Social Anxiety Disorder: Behavioural Characteristics
Associated with the Cortisol Stress Response

by

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Abstract

The present study evaluated the cortisol stress response and its relationship to several behavioural measures in SAD participants. It is hypothesized that SAD participants will show an exaggerated cortisol response to the Trier Social Stress Test (TSST) and differing positive and negative affects compared to controls, as well as correlations between the two measures.

SAD (n=12) and controls (n=12) underwent the TSST. Serial plasma cortisol samples were taken and self-report measures were completed.

The plasma cortisol levels were numerically higher in SAD at all time points compared to controls but the difference was not statistically significant. Cortisol response correlated inversely with childhood emotional abuse (p=0.01) and directly with positive affect (p=0.02) in SAD.
participants. Furthermore, SAD participants reported greater negative affect (prior to and after TSST) and more frequent emotional abuse than controls.

SAD is associated with changes in HPA axis activity and affective states that differ from controls.
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ACC: anterior cingulate cortex

ACT: acceptance and commitment therapy

ACTH: adrenocorticotropic hormone

ADIS-C: Anxiety Disorders Interview Schedule for Children

ADIS-IV-CP: Anxiety Disorders Interview Schedule for DSM-IV Child/Parent Version

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

ANS: autonomic nervous system

AS: anxiety sensitivity

AUC: area under the curve

AUD: alcohol use disorder

AVP: arginine vasopressin

BAI: Beck Anxiety Inventory

BDI: Beck Depression Inventory

BDI-II: Beck Depression Inventory II
BDZ: benzodiazepine

BMI: body mass index

CBT: Cognitive Behavioural Therapy

CIDI: Composite International Diagnostic Interview

CRH: corticotropin-releasing hormone

CTQ: Childhood Trauma Questionnaire

dACC: dorsal anterior cingulate cortex

DCS: D-cycloserine

DSM-IV: Diagnostic Statistical Manual of Mental Disorders

DSM-IV-TR: Diagnostic Statistical Manual of Mental Disorders Text Revision

EDTA: ethylenediaminetetra acetic acid

GABA: gamma-aminobutyric acid

gSAD: generalized social anxiety disorder

HAM-D: Hamilton Depression Scale

HPA: hypothalamic-pituitary-adrenal

I-125: Iodine-125

IPT: interpersonal psychotherapy
LSAS: Liebowitz Social Anxiety Scale

LSAS-SR: Liebowitz Social Anxiety Scale–self report

MAOI: monoamine oxidase inhibitor

MDD: major depressive disorder

mPFC: medial prefrontal cortex

ms: millisecond

µg: microgram

NEO-PI R: Revised NEO Personality Inventory

OCD: obsessive compulsive disorder

PANAS: Positive and Negative Affect Scale

PCC: posterior cingulate cortex

PD: panic disorder

PEP: post-event processing

pg: picogram

PTSD: post-traumatic stress disorder

PVN: paraventricular nucleus

rACC: rostral anterior cingulate cortex
RPM: revolutions per minute

sAA: salivary alpha-amylase

SAD: social anxiety disorder

SCID: Structured Clinical Interview for DSM

SFNE: Short Fear of Negative Evaluation Scale

SNRI: serotonin-norepinephrine reuptake inhibitor

SP: specific phobia

SPIN: Social Phobia Inventory

SSRI: selective serotonin reuptake inhibitor

SST: Social Skills Training

STAI: State-Trait Anxiety Inventory

TKS: Taijin Kyofusho syndrome

TSST: Trier Social Stress Test

USA: United States of America
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Chapter 1: Scientific Background

The purpose of this chapter is to:

• describe social anxiety disorder (SAD) and review its epidemiology, potential causes, impact, and course of illness;

• review the efficacy of treatment forms for SAD; and

• review neuroendocrine, particularly stress-induced cortisol, studies in SAD.

1.1 Epidemiology and Clinical Characteristics

Anxiety disorders are the most common class of mental illnesses with a point prevalence of 15-25% of the population (Antony, & Stein, 2009). The common forms of anxiety disorders include the following: Generalized Anxiety Disorder, Panic Disorder, Post-Traumatic Stress Disorder, Obsessive Compulsive Disorder (OCD), Specific Phobia, and Social Anxiety Disorder (SAD), the topic of this thesis. While a larger group of disorders (e.g. compulsive gambling, trichotillomania, etc.) are often said to be part of anxiety spectrum conditions. Despite the early onset in childhood and adolescence and chronic course of anxiety disorders, patients often seek help only in adulthood, more than a decade after the onset of the disorder (Christiana et al., 2000).
Compared to other mental illnesses, anxiety disorders are thought to be more highly comorbid with other illnesses, both mental and physical (Toft, Fink, Oernboel, Christensen, Frostholm, & Olesen, 2005). Up to one third of people with a lifetime diagnosis of an anxiety disorder meet criteria for two or more other anxiety disorders (Kessler, 1995). The presence of an anxiety disorder is also considered a reliable and strong predictor of subsequent development of substance use disorders as well as other comorbid mental illnesses. The societal costs of anxiety disorders are significant; Greenberg et al. (1999) estimated that the annual total societal cost of anxiety disorders in the United States over the 1990s was greater than $42 billion U.S. This estimate excludes the indirect costs of early-onset anxiety disorders through adverse life outcomes and increased risk of other disorders.

1.1.1 Epidemiology and Clinical Characteristics of Social Anxiety Disorder (SAD)

Social anxiety disorder (SAD) is one of the most common anxiety disorders, with an estimated lifetime prevalence of 10 percent (Kessler, 2003; Stein & Stein, 2008), but there has been a relative dearth of research on this condition (Keller, 2003). Prevalence is two times higher in females than in males and is also inversely related to socioeconomic status (Kessler, 2003), with higher rates reported among those from higher economic statuses. SAD often starts at an early age, often in late childhood and early adolescence, and impacts on secondary mental disorders, often preceding them (Kessler, 2003; Stein & Stein, 2008). It tends to run a chronic long-term course with continued high prevalence in adulthood and in later life (Cartney, McCabe, Veldbuizen, Corna, Streiner, & Herrmann, 2007). Of note is that only about 50 percent of those who experience SAD in their lifetime seek treatment for it, and of those who do, it is often fifteen to twenty years after onset (Stein & Stein, 2008). Epidemiological studies also
indicate that SAD is associated with academic difficulties and lower educational attainment (Lipsitz, 2000). As well, those with SAD are twice as likely to be financially dependent on others, and are more apt to collect welfare or disability benefits than those who do not have the disorder (Lipsitz, 2000).

There are two types of SAD: generalized SAD, which spans across various social situations and as such is more disabling, and non-generalized/discrete SAD, which is specific to certain social situations. Common and key elements of SAD are an overwhelming fear of being observed or negatively evaluated by others (Antony, & Stein, 2009; Stein, McQuaid, Laffaye, & McCahill, 1999) and a fear of embarrassment or humiliation (Woody & Nosen, 2009). Those with SAD are typically shy when they are in groups or with new people, and they have a tendency to be withdrawn in new settings. They can sometimes show physical signs of discomfort, but regardless of whether or not they show these signs, they worry that others will notice their discomfort, which in turn, leads to intense emotional and/or physical symptoms of anxiety. Hence, often those with SAD will try to avoid social situations even though these are the same situations that they crave to be successful in. This inherent tension or conflict underlines the stress-related nature of SAD. Consistent with this, those with SAD often have low self-esteem, are very self-critical, and often show symptoms of depression (Stein & Stein, 2008). As well, they are likely to make more excuses and apologies, doubt their ability to make a desired impression, and expect their performance to fall short of others’ expectations compared to those without SAD (Alden & Wallace, 1995; Antony & Stein, 2009). Finally, individuals with SAD experience increased negative self-focused cognitions that tend to worsen anxiety when social threat is anticipated (Schulz, 2008).
1.1.2 Common Comorbidities

Major Depressive Disorder (MDD) is one of the most common psychiatric comorbidities with SAD. Approximately 50 percent of people with SAD report having experienced MDD within their lifetime in comparison to 6 percent of people in the general population. In addition, people with SAD, or subthreshold SAD, are about three to four times more likely to experience MDD than the general population (Fehm, Beesdo, Jacobi, & Fiedler, 2008) and SAD often predates the onset of MDD (de Graaf, Bijl, Spijker, Beekman, & Vollebergh, 2003; Kessler, Stang, Wittchen, Stein, & Walters, 1999; Schatzberg, 1998; Schneier, 1992; Van Ameringen, Mancini, Styan, & Donison, 1991).

SAD and Alcohol Use Disorder (AUD) are also highly comorbid (Kessler et al., 1997). Grant et al. (2005) found that 48.2 percent of people with a lifetime diagnosis of SAD also met criteria for a lifetime diagnosis of AUD. This number is significantly higher than the lifetime prevalence of either alcohol abuse (12.2 percent) or alcohol dependence (5.4 percent) in the general population (Kessler, Berglund, Demler Jin, & Walters, 2005). Individuals with both AUD and SAD show more severe symptoms and greater impairment than those with only one of the two diagnoses (Buckner, Timpano, Zvolensky, Sachs-Ericsson, Schmidt, 2008; Schneier, Martin, Liebowitz, Gorman, Fyer, 1989; Thomas, Thevos, Randall, 1999). Taken together, these findings show that the SAD-AUD and SAD-MDD comorbidities are a significant mental health issue and one that affects a significant portion of the population.
1.1.3 Demographic and Cultural Factors in SAD

SAD is a common disorder found in most, if not all, cultures and its symptoms remain similar across cultures (Weissman, 1996). Similar mechanisms are thought to be responsible for SAD cross-culturally (Gilbert, 2001; Stein & Bouwer, 1997). However, SAD may express itself differently in different settings (Asmal & Stein, 2009).

It is worth noting that although SAD is more common in females in the West, males are more likely to seek treatment. Asmal & Stein (2009) believe that this could be related to perceived gender roles: males are expected to be dominant in society whereas shyness in females may be considered more normal. As well, immigrants have a higher risk of developing performance anxiety especially if they must communicate in a language that is not their mother tongue (Asmal & Stein, 2009).

Social learning involving culturally transmitted social goals and expectations can influence how SAD is expressed (Woody & Nosen, 2009). For instance, in Western society and particularly in North America, society generally encourages self-promotion and discourages submissiveness (Woody & Nosen, 2009), as such those who worry that they are being perceived as passive or shy may be more vulnerable to SAD. On the other hand, in the East and particularly in Asia, being less dominant and more avoidant is a socially encouraged behaviour (Kim, 1994; Oetzel, 1998a; Oetzel, 1998b), and therefore, SAD is expressed differently in these countries (Triandis, 1995). A good example is Taijin Kyofusho (TKS) syndrome, a particular variant of social anxiety seen in Japan and other East Asian cultures (Matsunaga, Kiriike, Matsui, Iwasaki, & Stein, 2001). It is described as “an individual’s intense fear that his or her body, its parts or its functions, displease, embarrass, or are offensive to other people in appearance, odour, facial expressions, or movements” by the Diagnostic Statistical Manual of Mental Disorders (DSM-IV)
(Woody & Nosen, 2009). Whereas the focus of SAD seems to be on embarrassing oneself, that of TKS is on embarrassing others (Woody & Nosen, 2009). However, SAD and TKS have phenomenological similarities since they both involve anxiety related to social situations, and leading to avoidance.

A number of etiological models have been proposed that are applicable to SAD as well as other forms of phobic disorders. Among them, Psychological models seem highly relevant.

1.2 **Psychological Models of Phobic Disorders**

Psychological models proposed for phobic disorders employ psychodynamic, behavioural, and cognitive frameworks. The proposed mediating mechanisms are briefly described below.

1.2.1 **Psychodynamic**

Goisman (1983) describes the classic psychoanalytic formulation of phobias as follows: anxiety-provoking impulse, usually primitive or socially unacceptable, repressed because acknowledging it is too threatening. This causes the displacement of the impulse and its anxiety onto a symbolically or temporally related object, creating a threatening stimulus that can be more easily avoided (Woody & Nosen, 2009). A further theory explains that the formation of a phobic symptom occurs so the anxiety can act like a realistic external fear and be avoided (Compton, 1992).
Modern psychodynamic theories tend to highlight the personal meaning of the feared stimulus, but also incorporate components of learning and cognitive theories. Fears of public display of inadequacy are thought to lead to engagement in avoidance behaviour in order to avoid being vulnerable or embarrassed in public (Salzman, 1968).

1.2.2 Behavioural

According to behavioural models, fears are learned through association, and thus neutral stimuli associated with a traumatic event may trigger a fear reaction on their own (Woody & Nosen, 2009). Based on this model, SAD is said to develop following exposure to negative or challenging stimuli during social interactions. When recalling their childhoods, individuals with SAD often report “traumatic conditioning experiences” related to social situations that they often relate to the development of SAD (Woody & Nosen, 2009). Furthermore, for those with limited social skills, operant conditioning principles may reinforce the avoidance of such situations and lead to negative reactions such as poor eye contact and reticence to engage others. There is an absence of positive reinforcement and prosocial behaviour, which compounds the anxiety related to social situations (Woody & Nosen, 2009).

It is not fully clear whether this altered social interaction displayed by SAD sufferers is contributed to by an actual lack of social skills or results from anxiety, which prevents the effective use of these skills (Woody & Nosen, 2009). According to some reports, while children with SAD were found to have similar social skills to other children, they often perceived them to be deficient (Cartwright-Hatton, Hodges, & Porter, 2003; Cartwright-Hatton, Tschernitz, &
Gomersali, 2005). This would suggest that in SAD, social skills may be present, but these skills are not applied appropriately (Woody & Nosen, 2009).

1.2.3 Cognitive

A cognitive model of panic proposed by Clark posits that an internal or external stimulus triggers perceived threat leading to apprehension, and the resulting bodily sensations are misinterpreted as catastrophic (Clark & Wells, 1995). This model has led to the suggestion that the misinterpretation of bodily sensations can contribute to maladaptive anxiety. Rapee and Heimberg have applied this notion in their model of SAD (1997), which suggests that individuals with SAD falsely perceive that they look just as nervous and uncomfortable as they feel in a social situation. Thus, SAD sufferers assess the consequences of being negatively evaluated in a social context, which results in increased anxiety that further negatively influences the mental representation of the self. Self-focused attention is higher in socially anxious individuals than in a healthy population (Mellings & Alden, 2000).

This model further suggests that individuals with SAD, perceiving others to be critical of them, anticipate humiliation and rejection (Rapee & Heimberg, 1997). In addition, there is evidence that SAD sufferers think that they lack the ability to control their behaviour and emotions unlike normal individuals (Cloitre, Heimberg, Liebowitz, & Girow, 1992; Leung & Heimberg, 1996) and so avoid social situations (Hofmann, 2005). Perceptions of control over anxiety were found to be a powerful mediator between the degree of social anxiety and the perceived consequences of negative social interaction (Hofmann, 2005). As well, it has been suggested that individuals with SAD tend to perform certain “safety” behaviours that can provide
protection and deny confirmation of their fear of negative evaluation (Woody & Nosen, 2009). For instance, in an investigation participants with SAD were told they were going to interact with either a critical or accepting partner. Although the partner behaved the same way in each condition (Alden & Bieling, 1998), SAD participants who expected a critical partner used more safety behaviours than controls, but no group differences were found when expecting an accepting partner. This has been proposed as suggesting the notion that deficient social skills alone could not explain the phobic behaviour. Other investigators have found that the use of safety behaviours relates to deficits in social understanding, social perception, and memory, though there was no direct evidence of causality (Hampel, 2011). It is also well documented that people with SAD are overly attentive to signs of negative evaluation from others, and tend to be attuned to criticism more than positive feedback (Veljaca & Rapee, 1998). They have been reported to interpret ambiguous social cues negatively (Amir, Foa, & Coles, 1998b; Stopa & Clark, 2000), and tend to miss positive social cues (Woody & Nosen, 2009).

1.3 Cognition in SAD

A core characteristic of anxiety disorders, in general, and SAD, in particular, is the altered thought processes underlying beliefs and cognitions and seen as a fundamental phenomenon of SAD. The following section provides an overview of the cognitive characteristics of SAD.
1.3.1 **Attentional Biases**

The human information-processing system has a limited capacity, thus an individual is only able to pay attention to one subset of stimuli at a time. Those with high trait anxiety, as well as those with syndromal anxiety conditions, are proposed to show greater attention bias to threatening stimuli. The literature reports such attentional bias being experimentally elicited using different paradigms, including the emotional Stroop task. The emotional Stroop task, which is related to the standard Stroop task, measures an individual’s response time when asked to name the colour of emotionally valenced words that are negative, positive, or neutral in valence. In those with anxiety disorders, including SAD (McNally & Reese, 2009), there is a longer response time for threat words than for non-threat words in comparison to healthy controls. In general, studies show that positive content rarely produces as much Stroop interference as threatening content. An exception may occur if this positive content is conceptually related to one’s main concern or a situation that may be related to the anxiety. Studies have also found that such Stroop effect can be nullified when anxiety sufferers are anticipating an imminent, extremely stressful event, such as individuals with SAD giving a speech in front of others (McNally & Reese, 2009).

This presence of increased attention to threatening stimuli in individuals with SAD is further supported by an event-related potential study, which showed that during masked and unmasked Stroop task of angry face processing, SAD participants showed an early attentional bias for social threat (van Peer, 2010). In other words, even at early stages of information processing, social threat stimuli automatically attract more attention in those with SAD. In a variant of the dot-probe paradigm, another strategy used to assess selective attention to threatening stimuli, those with SAD showed attentional avoidance to both positive and negative
emotions when anticipating giving a speech. When such expectation of having to give a speech was absent, there was no difference in attentional avoidance between high- and low-anxiety participants (Mansell, Clark, Ehlers, & Chen, 1999). Another study found that people with SAD were quicker at detecting angry versus happy faces than a control group using a visual probe task (Mogg, Philippot, & Bradley, 2004).

It has been noted that when experiencing anxiety, even relatively non-threatening stimuli are often interpreted as threatening, causing attentional bias towards these stimuli. This observation is supported by Wilson and Macleod’s (2003) study showing that those with high trait anxiety respond to moderate threat, perceiving it to be higher. More specifically, people with high and low trait anxiety showed similar attentional avoidance for minimal anger and intense anger situations (Wilson & MacLeod, 2003). The groups differed under the moderate anger situation, in that high trait anxious participants showed increased attention in comparison to participants with low trait anxiety. The possible contribution of attentional bias in phobic disorders is well summarised by Pflugshaupt (2005) who states that: “As a consequence of initial hypervigilance, phobics are more likely to detect potentially threatening events and thus perceive the world as a dangerous place, while subsequent cognitive avoidance prevents objective evaluation and habituation to such events.” Taken together, these findings suggest that people with SAD may be more inclined to perceive increased stress in situations and may be more likely to use avoidance as a coping strategy than those without SAD.
1.3.2  *Interpretation Biases*

Increased anxiety can be related to a tendency to interpret ambiguous information as threatening. Butler and Mathews (1983) found that when interpreting ambiguous scenarios, both depressed and anxious individuals interpreted the ambiguous situations as more threatening than the control group. As well, Macleod and Cohen (1993) found that those with high trait anxiety were more likely to place a threatening interpretation on ambiguous sentences whereas those with low trait anxiety tended to do the opposite. Similarly, in another study, Amir et al. (2005) developed videotaped scenarios where an actor would approach the camera saying a negative, positive, or ambiguous comment. Participants were told to imagine themselves to be the recipients of these comments and asked to rate the emotional valence of each comment. Authors report that those with SAD rated the ambiguous scenarios as more emotionally negative, thereby confirming the presence of an interpretive bias.

In another paradigm to elicit the interpretation bias, participants read sentences ending in a homograph (words with different meanings but similar spelling) or nonhomograph that had either a socially threatening or nonthreatening potential meaning. Participants were then asked to decide whether a word appearing either 100 milliseconds or 850 milliseconds later was related to the sentence. Using this paradigm, Amir et al. (1998) found that in the SAD group, there were decreased decision latencies at 100ms implying earlier activation of the inappropriate meaning of social threat sentences. The opposite occurred at 850ms indicating increased decision latencies. These findings suggest initial automatic threat activation followed by an inhibition of this interpretation in response to ambiguity (Amir, Foa, & Coles, 1998a). This resembles the vigilance-avoidance style of threat-related information processing described in the previous
section (McNally & Reese, 2009) and is proposed as a mechanism to cope with the initially threatening information.

Post-event processing (PEP) was proposed by Clark and Wells (1995) as a possible central mechanism for maintaining social anxiety symptoms. PEP was defined as a “detailed review of a recent social situation” (Clark & Wells, 1995) and involves re-experiencing that scenario (Abbott & Rapee, 2004; Dannahy & Stopa, 2007). This is said to lead to intensified negative self-appraisals and recall of memories of past social failures that become repetitive and uncontrollable, further strengthening dysfunctional assumptions and reinforcing avoidance behaviours in the future (Field & Morgan, 2004; Hackmann, Clark, & McManus, 2000; Kocovski, Endler, Rector, & Flett, 2005; Morgan & Banerjee, 2008; Rachman, Grüter-Andrew, & Shafran, 2000). Those with high social anxiety (Brozovich & Heimberg, 2011; Dannahy & Stopa, 2007; Edwards, Rapee, & Franklin, 2003; Kocovski, Endler, Rector, & Flett, 2005; Mellings & Alden, 2000) and those with a clinical diagnosis of SAD (Abbott & Rapee, 2004; Perini, Abbott, & Rapee, 2006) have been noted to experience PEP after stressful social interactions. Interestingly, this phenomenon of PEP occurs specifically following social stimuli and is not triggered by other phobic situations (Fehm, Schneider, & Hoyer, 2007). Kiko et al. (2012) evaluated PEP in which state and trait anxiety levels were examined in relation to a speech and a social encounter, and found that it was best predicted by the presence of situational anxiety and dysfunctional cognitions. As well, PEP was predicted by the presence of trait anxiety following social interaction, whereas the presence of self-consciousness was a predictor for the speech task only (Kiko et al., 2012). These findings led to the suggestion that PEP may result from continued activation of negative dysfunctional cognitions and anxiety surfacing from past social situations. Such notion is supported by the observation that individuals with SAD preserve
learned negative associations to social cues for longer time periods than the normal population (Hermann, Ziegler, Birbaumer, & Flor, 2002; Lissek et al., 2008).

In conclusion, those with SAD seem to show an attenuated positivity bias compared to those without SAD, rather than the presence of a purely negative interpretation bias. Thus, these individuals seem to have difficulties making positive interpretations for ambiguous social stimuli (McNally & Reese, 2009) and such reduction in positive bias has been proposed to be a key feature in the pathophysiology of SAD.

1.4 Treatment of SAD

Several forms of interventions are proposed to be effective in the treatment of SAD. Broadly they are pharmacological, psychological, and/or a combination of the two. They are outlined below.

1.4.1 Pharmacological Treatments

Several classes of antidepressants have been shown to reduce the symptoms of SAD. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are first line medications for SAD (Davidson, 2003). SSRIs act by increasing the extracellular level of serotonin by inhibiting its reuptake (Davidson, 2003). SSRI treatment is the most widely used pharmacological treatment for SAD based on their safety, tolerability, and effectiveness in various treatment studies of SAD (Van Amerigan, Mancini, Pipe, & Bennett, 2004b). First choice SSRIs include: fluvoxamine CR (Luvox CR), paroxetine (Paxil), paroxetine
CR (Paxil CR), and sertraline (Zoloft). Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has been shown to be effective for SAD as well (Liebowitz, Mangano, Bradwejn, & Asnis, 2005; Stein, Pollack, Bystritsky, Kelsey, & Mangano, 2005). SNRIs act by increasing the extracellular level of serotonin and norepinephrine by inhibiting their reuptake.

Evidence of the efficacy of the older antidepressant MAOI treatment for SAD was established in the 1970s and was shown to be robust (Gelernter et al., 1991; Heimberg et al., 1998; Liebowitz, Gorman, Fyer, & Klein, 1985; Liebowitz et al., 1992; Liebowitz & Liebowitz, 1999). MAOIs act by inhibiting the activity of the family of monoamine oxidase enzymes; the key enzymes involved in the metabolic break down of monoamines, and thereby increasing monoamine activity. The use of MAOIs has declined due to the possible dangerous side effects, for example serotonin syndrome, and the need for a special diet low in tyramine. As well, drug-drug and drug-food interactions associated with MAOI treatment are problematic and require close monitoring. In a practical sense, MAOIs are not to be used in conjunction with certain over-the-counter medications such as pain and asthma medications, and if combined with certain foods, they may result in dangerously high blood pressure or a stroke. They are still prescribed for SAD, however, for those who do not respond to other medications.

Benzodiazepines (BDZs) are also thought to be effective in symptomatically treating anxiety symptoms of SAD. They act by enhancing the inhibitory gamma-aminobutyric acid (GABA) neurotransmission (Van Ameringen, Mancini, & Patterson, 2009). Clonazepam (a benzodiazepine) has also been shown to reduce SAD symptoms faster than antidepressants (Davidson, 2003). In a clinical trial, BDZs were shown to be as effective as SSRIs and more effective than placebo (Fedoroff & Taylor, 2007). However, they have potential for addiction, are known to cause rebound anxiety upon discontinuation, and do not treat common comorbid
conditions to SAD such as depression (Davidson, 2003). BDZs are usually used in combination with another pharmacological agent or when quick relief of symptoms is required (Van Ameringen, Mancini, & Patterson, 2009).

More recently, atypical antipsychotics have been shown to have anxiolytic effects in both animal models (Moore, Rees, Sanger, & Tye, 1994) and clinical trials (Klieser et al., 1999; Tollefson, Sanger, Beasley, & Tran, 1998). There is some evidence for their benefit in the treatment of SAD. For instance, monotherapy with the atypical antipsychotic, Quetiapine, showed positive results in an open-label trial of SAD (Schutters, van Megen, & Westenberg, 2005). In a placebo-controlled trial with flexible dose olanzapine, another atypical antipsychotic agent, those with SAD showed significant improvement on primary outcome measures (Barnett, Kramer, Casat, Connor, & Davidson, 2002). In the short-term, atypical antipsychotics are well tolerated, though long-term use may result in significant adverse effects such as weight gain, diabetes, and high cholesterol (Newcomer, 2004). In general, atypical antipsychotics are typically used for SAD as adjunctive agents or in those who do not respond to other medications, though further research is still needed in this area (Van Ameringen, Mancini, & Patterson, 2009).

1.4.2 Psychological Treatments

Although several modalities of psychological treatment for SAD have been evaluated, cognitive behavioural therapy (CBT) remains the psychological intervention of choice (Ponniah & Hollon, 2008). CBT is an “action-oriented form of psychosocial therapy that assumes that maladaptive, or faulty, thinking patterns cause maladaptive behavior and “negative” emotions. The treatment focuses on changing an individual’s thoughts (cognitive patterns) in order to
change his or her behavior and emotional state.” (Antony & Stein, 2009; Gale Encyclopedia of Medicine, 2008). Several reviews and meta-analyses have found CBT to be efficacious in anxiety disorders (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). The treatment gains from CBT have been found to be durable for most anxiety disorders in general, but for SAD specifically (Buckner, Ledley, Heimberg, & Schmidt, 2008b; Fedoroff & Taylor, 2001; Feske & Chambless, 1995; Gould, Buckminster, Pollack, Otto, & Yap, 1997; Heimberg, 2002; Ledley & Heimberg, 2005; Rodebaugh, Holaway, & Heimberg, 2004; Taylor, 1996). As with pharmacological therapies, CBT is associated with significant quality of life improvements (Eng, Coles, Heimberg, & Safren, 2001; Safren, Heimberg, Brown, & Holle, 1997).

Another form of psychological therapy referred to as exposure treatment is thought to reduce anxiety by encouraging the participant to imagine or directly confront anxiety-provoking situations or stimuli while remaining psychologically engaged (Magee, Erwin, & Heimberg, 2009). It is suggested that exposure therapy functions through the assimilation of new learning with the original anxiety response (Bouton, 2002). Exposure therapy is usually more effective when used in combination with cognitive restructuring and other similar techniques (Juster & Heimberg, 1995), since cognitive distortion with fear of negative evaluation by others is a core characteristic of SAD (Butler, 1985; Turk, Fresco, & Heimberg, 1999).

Exposure-based CBT involves both exposure as well as a cognitive restructuring, and has been documented by the International Consensus Group on Depression and Anxiety as demonstrating good evidence for its efficacy (Ballenger et al., 1998). Several studies have shown the superior efficacy of combined cognitive and exposure techniques compared to several control conditions. These include waitlist control conditions (Butler, Cullington, Munby, Amies, & Gelder, 1984; Hope, Heimberg, & Bruch, 1995), educational support (Heimberg et al., 1990;
Heimberg, Holt, Schneier, Spitzer, & Liebowitz, 1993; Heimberg et al., 1998), and placebo medication (Heimberg et al., 1998). Several meta-analyses on psychological treatments for SAD suggest that including an exposure component to CBT increases its efficacy in this population (Zaider & Heimberg, 2003), and in turn, addition of cognitive techniques to exposure paradigms can decrease the amount of exposure necessary to arrive at similar results (Turk, Coles, & Heimberg, 2002).

Social Skills Training (SST) is another form of therapy used to treat SAD. It is based on the assumption that SAD is associated with a lack of social skills, triggering negative reactions from others and leading to negative personal evaluation, distress, and poor self-esteem (Magee, Erwin, & Heimberg, 2009). Research on the effectiveness of SST in SAD is scarce, and thus far, there are no reports that SST on its own is more effective than control conditions (Magee, Erwin, & Heimberg, 2009). However, there is some evidence that the addition of SST to group CBT improves the latter’s effectiveness (Herbert et al., 2005). This study reported all participants who received treatment benefitted but the improvement was more within the combination of CBT and SST compared to either treatment alone (Herbert et al., 2005).

Relaxation strategies are also used to treat SAD and these are aimed at decreasing physiological arousal before or during an anxiety-provoking situation. One such strategy is progressive muscle relaxation (Bernstein, Borkovec, & Hazlett-Stevens, 2000), which is used to manage the physiological arousal that comes with increasing anxiety levels. Progressive muscle relaxation alone has minimal effect on SAD symptoms (Al-Kubaisy et al., 1992; Alström, Nordlund, Persson, Härding, & Ljungqvist, 1984). Applied relaxation is a technique that uses a combination of gradual exposure to a feared situation and progressive muscle relaxation. Individuals are first told to become aware of the physiological symptoms associated with
anxiety, and then progressive muscle relaxation starts in conjunction with non-anxiety provoking situations that slowly change to anxiety-provoking ones (Öst, 1987). Applied relaxation therapy has been shown to be more effective than waitlist controls conditions (Jerremalm, Jansson, & Öst, 1986) and equally as effective as SST (Öst, Jerremalm, & Johansson, 1981). In a more recent randomized control trial, people with SAD were assigned to undergo cognitive therapy, exposure plus applied relaxation, or a waitlist control condition. Results showed efficacy for both treatment groups, though the cognitive therapy was the most effective (Clark et al., 2006).

Interpersonal psychotherapy (IPT) is a time-limited therapy based on the idea that mental health disorders develop and are maintained in a psychosocial and interpersonal context (Magee, Erwin, & Heimberg, 2009). IPT has been found to be an effective treatment in major depression (Elkin et al., 1989), dysthymia (Markowitz, 1994), bulimia nervosa (Wilfley et al., 1993), and other conditions. In the context of SAD, the goal of IPT is for the participant to grasp the link between SAD symptoms and one’s interpersonal conflicts. In an uncontrolled study using IPT, the majority of SAD participants were classified as responders (Lipsitz, Markowitz, Cherry, & Fryer, 1999). More recent studies have shown that though IPT may not be as effective as CBT in the treatment of SAD, it can be beneficial for many individuals with SAD (Bohn, Aderka, Schreiber, Stangier, & Hofmann, 2013; Stangier, Schramm, Heidenreich, Berger, & Clark, 2011).

Acceptance and commitment therapy (ACT) is a fairly new psychological intervention and has not been fully evaluated in SAD. The rationale for the use of ACT is that mental health disorders are related to one’s “psychological inflexibility and avoidance of internal and external experiences” (Magee, Erwin, & Heimberg, 2009). In ACT, participants are encouraged to choose life directions that are aligned with their values and to commit to taking action towards these
values. Preliminary studies suggest that ACT may be a useful treatment option for several mental health disorders including anxiety disorders (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). One investigation compared CBT with ACT in the treatment of participants with public speaking anxiety and reported that the latter was more effective (Block & Wulfert, 2000). Further research is needed to determine the effectiveness of ACT for SAD.

1.4.3 Combination of Psychological and Pharmacological Interventions

To date few studies have addressed the use of the combination of both psychological and pharmacological components to treat SAD. Among reported studies, the results are mixed with several early studies reporting that combination therapy was no more effective than placebo or than either treatment alone (Clark & Agras, 1991; Falloon, Lloyd, & Harpin, 1981). More recently, an investigation that compared treatment with group CBT, phenelzine, combination of group CBT and phenelzine, and pill placebo alone, found that the combination of group CBT and phenelzine was superior to the other three interventions (Heimberg & Becker, 2002). Subsequently, Davidson et al.’s (2004) study compared the treatment of fluoxetine, group CBT, the combination of fluoxetine and group CBT, and placebo. They found that all three treatments (fluoxetine, group CBT, and the combination of fluoxetine and group CBT) were equally effective and were all more effective than the placebo condition (Davidson et al., 2004). Bandelow et al.’s (2007) meta-analysis compared the efficacy of combining psychological and pharmacological interventions in SAD to either intervention alone, and showed that there was a limited number of studies addressing this topic. Results of this analysis showed that the only significant difference that was detected was that the combination of CBT and medication was significantly more effective than the combination of CBT and placebo, suggesting that the
combination of a psychological and a pharmacological intervention may be more effective than a psychological intervention alone (Bandelow, Seidler-Brandler, Becker, Wedekind, & Rüther, 2007).

More recently, the benefit of combining psychological therapies with pharmacological agents other than antidepressants have been evaluated. Research shows that fear-relevant information processing is mediated by glutamatergic pathways (Falls, Miserendino, & Davis, 1992; Santini, Muller, & Quirk, 2001; Zwanzger, 2009) and D-cycloserine (DCS), an N-methyl-D-aspartate agonist, was noted to improve the effect of exposure trials in animals (Parnas, Weber, & Richardson, 2005) as well as humans (Ressler et al., 2004) through impact on learning and memory (Myers & Davis, 2002; Schwartz, Hashtroudi, Herting, Schwartz, & Deutsch, 1996). Hofmann et al. (2006) looked at twenty-seven participants with SAD who received either CBT alone or a combination therapy of CBT and DCS. It was reported that participants who received combination therapy had less social anxiety during exposure compared to those who received CBT alone (Hofmann et al., 2006). These results were subsequently replicated in a larger sample of 110 participants in a more recent study (Guastella et al., 2008). These results provide evidence that DCS may enhance psychological treatment of SAD but additional studies are needed for confirmation.

1.5 Factors Influencing the Expression of SAD: Developmental, Personality and Neurobiological Considerations

SAD is a multifaceted illness whose pathophysiology is not fully elucidated. A multifactorial model has been proposed with developmental (childhood trauma, emotional abuse,
and certain parenting styles), personality (neuroticism, positive affectivity, perfectionism, and shyness), and neurobiological (neurotransmitters, neuroanatomical dysfunction, genetic vulnerability, etc.) factors being implicated. The related literature is below.

1.5.1 *Developmental Factors and SAD*

Many mental health disorders have their antecedents in early life. Large prospective studies have shown the relationship between childhood experience of emotional distress and the subsequent development of anxiety disorders in adulthood (Poulton, Grisham, & Andrews, 2009). They report that adults with early onset anxiety disorders are likely to have experienced anxiety as children and adolescents, and often reported depression in early life. Of note, externalizing disorders or psychosis did not increase the likelihood of developing an anxiety disorder as an adult (Poulton, Grisham, & Andrews, 2009).

The onset of the various anxiety disorders appears to have a developmental link. “Phases” of anxiety development are thought to be part of the human developmental trajectory and the order of their onset have been noted to parallel the ability of the child to conceptualize threats and understand the consequences of the fear. Separation anxiety and specific phobias usually begin in early childhood, SAD tends to begin in middle childhood, and panic disorder tends to have its onset in early adolescence (Poulton, Grisham, & Andrews, 2009). Current developmental theories have proposed the contribution of temperament, parenting styles, family relationships, and aversive childhood experiences for the development of anxiety disorders (Antony & Stein, 2009). For example, there appears to be a relationship between the development of anxiety disorders and controlling and overprotective parenting styles (Hudson & Rapee, 2009). It has also been shown that a child’s temperament plays a role in its relationship
with the parent. Thus, children who are shy, inhibited, anxious, or depressed tend to bring about overprotective behaviours in parents, which, in turn, leads to low self-confidence, self-efficacy, and autonomy, further increasing the vulnerability to anxiety (Hudson & Rapee, 2009). The role of peer interactions appears to be relevant in the pathophysiology of SAD. It has been proposed that reduced positive peer appraisal, increased peer victimization, and decreased friendship quality may be associated with SAD (Beidel, Turner, & Morris, 1999; Flanagan, 2008; La Greca & Harrison, 2005; Storch & Masia-Warner, 2004). Furthermore, Flanagan et al. (2008) found that increased levels of SAD are often associated with poor levels of social skills, which in turn contributes to increased social withdrawal as well as negative social appraisals. However, quality of peer appraisal and the presence of peer victimization appeared to significantly influence levels of social anxiety, even more so than the influence of social behaviour (Flanagan, 2008). This is consistent with developmental models that suggest that multiple pathways can influence the pathophysiology of SAD (Ollendick & Hirshfeld-Becker, 2002).

Traumatic events in early life have been proposed as an important risk factor for the development of SAD (Antony & Stein, 2009). Trauma is thought to influence and alter the normal stress response, impacting on the resilience to cope with repetitive stressors. Cortisol is a key hormone implicated in the stress response and has been suggested to play a role in mediating such adversity (Khan, King, Abelson, & Liberzon, 2009). In support of this, an investigation showed that individuals with SAD and a history of childhood abuse had greatly enhanced cortisol reactivity to a psychosocial stress task in comparison to those with SAD but without a history of childhood abuse and with healthy controls with no history of childhood abuse (Elzinga, Spinhoven, Berretty, de Jong, & Roelofs, 2010). In addition to this, Van der Vegt et al. (2010) showed that people who have experienced severe childhood maltreatment have decreased cortisol secretion in comparison to healthy controls. In general, studies confirm that those with
SAD report higher rates of childhood emotional abuse compared to normal populations and possibly even other anxiety disorders (e.g. panic disorder) (Lochner et al., 2010). Interestingly, it is emotional abuse, more so than physical or sexual abuse, that has been associated with the diagnosis of SAD (Asher & Coie, 1990; Lochner et al., 2010).

1.5.2 **Personality, Affect, and SAD**

Various studies have supported the role of neuroticism in both mood and anxiety disorders (Pagura, Cox, & Enns, 2009). Neuroticism is a personality trait defined by the experience of negative emotional states such as anxiety, anger, envy, and guilt. Trull & Sher (1994) evaluated the relationship between DSM-III Axis I disorders and the Five-Factor Model of Personality using a large nonclinical sample of young adults. They reported that participants with anxiety disorders were higher in neuroticism and openness factors, and lower in extraversion, agreeableness, and conscientiousness factors than those with no anxiety disorder. This study further found that certain personality factors were more sensitive to specific anxiety disorders. For SAD, high neuroticism and low extraversion were found to be especially relevant while agreeableness was less so (Trull & Sher, 1994). This finding is supported by several other reports and in keeping with the suggestion that higher neuroticism in general is related to distress-related anxiety disorders (Bienvenu, Hettema, Neale, Prescott, & Kendler, 2007; Bienvenu et al., 2004; Norton, Cox, Hewitt, & McLoed, 1997).

Positive and negative affect represent mood dimensions that describe specific positive or negative emotions relating to how people interact with others in their environment (Bushman & Crowley, 2010). Positive affect is reported to be low in individuals with SAD and depression.
(Brown, Chorpita, & Barlow, 1998) and this was true even after controlling for the degree of negative affect present in these participants. Individuals with SAD are known to possess consistently high levels of negative affect and low levels of positive affect (Buckner, Heimberg, Ecker, & Vinci, 2013). Furthermore, negative affect is thought to be an important vulnerability factor in the development of anxiety disorders (Brown, Chorpita, & Barlow, 1998). In addition, individuals with SAD are often noted to experience difficulties with emotional regulation (Farmer & Kashdan, 2012). As previously stated, individuals with SAD tend to have high levels of neuroticism and low levels of extraversion. This relationship between low levels of extraversion and higher social anxiety has been noted consistently in both clinical and in nonclinical populations (Pagura, Cox, & Enns, 2009). Extraversion appears to be the only higher-order personality dimension significantly (and inversely) associated with SAD after controlling for gender and general distress (Trull & Sher, 1994).

Shyness (which overlaps with low extraversion) has been suggested as a risk factor for the development of SAD (Pagura, Cox, & Enns, 2009). Cross-sectional studies have reported a direct relationship between the degree of shyness and the increased probability of having SAD in a large sample of college students (Chavira, Stein, & Malcarne, 2002) a finding replicated in the general population (Cox, MacPherson, & Enns, 2005). Behavioural inhibition, an overlapping concept with social inhibition and withdrawal, is said to occur in vulnerable individuals when responding to novel stimuli, and has been proposed as a key contributor to social anxiety (Kagan & Snidman, 1999; Rapee & Spence, 2004). Children exhibiting behavioural inhibition have been reported as more likely (though not always) to develop SAD in later life (Biederman, Hirshfeld-Becker, Rosenbaum, Herot, & et al, 2001; Hayward, Killen, Kraemer, & Taylor, 2000; Schwartz, Snidman, & Kagan, 1999). There is also evidence to suggest that within behavioural inhibition,
the social reticence component may better predict the later development of SAD in comparison to the experience of physical fear (Neal, Edelmann, & Glachan, 2002).

Self-criticism is another trait of neuroticism in the Five-Factor Model. Self-criticism is defined as “persistent and harsh self-scrutiny and self-evaluation” and was proposed as a vulnerability factor for depression (Blatt, 1974). More recently research has focused on the relationship between self-criticism and SAD. A recent report suggests that individuals with current or past SAD tend to exhibit higher self-criticism than individuals free of psychiatric morbidity (Pagura, Cox, & Enns, 2009). The effect remained even after controlling for current emotional distress, neuroticism, and lifetime presence of mood, anxiety, and substance use disorders. In another investigation, self-criticism levels were found to be highest in those with SAD and comorbid depression compared to those with depression alone, though both groups exhibited higher degrees of it (Cox et al., 2000). The same group of investigators also demonstrated a direct correlation between the degree of self-criticism and severity of SAD, a relationship that persisted even after controlling for depressed mood (Cox, Walker, Enns, & Karpinski, 2002). Furthermore, they note that both the intensity of self-criticism and symptom severity decreased in parallel following treatment.

Another trait that has been studied in relation to SAD is perfectionism. Compared to a healthy control group, those with SAD scored higher on concern over mistakes, doubts about actions, and parental criticism (Juster, Heimberg, Rector, Mattia, & Faccenda, 1996; Lundh & Öst, 1996; Saboonchi & Lundh, 1997; Saboonchi, Lundh, & Öst, 1999). Individuals with SAD also scored higher on socially prescribed perfectionism compared to controls and exhibited a greater degree of certain perfectionistic traits compared to participants with other anxiety disorders (Alden, Bieling, & Wallace, 1994). For example, an investigation found that in SAD,
individuals had significantly higher scores on concern over mistakes, doubts about action, parental criticism, and socially prescribed dimensions of perfectionism than individuals with panic disorder, OCD, and specific phobia (Antony, Purdon, Huta, & Swinson, 1998). These findings were reinforced by Saboonchi et al. (1999) who showed that those with SAD scored higher on concern over mistakes and doubts about action compared to those with panic disorder.

Anxiety sensitivity (AS), an individual trait and personality factor, is a well-established cognitive risk factor for developing anxiety conditions, including SAD (McNally, 1996; Rapee & Medoro, 1994; Reiss, 1991). AS is defined as a trait-like, firmly held belief in the danger of anxiety symptoms, and is reported to be elevated in individuals with SAD (Taylor, Kock, & McNally, 1992). However, others have suggested that both may be manifestations of the same condition with significant overlap. It has been found that in non-generalized SAD, AS predicted a large part of the variance among undergraduate students, but less so in the generalized form (Norton et al., 1997). This has led to the suggestion that AS may play a larger role in the pathophysiology of non-generalized SAD while self-criticism may be more relevant to generalized SAD (Pagura, Cox, & Enns, 2009). An investigation reported that in a community sample of German women, after controlling for neuroticism, a significant association between SAD and several facets of AS (e.g. fear of publicly observable symptoms) was found (McWilliams, Becker, Margraf, Clara, & Vriends, 2007). It has also been proposed that AS may increase vulnerability to substance use in an effort to self-medicate to cope with anxiety (Stewart, Samoluk, & MacDonald, 1999). Individuals with AS also appear to be abusing substances with anxiolytic properties, such as alcohol and benzodiazepines (Conrod, Pihl, Stewart, & Dongier, 2000; DeHaas, Calamari, & Bair, 2002; Lejuez, Paulson, Daughters, Bornovalova, & Zvolensky, 2006; Norton et al., 1997).
1.5.3 **Neurobiology and SAD**

Several neurobiological models have been proposed for the aetiology of SAD. These include mono-aminergic theories, effect of stress and HPA axis alterations, as well as changes in the neural circuits and genetic vulnerability.

1.5.3.1 Neurotransmitters

As with other anxiety disorders and depression, the most prominent among the biological theories is the monoamine hypothesis, in particular involving neurotransmitters serotonin and gamma-Aminobutyric acid (GABA).

Serotonin function has been widely evaluated in SAD. Challenge studies using m-chlorophenylpiperazine (m-CPP), a partial serotonin agonist, and fenfluramine, a serotonin-releasing agent, have implicated serotonin abnormalities in SAD (Hollander et al., 1998). Studies have demonstrated an increase in anxiety following the administration of these agents in individuals with SAD, suggesting that serotonin dysfunction plays a role in SAD. The role of serotonin in SAD has been further explored using SSRIs in various studies that have shown, as discussed above, that SSRIs alleviate symptoms of SAD (Stein, Liebowitz, Lydiard, Pitts, & et al, 1998).

GABA is also thought to play a role in SAD. Benzodiazepines, thought to be acting on the GABA$_A$ receptor, appear to provide short-term relief of SAD symptoms. A clinical trial found a 55–60 percent difference in therapeutic response rates between those with SAD
receiving the benzodiazepine clonazepam (80 percent therapeutic response rate) in comparison to those receiving placebos (20–25 percent therapeutic response rate) (Davidson et al., 1993). In addition, GABA research has shown a potential direct link between anxiety and AUD (Nutt, 1999) because alcohol consumption enhances GABA activity and this increase in GABA could decrease anxiety (Tran & Smith, 2008). Thus, GABA may be involved in the development of SAD-AUD comorbidity through this putative positive reinforcement mechanism, similar to that of the serotonin mechanism.

Dopamine is another neurotransmitter thought to have a pathophysiological role in SAD. Neuroimaging findings have indicated that there is an association between SAD and low binding of dopamine receptors (Schneier et al., 2000). Studies have shown that SAD can be triggered by drugs that block dopamine transmission (Mikkelsen, Detlor, & Cohen, 1981) and that monoamine oxidase inhibitors (MAOIs), which are dopamine-enhancing, can alleviate symptoms of SAD (Liebowitz, Campeas, & Hollander, 1987).

Additionally, several genetic vulnerabilities have been proposed as being connected to SAD. Bievenu et al. (2007) report, in a twin study, that genetic correlations were found between extraversion and SAD (negative correlation) as well as neuroticism and SAD (positive correlation). The authors suggest that genetic factors impacting on individual differences in neuroticism and extraversion account for most of the genetic vulnerability to SAD. Reports also suggest that individuals with first-degree relatives with SAD are about three times more likely to have SAD themselves, compared to the general population (Ollendick & Hirshfeld-Becker, 2002). Individuals with the serotonin transporter gene promoter polymorphism (5-HTTLPR) who have the short-short allele show increased sensitivity to stressors, and those who had experienced childhood maltreatment showed higher levels of anxiety sensitivity, which renders
them more vulnerable to the development of mood and anxiety disorders (Stein, Schork, & Gelernter, 2008). Furthermore, Furmark et al. (2004) reported that individuals with SAD with the serotonin transporter gene (5-HTT) promoter polymorphism with one or two copies of the short allele exhibited higher levels of anxiety-related traits (anxiety symptom severity), state anxiety, and increased amygdala activation in response to a stressor compared to those with two copies of the long allele.

1.5.3.2 Neuroanatomical Findings

Neuroimaging studies, specifically fMRI investigations, confirm the key role of the amygdala and the neural circuits associated with it, in the aetiology of all forms of anxiety disorders. The key structures that are implicated in the “anxiety context” in addition to the amygdala include the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), the insula, the hippocampus, and the posterior cingulate cortex (PCC). Alterations in the neural circuitry constituted by these structures appear to be relevant to the neural basis of SAD and other anxiety conditions.

Most anxiety disorders are characterized by an inflated fear response to stimuli that are specific to each anxiety disorder (Britton & Rauch, 2009). In SAD, the stimulus is a social situation or interaction. It is posited that stimulus-driven anxiety, seen in SAD, post-traumatic stress disorder (PTSD), specific phobia (SP), and panic disorder (PD), involves bottom-up processing (i.e. attending first to specific situational stimuli relating to the threat before processing the whole picture). The bottom-up processing model has been proposed as a useful
framework to understand the implications of the dysfunctions in several key neuroanatomical structures implicated in the pathophysiology of SAD and is reviewed below.

a) Amygdala: The amygdala has been associated with stress, fear, and anxiety responses (Mueller, 2010; Roozendaal, 2009; Slavich, 2010; Wang, 2005). Those with SAD show increased bilateral amygdala activation in response to facial stimuli (for example neutral faces, neutral faces paired with negative odours, and harsh faces) and social situations in comparison to healthy controls (Britton & Rauch, 2009; Stein & Stein, 2008). The extent of amygdala activation has been correlated with the severity of social anxiety (Shah, 2009). For instance, during an emotion identification task, in response to harsh vs. happy faces, symptom severity was associated with increased amygdala activity in SAD participants (Phan, Fitzgerald, Nathan, & Tancer, 2006). It has also been shown that in anticipation of a public speech task, a feared social situation for most with SAD, those with SAD showed increased amygdala activation in comparison to healthy controls. This increased amygdala activation was correlated with fear ratings (Tillfors et al., 2001).

Recent pathophysiological models of anxiety disorders propose that the amygdala is hyperresponsive to threat stimuli and is the key neuroanatomical region mediating the response to such increased threat sensitivity to stimuli in those with anxiety disorders (Etkin, 2007; Hahn et al., 2011; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Phan, Fitzgerald, Nathan, & Tancer, 2006; Prather et al., 2001; Rauch, Shin, & Wright, 2003; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002b).

b) Anterior cingulate cortex (ACC): The ACC is divided into two sections, the rostral ACC (rACC), thought to process the more emotional tasks, and the dorsal ACC (dACC), thought to process the more cognitive tasks (Bush, Luu, & Posner, 2000). Altered activity of the ACC
seen in anxiety disorders has been proposed to represent heightened sensitivity or lowered perceptual thresholds to different stimuli (Britton & Rauch, 2009). In SAD, a greater dACC response to harsh compared to neutral faces has been reported in healthy controls, emphasizing these participants’ attentional bias to social threats (Phan, Fitzgerald, Nathan, & Tancer, 2006). Interestingly, in anticipation of giving a public speech, healthy controls had higher ACC activation than those with SAD, and Britton & Rauch (2009) posit that this could be due to an inability in those with SAD to regulate emotion during socially stressful events.

c) Medial prefrontal cortex (mPFC): The mPFC is thought to co-activate with the amygdala and also play a regulatory role in modulating the latter’s activity (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ongur & Price, 2000). Cognitive tasks are noted to increase mPFC activity and decrease that of the amygdala (Taylor, Phan, Decker, & Liberzon, 2003) and both of these regions are proposed to play a role in re-assessing or suppressing negative emotions (Ochsner, Bunge, Gross, & Gabrieli, 2002) and in regulatory processes thought to be defective in anxiety disorders. In SAD, specifically, dorsal mPFC activation in response to angry faces was noted to be greater compared to healthy participants, and was attributed to activity needed to control exaggerated amygdala responses (Britton & Rauch, 2009; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002b; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004). In another investigation, during a public speech task, SAD participants showed decreased activation in their ventral mPFC compared to healthy controls (Tillfors et al., 2001). Britton & Rauch (2009) note these findings to be in agreement with recent converging evidence that the ventral mPFC is usually inversely related to fear expression and amygdala activation (Milad & Quirk, 2002; Phelps, Delgado, Nearing, & LeDoux, 2004; Shin et al., 2004). It is also thought that the hyperresponsiveness of the amygdala to threat stimuli may also be associated with a “deficient” top-down regulation by the medial prefrontal cortex (mPFC) (Britton & Rauch, 2009).
d) Insula: The insula is involved in somatic and visceral responses, and interoceptive awareness, and is thought to play a key role in the pathophysiology of anxiety disorders. Functional neuroimaging studies have shown that individuals with generalized SAD have enhanced insula activation when exposed to negative images versus neutral images or faces in comparison to healthy controls (Stein & Stein, 2008) and the extent of this activation was positively correlated with trait anxiety (Shah, 2009). However, other studies found no group differences in harsh vs. happy faces in SAD participants vs. healthy control participants (Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002a). Interestingly, increased activation of the insula was noted in SAD participants compared to healthy controls in anticipation of a speech task (Loberbaum et al., 2004), while decreased activation of the insula was noted in SAD participants during a public speaking task compared with a private speech task (Tillfors et al., 2001).

e) Hippocampus: The hippocampus is a brain region with a key role in memory function and has also been suggested to play a role in the pathophysiology of anxiety disorders (Maren, 2005). Several fMRI studies have reported that participants with SAD have greater hippocampal and parahippocampal activation when viewing harsh faces compared to healthy controls (Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002a; Straube, Kolassa, Glauer, Mentzel, & Miltner, 2004). Similarly, in anticipation of giving a public speech, people with SAD also showed greater hippocampal activation than healthy controls (Loberbaum et al., 2004).

f) Posterior cingulate cortex (PCC): The PCC also plays an important role in memory function and has also been implicated in the pathophysiology of anxiety disorders (Britton & Rauch, 2009). While the studies looking at the relationship of PCC function and SAD are sparse,
there is at least one report of SAD participants showing reduced activation of the PCC compared to the healthy control group during a public speech task (Tillfors et al., 2001).

1.6 Linking Stress and Anxiety: The Role of the Hypothalamic-Pituitary-Adrenal (HPA) Axis

There is good evidence to suggest that stressors influence the onset and course of anxiety disorders including SAD. Clarifying the mechanisms that mediate this relationship is relevant to understanding the pathophysiology of SAD. The following section will review stress reactivity and the HPA axis function in SAD.

The general physiological reaction to stress, often referred to as the “fight or flight response”, is expressed through two systems: the sympathetic nervous system, which is part of the autonomic nervous system (ANS), and the endocrine system (Atkinson & et al., 1996; Carlson, 1994). The ANS responds to stressors in the short term and reacts instantly and directly. The endocrine system responds to stressors over a longer time period, and reacts more slowly and widely (Gross, 1998a). It is the synergy and the balance between these two systems that is thought to be responsible for the broad-based response to stress, which incorporates both immediate and long-term effects. The biological stress response in humans include the following, among others: (a) increased heart rate, blood pressure, and respiration (providing increased oxygen supply to the heart, lungs, and muscles); (b) increased blood sugar levels (providing availability of energy for higher temporary metabolism); (c) blood thickening (enable increased oxygen availability and more efficient immune response); and (d) secretion of stress hormones (epinephrine, norepinephrine, adrenocorticotropic hormone, glucocorticoids) and endorphins,
both indicators of adaptive defenses to stress (Atkinson & et al., 1996; Hanson, 1986; Kandel, 1991). Together, these responses provide the physiologic mechanisms for adaptation to stress and maintenance of homeostasis.

1.6.1 **HPA Axis and Cortisol**

In the present study, the emphasis was on the neuroendocrine response to stress – with a focus on the HPA axis and the stress hormone cortisol. Cortisol is produced and secreted into the bloodstream by cells of the adrenal cortex. The adrenal cortex is part of a broader, physiological, system known as the hypothalamic-pituitary-adrenal axis (HPA axis), which is shown below in Figure 1. The body’s principal neuroendocrine stress system starts with neurons in the paraventricular nucleus (PVN) in the hypothalamus that respond to threat or stress signals from the corticolimbic circuitry. The PVN neurons then secrete the peptides corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH and AVP are transported by the portal blood system to the anterior pituitary gland. Together, CRH and AVP stimulate the release of adrenocorticotropin hormone (ACTH). ACTH then stimulates the adrenal gland cells, located in two different layers of the adrenal cortex, the zona fasciculata and the reticularis layers, which release glucocorticoids including cortisol (Khan, King, Abelson, & Liberzon, 2009).

During normal or basal conditions, HPA activity fluctuates with circadian rhythms. CRH and AVP are released in a pulsatile manner (1–3 secretory episodes per hour). In humans, these pulses are highest in amplitude in the morning and gradually decrease throughout the day. This causes the regular diurnal pattern seen for ACTH and cortisol where the highest levels are seen in the morning, and lowest levels are seen in the evening (Khan, King, Abelson, & Liberzon,
2009). This pattern of secretion is very sensitive to change affected by various factors including changes in systemic conditions (for example medications, light, or feeding schedules), changes in one’s internal environment (for example physical activity or hypoglycemia induced by insulin), or the onset of stress (Khan, King, Abelson, & Liberzon, 2009) among others.
Figure 1: The functioning of the HPA axis (Taft & Oak Park Behavioral Medicine, LLC., 2012)
Glucocorticoids play an important role in the physiological system and are secreted in response to stress. Their role includes redirecting energy stores in order to cope with stress or perceived threats, as well as providing a negative feedback signal to prevent the overcompensation of stress-activated defense systems. This is important, as excess glucocorticoids can have detrimental effects. For example, excess cortisol can cause adrenal hypertrophy and thymus hypotrophy, and is also implicated in the pathogenesis of different conditions including diabetes, asthma, hypertension, affective disorders, and many neuropsychiatric conditions. Glucocorticoids elevate blood glucose through the stimulation of gluconeogenesis in the liver and lypolisis, and the inhibition of insulin secretion, thereby suppressing the immune system and inflammatory activity, and ending the stress response via the inhibition of CRH and ACTH (Khan, King, Abelson, & Liberzon, 2009).

1.6.2 Depression, Anxiety, and the HPA axis

There is a considerable amount of research examining depression and HPA axis function, and the following overview will provide a context for the ensuing focus on HPA function in anxiety disorders including social phobia.

Research has shown that in depressive illness, there is an altered physiological response to stress as well as increased perception of stress. Depressive episodes are often precipitated by stressful life events. Results show that the majority of individuals with clinical depression had experienced a major stressful life event in the year prior to the onset of the episode (Paykel, 1978). Daily minor stressful events have also been shown to play a role in the perpetuation of depression. Thus, minor stressors referred to as “hassles” add to negative affect, and cognitions
in those already suffering from depressive illnesses (van Eck, Nicolson, & Berkhof, 1998). Those with depression have been noted to interpret both positive and negative events as stressful and perceive a greater number of stressors in general. Such increased perceived stressors are often associated with treatment resistance and greater severity of depression (Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006; Peeters, Nicholson, & Berkhof, 2003; Ravindran, Matheson, Griffiths, Merali, & Anisman, 2002).

Research dating back to the late 1950’s (Board, Wadeson, & Persky, 1957) initially noted that individuals with MDD have altered activity of their HPA axis. Since then, numerous studies have confirmed this finding. More specifically, studies have reported the following cortisol abnormalities in those suffering from MDD: (a) increase in cortisol secretion (Pariante & Lightman, 2008); (b) dexamethasone non suppression (Pariante & Lightman, 2008); (c) increased cortisol response to ACTH challenge tests (Amsterdam, Winokur, Abelman, Lucki, & Rickel, 1983); (d) attenuated cortisol awakening response (Huber, Issa, Schik, & Wolf, 2006); and (e) elevated total and free cortisol concentrations in their urine (Carroll, Curtis, & Mendels, 1976).

In spite of the common comorbidity of anxiety and depression, studies evaluating the link between anxiety disorders and HPA axis abnormalities have reported inconsistent results (Shin, 2010). Studies have found increases, decreases, or no changes in HPA activity in response to stress in those with anxiety disorders (Abelson, Khan, Liberzon, & Young, 2007; Curtis, Buxton, Lippman, Nesse, & Wright, 1976; Yehuda, Giller, Southwick, Lowy, & Mason, 1991; Yehuda, 2006). However, reports of elevated HPA response in those with comorbid MDD and anxiety disorder appears to be more consistent compared to those with MDD alone, suggesting that
anxiety disorders under certain conditions, may be linked to heightened HPA reactivity (Young, Abelson, & Cameron, 2004).

1.6.3 SAD and the HPA Axis

As with other anxiety disorders, studies characterizing the neuroendocrine profile of SAD participants are sparse and report inconsistent results. There are no consistent reports of abnormal basal cortisol levels in SAD participants compared to healthy control groups (Khan, King, Abelson, & Liberzon, 2009). In addition, there is a lack of uniform findings in studies examining cortisol levels in response to social stress-inducing situations.

To date, eleven studies exist in the literature examining the relationship between SAD, cortisol, and stress. Whereas some studies show an increased cortisol response following stress in individuals with SAD (Condren, O’Neill, Ryan, Barrett, & Thakore, 2002; Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001; Roelofs et al., 2009; van West, Claes, Sulon, & Deboutte, 2008; Yoon, 2012), others show either a decreased cortisol response (Beaton et al., 2006; Shirotsuki et al., 2009) or no difference at all in cortisol response between SAD participants and healthy controls (Levin, 1993; Martel et al., 1999; van Veen et al., 2008; Vreeburg et al., 2010).

See Table 1 on page 44. A review of these studies are provided below:

i) Studies Showing Increased Cortisol Response in SAD Participants

In a study by Furlan et al. (2001), adult SAD participants showed either increases or decreases in salivary cortisol response to a speech task. However, the dominant response appeared to be an increase in cortisol, as evidenced by the 90 percent increase in cortisol in those
participants who showed increases, in comparison to a more modest 32 percent decrease
evidenced in the participants who showed decreases. Researchers also observed that only the
acute cortisol response to psychological stress in SAD differed from controls. Participants in this
study were clinically assessed for generalized SAD as the primary diagnosis, and the absence of
psychiatric illnesses using the DSM-IV (Furlan, DeMartinis, Schweizer, Rickels, & Lucki,
2001).

Using a stress induction involving a mental arithmetic task and a memory task in front of
an audience, Condren et al. (2002) found that when the plasma cortisol response was calculated
using the difference between baseline and the maximum values, it was significantly higher in
SAD participants compared to controls. Participants in this study were clinically assessed using
the DSM-IV (SCID) and were adults who either had no psychiatric disorders, in other words the
control participants, or had the generalized subtype of SAD (Condren, O’Neill, Ryan, Barrett, &
Thakore, 2002).

A study by van West et al. (2008) measured HPA axis activity using salivary cortisol in
prepubertal children who were six to twelve years of age suffering from SAD, with similar aged
healthy controls. Of note is that half of the SAD participants in this study had a comorbid anxiety
disorder. Using a modified Trier Social Stress Test (TSST), researchers found that those with
SAD had a higher salivary cortisol response to a public speaking task than controls (van West,
Claes, Sulon, & Deboutte, 2008). Participants were clinically assessed with the ADIS-IV-CP, the
children’s version of DSM-IV (van West, Claes, Sulon, & Deboutte, 2008).

Roelofs et al. (2009) found that adult SAD participants, diagnosed using the DSM-IV
criteria, had greater salivary cortisol responses than controls following the TSST, a commonly
used and validated test involving a speech and mental arithmetic task. It was also noted that the
extent of cortisol reactivity was positively correlated with the degree of avoidance behaviour (Roelofs et al., 2009).

Most recently, Yoon et al. (2012) evaluated cortisol response measured in saliva to speech and memory tasks in three groups of participants: those with gSAD alone, gSAD and comorbid depression, and healthy controls. Participants with gSAD alone had a higher cortisol response compared to the other two groups. Participants were diagnosed using the Diagnostic Statistical Manual of Mental Disorders (DSM-IV - SCID) (Yoon, 2012).

ii) Studies Showing Decreased Cortisol Response in SAD Participants

In the study by Beaton et al. (2006), adult participants were clinically assessed using the DSM-IV (SCID) and the Social Phobia Inventory (SPIN). Results of this study in response to a speech task, participants with symptoms of SAD had lower salivary cortisol levels compared to controls. In a follow-up investigation, they further found that adults who self-reported high trait shyness showed decreased cortisol at baseline and fifteen minutes post-task. Of note is that these participants did not have syndromal SAD (Beaton et al., 2006).

In a similar investigation, Shirotsuki et al. (2009) reported that in response to the TSST as a psychosocial stressor, male college students with high trait social anxiety showed lower salivary cortisol reactivity than those with low trait social anxiety. None of the participants in this study had a clinically significant mental disorder, and the Short Fear of Negative Evaluation Scale (SFNE) was used to assess trait social anxiety (Shirotsuki et al., 2009).
iii) Studies Showing No Difference in Cortisol Response Between SAD and Healthy Control Participants

In an early investigation by Levin et al. (1993), participants were assessed using the DSM-III-R and plasma cortisol response to a public speaking task was measured. Results showed that cortisol levels did not differ between participant groups. However, it was noted that the adult SAD participants devoid of comorbidities reported less confidence in a public speaking task than the healthy control participants.

Martel et al. (1999) found significant increases in salivary cortisol levels in anticipation of the TSST in both SAD and control participants, but found no significant group differences. Participants were adolescent girls and were clinically assessed for SAD using the Anxiety Disorders Interview Schedule for Children (ADIS-C). Individuals with other anxiety disorders in addition to SAD were also included in this study (Martel et al., 1999).

In a study by van Veen et al. (2008), adult participants were clinically assessed using the DSM-IV and those with gSAD were found to have higher diurnal/post-dexamethasone salivary alpha-amylase (sAA) levels than control participants. However, no differences in salivary cortisol levels between the two groups were found under basal, non-challenging conditions (van Veen et al., 2008).

Evaluating participants with a spectrum of anxiety disorders using the Beck Anxiety Inventory (BAI) and the Composite International Diagnostic Interview (CIDI), Vreeburg et al. (2010) found no significant salivary basal cortisol difference between adults with SAD and controls. Of note is that there was no specific stress provocation in this study (Vreeburg et al., 2010).
**Table 1: Summary of Studies Evaluating Basal Cortisol and Cortisol Response to Stress in SAD**

*Participants*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Key Findings</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased Cortisol Response in SAD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furlan et al. (2001)</td>
<td>SAD participants showed a sharp rise (90% increase) in cortisol in response to a speech stress task compared to controls. This group difference was only observed for the acute cortisol response.</td>
<td>Adults with SAD</td>
</tr>
<tr>
<td>Condren et al. (2002)</td>
<td>Participants with SAD had higher cortisol levels compared to control participants in response to a social stressor (mental arithmetic and memory task)</td>
<td>Adults with SAD</td>
</tr>
<tr>
<td>van West et al. (2008)</td>
<td>SAD participants had higher salivary cortisol response to a public speaking task (modified TSST for children) compared to controls</td>
<td>Children (6-12 years old) with SAD</td>
</tr>
<tr>
<td>Roelofs et al. (2009)</td>
<td>SAD participants had higher cortisol responses than controls in response to the TSST.</td>
<td>Adults with SAD</td>
</tr>
<tr>
<td>Yoon et al. (2012)</td>
<td>SAD participants had increased salivary cortisol levels compared to control and MDD/SAD participants in response to a public speech task</td>
<td>Adults with SAD</td>
</tr>
<tr>
<td><strong>Decreased Cortisol Response in SAD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beaton et al. (2006)</td>
<td>SAD participants had lower salivary cortisol levels compared to controls before and after a speech task. High trait shyness was also linked to lower salivary cortisol in individuals with SAD during the speech task.</td>
<td>Adults</td>
</tr>
<tr>
<td>Shirotsuki et al. (2009)</td>
<td>Male college students with high trait social anxiety showed lower cortisol reactivity, compared to those with low trait anxiety, in response to the TSST.</td>
<td>Male College Students</td>
</tr>
<tr>
<td><strong>No difference in Cortisol Response Between Groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levin et al. (1993)</td>
<td>Cortisol levels did not differ between SAD and control participant groups in response to the TSST, though SAD participants reported feeling less confident.</td>
<td>Adults with SAD</td>
</tr>
<tr>
<td>Martel et al. (1999)</td>
<td>No difference in cortisol levels was found between control and SAD participants. Results showed significant increases in salivary cortisol levels in anticipation of the TSST in both groups.</td>
<td>Adolescent Females with SAD</td>
</tr>
<tr>
<td>van Veen et al. (2008)</td>
<td>No differences in salivary cortisol levels were found between SAD and control participants (in basal, non-challenging conditions).</td>
<td>Adults with SAD</td>
</tr>
<tr>
<td>Vreeburg et al. (2010)</td>
<td>Participants with a current anxiety disorder had higher awakening cortisol levels. No difference in awakening cortisol levels was found between SAD participants alone and control participants.</td>
<td>Adults with anxiety disorders</td>
</tr>
</tbody>
</table>
1.7 Summary of Literature and Rationale for the Current Investigation

Taken together, the above studies confirm that there is significant alteration in HPA activity in individuals with SAD. However, the nature and direction remains unclear, with several factors being proposed as contributing to the conflicting findings. The following observations may be relevant in evaluating the above literature:

- Positive cortisol response to stress provocations in SAD participants was reported more frequently compared to findings of blunted response.

- Basal cortisol was consistently found to be unaffected in those with SAD.

- In the two studies that reported decreased cortisol levels in response to stress provocation, the participants had trait anxiety/shyness and did not have syndromal conditions.

Based on the existing literature, then, there is evidence to suggest that elevated cortisol in response to social stress to be a biomarker for SAD. However, methodological limitations of the published studies to date may need to be addressed to confirm this observation. To address these above issues, the following novel approaches were included in this investigation:

- Stress induction – Only a limited number of studies examined stress induction and four of these utilized the TSST, the gold standard for social stress induction as a standardized and validated stress provocation method. Although different social stress provocations have been used in the literature, the TSST is arguably the most validated. The TSST provides an induction of moderate psychological,
social stress in a laboratory setting (Kirschbaum, Pirke, & Hellhammer, 1993) that consists of a ten-minute anticipation period and a ten-minute test period of a public speech and a mental arithmetic task. This protocol has been found to induce significant changes in cortisol levels (Kirschbaum, Pirke, & Hellhammer, 1993) and confirmed to be effective in activating the HPA axis and sympathetic nervous system (Kern et al., 2008; Kirschbaum & Hellhammer, 1999; Schommer, Hellhammer, & Kirschbaum, 2003). In a placebo TSST (consisting of a speech task and a mental arithmetic task without the social-evaluative threat) versus the TSST paradigm, the TSST has been found to provoke a strong cortisol response, which is significantly different than that seen under the placebo condition (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009). The present study used the TSST in the validated method and employed plasma cortisol levels as a measure of the neuroendocrine stress response (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009).

- **Basal versus stress-induced cortisol measures** – Few past studies employed both basal and stress induced cortisol measures. Most investigations used socially stressful conditions to compare cortisol levels, while other studies measured only basal cortisol levels (van Veen et al., 2008; Vreeburg et al., 2010). In the present study, both basal and stress induced cortisol levels will be measured.

- **Heterogeneity of study populations to date: comorbidity, gender, and age** – Comorbidity in past studies may have contributed to increased variability of their results. The majority of investigations included participants with clinically significant SAD, while two studies used non-clinical participants who scored high on trait dimensions of anxiety (Beaton et al., 2006; Shirotsuki et al., 2009). It is
also worth noting that studies had variations in the inclusion and exclusion criteria used to select SAD participants, and often included SAD participants with significant comorbidities. As well, although most studies used adult participants of both genders, others used different age and sex criteria. For example, Van West et al. (2008) used children participants six to twelve years of age, and Shirotsuki et al. (2009) only recruited male adult students as participants. As well, Beaton (2006) recruited undergraduate students of both genders, and Martel et al. (1999) only recruited female adolescent participants.

The present study recruited adult participants of both genders, with SAD as their primary diagnosis. Approximately 83% of participants were devoid of significant comorbidities. However, two participants met criteria for GAD. All participants were devoid of depression.

- **Plasma versus salivary cortisol** – While saliva samples are easier to obtain, plasma levels give a more direct measure of blood cortisol levels with a better temporal resolution, thereby allowing for a more precise time-course measurement (Perogamvros, Keevil, Ray, & Trainer, 2010; Yates, Ross, Hallford, Hill, & Wesley, 2008). The decreased temporal resolution associated with salivary cortisol measurements may have contributed to conflicting findings of the published studies. Therefore, the decision was made to assess plasma levels of cortisol in the current study.
1.8 Aims and Hypotheses of the Present Study

The following section outlines the aims and hypotheses of the current study.

1.8.1 Aims

- To determine if there are any differences in cortisol response to the TSST between the participants in the SAD and control groups.

- To compare the TSST induced affective states (evaluating both positive and negative affect, separately) in the two groups of participants.

- To examine the relationship between serial plasma cortisol levels as a response to the TSST and measuring affective states (looking at both positive and negative affect, separately).

1.8.2 Hypotheses

Based on the proposed aims, the following hypotheses were formulated:

**Hypothesis 1:**

Individuals with SAD will show an exaggerated stress reactivity response on the TSST in comparison to healthy controls. Such exaggerated response will manifest as a higher plasma cortisol response.
Hypothesis 2a):

The Positive and Negative Affect Scale (PANAS), given before and after the stressor, will show decreased positive affect in the SAD group in comparison to the healthy control group. There will also be a time effect, where the SAD group will show a decrease in positive affect post-TSST compared to pre-TSST.

Hypothesis 2b):

The Positive and Negative Affect Scale (PANAS), given before and after the stressor, will show increased negative affect in the SAD group in comparison to the healthy control group. There will also be a time effect, where the SAD group will show an increase in negative affect post-TSST compared to pre-TSST.

Hypothesis 3:

Significant correlations will be seen between the plasma cortisol levels and measures of both positive and negative affect.
Chapter 2 : Methods

The purpose of this chapter is to:

• provide an overview of the study design;
• describe the TSST stress protocol;
• describe the approach to statistical analysis.

2.1 Overview, Overall Design, and Participants

2.1.1 Overall Design

Participants who fulfilled the inclusion and exclusion criteria went through two visits – the first one for screening purposes and the second one for participants to undergo a stress procedure, have plasma cortisol samples taken (biological component), and complete various tasks that look at anxiety symptoms, stress and coping measures, and childhood trauma (behavioural component). Hormonal response to a social stress induction (the TSST) was compared across two groups, namely, individuals with SAD and a healthy control group. Details are more fully described in the study procedures section below.
2.1.2 Participants

Twelve participants who met diagnostic criteria for SAD and twelve volunteers with no history of psychiatric disorders were recruited. SAD participants were recruited from referrals coming into the Centre for Addiction and Mental Health (CAMH) as well as from the CAMH website and advertisements placed in University Health Network hospitals. Healthy volunteers were recruited from flyers posted around the University of Toronto campus, community boards, and University Health Network hospitals. Participants who responded to flyers were briefly screened over the telephone before they were asked to come in. Healthy controls were matched to the patient group by gender and age. All participants went through an informed consent process and signed a consent form prior to enrolment in the study. This study received CAMH Research Ethics Board approval.

Inclusion Criteria for Participants with SAD

- Male or female between eighteen to sixty-five years of age
- Meet diagnostic criteria for SAD
- Physically healthy
- Able to provide consent

Exclusion Criteria for Participants with SAD

- Diagnosis of major depression, dysthymia, bipolar I & II, or any other Axis I disorder as a primary diagnosis
• Any significant current or past history of substance abuse/dependence

• Acute or high risk of suicidality during the past six weeks

• Psychotic symptoms

• Diagnosis of anorexia nervosa and/or bulimia nervosa

• Major medical illnesses, for example asthma, heart disease, Crohn’s disease, rheumatoid arthritis, diabetes, hepatitis C, etc.

• Medications such as atypical antipsychotics, psychostimulants, mood stabilizers, benzodiazepine, and mirtazapine less than two weeks prior to enrolment

• Medications such as antibiotics and most steroid medications

• Pregnancy

• Major recent life stressors, for example death of a loved one, divorce, job loss, moving, etc.

**Note:** Participants were included in the study whether or not they were taking antidepressant medication. Those who were on antidepressant medication must have been taking this medication at a stable dose for at least two weeks prior to study enrolment in order to be included in the study.

**Inclusion Criteria for Healthy Volunteers**
• Male or female between eighteen to sixty-five years of age

• Physically healthy

• Able to provide consent

Exclusion Criteria for Healthy Volunteers

• Any current or history of symptoms associated with any Axis I or II disorder

• History of substance abuse/dependence

• Major medical illnesses, for example asthma, heart disease, Crohn’s disease, rheumatoid arthritis, diabetes, hepatitis C, etc.

• Medications such as antibiotics and most steroid medications

• Pregnancy

• Major recent life stressors, for example death of a loved one, divorce, job loss, moving, etc.

2.2 Measures: Stress Protocol–Behavioural and Biological

2.2.1 Behavioural Measures

Participants completed the following behavioural measures:

• The Liebowitz Social Anxiety Scale–self-report (LSAS-SR) (Liebowitz, Campeas, & Hollander, 1987): The LSAS is a twenty-four-item scale providing separate scores for
fear and avoidance in social and performance situations over the past week. The LSAS-SR shows high internal validity and compares well to the clinician-administered version of the LSAS (Fresco et al., 2001). The LSAS-SR asks participants to provide ratings on a four-point likert scale from 0–3. The fear subscale ranges from 0 being “none” to 3 being “severe” and the avoidance subscale ranges from 0 being “never” to 3 being “usually.”

- Social Phobia Inventory (SPIN) (Connor et al., 2000): As Beaton et al. (2006) state: “The Social Phobia Inventory measure is a 17-item self-report measure of fear, avoidance, and physiological symptoms associated with social phobia and social anxiety”. SPIN items focus on fears of talking and socializing with others and fears of experiencing and exhibiting physiological signs of anxiety, such as blushing or sweating (Connor et al., 2000).

- State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970): The STAI is a validated twenty-item self-report assessment device, which includes separate measures of state and trait anxiety. The state anxiety portion is twenty questions long, on a four-point likert scale ranging from 1 to 4, where 1 represents “not at all” and 4 represents “very much so” and the trait anxiety portion is also twenty questions long, on a four-point likert scale ranging from 1 to 4, where 1 represents “almost never” and 4 represents “almost always.”

- Hamilton Depression Rating Scale 29-item (HAM-D-29) (Hamilton, 1967): This clinician-rated scale measures depressive symptom severity. Scores were obtained for the first seventeen items representing the core symptoms of depression, as well as twenty-nine–item scores which include items specific to subtypes of depression, for example
atypical depression. All raters were required to successfully complete training specific to this measure (McKay, 2009).

- Beck Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996): This self-report questionnaire has twenty-one items measuring an individual’s depressive symptoms in the past week. Scores can range from 0 to 63 (Roelofs et al., 2009).

- Childhood Trauma Questionnaire (CTQ) (Bernstein & Fink, 1998): This self-report questionnaire consists of twenty-eight questions rated on a five-point likert scale as one of the following: never true, rarely true, sometimes true, often true, and very often true. This questionnaire assesses childhood maltreatment and has various subscales looking at emotional, physical, and sexual facets of childhood abuse or neglect.

- Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988): This is a twenty-item self-report measure containing two scales, one of positive emotions, and one of negative emotions. Participants indicated the extent to which they felt the various emotions on a five-point likert scale, where 1 represents “very slightly or not at all” and 5 represents “extremely.” Separate scores for positive and negative affects were obtained (McKay, 2009).

2.2.2 Biological Measures

In this study, plasma cortisol samples were taken as described below. Serial plasma cortisol samples were obtained before and after the stress induction (the TSST). The method used is outlined in the publication by Raspopow et al. (2010): “a 19-gauge needle with a 5 foot
line was used for blood withdrawal, and the rate of withdrawal over the 120 minute sampling period was controlled by a Dakmed continuous withdrawal pump (Dakmed Inc., Buffalo, NY).” Following their method, the needle was covered with a cloth in order to prevent participants from viewing the blood being withdrawn (Raspopow, Abizaid, Matheson, & Anisman, 2010). Samples were taken at baseline (right before the stress task) and ten, thirty, forty-five, and sixty minutes post stress task directly into vacutainer test tubes coated with EDTA, with each sample consisting of approximately 5 mL of blood, with a total of 40 mL being taken across the 105 minute period, including the minimal amount drawn between sampling times to prevent the line from clogging.

2.2.3 Stress Protocol

The TSST (Kirschbaum, Pirke, & Hellhammer, 1993) was used in the present study for the stress protocol. Based on the procedures developed by Kirschbaum et al. (1993), social stress was induced by placing participants in a novel situation in which they believed they were being socially evaluated. The task required participants to make a five-minute speech and to complete a five-minute arithmetic challenge for which they had to count backwards from 1022 in intervals of thirteen in front of a panel of three confederates. These tasks were preceded by an anticipation period of ten minutes during which participants prepared for their speeches. Participants were asked to think of themselves as job applicants (Roelofs et al., 2009) and were informed that the panel members were behavioural analysts who would be assessing them for signs of anxiety. To heighten the feeling of being evaluated, participants were also led to believe that a microphone and video camera would be used to provide video and audio recordings for the assessment of any anxiety symptoms (McKay, 2009). As outlined by Roelofs et al. (2009): “In the event that
participants reported being unable to proceed with the free speech, they received a modified version of the TSST, with up to three measures helping participants to fulfill the task, without dropping out. The measures were in fixed order as follows, and the next step was only applied if necessary: 1) giving verbal encouragements during the free speech; 2) structured interview instead of free speech, involving direct questions about job application; and 3) pre-term cancellation of free speech, and immediate continuation with the mental arithmetic task.”

2.3 Study Procedures

2.3.1 Visit 1: Screening/Baseline Procedures

All participants underwent a diagnostic interview (SCID) (First & et al., 1995) to confirm the diagnosis of SAD and in the case of the controls, to confirm the absence of any psychiatric disorders. All SAD participants had their primary diagnosis of SAD confirmed previously by a psychiatrist. Demographic information, medical history, psychiatric history, and current treatment information was obtained. As well, height, weight, and waist/hip ratio was measured and body mass index (BMI) was calculated. Blood pressure and heart rate vitals were also obtained. In order to control for menstrual phase, information regarding menstrual cycles was obtained from female participants. Participants were also asked to complete various questionnaires, including the LSAS and the STAI.
2.3.2 Visit 2: Experimental Stress Induction

For the second visit, participants were asked to come in for what they believed to be a moderate social stress task in the afternoon. Participants were asked to refrain from eating or doing rigorous exercise within two hours prior to their visit. Participants were reminded that they could stop their participation in the study at any time. Information regarding food consumption for that day was collected in order to make sure participants had not eaten within the past two hours. Participants remained seated throughout the experiment and an indwelling catheter was inserted in their non-dominant arm, and blood was taken automatically at a very slow rate using a Dakmed pump. Participants were then given an introduction to the visit procedures and were left in the room for a period to relax. Hormone samples, blood pressure, and heart rate were taken at various time points before the stress induction began. Participants were also asked to complete the PANAS prior to the TSST. Twenty minutes after the participants arrived, panel members entered the room and gave them instructions about the task they needed to do, namely to prepare a speech. Participants were given the opportunity to ask questions for clarification and then panel members exited the room to allow the participants to prepare for the task.

After a period of ten minutes, panel members were brought back into the experiment room. A microphone, tape recorder, and video camera were placed in front of the participants and they were instructed to begin their speeches. If a participant finished speaking before the five-minute time limit was over, panel members remained silent for twenty seconds and then asked a list of scripted questions. Panel members paused for ten seconds between each scripted question before moving on to the next question. After the speech task, participants were given instructions for a mental arithmetic challenge where they were asked to count backwards from 1022 in intervals of thirteen. If participants made an error doing this, a panel member would
inform them of the error and instruct them to start the task over again. This continued until the five-minute time limit was over.

Participants were then instructed to await further instructions and the panel members exited the room. At this time, the participants completed the post-TSST PANAS. The experimenter instructed the participants to rest while further serial plasma cortisol samples were obtained. In all, samples were taken two minutes after arrival, immediately prior to the stress induction, and then ten minutes, thirty minutes, forty-five minutes, and sixty minutes post stressor. The total volume of blood drawn in this challenge was 40 mL. The experimenter kept conversation with the participant to a minimum in order to standardize the experiment and deferred questions until the end of the experiment at which time participants were debriefed and compensated for their time.

Figure 2: Serial Plasma Cortisol Sample Schedule
2.4 Biological Assay Analysis

The candidate completed the analysis of the plasma cortisol samples under the supervision of Dr. Hymie Anisman and his laboratory at Carleton University. All of the procedures were conducted in duplicate, and provided less than 8 percent inter- and intra-assay variability. Assays were performed in a single run to preclude inter-assay variability. For the purpose of cortisol determinations, blood was collected in tubes containing 10 µg of EDTA and centrifuged within an hour of having taken the sample for fifteen minutes at 3600 RPM, and the plasma was aliquoted for each assay and then stored in a freezer at -80 °C for subsequent determinations using commercial radioimmunoassay (I-125) kits (Linco, St. Charles, MO and MP Biomedicals, Solon, OH) following the procedures described in the biological measures section. The sensitivity of the assays was approximately 8pg/mL.

2.5 Data Analysis

Descriptive statistics for quantitative demographic measures, for example age, was compared across groups with independent samples t tests. Cortisol levels were compared throughout the stress protocol between SAD and control groups with repeated measures Analysis of Variance (ANOVA), using the general linear model, peak change, and change from baseline, as well as with area under the curve (AUC). AUC was measured in two different ways, following Pruessner et al.’s (2003) formulae as shown (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).
1) \( AUC_G = \sum (m(i+1) + m_i) / 2 \)

Note: This formula calculates AUC with respect to ground.

2) \( AUC_I = AUC_G - m_1 \cdot \sum t_i \)

Note: This formula calculates AUC with reference to the first value and ignores the distance from zero for all measurements.

Due to technical difficulties, the sixth plasma cortisol sample was not obtained for two SAD participants and one control participant. As such, missing data was imputed for these three participants using the series mean.
Chapter 3 : Results

The purpose of this chapter is to:

- present baseline clinical and demographic characteristics of the SAD and control participants;
- present the cortisol stress response to the TSST, as measured by serial plasma cortisol levels in the SAD and control participants, and evaluate potential associations between the neuroendocrine findings and behavioural data;
- present group differences in the behavioural measures between SAD participants and matched healthy control participants.

Any statistical differences for measures were based on $p < 0.05$ level of significance.

3.1 Demographic and Clinical Variables

3.1.1 Demographic Variables

Twenty-four individuals, including eight females and sixteen males, consented to participate in this study. The SAD group comprised of twelve participants, of which four were female and eight were male, as with the control group. The SAD group was both age ($\pm 5$ years) and gender-matched to the control group. The mean age of participants was 32.42 ($SD=10.13$),
with a range from 19 to 54 years old. The mean age of participants with SAD was 33.00 (SD=10.43) while that of control participants was 31.83 (SD=10.26). There were no significant age differences between the two groups. See Table 2A for demographic variables.
Table 2A: Demographic variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>66.7%, n=8</td>
<td>66.7%, n=8</td>
</tr>
<tr>
<td>Age</td>
<td>33.00 ± 3.01 (19-54)</td>
<td>31.83 ± 2.96 (21-51)</td>
</tr>
<tr>
<td>Years of Education</td>
<td>15.75 ± 0.41 (13-18)</td>
<td>17.75 ± 0.87 (12-22)</td>
</tr>
<tr>
<td>Level of Education</td>
<td>5.58 ± 0.31 (4-8)</td>
<td>6.67 ± 0.43 (3-8)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.27 ± 1.33 (19.40-35.76)</td>
<td>25.39 ± 1.29 (21.61-37.49)</td>
</tr>
</tbody>
</table>
3.1.2 Clinical Variables

The clinical data that was evaluated included measures of anxiety, depression, and childhood trauma, as discussed below.

3.1.2.1 Diagnostic Measurements: Anxiety Measures

All participants, from both the SAD and control groups, underwent a structured clinical interview (SCID – a tool with standardized questions that helps health professionals make more accurate diagnoses of various mental illnesses) for diagnostic purposes. All SAD participants fulfilled DSM-IV-TR criteria for SAD, which was their primary diagnosis, as confirmed by a psychiatrist in the Mood and Anxiety program at the Centre for Addiction and Mental Health (CAMH), and were absent of significant comorbidities. Of the twelve participants, two met DSM-IV-TR criteria for generalized anxiety disorder, six met DSM-IV-TR criteria for past major depressive episode, and one met DSM-IV-TR criteria for past dysthymia. Fifty percent (n=6) of the SAD participants were receiving either an SSRI or an SNRI medication for the treatment of SAD at the time of study participation, but ANOVA revealed no significant effect of the medication on baseline cortisol levels.

Severity of Anxiety Measurements:

Several measures were used to measure the severity of participants’ anxiety, specifically SAD. On the LSAS (the primary measure of social anxiety severity), the mean total score for the SAD group was 64.56 (SD=12.96), with no significant differences between those with and without a comorbid disorder. This average indicates that the illness severity of SAD participants was in the moderately severe (55-65) range. The SAD group scored significantly higher
compared to the control group on all anxiety measures including LSAS, SPIN, and STAI for both the state and trait subscales. Independent samples t-tests were used to compare means between groups. First, for the LSAS, the SAD group scores ($M=64.56$, $SD=12.96$) were significantly higher than the control group scores ($M=30.18$, $SD=15.75$) ($t(18) = 5.25$, $p<.001$, with an effect size of $d=.86$). Second, the SPIN showed significant group differences between the SAD participants ($M=53.67$, $SD=9.96$) and the control participants ($M=28.56$, $SD=8.04$) ($t(19) = 6.19$, $p<.001$, with an effect size of $d=.09$) where the SAD participants demonstrated significantly higher scores. Finally, on the STAI, the SAD group scored significantly higher on the trait anxiety subscale ($M=49.83$, $SD=4.37$) compared to the control group ($M=34.11$, $SD=8.46$) ($t(19) = 5.56$, $p<.001$, with an effect size of $d=8.01$) as well as on the state anxiety subscale [SAD group: ($M=41.08$, $SD=8.34$); control group: ($M=32.82$, $SD=7.88$); ($t(21) = 2.44$, $p=.02$, with an effect size of $d=.007$)]. These results confirmed that the SAD group reached clinical levels of anxiety, whereas the control group did not, validating the group difference between the two groups. These results are presented in Table 2B below.

3.1.2.2 Depression Measures

None of the participants met DSM-IV-TR criteria for current syndromal depression. In this study, the aim was for the SAD and control participants to be free of any significant depression, as its presence would impact on the HPA axis activity. Participant total HAM-D and the BDI scores did not reach levels of clinical significance (for example, HAM-D $\geq 8$; BDI $\geq 14$), validating that both participant groups were devoid of current depression. Nonetheless, it should be noted that the SAD group did show greater presence of subsyndromal depressive symptoms compared to the control group, as measured by both the HAM-D and BDI.
Independent samples t-tests were used to compare the means between the two groups. On the HAM-D, participants with SAD ($M=4.00$, $SD=1.60$) scored significantly higher than control participants ($M=.75$, $SD=1.29$) ($t (22) = 5.49$, $p=<.001$, with an effect size of $d=.21$). On the BDI, SAD participants ($M=11.50$, $SD=6.13$) had significantly higher scores than the control group ($M=4.64$, $SD=3.72$) ($t (21) = 3.21$, $p=.004$, with an effect size of $d=2.07$). It should be noted that the higher HAM-D/BDI scores in SAD participants were at least in part driven by significantly high scores on the anxiety items, which may have significant weight in these measures. Results can be seen in Table 2b below.

3.1.2.3 Childhood Trauma Measures

Childhood trauma was evaluated using the Childhood Trauma Questionnaire (CTQ). Independent samples t-tests were used to test for group differences. Group differences were found for childhood trauma measures. The SAD group ($M=1.95$, $SD=.25$) had a significantly higher mean total score on the CTQ compared to the control group ($M=1.54$, $SD=.21$) ($t (18) = 3.91$, $p=.001$, with an effect size of $d=.08$). SAD participants ($M=2.64$, $SD=.78$) also had a significantly higher mean score for the emotional abuse subscale of the CTQ compared to the control group ($M=1.40$, $SD=.44$) ($t (19) = 4.39$, $p=<.001$, with an effect size of $d=1.98$). Results are presented in Table 2B below.
Table 2B: Clinical measures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSAS total score</td>
<td>64.56 ± 4.32 (53-95)*</td>
<td>30.18 ± 4.75 (11-57)</td>
</tr>
<tr>
<td>SPIN total score</td>
<td>53.67 ± 2.87 (33-68)*</td>
<td>28.56 ± 2.68 (19-40)</td>
</tr>
<tr>
<td>STAI State Anxiety Total</td>
<td>41.08 ± 2.41 (27-53)*</td>
<td>32.82 ± 2.38 (21-43)</td>
</tr>
<tr>
<td>STAI Trait Anxiety Total</td>
<td>49.83 ± 1.26 (40-55)*</td>
<td>34.11 ± 2.82 (23-44)</td>
</tr>
<tr>
<td>HAM-D 17 total score</td>
<td>4.00 ± 0.46 (2-7)*</td>
<td>0.75 ± 0.37 (0-4)</td>
</tr>
<tr>
<td>BDI total score</td>
<td>11.50 ± 1.77 (0-20)*</td>
<td>4.63 ± 1.12 (0-10)</td>
</tr>
<tr>
<td>CTQ total score</td>
<td>54.60 ± 7.12 (45-71)*</td>
<td>43.20 ± 5.87 (37-56)</td>
</tr>
<tr>
<td>CTQ Emotional Abuse Total</td>
<td>13.18 ± 3.92 (7-20)*</td>
<td>7.00 ± 2.21 (5-12)</td>
</tr>
</tbody>
</table>

* Denotes significantly different than control group (p<0.05)
3.2 Cortisol Measures – Hypothesis 1

Past research has shown that cortisol data often requires statistical transformation due to outliers and non-normal distributions. In this study, normality was examined for important study variables. This was done using the Explore function of SPSS-16. In order to determine whether the cortisol data was normally distributed, an a priori cut-off of \( p > .01 \) on the Kolmogorov-Smirnov (K-S) test was determined and used. In other words, variables that had a distribution with a K-S statistic of \( p > .01 \) were considered normally distributed. Normality tests revealed the need to transform the cortisol data and data was transformed by square root. The square rooted data was used for these calculations.

A two-way repeated measures ANOVA was used to examine differences in cortisol levels between SAD participants and control participants before and after the stress induction. This test revealed no significant main effect of group \((F (1,22) = 0.84, p = 0.37)\) or group x time interaction difference \((F (5,110) = 0.16, p = 0.98)\). However, a significant main effect of time was found \((F (5,110) = 3.72, p = 0.004)\). A power analysis revealed that the effect size is \( d=0.22 \), the observed power is 0.18, and the partial eta squared is 0.037. In order to achieve a power of 0.8 with this study, a sample size of \( n=81 \) (per group) would have been needed.

A few possible covariates were chosen at the beginning of the study to evaluate if they bias the results. These include: childhood emotional abuse, childhood physical abuse, BMI, and age. Correlational analyses revealed an association between childhood emotional abuse and AUC for the SAD group, as well as BMI and AUC for all participants. No significant correlations were found between childhood physical abuse/age and cortisol response measures of AUC and peak change, thus they were not used as covariates. Significant correlations were found between childhood emotional abuse and \( \text{AUC}_G \) \((r= -.80, p=.01)\) (Spearman correlation) as well as BMI
and AUC$_1$ ($r = .81$, $p = .005$) (Pearson correlation). Both the Pearson and Spearman correlations were significant. An ANCOVA examining childhood emotional abuse and BMI as covariates did not affect these results.

The results showed that the plasma cortisol levels were numerically higher in the SAD participants at all time points compared to controls. However, this difference did not reach statistical significance. Furthermore, while cortisol levels changed significantly at the measurement points during the experimental procedure, there were no significant differences noted between groups (See Figure 3).
**Figure 3**: Mean Cortisol Response (±SEM) Over Time to TSST in SAD vs. Control Participants.

(X-axis values: -30 = Time 1/Baseline, -5 = Time 2/Anticipatory, 10 = Time 3/Recovery Sample 1, 30 = Time 4/Recovery Sample 2, 45 = Time 5/Recovery Sample 3, 60 = Time 6/Recovery Sample 4)

- Main effect of group: p = 0.37
- Main effect of time: p = 0.004
- Group x time interaction: p = 0.98
Area under the curve (AUC) was also calculated to compare cortisol reactivity between groups. A one-way ANOVA did not show significant differences between the SAD and control groups (AUC<sub>G</sub>: F (1,23) = .84, p = .37, as shown in Figure 4A below; AUC<sub>I</sub>: F (1,23) = .06, p = .81, as shown in Figure 4B below).

**Figure 4**: Mean Cortisol Stress Response (±SEM) to TSST in SAD vs. Control participants

**Figure 4A**: Mean AUC<sub>G</sub> (Area Under the Curve from ground level zero reference)
Figure 4B: Mean $AUC_1$ (Area Under the Curve from baseline reference)

Mean $AUC_1$ in SAD vs. Control Participants

Participant Group

Error Bars: +/- 1 SE

$p = 0.81$
Peak percentage change in cortisol response was also calculated and compared between the SAD and control groups. A one-way ANOVA did not reveal any significant differences between the two groups of participants (F (1,23) = .12, p = .73) (see Figure 4C below).

**Figure 4C: Mean Peak Change**

![Mean Peak Change in SAD vs. Control Participants](image)

- **Participant Group**: Social Anxiety, Control
- **Error Bars**: +/- 1 SE
- **p = 0.73**
In addition, change from baseline was calculated and compared between the SAD and control groups. A one-way ANOVA did not show significant differences between the two groups (F (1,22) = .34, p = .57) (see Figure 4D below).

**Figure 4D:** Mean change from baseline (Difference between Cortisol Sample 2 and Cortisol Sample 1)

![Figure 4D](chart)

The above results suggest that Hypothesis 1 was not supported, as no significant difference in cortisol response measures was found between the SAD and control groups.
3.3 Positive and Negative Affect Measures (PANAS) – Hypotheses 2a and 2b

3.3.1 Positive Affect – Hypothesis 2a

Group differences were evaluated for the positive affect measures (from the PANAS) that were administered before and after the stress induction, using independent samples t-tests. While PANAS positive affect scores were higher in the control group vs. SAD participants, this difference did not reach statistical significance. The SAD and control groups began with similar scores for positive affect on the PANAS pre-stressor, but diverged post-stressor with SAD participants showing a slight decrease in positive affect and control participants showing a slight increase. The difference in positive affect scores on the PANAS post-stressor showed a trend, approaching significance, with SAD participants reporting lower positive affect (M = 20.92, SD = 6.24) compared to control participants (M = 25.92, SD = 7.30) (t (22) = -1.80, p = .09) (see Figure 5A below).

A two-way repeated measures ANOVA was used to examine differences in positive affect levels between the SAD and control participants before and after the stress induction. This test revealed no significant main effect of group (F (1,22) = 2.44, p = 0.13), group x time interaction difference (F (1,44) = 2.05, p = 0.17), or time (F (1,44) = 0.01, p = 0.92). A power analysis revealed that the effect size for the time by group interaction is d = 0.30, the observed power is 0.29, and the partial eta squared is 0.085. In order to achieve a power of 0.8 for the time by group interaction with this study, a sample size of n = 45 (per group) would have been required. A number of possible covariates were chosen at the beginning of the study to see if they would impact the results of the study including childhood emotional and physical abuse, BMI, and age. Correlational analyses revealed an association between BMI and positive affect pre-TSST. Significant positive correlations were found between BMI and positive affect scores
pre-TSST for all participants (r = .76, p = .007) (Pearson correlation reported, both Pearson and Spearman correlations were significant).
**Figure 5:** Mean Affect Scores (from PANAS) (±SEM) in SAD vs. Control Participants

**Figure 5A:** Mean Positive Affect Scores Pre- and Post-TSST (±SEM)

<table>
<thead>
<tr>
<th>PANAS Positive Affect Score</th>
<th>Positive Affect Pre TSST</th>
<th>Positive Affect Post TSST</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Control</td>
<td>28</td>
<td>26</td>
</tr>
</tbody>
</table>

Main effect of group: p = 0.13
Main effect of time: p = 0.92
Group x time interaction: p = 0.17
Effect of group, positive affect post-TSST: p = 0.09
No significant correlations were found between positive affect and childhood emotional or physical abuse or age, thus they were excluded as covariates. An ANCOVA examining BMI as a covariate did not influence these results.

These results suggest that positive affect did not change significantly across the experimental procedure and that though the SAD and control participants showed divergent patterns in positive affect over time, these results were non-significant. This is in partial support of hypothesis 2a, showing that although neither group had a significant change in positive affect, they did show a trend where each group was moving in opposite directions over time with positive affect decreasing in the SAD and increasing in the control group.

3.3.2 **Negative Affect – Hypothesis 2b**

Group differences were evaluated for the positive and negative affect measures (from the PANAS) that were administered before and after the stress induction using independent samples t-tests. There were significant differences between the SAD and control groups, with SAD participants reporting greater negative affect ($M = 16.83$, $SD = 5.62$) compared to control participants ($M = 11.75$, $SD = 1.66$) ($t(22) = 3.00$, $p = .007$, with an effect size of $d = .70$) before the stress induction. SAD participants reported even greater negative affect ($M = 19.92$, $SD = 5.65$) after the stress induction compared to control participants ($M = 12.73$, $SD = 3.29$) ($t(21) = 3.68$, $p = .001$, with an effect size of $d = .80$) (see Figure 5B below).

A two-way repeated measures ANOVA was used to examine differences in negative affect levels between the SAD and control participants before and after the stress induction. This test revealed a significant main effect of group ($F(1,22) = 16.51$, $p = .001$) and a significant
main effect of time ($F(1,44) = 4.54, p = 0.045$). However, no group \texttimes time interaction difference was found ($F(1,44) = 0.76, p = 0.39$). A power analysis revealed that the effect size for the time by group interaction is $d = 0.22$, the observed power is 0.18, and the partial eta squared is 0.034. In order to achieve a power of 0.8 for the time by group interaction in this study, a sample size of $n = 80$ (per group) would have been needed.
Figure 5B: Mean Negative Affect Scores Pre- and Post-TSST (±SEM)

* denotes significantly different than control group (p<0.05)

Main effect of group: p = 0.001
Main effect of time: p = 0.045
Group x time interaction: p = 0.39
Several covariates were chosen at the beginning of the study to see if they would have a confounding effect on plasma cortisol measures including childhood emotional and physical abuse, BMI, and age. Significant correlations were found between childhood emotional abuse (subscale of the Childhood Trauma Questionnaire) and negative affect pre-TSST ($r = .70$, $p = .000$) as well as negative affect post-TSST ($r = .62$, $p = 0.004$) for all participants. BMI and negative affect post-TSST were also correlated for all participants but to a lesser extent ($r = .58$, $p = .049$). No significant correlations were found between negative affect measures and childhood physical abuse and age, thus these were excluded as covariates. Similarly, since childhood physical abuse and age did not correlate with negative affect, they were also not used as covariates. An ANCOVA examining childhood emotional abuse and BMI as covariates did not affect these results.

The results show that negative affect was significantly higher in the SAD group compared to the control group both before and after the TSST, however there were no significant changes in negative affect across the experimental procedure for either group of participants. It is worth noting that the SAD group did show a slight increase in negative affect post-TSST, though this did not reach significance. This is in partial support of hypothesis 2b, confirming the group differences in negative affect levels and there was a modest (non-significant) increase over time, but there was no group by time interaction. The possible implications of these findings are discussed in Chapter 4.
3.4 Correlations between Cortisol Response Measures and Positive or Negative Affect – Hypothesis 3

Pearson and Spearman correlations were conducted to determine if there was any relationship between plasma cortisol changes following the TSST and the behavioural measure of affect, as measured by the PANAS.

Significant associations between AUC and positive affect were found. When examining the SAD group alone, positive affect scores (PANAS, positive affect subscale) pre- \( (r = .68, p = .02) \) (see Figure 6A) and post-stress induction \( (r = .67, p = .02) \) (see Figure 6B) were positively related to AUC. This supports hypothesis 3 that proposed a direct relationship between positive affect and cortisol response measures (see Figures 6A to C).
Figure 6: Significant Correlations (p<0.05) Between Cortisol Measures and Positive Affect

Figure 6A: $AUC_I$ (Area Under the Curve from Baseline Reference) and Positive Affect Pre-TSST

Relationship Between $AUC_I$ and Positive Affect Pre-TSST (SAD group only)

$p = 0.02$
Figure 6B: AUC₁ (Area Under the Curve from Baseline Reference) and Positive Affect Post-TSST

Relationship Between AUC₁ and Positive Affect Post-TSST (SAD group only)

\[ p = 0.02 \]
A significant correlation was also noted between peak change and positive affect for the SAD group, which showed a significant positive correlation between peak percentage change and positive affect post-stressor (PANAS, positive affect subscale) \((r = .58, p = .049)\) (see Figure 6C below). This also supports the hypothesis that positive affect will correlate with cortisol response measures.

Negative affect did not correlate with any cortisol response measures in this study.

**Figure 6C: Peak Change and Positive Affect Post-TSST**

![Graph showing the relationship between peak change and positive affect post-TSST](image-url)
Chapter 4 : Discussion

The purpose of this chapter is to:

- review the main findings of the study;
- discuss how these findings relate to the proposed hypotheses of the thesis as well as with previously published literature;
- discuss the implications of these results for SAD;
- describe the strengths and limitations of the study, and propose possible avenues for future research.

4.1 Cortisol and Stress Induction

The study had two main purposes: firstly to investigate the endocrine and affective response to a social stressor, the TSST, in an SAD population in comparison to a healthy control population; and secondly, to explore the possible relationships between the plasma cortisol response and several behavioural measures.

Several findings from the current study are consistent with previously published literature (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009). The TSST produced a robust effect in plasma cortisol levels over time in both groups, supporting the notion that the TSST is effective
and reliable as a stress induction manipulation. This was evidenced by the fact that a cortisol increase was found in response to the TSST. The changes in the PANAS scores further confirm the efficacy of the TSST as a stress induction tool, as increases in negative affect following the manipulation were observed in both groups of participants.

An interesting observation from this study is that none of the SAD participants used the modifications offered to them in case they found the TSST speech task intolerable. This option was created especially for the SAD participants (Roelofs et al., 2009), and offered to them as an ‘escape’ in case of extreme distress during the social stressor. It would appear that SAD participants might have greater tolerance of socially stressful situations than they perceive or than is often believed by clinicians. In other words, although SAD participants do not enjoy social interactions and find them stressful, they are still able to partake in forced social situations despite experiencing anxiety and negative affect.

Another notable finding of this investigation is that the effect of the social stressor had opposite impact on the two affective states of these individuals – increasing negative and decreasing positive affect. Another finding of note was that in those with SAD, the peak cortisol response occurred during the anticipatory stress period while in control participants, it occurred during the first recovery sample post-TSST. This raises the possibility that the highest stress moment for SAD individuals are prior and in anticipation of the stressful event or social interactions and not during or after its occurrence.

The current study did not find any significant differences in baseline cortisol or stress-induced cortisol levels between SAD participants and controls. Past findings have shown either no cortisol change or increased cortisol in response to stress in SAD compared to control participants. The current investigation did find important behavioural differences between the
two groups in response to the TSST. The significance of these findings as well as the possibility that the stress responses in SAD may be linked to such behavioural differences is discussed below.

4.2 SAD, Positive and Negative Affect, and the Stress Response

It is well documented that individuals with SAD exhibit significant initial hypervigilance when coming across objects or situations with negative associations, which in turn leads to an increase in the likelihood of further perceiving these as negative (Hofmann, 2007), and contributing to an early attentional bias (van Peer, 2010; van Peer et al., 2007; van Peer, Spinhoven, Dijk, & Roelofs, 2009). As well, there is evidence that SAD sufferers tend to bias their attention away from positive stimuli, and show decreased positivity (Taylor, 2010) and increased negativity compared to those without SAD (Brown, Chorpita, & Barlow, 1998). Thus it may be inferred that for SAD sufferers positive experiences are often short-lived, and tend to be less frequent and of low intensity (Kashdan, Weeks, & Savostyanova, 2011). In addition, individuals with SAD often experience fear responses to positive evaluation (Kashdan, Weeks, & Savostyanova, 2011).

Consistent with the above findings, the current study also showed decreased positivity in SAD participants, as evidenced by a decrease in positive affect post-TSST compared to the controls. Although this difference was not significant, it showed a clear trend that approached significance. The degree of negative affect was also significantly higher for the SAD participants both pre- and post-TSST compared to control participants. In addition, state anxiety, considered
an indication of early threat detection (Choi, Padmala, & Pessoa, 2012), was significantly higher in the SAD participants compared to the control group.

When the relationship between measures of positive affect and cortisol response were examined, a direct correlation was noted between the two in SAD participants. This is in keeping with previous reports, which found a direct relationship between cortisol levels and positive emotions (Ong, Fuller-Rowell, Bonanno, & Almeida, 2011; Waismel-Manor, Ifergane, & Cohen, 2011). The current investigation is the first to report the positive correlation between the cortisol stress response and positive affect in SAD. The mechanism mediating this relationship is not fully elucidated. It is speculated that individuals with SAD who experience positive affect find this to be an uncommon emotion, and it is this experience of unfamiliarity that is perceived as a form of stress and may lead to the induction of a cortisol response. This explanation is consistent both with the findings of this study that showed a trend toward lowered levels of positive affect in SAD participants post-TSST and with past literature indicating that those with SAD have decreased positive emotions and experiences (Finkel et al., 2006; Kashdan, Weeks, & Savostyanova, 2011; McNally & Reese, 2009; Taylor, 2010; Vohs, Baumeister, & Ciarocco, 2005). The current study found no significant correlations between negative affect and cortisol response. However, previous studies show that cortisol post-TSST was inversely correlated with negative affect (Het, Schoofs, Rohleder, & Wolf, 2012). A further investigation showed that women treated with cortisol prior to exposure to an acute social stressor (TSST) had significantly less negative mood states compared to the control group (Het & Wolf, 2007).

The evidence for altered interpretation biases from the current study, along with previous published literature suggest that another important contribution to the cortisol response in SAD participants relates to their decreased positivity in various domains of life. In terms of the stress
response in SAD, these results would predict that individuals with SAD, who also show decreased positivity, would show a decreased cortisol stress response compared to others. Notably, the current findings, supported by those of earlier studies, may be important for future research on the behavioural correlates of SAD that may be associated with the stress response.

4.3 SAD, Childhood Trauma, and the Stress Response

SAD is known to start early in life. Individuals with SAD often report encountering peer victimization early in life, experiencing less positive peer appraisals, and tending to withdraw from social situations during developmental years (Beidel, Turner, & Morris, 1999; Flanagan, 2008; La Greca & Harrison, 2005; Storch & Masia-Warner, 2004). Childhood trauma has been proposed as a significant risk factor for SAD (Asher & Coie, 1990; Lochner et al., 2010). Past research has shown that individuals with SAD tend to report higher rates of childhood trauma, and in particular emotional abuse, compared to healthy individuals (Asher & Coie, 1990; Lochner et al., 2010). Furthermore, history of emotional abuse was also correlated with greater symptom severity, decreased quality of life, and greater disability (Bruce, Heimberg, Blanco, Schneier, & Liebowitz, 2012). The current study’s findings are in keeping with the published literature confirming significantly higher levels of childhood emotional abuse in SAD participants compared to controls.

Childhood trauma, including emotional abuse, has been previously reported to be associated with the altered stress response. Commonly, this manifests as a blunted cortisol response (Bergen et al., 2012; Carpenter et al., 2009; Carpenter et al., 2007; van der Vegt, van der Ende, Huizink, Verhulst, & Tiemeier, 2010). Several previous studies found group
differences in cortisol levels when comparing those who have experienced childhood trauma to those who did not. In one study, greater childhood maltreatment in people with anxiety disorders was associated with lower cortisol levels (van der Vegt, van der Ende, Huizink, Verhulst, & Tiemeier, 2010). Another study reported similar reductions in cortisol levels with chronic exposure to severe and threatening life events (Bergen et al., 2012). Increased stress reactivity in individuals who have experienced childhood maltreatment has been found to lead to hypervigilance, poor anger management, and interpersonal difficulties (Boyce & Ellis, 2005; Ellis, Essex, & Boyce, 2005). Cook et al. (2012) showed that in youth who have experienced significant childhood abuse, a heightened cortisol response to the TSST was associated with decreased interpersonal competence and anger regulation. However, in youth without such history, the opposite was true and a heightened cortisol response was associated with increased interpersonal competence and anger regulation (Cook, Chaplin, Sinha, Tebes, & Mayes, 2012).

Furthermore, Carpenter et al. (2007) found that, in response to a stress challenge, healthy adults who experienced moderate to severe childhood maltreatment showed decreased cortisol reactivity in response to the TSST compared to a control group (Carpenter et al., 2007). In another study by the same group, childhood emotional abuse, independent of other forms of childhood maltreatment, predicted decreased cortisol reactivity, an effect that was found to be cumulative over time (Carpenter et al., 2009). Fries et al. (2005) have suggested that this blunted cortisol response (also termed hypocortisolism) may occur after an extended period of hyperactivity of the HPA axis attributed to long-term exposure to chronic stress. This blunted cortisol reactivity is seen as an adaptive compensatory response that may have beneficial effects (Fries, 2005). This notion is supported by previous findings that there is initial HPA axis activation and increased cortisol reactivity with the onset of trauma, but over time and as the stressor becomes chronic or disappears, blunted response occurs (Miller, Chen, & Zhou, 2007).
The findings from the current investigation are similar to these previous results, showing an inverse relationship between childhood emotional abuse and cortisol response and confirming the reduction in cortisol reactivity to stress in SAD sufferers with a history of emotional abuse. Such “sensitization” effects of childhood emotional abuse are also likely to make SAD participants more vulnerable to reduction in positive and increase in negative affect (Ayoub et al., 2006).

4.4 Methodological Considerations

The main strength of the current study is that it utilized a standardized and validated protocol, the TSST, for the social stress induction. In addition, it used validated behavioural measures to evaluate affective states in study participants and used a semi-structured interview for diagnosis. The measurement of cortisol levels through plasma rather than saliva provided a more direct and temporally precise measure. However, the present study also had several limitations, which are highlighted below.

The sample size was small thus limiting the statistical power and as such, the results were largely correlational. Any replication study would need to employ a larger sample size in order to extend the present findings relating to behavioural characteristics and cortisol, and to allow for the expression of group differences. As well, the unequal number of female vs. male participants may have influenced the findings, and gender differences in behavioural and/or stress reactivity measures were not evaluated due to small and unequal numbers of each gender.

Although baseline cortisol levels in the study were low relative to post-stress cortisol levels, the fact that the former was taken on the day of the stress induction itself may be
considered another deficiency. It is possible that the anticipatory anxiety may have contributed to alterations in cortisol levels even at baseline. Obtaining a baseline cortisol sample on a non-experimental day to avoid the effect of such anticipatory anxiety could provide a more valid characterization. Additionally, the fact that half the SAD participants were on an SSRI or an SNRI and half were not on medication may have acted as another confounding variable.

Finally, most of the behavioural measures in the study were done at baseline, and not immediately before or after the TSST. Although the baseline measures have provided interesting and important information, measurements immediately before and soon after the TSST may have provided valuable data on the direct effect of stress induction on such measures.

4.5 Recruitment Challenges of the Investigation

For the current study, SAD participants were recruited through ads posted around CAMH, UHN hospitals, as well as on the University of Toronto St. George campus. Participants were also recruited through the Mood and Anxiety Clinic at CAMH, mainly through some physicians affiliated with this study. The support of the excellent multidisciplinary team at the Mood and Anxiety Clinic was crucial for the recruitment of SAD participants for this study. Nonetheless, recruitment of SAD participants devoid of comorbidities who are comfortable with a serial blood draw is not easy. Furthermore, although many calls were received from interested potential participants, only one in five callers were actually eligible for the study. The nature of the illness also made it a challenge to contact and communicate with prospective participants, who often tended to avoid telephone interaction.
In the current study, two thirds of the participants were male in spite of significant effort to enrol female participants. This can be attributed to two reasons. Firstly (as noted in past literature) although SAD is more prevalent in females, males are more likely to seek treatment and to come forward as potential participants for such investigations (Kessler, 2003). Secondly, even though significant numbers of females were initially interested in participating, many were deterred by the need for blood draw.

In the future, the recruitment process for similar studies with SAD participants would be facilitated if studies were run at, or in affiliation with, clinics for people with SAD. By doing this, one could potentially also amass a larger sample size in a shorter time frame. There are, unfortunately, few ways to reduce the potential deterrent value of the blood draw, other than by switching to salivary sample collection, which has its own disadvantages as described previously. In order to increase contact with potential SAD participants, it may be of value to contact them via e-mail whenever possible. Although this is not the most confidential means of communication, it could be useful for the discussion of generic information relating to the study and booking study visit appointments. In addition, scheduling face-to-face visits in order to discuss the study and answer any questions potential participants may have, may be more effective than speaking over the phone.
4.6 Future Directions

The current investigation adds to the existing knowledge on the relationship between social stress and HPA axis activity in SAD participants. It also provides evidence for the adverse influence of childhood emotional abuse on the condition. Although most anxiety disorders begin early in life, help-seeking is often delayed by a number of years. However, if the various aforementioned vulnerabilities were addressed earlier in life, perhaps the development of an anxiety disorder could be attenuated or prevented. The identification of the various vulnerabilities that may be associated with the stress response and onset of SAD during childhood and adolescence thus warrants closer examination.

As previously mentioned, SAD sufferers tend to report higher rates of childhood trauma and emotional abuse, compared to normal populations (Asher & Coie, 1990; Lochner et al., 2010) and those who have experienced childhood maltreatment tend to show blunted cortisol responses (Bergen et al., 2012; Carpenter et al., 2009; Carpenter et al., 2007; van der Vegt, van der Ende, Huizink, Verhulst, & Tiemeier, 2010). Thus the blunted cortisol response has been proposed to be a putative protective mechanism in individuals with SAD who have experienced significant childhood maltreatment. Further explorations of the relationship between childhood abuse, SAD, and altered cortisol levels, as well as determination of contextual factors that influence benefit/harm from such responses, are needed.

Another useful area for future research is the role of cognitive biases in the causation and maintenance of SAD and the implications for treatment. People with SAD tend to have decreased positivity and a bias towards detecting threat in social situations (Taylor, 2010; van Peer, 2010). The present study identifies positive affect as a factor associated with the stress
response that may influence such bias. As a possible “behavioural marker” for SAD, further examination of this potential association could help identify those areas of cognitive biases that play an important role in the SAD stress response. Also worthy of further exploration is the role of anticipatory anxiety in SAD and its links to the stress response as well as to cognitive biases, such as the initial interpretation of ambiguous stimuli as threatening. These results, taken together, could also provide information on future therapies aimed at modifying the cognitions and anxiety reactivity of people with SAD. Training individuals with SAD in prosocial behaviour (Turner, Beidel, & Cooley-Quille, 1997) and emotional literacy (Mayer, Salovey, & Caruso, 2008) would further complement other interventions.

The degree of positivity was found to be an important factor influencing the stress response of individuals with SAD in the current study. Past research has shown that cognitive interventions (with interpretation of symptom perception) for SAD have been successful in teaching these individuals to interpret ambiguous stimuli as neutral rather than threatening (Amir, Bomyea, & Beard, 2010; Amir & Taylor, 2012). Future research could focus on further exploration of techniques to increase positivity, for example by using computerized interpretation modification programs to provide benefit. Computer-based interventions would further improve accessibility and provide an avenue for standardized feedback to participants. Such feedback has been shown to improve positivity and decrease the prevalence of negative emotions (Emmons & McCullough, 2003; Lyubomirsky, Sheldon, & Schkade, 2005; Seligman, Steen, Park, & Peterson, 2005).

An important observation in the current study was that none of the SAD participants needed or wanted to opt for the modified TSST (Roelofs et al., 2009). The SAD participants were, on average, in the moderate to marked range of social anxiety severity, as determined by
the LSAS. Even with this degree of severity and while reporting the experience of the TSST to be very stressful, they were still willing to endure it. This observation may have implications for future research and areas of treatment aimed at individuals with significant SAD, and also provides a rationale for exploring the impact that brief social stressors have on people with SAD. Currently, it is unclear if such minor social stressors have cumulative or long-term effects. It has been previously reported that those with SAD who suppress their unwanted thoughts after a stressful event may benefit from it and may be less shy afterwards (Magee & Zinbarg, 2007). This potential beneficial effect of exposure to minor stressful events or unwanted thoughts is in keeping with behavioural literature and emphasizes the benefit of graduated exposure therapy. Past research has shown support for the use of exposure techniques alone in the treatment of SAD, which has been shown to be as effective as cognitive behavioural treatment (Feske & Chambless, 1995). Virtual reality exposure therapy has also been shown to be effective in the treatment of anxiety disorders, though not in SAD specifically (Powers & Emmelkamp, 2008). In the future, virtual reality exposure therapy as a stand-alone treatment for SAD should be evaluated, as it may be useful in individuals with significant SAD, who have difficulties enduring the anxiety associated with direct exposure.
4.7 Conclusions

The current study found no significant group difference in cortisol response to the TSST between SAD and control participants. However, results did show an inverse correlation between cortisol response and emotional abuse in SAD participants as well as a positive correlation between cortisol response and positive affect in SAD participants. In addition, negative affect (both pre and post-TSST) was significantly higher in SAD participants compared to controls. SAD participants also reported significantly higher rates of childhood trauma and emotional abuse compared to control participants. The finding that certain behavioural characteristics of the SAD population may play a role in their cortisol reactivity pattern could have implications for future research on this topic.

The current investigation aimed to address several methodological challenges of past studies including: lack of a standardized stress protocol, heterogeneity of the SAD participant group, and use of saliva rather than plasma in order to measure cortisol levels. To address these issues, this study used the TSST (a standardized and validated stress protocol) as the stress induction, included only SAD participants devoid of significant comorbidities, and used plasma to measure cortisol levels. Although these past challenges were addressed, the current investigation also had limitations including small sample size and unequal numbers of female vs. male participants.

It is suggested that notwithstanding the methodological deficiencies, the findings of this study provide a significant increment in knowledge to the current literature on the pathophysiology of SAD. Some of its findings may provide useful pointers in the clinical management of this population.
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