance-induced stress can influence right VLPFC activation: An fMRI study in healthy subjects and in patients with social phobia. *Human Brain Mapping*, *33*(8), 1973–1986.

Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*(7042), 673–676.

Laakso, A. (2000). Prediction of detached personality in healthy subjects by low dopamine transporter binding. *American Journal of Psychiatry*, *157*(2), 290–292.

Labuschagne, I., Phan, K. L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., et al. (2010). Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology*, *35*(12), 2403–2413.

Labuschagne, I., Phan, K. L., Wood, A., Angstadt, M., Chua, P., Heinrichs, M., et al. (2011). Medial frontal hyperactivity to sad faces in generalized social anxiety disorder and modulation by oxytocin. *The International Journal of Neuropsychopharmacology*, 1–14.

Lanzenberger, R., Mitterhauser, M., Spindelegger, C., Wadsak, W., Klein, N., Mien, L. K., et al. (2007). Reduced serotonin-1A receptor binding in social anxiety disorder. *Biological Psychiatry*, *61*(9), 1081–1089.

Lanzenberger, R., Wadsak, W., Spindelegger, C., Mitterhauser, M., Akimova, E., Mien, L. K., et al. (2010). Cortisol plasma levels in social anxiety disorder patients correlate with serotonin-1A receptor binding in limbic brain regions. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *13*(9), 1129–1143.

Laukka, P., Åhs, F., Furmark, T., & Fredrikson, M. (2011). Neurofunctional correlates of expressed vocal affect in social phobia. *Cognitive, Affective, & Behavioral Neuroscience*, *11*(3), 413–425.

Li, D., Chokka, P., & Tibbo, P. (2001). Toward an integrative understanding of social phobia. *Journal of Psychiatry and Neuroscience*, *26*(3), 190–202.

Liao, W., Chen, H., Feng, Y., Mantini, D., Gentili, C., Pan, Z., et al. (2010a). Selective aberrant functional connectivity of resting state networks in social anxiety disorder. *NeuroImage*, *52*(4), 1549–1558.

Liao, W., Qiu, C., Gentili, C., Walter, M., Pan, Z., Ding, J., et al. (2010b). Altered effective connectivity network of the amygdala in social anxiety disorder: A resting-state fMRI study. *PLoS ONE*, *5*(12), e15238.

Liao, W., Xu, Q., Mantini, D., Ding, J., Machado-de-Sousa, J. P., Hallak, J. E. C., et al. (2011). Altered gray matter morphometry and resting-state functional and structural connectivity in social anxiety disorder. *Brain Research*, *1388*, 167–177.

Liberzon, I., King, A. P., Britton, J. C., Phan, K. L., Abelson, J. L., & Taylor, S. F. (2007). Paralimbic and medial prefrontal cortical involvement in neuroendocrine responses to traumatic stimuli. *American Journal of Psychiatry*, *164*(8), 1250–1258.

Liberzon, I., Phan, K. L., Decker, L. R., & Taylor, S. F. (2003). Extended amygdala and emotional salience: A PET activation study of positive and negative affect. *Neuropsychopharmacology*, *28*(4), 726–733.

Lieberman, M. D. (2007). Social cognitive neuroscience: A review of core processes. *Annual Review of Psychology*, *58*(1), 259–289.

Lorberbaum, J. P., Kose, S., Johnson, M. R., Arana, G. W., Sullivan, L. K., Hamner, M. B., et al. (2004). Neural correlates of speech anticipatory anxiety in generalized social phobia. *Neuroreport*, *15*(18), 2701–2705.

Maddock, R. J. (1999). The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends in Neurosciences*, *22*(7), 310–316.

Mantini, D., Corbetta, M., Perrucci, M. G., Romani, G. L., & Del Gratta, C. (2009). Large-scale brain networks account for sustained and transient activity during target detection. *NeuroImage*, *44*(1), 265–274.

Mantini, D., Perrucci, M. G., Gratta, C. D., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences*, *104*(32), 13170–13175.

Marteinsdottir, I., Furmarkt, T., Tillfors, M., Ågren, H., Hartvig, P., Fredrikson, M., et al. (2001). Presynaptic serotonin imaging in social phobia using [3-11C]-5-hydroxy-L-tryptophan and PET. *NeuroImage*, *13*(6, Supplement), 1070.

Martel, F. L., Hayward, C., Lyons, D. M., Sanborn, K., Varady, S., & Schatzberg, A. F. (1999). Salivary cortisol levels in socially phobic adolescent girls. *Depression and Anxiety*, *10*(1), 25–27.

McTeague, L. M., Shumen, J. R., Wieser, M. J., Lang, P. J., & Keil, A. (2011). Social vision: Sustained perceptual enhancement of affective facial cues in social anxiety. *NeuroImage*, *54*(2), 1615–1624.

Milham, M. P., Nugent, A. C., Drevets, W. C., Dickstein, D. S., Leibenluft, E., Ernst, M., et al. (2005). Selective reduction in amygdala volume in pediatric anxiety disorders: A voxel-based morphometry investigation. *Biological Psychiatry*, *57*(9), 961–966.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*(1), 167–202.

Miner, C. M., Davidson, J. R., Potts, N. L., Tupler, L. A., Charles, H. C., & Krishnan, K. R. (1995). Brain fluoxetine measurements using fluorine magnetic resonance spectroscopy in patients with social phobia. *Biological Psychiatry*, *38*(10), 696–698.

Mitchell, J. P., Banaji, M. R., & Macrae, C. N. (2005). The link between social cognition and self-referential thought in the medial prefrontal cortex. *Journal of Cognitive Neuroscience*, *17*(8), 1306–1315.

Moser, J. S., Hajcak, G., Huppert, J. D., Foa, E. B., & Simons, R. F. (2008). Interpretation bias in social anxiety as detected by event-related brain potentials. *Emotion*, *8*(5), 693–700.

Mueller, E. M., Hofmann, S. G., Santesso, D. L., Meuret, A. E., Bitran, S., & Pizzagalli, D. A. (2009). Electrophysiological evidence of attentional biases in social anxiety disorder. *Psychological Medicine*, *39*(7), 1141–1152.

Mueller, S. C., Aouidad, A., Gorodetsky, E., Goldman, D., Pine, D. S., & Ernst, M. (2013). Gray matter volume in adolescent anxiety: An impact of the brain-derived neurotrophic factor Val66Met polymorphism? *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(2), 184–195.

Nakao, T., Sanematsu, H., Yoshiura, T., Togao, O., Murayama, K., Tomita, M., et al. (2011). fMRI of patients with social anxiety disorder during a social situation task. *Neuroscience Research*, *69*(1), 67–72.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–457.

Ochsner, K. N. (2004). Current directions in social cognitive neuroscience. *Current Opinion in Neurobiology*, *14*(2), 254–258.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences*, *9*(5), 242–249.

Pannekoek, J. N., Veer, I. M., van Tol, M. -J., van der Werff, S. J. A., Demenescu, L. R., Aleman, A., et al. (2013). Resting-state functional connectivity abnormalities in limbic and salience networks in social anxiety disorder without comorbidity. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *23*(3), 186–195.

Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry*, *60*(4), 383–387.

Phan, K. L., Coccaro, E. F., Angstadt, M., Kreger, K. J., Mayberg, H. S., Liberzon, I., & Stein, M. B. (2013). Corticolimbic brain reactivity to social signals of threat before and after sertraline treatment in generalized social phobia. *Biological Psychiatry*, *73*(4), 329–336.

Phan, K. L., Fitzgerald, D. A., Cortese, B. M., Seraji-Bozorgzad, N., Tancer, M. E., & Moore, G. J. (2005). Anterior cingulate neurochemistry in social anxiety disorder: 1H-MRS at 4 Tesla. *Neuroreport*, *16*(2), 183–186.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., & Tancer, M. E. (2006). Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biological Psychiatry*, *59*(5), 424–429.

Phan, K. L., Orlichenko, A., Boyd, E., Angstadt, M., Coccaro, E. F., Liberzon, I., & Arfanakis, K. (2009). Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. *Biological Psychiatry*, *66*(7), 691–694.

Phan, K. L., Sripada, C. S., Angstadt, M., & McCabe, K. (2010). Reputation for reciprocity engages the brain reward center. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(29), 13099–13104.

Phan, K. L., Taylor, S. F., Welsh, R. C., Decker, L. R., Noll, D. C., Nichols, T. E., et al. (2003). Activation of the medial prefrontal cortex and extended amygdala by individual ratings of emotional arousal: A fMRI study. *Biological Psychiatry*, *53*(3), 211–215.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, *16*(2), 331–348.

Potts, N. L., Davidson, J. R., Krishnan, K. R., & Doraiswamy, P. M. (1994). Magnetic resonance imaging in social phobia. *Psychiatry Research*, *52*(1), 35–42.

Potts, N. L., Davidson, J. R., Krishnan, K. R., Doraiswamy, P. M., & Ritchie, J. C. (1991). Levels of urinary free cortisol in social phobia. *The Journal of Clinical Psychiatry*, *52*(Suppl), 41–42.

Prater, K. E., Hosanagar, A., Klumpp, H., Angstadt, M., & Phan, K. L. (2013). Aberrant amygdala–frontal cortex connectivity during perception of fearful faces and at rest in generalized social anxiety disorder. *Depression and Anxiety*, *30*(3), 234–241.

Pujol, J., Giménez, M., Ortiz, H., Soriano-Mas, C., López-Solà, M., Farré, M., et al. (2013). Neural response to the observable self in social anxiety disorder. *Psychological Medicine*, *43*(04), 721–731.

Qiu, C., Liao, W., Ding, J., Feng, Y., Zhu, C., Nie, X., & Gong, Q. (2011). Regional homogeneity changes in social anxiety disorder: A resting-state fMRI study. *Psychiatry Research: Neuroimaging*, *194*(1), 47–53.

Quadflieg, S., Mohr, A., Mentzel, H. J., Miltner, W. H. R., & Straube, T. (2008). Modulation of the neural network involved in the processing of anger prosody: The role of task-relevance and social phobia. *Biological Psychology*, *78*(2), 129–137.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–682.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: A brief history of an evolving idea. *NeuroImage*, *37*(4), 1083–1090.

Richey, J. A., Rittenberg, A., Hughes, L., Damiano, C. R., Sabatino, A., Miller, S., et al. (2012). Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Social Cognitive and Affective Neuroscience*.

Roelofs, K., van Peer, J., Berretty, E., Jong, P., de Spinhoven, P., & Elzinga, B. M. (2009). Hypothalamus–pituitary–adrenal axis hyperresponsiveness is associated with increased social avoidance behavior in social phobia. *Biological Psychiatry*, *65*(4), 336–343.

Rossignol, M., Campanella, S., Maurage, P., Heeren, A., Falbo, L., & Philippot, P. (2012). Enhanced perceptual responses during visual processing of facial stimuli in young socially anxious individuals. *Neuroscience Letters*, *526*(1), 68–73.

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Gotimer, K., et al. (2009). Functional connectivity of the human amygdala using resting state fMRI. *Neuroimage*, *45*(2), 614–626.

Russ, S. J., Herbert, J., Cooper, P., Gunnar, M. R., Goodyer, I., Croudace, T., & Murray, L. (2012). Cortisol levels in response to starting school in children at increased risk for social phobia. *Psychoneuroendocrinology*, *37*(4), 462–474.

Sareen, J., Campbell, D. W., Leslie, W. D., Malisza, K. L., Stein, M. B., Paulus, M. P., et al. (2007). Striatal function in generalized social phobia: A functional magnetic resonance imaging study. *Biological Psychiatry*, *61*(3), 396–404.

Scherer, K. R. (1989). Vocal correlates of emotional arousal and affective disturbance. In H. Wagner, & A. Manstead (Eds.), *Handbook of social psychophysiology* (pp. 165–197). Oxford: John Wiley & Sons.

Schmidt, S., Mohr, A., Miltner, W. H. R., & Straube, T. (2010). Task-dependent neural correlates of the processing of verbal threat-related stimuli in social phobia. *Biological Psychology*, *84*(2), 304–312.

Schmitz, J., Scheel, C. N., Rigon, A., Gross, J. J., & Blechert, J. (2012). You don't like me, do you? Enhanced ERP responses to averted eye gaze in social anxiety. *Biological Psychology*, *91*(2), 263–269.

Schmitz, T. W., & Johnson, S. C. (2006). Self-appraisal decisions evoke dissociated dorsal--ventral aMPFC networks. *NeuroImage*, *30*(3), 1050–1058.

Schneider, F., Weiss, U., Kessler, C., Müller-Gärtner, H. -W., Posse, S., Salloum, J. B., et al. (1999). Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biological Psychiatry*, *45*(7), 863–871.

Schneier, F. R. (2000). Low dopamine D2 receptor binding potential in social phobia. *American Journal of Psychiatry*, *157*(3), 457–459.

Schneier, F. R. (2006). Social anxiety disorder. *New England Journal of Medicine*, *355*(10), 1029–1036.

Schneier, F. R., Abi-Dargham, A., Martinez, D., Slifstein, M., Hwang, D. -R., Liebowitz, M. R., & Laruelle, M. (2009a). Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. *Depression and Anxiety*, *26*(5), 411–418.

Schneier, F. R., Kent, J. M., Star, A., & Hirsch, J. (2009b). Neural circuitry of submissive behavior in social anxiety disorder: A preliminary study of response to direct eye gaze. *Psychiatry Research: Neuroimaging*, *173*(3), 248–250.

Schneier, F. R., Pomplun, M., Sy, M., & Hirsch, J. (2011a). Neural response to eye contact and paroxetine treatment in generalized social anxiety disorder. *Psychiatry Research*, *194*(3), 271–278.

Schneier, F. R., Rodebaugh, T. L., Blanco, C., Lewin, H., & Liebowitz, M. R. (2011b). Fear and avoidance of eye contact in social anxiety disorder. *Comprehensive Psychiatry*, *52*(1), 81–87.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science*, *300*(5627), 1952–1953.

Shah, S. G., Klumpp, H., Angstadt, M., Nathan, P. J., & Phan, K. L. (2009). Amygdala and insula response to emotional images in patients with generalized social anxiety disorder. *Journal of Psychiatry & Neuroscience: JPN*, *34*(4), 296–302.

Sladky, R., Höflich, A., Atanelov, J., Kraus, C., Baldinger, P., Moser, E., et al. (2012). Increased neural habituation in the amygdala and orbitofrontal cortex in social anxiety disorder revealed by fMRI. *PLoS ONE*, *7*(11), e50050.

Soravia, L. M., Heinrichs, M., Aerni, A., Maroni, C., Schelling, G., Ehlert, U., et al. (2006). Glucocorticoids reduce phobic fear in humans. *Proceedings of the National Academy of Sciences*, *103*(14), 5585–5590.

Spokas, M., Luterek, J. A., & Heimberg, R. G. (2009). Social anxiety and emotional suppression: The mediating role of beliefs. *Journal of Behavior Therapy and Experimental Psychiatry*, *40*(2), 283–291.

Sripada, C. S., Angstadt, M., Banks, S., Nathan, P. J., Liberzon, I., & Phan, K. L. (2009). Functional neuroimaging of mentalizing during the trust game in social anxiety disorder. *Neuroreport*, *20*(11), 984–989.

Sripada, C. S., Angstadt, M., Liberzon, I., McCabe, K., & Phan, K. L. (2013). Aberrant reward center response to partner reputation during a social exchange game in generalized social phobia. *Depression and Anxiety*, *30*(4), 353–361.

Stein, D. J., Westenberg, H. G. M., & Liebowitz, M. R. (2002). Social anxiety disorder and generalized anxiety disorder: Serotonergic and dopaminergic neurocircuitry. *The Journal of Clinical Psychiatry*, *63*(Suppl 6), 12–19.

Stein, M. B., Goldin, P., Sareen, J., Zorrilla, L. T. E., & Brown, G. G. (2002). Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Archives of General Psychiatry*, *59*(11), 1027–1034.

Stein, M. B., & Leslie, W. D. (1996). A brain single photon-emission computed tomography (SPECT) study of generalized social phobia. *Biological Psychiatry*, *39*(9), 825–828.

Stein, M. B., & Stein, D. J. (2008). Social anxiety disorder. *The Lancet*, *371*(9618), 1115–1125.

Stopa, L., & Clark, D. M. (2000). Social phobia and interpretation of social events. *Behaviour Research and Therapy*, *38*(3), 273–283.

Straube, T., Kolassa, I. -T., Glauer, M., Mentzel, H. -J., & Miltner, W. H. R. (2004). Effect of task conditions on brain responses to threatening faces in social phobics: An event-related functional magnetic resonance imaging study. *Biological Psychiatry*, *56*(12), 921–930.

Straube, T., Mentzel, H. -J., & Miltner, W. H. R. (2005). Common and distinct brain activation to threat and safety signals in social phobia. *Neuropsychobiology*, *52*(3), 163–168.

Sung, S. C., Porter, E., Robinaugh, D. J., Marks, E. H., Marques, L. M., Otto, M. W., et al. (2012). Mood regulation and quality of life in social anxiety disorder: An examination of generalized expectancies for negative mood regulation. *Journal of Anxiety Disorders*, *26*(3), 435–441.

Syal, S., Hattingh, C. J., Fouche, J. -P., Spottiswoode, B., Carey, P. D., Lochner, C., & Stein, D. J. (2012). Grey matter abnormalities in social anxiety disorder: A pilot study. *Metabolic Brain Disease*, *27*, 299–309.

Tafet, G. E., Feder, D. J., Abulafia, D. P., & Roffman, S. S. (2005). Regulation of hypothalamic-pituitary-adrenal activity in response to cognitive therapy in patients with generalized anxiety disorder. *Cognitive, Affective, & Behavioral Neuroscience*, *5*(1), 37–40.

Talati, A., Pantazatos, S. P., Schneier, F. R., Weissman, M. M., & Hirsch, J. (2013). Gray matter abnormalities in social anxiety disorder: Primary, replication, and specificity studies. *Biological Psychiatry*, *73*(1), 75–84.

Tancer, M. E., Mailman, R. B., Stein, M. B., Mason, G. A., Carson, S. W., & Golden, R. N. (1994). Neuroendocrine responsivity to monoaminergic system probes in generalized social phobia. *Anxiety*, *1*(5), 216–223.

Tiihonen, J., Kuikka, J., Bergström, K., Lepola, U., Koponen, H., & Leinonen, E. (1997). Dopamine reuptake site densities in patients with social phobia. *The American Journal of Psychiatry*, *154*(2), 239–242.

Tillfors, M., Furmark, T., Marteinsdottir, I., Fischer, H., Pissiota, A., Långström, B., & Fredrikson, M. (2001). Cerebral blood flow in subjects with social phobia during stressful speaking tasks: A PET study. *American Journal of Psychiatry*, *158*(8), 1220–1226.

Tillfors, M., Furmark, T., Marteinsdottir, I., & Fredrikson, M. (2002). Cerebral blood flow during anticipation of public speaking in social phobia: a PET study. *Biological Psychiatry*, *52*(11), 1113–1119.

Tupler, L. A., Davidson, J. R. T., Smith, R. D., Lazeyras, F., Charles, H. C., & Krishnan, K. R. (1997). A repeat proton magnetic resonance spectroscopy study in social phobia. *Biological Psychiatry*, *42*(6), 419–424.

Uhde, T. W., Tancer, M. E., Gelernter, C. S., & Vittone, B. J. (1994). Normal urinary free cortisol and postdexamethasone cortisol in social phobia: Comparison to normal volunteers. *Journal of Affective Disorders*, *30*(3), 155–161.

van Ameringen, M., Mancini, C., Szechtman, H., Nahmias, C., Oakman, J. M., Hall, G. B. C., et al. (2004). A PET provocation study of generalized social phobia. *Psychiatry Research: Neuroimaging*, *132*(1), 13–18.

van der Wee, N. J., van Veen, J. F., Stevens, H., van Vliet, I. M., van Rijk, P. P., & Westenberg, H. G. (2008). Increased serotonin and dopamine transporter binding in psychotropic medication–naïve patients with generalized social anxiety disorder shown by 123I-β-(4-iodophenyl)-tropane SPECT. *Journal of Nuclear Medicine*, *49*(5), 757–763.

van Overwalle, F. (2009). Social cognition and the brain: A meta-analysis. *Human Brain Mapping*, *30*(3), 829–858.

van Tol, M. J., Demenescu, L. R., van der Wee, N. J. A., Kortekaas, R., Marjan, M. A. N., Boer, J. A. D., et al. (2012). Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. *Biological Psychiatry*, *71*(7), 593–602.

van Tol, M. J., & van der Wee, N. A. (2010). Regional brain volume in depression and anxiety disorders. *Archives of General Psychiatry*, *67*(10), 1002–1011.

van Veen, J. F., van Vliet, I. M., DeRijk, R. H., van Pelt, J., Mertens, B., & Zitman, F. G. (2008). Elevated alpha-amylase but not cortisol in generalized social anxiety disorder. *Psychoneuroendocrinology*, *33*(10), 1313–1321.

van West, D., Claes, S., Sulon, J., & Deboutte, D. (2008). Hypothalamic-pituitary-adrenal reactivity in prepubertal children with social phobia. *Journal of Affective Disorders*, *111*(2–3), 281–290.

Veit, R., Flor, H., Erb, M., Hermann, C., Lotze, M., Grodd, W., & Birbaumer, N. (2002). Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. *Neuroscience Letters*, *328*(3), 233–236.

Vogt, B.A., Laureys, S. (2005). Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. In: Laureys, S., editor. *Progress in Brain Research*, Elsevier, *150*, 205–217.

Vreeburg, S. A., Zitman, F. G., van Pelt, J., DeRijk, R. H., Verhagen, J. C. M., van Dyck, R., et al. (2010). Salivary cortisol levels in persons with and without different anxiety disorders. *Psychosomatic Medicine*, *72*(4), 340–347.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*, *59*(6), 1037–1050.

Walker, D. L., & Davis, M. (2002). The role of amygdala glutamate receptors in fear learning, fear-potentiated startle, and extinction. *Pharmacology Biochemistry and Behavior*, *71*(3), 379–392.

Warwick, J. M., Carey, P. D., Cassimjee, N., Lochner, C., Hemmings, S., Moolman-Smook, H., et al. (2012). Dopamine transporter binding in social anxiety disorder: The effect of treatment with escitalopram. *Metabolic Brain Disease*, *27*(2), 151–158.

Warwick, J. M., Carey, P., Jordaan, G. P., Dupont, P., & Stein, D. J. (2008). Resting brain perfusion in social anxiety disorder: A voxel-wise whole brain comparison with healthy control subjects. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(5), 1251–1256.

Warwick, J. M., Carey, P., der Linden, G. V., Prinsloo, C., Niehaus, D., Seedat, S., et al. (2006). A comparison of the effects of citalopram and moclobemide on resting brain perfusion in social anxiety disorder. *Metabolic Brain Disease*, *21*(2–3), 230–241.

Waugh, C. E., Hamilton, J. P., Chen, M. C., Joormann, J., & Gotlib, I. H. (2012). Neural temporal dynamics of stress in comorbid major depressive disorder and social anxiety disorder. *Biology of Mood & Anxiety Disorders*, *2*(1), 11.

Yang, T. T., Menon, V., Reid, A. J., Gotlib, I. H., & Reiss, A. L. (2003). Amygdalar activation associated with happy facial expressions in adolescents: A 3-T functional MRI study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*(8), 979–985.

Yoon, K. L., Fitzgerald, D. A., Angstadt, M., McCarron, R. A., & Phan, K. L. (2007). Amygdala reactivity to emotional faces at high and low intensity in generalized social phobia: A 4-Tesla functional MRI study. *Psychiatry Research: Neuroimaging*, *154*(1), 93–98.

Yoon, K. L., & Joormann, J. (2012). Stress reactivity in social anxiety disorder with and without comorbid depression. *Journal of Abnormal Psychology*, *121*(1), 250–255.

Yoon, K. L., & Zinbarg, R. E. (2008). Interpreting neutral faces as threatening is a default mode for socially anxious individuals. *Journal of Abnormal Psychology*, *117*(3), 680–685.

Young, E. A., Abelson, J. L., & Cameron, O. G. (2004). Effect of comorbid anxiety disorders on the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression. *Biological Psychiatry*, *56*(2), 113–120.

Ziv, M., Goldin, P., Jazaieri, H., Hahn, K. S., & Gross, J. J. (2013). Is there less to social anxiety than meets the eye? Behavioral and neural responses to three socio-emotional tasks. *Biology of Mood & Anxiety Disorders*, *3*(1), 5.

Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimarães, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology*, *7*(1 suppl), 82–88.

Zuardi, A. W., Crippa, J. A. S., Hallak, J. E. C., Moreira, F. A., & Guimarães, F. S. (2006). Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Brazilian Journal of Medical and Biological Research*, *39*(4), 421–429.