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Concordance in salivary cortisol and subjective anxiety to the trier social stress test in social anxiety disorder

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ABSTRACT

Background: Social anxiety disorder (SAD) is characterised by an excessive fear of negative social evaluation. There is a limited understanding of how individuals with SAD react physiologically and subjectively to social stress.

Method: The Trier Social Stress Test (TSST), an acute social stress task, was completed by 40 SAD individuals (50% female) and 41 healthy controls (matched on age, sex, and education) to examine salivary cortisol and self-reported stress reactivity. Salivary cortisol concentrations and self-reported affect (anxiety, sadness, tiredness, withdrawal, and happiness) were assessed at baseline and across nine-time points during the TSST.

Results: Bayesian salivary cortisol analyses revealed no group differences in salivary cortisol levels at baseline or during the TSST, with results comparative after the removal of 17 cortisol non-responders (21%). Contrastingly, the groups significantly differed on self-reported affect. At baseline, the SAD group (vs. controls) reported heightened negative affect and diminished happiness. In response to the TSST, the SAD group (vs. controls) displayed greater negative affect reactivity and diminished happiness reactivity, and significantly higher rates of change in their anxiety and sadness over time. After accounting for differences in the temporal resolution of self-reported versus cortisol responses, a moderate positive association was found between salivary cortisol and anxiety reactivity to social stress that was comparable between the groups.

Conclusions: Despite elevated subjective anxiety, our findings suggest concordance in psychobiological stress reactivity in SAD and healthy controls. We discuss the possibility of heightened subjective sensitivity to social evaluative stress as a core treatment target for SAD.

1. Introduction

Social anxiety disorder (SAD) is a debilitating mental health disorder characterized by excessive fear of scrutiny or negative evaluation by others that significantly disrupts everyday social functioning (Heimberg & Magee, 2014). Individuals with SAD have a greater risk of school drop-out, under-employment, lower workplace productivity and socio-economic status, and poorer well-being, interpersonal relationships, and quality of life (Patel, Knapp, Henderson, & Baldwin, 2002). Behaviourally, a large body of research shows that SAD individuals consistently demonstrate heightened anxiety, fear, other negative feelings, and biased (negative) cognitions in response to acute social stressors when compared to healthy controls (Jamieson, Nock, & Mendes, 2013; Klumbies, Braeuer, Hoyer, & Kirschbaum, 2014; Mauss, Wilhelm, & Gross, 2003). However, research into physiological responses to acute social stress among those with SAD compared to controls has produced varying results (Klumbies et al., 2014; Krämer et al., 2012; Roelofs et al. 2009; van West, Claes, Sulon, & Deboutte, 2008). Understanding how individuals with SAD physiologically react to social situations is critical to fully understand the underlying pathophysiology of SAD as well as to improve well-being and inform treatment strategies for those with the disorder.

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Physiologically, the interpretation of stimuli as stressors leads to the activation of two major components of the stress response system, the sympathetic-adreno-medullar (SAM) axis and the hypothalamus-pituitary-adrenal (HPA) axis. Activation of the SAM axis results in the secretion of noradrenaline and norepinephrine along with cardiovascular changes and forms the first phase of the stress response that provides rapid physiological adaptation and short-lasting responses (e.g., vigilance, alertness) (Godoy, Rossignoli, Delfino-Pereira, Garcia-Cairasco, & de Lima Umeoka, 2018). The HPA axis leads to the secretion of glucocorticoids and forms the secondary (hormonal) phase characterised by a slower but long-lasting response (Godoy et al., 2018). Although the SAM axis is considered a more reliable marker of physical stress, the HPA axis is thought to be a better marker in response to psychosocial stress (Godoy et al., 2018), with cortisol being the most commonly reported physiological marker of the acute social stress response (Grace, Labuschagne, Rendell, Terrett, & Heinrichs, 2019). Moreover, the HPA axis response to stress is also thought to be a determining factor of disease onset and progression (Kudielka, Wüst, Kirschbaum, & Hellhammer, 2007) as well as treatment response (Fries, Hellhammer, & Hellhammer, 2006).

Among individuals with SAD, research into physiological responses to acute social stress has produced varying results. Some studies report no group differences in the salivary cortisol, plasma cortisol, heart rate, or salivary enzyme alpha-amylase reactivity to an acute social stressor in individuals with SAD compared to controls (Klumbies et al., 2014; Krämer et al., 2012; Martel et al. 1999) and non-clinical high and low socially anxious individuals (I. Mauss, Wilhelm, & Gross, 2004; von Dawans, Trueg, Kirschbaum, Fischbacher, & Heinrichs, 2018; Wilhelm, Kochar, Roth, & Gross, 2001), despite heightened subjective anxiety. Other research has found that in addition to heightened subjective anxiety, individuals with SAD display significantly higher salivary and plasma cortisol reactivity, but no difference in blood pressure or corticotrophin reactivity, to acute social stressors relative to controls (Condren, O'Neill, Ryan, Barrett, & Thakore, 2002; Furlan, Demartinis, Schweizer, Rickels, & Lucki, 2001; Roelofs et al., 2009; van West et al., 2008).

Several reasons may account for these inconsistent findings, including variability across studies in the social stress tasks used, sample characteristics, such as participant sex (Zorn et al. 2017), age (e.g., studies involving children: Klumbies et al., 2014; Krämer et al., 2012; van West et al., 2008), presence of comorbidities such as depression (Yoon & Joormann, 2012), the presence of within-group differences such as cortisol responders and non-responders (Klumbies et al., 2014), the physiological outcome of interest (e.g., salivary vs. plasma cortisol, heart rate, blood pressure, salivary alpha-amylase), and the data analytic approach (e.g., (non) linear change slope vs. area under the curve).

In addition to methodological variations, studies have not specifically tested the association between self-reported and physiological reactivity to social stress in SAD, despite claiming discordance between the two response systems (Jamieson et al., 2013; Klumbies et al., 2014). It has long been assumed that there is coherence in our self-reported, physiological, and behavioural responses to stress, which serve an adaptive function (Ekman, 1992; Lazarus, 1991; Levenson, 1994). However, it is now widely understood that although different stress response systems are interrelated, there may be a lack of strong coherence among them (Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005) and considerable individual differences in their degree of concordance (Sommerfeldt, Schaefer, Brauer, Ryff, & Davidson, 2019). A review of 30 studies that examined associations between cortisol reactivity and self-reported responses to social stress among healthy controls found that only 27% ($n = 8$) reported significant correlations among physiological and self-reported responses (Campbell & Ehlert, 2012).

Reasons for such low coherence between these self-reported and physiological stress response systems are unclear. One possible explanation could be that the previously calculated associations did not account for the different temporal dynamics of these systems, i.e., the slow-acting endocrine response lagging behind the more immediate psychological responses. Further, studies have predominantly assessed self-reports only at pre- and post-stressor (two time-points), thereby potentially missing the highly sensitive, time-contingent changes in emotional states that precede the slow-acting HPA axis response (Schlotz et al. 2008). Assessing over multiple time points during the stressor (e.g., Hellhammer & Schubert, 2012) and accounting for the expected time lag between the different response systems, Schlotz et al. (2008) found a strong positive relationship between state anxiety and cortisol response in healthy controls, suggesting there may be substantial coherence between subjective and salivary cortisol responses to stress, at least in healthy cohorts.

Another important factor to consider when examining concordance between different stress response systems is whether the assessment is between-person or within-person. Between-person concordance refers to the extent to which individuals who score high on one measure (e.g., self-reported anxiety) also tend to score high on another measure (e.g., cortisol) either at a single time-point or on average across time. Within-person concordance, however, refers to the extent to which multiple measures (e.g., self-reported anxiety and cortisol level) are correlated over multiple time points within a single individual. Thus, within-person concordance estimates reflect how two or more measures track each other across repeated assessments, i.e., over time (Sze, Gyurak, Yuan, & Levenson, 2010). Within-person (rather than between-person) concordance indices reflect the theorised coherence among emotional/stress response systems (Mauss, 2005). Despite suggestions of a lack of coherence or discordance between anxiety and salivary cortisol reactivity to social stress in healthy individuals (Campbell & Ehlert, 2012) and individuals with SAD (Klumbies et al., 2014), there are limitations to these conclusions. That is, these studies have examined the relationship between physiological and self-reported stress reactivity independently rather than directly testing their relations, and have often not accounted for the differences in temporal dynamics of the response systems.

In the current study, we examined self-reported and salivary cortisol stress reactivity to the Trier Social Stress Test (TSST) (Kirschbaum, Pirke, & Hellhammer, 1993) in individuals with SAD and healthy controls and (i) compared groups on self-reported and salivary cortisol reactivity and distinguished between cortisol responders and non-responders, and (ii) statistically tested for within-person concordance between the self-reported anxiety and salivary cortisol stress responding, accounting for differences in temporal dynamics in the response systems. We compared groups on subjective and salivary cortisol (HPA axis) reactivity and distinguished between cortisol responders and non-responders. We assessed HPA axis cortisol reactivity because of the well-established role of glucocorticoid signalling in the brain and psychological processes (Gray, Kogan, Marrocco, & McEwen, 2017) and because cortisol was the most commonly reported physiological marker of the acute stress response involving the TSST (Grace et al., 2019). Based on previous research comparing cortisol responses to the TSST among individuals with SAD versus healthy controls (Klumbies et al., 2014), our hypotheses were threefold: Firstly (hypothesis 1; H1), we expected no group differences in salivary cortisol concentration at baseline or across the social stress protocol, consistent with more recent evidence from clinical (Klumbies et al., 2014; Krämer et al., 2012) and non-clinical studies (I. Mauss et al., 2004; von Dawans et al., 2018; Wilhelm et al., 2001). Secondly (H2), we expected individuals with SAD to report heightened subjective stress (evident in greater negative affect and lower happiness) at baseline and in response to the social stress protocol relative to the healthy controls (Klumbies et al., 2014; Krämer et al., 2012; Wilhelm et al., 2001; Yoon & Joormann, 2012). Lastly (H3), given the lack of studies directly assessing concordance or discordance between self-report and salivary cortisol stress responses (Klumbies et al., 2014; Krämer et al., 2012; Yoon & Joormann, 2012), we explored such evidence among SAD versus healthy control participants, accounting for the different temporal nature of the self-reported and

physiological response systems (Schlotz et al., 2008).

2. Methods

2.1. Study design and participants

The structure of the current study was according to it being embedded in a broader study, with participants completing two lab visits and one week of ecological momentary assessment. Participants completed the TSST (Kirschbaum et al., 1993) during their second lab visit which occurred approximately 4 days after the initial lab. Following telephone screening, participants were invited to their first visit during which they completed questionnaires and were briefed on the protocol for the ecological momentary assessment. For the second lab visit, participants were not told of the nature of this visit until the night prior when they were informed that the visit will include a social stress task. The TSST protocol was based on the recently updated recommendations and manual for an 85-minute protocol (Grace et al., 2019).

After recruiting 96 participants, a total of 81 participants comprising 40 individuals with SAD (20 females) and 41 healthy controls (20 females), matched in age, sex, and total years of education, participated in this study; 15 participants did not commence or complete the study after successful screening for exclusion criteria. Participants were recruited using local online advertisements and flyers. General inclusion criteria required participants to be aged 18–55 years, non-smoking, medication free and not currently engaged in psychotherapeutic intervention, free of substance abuse, to have no clinically significant medical (e.g., diabetes, cancer), neurodevelopmental disorder (e.g., attention-deficit/hyperactivity disorder) or neurological condition, and be proficient in English. Due to interactions between menstruation cycle phases and cortisol response (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999), females were tested in the luteal phase of their cycle. Table 1 presents the demographic and clinical details for each group, as well as the number of cortisol non-responders.

The SAD participants needed a current or suspected diagnosis of SAD as confirmed with the Mini-International Neuropsychiatric Interview (MINI 7.0.2 Full and MINI 7.0.2 Screen; English version for the DSM-5; Sheehan et al., 1998; conducted by C.G.) and also a score of ≥ 36 on the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998) and ≥ 30 on the Leibowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). Participants with a history of post-traumatic stress disorder, a psychotic disorder (e.g., bipolar disorder or schizophrenia), a current major depressive episode, an intellectual disability, or a neurodevelopmental disorder were excluded from participation. In the presence of comorbid disorders, generalised anxiety disorder (GAD) and symptoms of low mood (but not a current depressive episode) were to be accepted provided that social anxiety was the primary concern. Potential comorbidities identified on the MINI screen questionnaire (e.g., GAD) were followed up with the corresponding MINI module (e.g., Module N; GAD).

No participant in this study was reported to meet the criteria for a comorbid disorder in the current participant group. Further, the presence of any other clinically significant medical (e.g., diabetes, cancer), neurodevelopmental disorder (e.g., attention-deficit/hyperactivity disorder), or neurological condition excluded individuals from participation. Control participants were to have no current or suspected diagnosis of any mental illness (using MINI 7.0.2). The two groups were further characterized by participants completing the Depression Anxiety Stress Scale (DASS-21; Lovibond & Lovibond, 1995) to assess depressive, anxiety, and stress symptoms. Written informed consent was provided by all participants before their inclusion in the study and ethical approval for the conduct of the study was granted by the Australian Catholic University Human Research Ethics Committee. Participants were remunerated on a pro-rata basis up to a total of AUD 150.00 provided in voucher format. The maximum payment was provided if participants had compliance between 70% and 80%, with compliance rates < 70% incurring the $20.00 deduction in the final payment.

Table 1
Demographic and clinical characteristics and cortisol responder status for social anxiety disorder and healthy control participants.

N = 81		SAD (*n* = 40)	Controls (*n* = 41)	Test	*p*	*df*
Gender (Female)	n (%)	20 (50.0)	20 (48.8)	χ^2 = 0.01	0.913	1
Age (Years)	M (SD)	28.42 (7.90)	25.75 (6.36)	*t* = 1.68	0.098	79
Education (Total Years)	M (SD)	16.18 (2.25)	16.57 (2.09)	*t* = 0.83	0.412	79
Hormonal contraceptives	n (%)	7 (17.5)	12 (29.3)	χ^2 = 1.56	0.211	1
Cortisol non-responders	n (%)	10 (25.0)	7 (17.1)	χ^2 = 0.77	0.381	1
SIAS	M (SD)	57.00 (9.26)	16.08 (10.30)	*t* = 18.69	< 0.001	78
LSAS	M (SD)	78.70 (19.05)	24.26 (16.25)	*t* = 13.21	< 0.001	73
DASS-21 Depression	M (SD)	17.00 (8.61)	3.56 (3.62)	*t* = 9.20	< 0.001	79
DASS-21 Anxiety	M (SD)	18.85 (8.18)	4.15 (5.34)	*t* = 9.61	< 0.001	79
DASS-21 Stress	M (SD)	24.70 (8.16)	8.29 (5.96)	*t* = 10.35	< 0.001	79

Notes. N = 81. M(SD) = mean (standard deviation), n (%) = number (percentage), SAD = social anxiety disorder, SIAS = social interaction anxiety scale, LSAS = Leibowitz social anxiety scale, DASS-21 = depression anxiety stress scale, χ^2 = chi-square test, *t* = *t*-test of independence, *p* = *p*-value significance, *df* = degrees of freedom.

2.2. Assessments

The current study was embedded in a larger study, with participants completing two lab visits and one week of ecological momentary assessment. Participants completed the TSST (Kirschbaum et al., 1993) during their second lab visit, occurring 4 days after the initial lab visit. Participants were only informed of the nature of their second lab visit the night prior, then told the visit will include a social stress task. The TSST protocol was based on the recently updated recommendations and manual for an 85-minute protocol (Grace et al., 2019) consisting of a waiting period (20 min), task introduction (5 min), anticipatory period (5 min), speech task (5 min), surprise arithmetic task (5 min), debriefing (10 min) and recovery (35 min); see Fig. 1. The speech and arithmetic tasks were completed in front of a panel of 3 independent mixed-gender "managers". Salivary cortisol and self-reported affect were obtained at nine time points across the TSST protocol.

Salivary cortisol sampling was completed using Salivettes (Sarstedt; see Grace et al., 2019 testing manual supplement for procedure). Following collection, samples were stored at − 80 degrees Celsius until analysed. Samples underwent one freeze-thaw cycle and were analysed by Stratech Scientific APAC PTY Ltd using commercially available immunoassay kits (Salimetrics, USA) according to the manufacturer's instructions. Thawed samples were centrifuged at 1500 x *g* for 15 min to obtain clear saliva that was then added to the assay wells and analysed in duplicate. Salivary cortisol correlates strongly with matched serum cortisol concentrations; $r = 0.91$, assay sensitivity equal to 0.08nmol/L (0.003 μg/dL) (Gozansky, Lynn, Laudenslager, & Kohrt, 2005). In our samples, intra- and inter-assay coefficients of variation were at 4.3% and 4.6% respectively for salivary cortisol. All analyses were within the set proficiency standard. Seven samples had insufficient volume for analysis and were noted as missing. Five of these samples were from one participant, who was excluded from further physiological analyses, and the two remaining missing samples were replaced (see Statistical analysis). Therefore, final salivary cortisol analyses were conducted on 40 SAD and 40 healthy control participants.

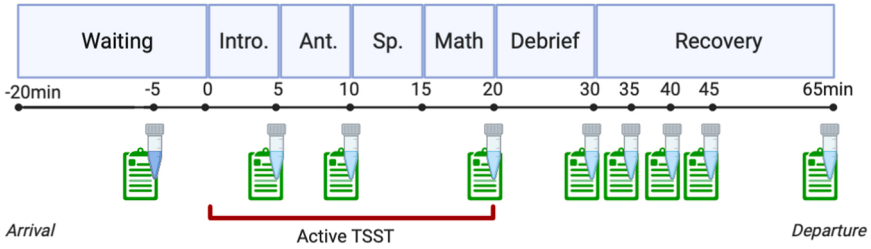

Fig. 1. An illustration of the phases involved in the administered Trier Social Stress Test (TSST) consisting of a waiting period, task introduction (Intro.), anticipatory period (Ant.), speech (Sp.) and arithmetic tasks (Math), debriefing, and recovery. Cortisol sampling and affect assessments were sampled across nine time points. Modified from Grace et al. (2019) and created in BioRender.com.

A modified version of the Visual Analogue Mood Scale (VAMS; Bond & Lader, 1974) was used to assess self-reported affect using five items: Happy, Sad, Tired, Anxious, and Withdrawn. For each affect item, participants rated how much they were experiencing the feeling at the time using a sliding scale from 0 (not at all) to 100 (very much) on an iPad. We included these items to reduce the demands of additional assessments and the potential burden to participants given the nature of our participant group and the intensity of the TSST (see Grace et al., 2019). We specifically included these items as they were deemed to capture different types of emotions including basic positive affect (happy), basic negative non-threatening affect (sad), basic negative threatening affect (anxiety), and affect relating specifically to the impact of the TSST (tired, as a measure of discomfort; and withdrawal as a measure of wanting to leave the space/discomfort with the space).

2.3. Statistical analysis

Data analyses were conducted using the Statistical Package for the Social Sciences (SPSS; IBM Corp, 2015), Stata (StataCorp. 2019), and JASP (JASP Team, 2019). Data were first checked for missing values, outliers, and normality of continuous data. Participants with ≤ 3 (out of 9) salivary cortisol samples had their missing values replaced with the expectation-maximization algorithm in SPSS ($n = 2$). Missing values for the mood scales were also replaced using the expectation-maximization algorithm (time points 1–4 and 9) in SPSS ($n = 2$). Participants with ≥ 4 salivary cortisol samples missing ($n = 1$) were excluded from any physiological analyses. Bayesian analyses were conducted to estimate the strength of evidence for null effects. The level of significance was set at $\alpha = 0.05$ for all frequentist analyses (two-tailed).

Preliminary analyses involved checking for salivary cortisol responders and non-responders using the threshold of baseline-to-peak cortisol increases of 1nmol/l (0.036245 μg/dL) (Miller, Plessow, Kirschbaum, & Stalder, 2013). To calculate baseline-to-peak cortisol increase, each participant's baseline cortisol concentration (i.e., collected at 5 min before TSST-onset) was subtracted from their peak, defined as the highest salivary cortisol concentration evident between samples 6–8 (i.e., 35–45 min post-TSST-onset). Next, *baseline analyses* were performed on salivary cortisol and self-reported affect using the first (of nine) samples collected. Given our expectation of no group differences (SAD vs. controls) for salivary cortisol at baseline (H1), we used Bayesian hypothesis testing (van Doorn et al., 2020) to estimate the degree of evidence for the null hypothesis, i.e., $H0 : \delta = 0$ (over the alternate hypothesis) using JASP and a Bayesian Mann-Whitney U test (Rouder, Speckman, Sun, Morey, & Iverson, 2009). The null hypothesis postulates that there is no difference in baseline salivary cortisol between the groups and therefore $H_0 : \delta = 0$. The Bayes factor expresses the strength of evidence in favour of one hypothesis compared to another. We reported Bayes factor as BF_{01}, which indicates evidence in favour of the null hypothesis H_0 (over the alternative hypothesis, H_1), and BF_{10} where there is evidence in favour of H_1 (over H_0). For the baseline self-reported data (H2), a series of standard Mann-Whitney U tests were performed given our expectations of significant group differences.

For H3, the *area under the curve (AUC) analyses* were then calculated using data from all nine time points to quantify total cortisol and self-reported affect reactivity to the TSST. Two formulas for the calculation of AUC derived from the trapezoid formula include the 'area under the curve with respect to increase' (AUC_i) and the 'area under the curve with respect to ground' (AUC_g) (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The AUC_i captures change over time (either increases or decreases) in cortisol levels relative to the initial value (i.e., without regard for zero) and is therefore thought to be indicative of stress reactivity to the TSST, while the AUC_g indicates the total systemic cortisol output to the stressor to the stressor. The formulas used to derive AUC_i and AUC_g, respectively:

$$AUC_i = \left(\sum_{i=1}^{n-1} \frac{\left(m_{(i+1)} + m_i\right)^{\circ} t_i}{2} \right) - \left(m_1{}^{\circ} \sum_{i}^{n-1} t_i \right)$$

$$AUC_g = \sum i \quad = 1n - 1\left(m_{(i+1)} + m_i\right)^{\circ} t_i 2$$

Here, t_i denotes the time interval between each pair of successive measurements, m_i the individual measurement of salivary cortisol/affect, and n the total number of measurement occasions.

Lastly, *concordance analyses* were conducted between self-reported (anxiety; considered the most relevant subjective experience to the social stressor) and physiological (cortisol) responses during the TSST using within-person correlations (H3). Two statistical approaches may be used to examine how within-person concordance is associated with an individual-difference variable, i.e., group status (SAD vs. controls). The first is a two-step approach, in which a within-person correlation coefficient is calculated separately for each participant in the first step, and subsequently, these within-person correlation coefficients are correlated with the individual-differences variable in the second step. The second approach involves linear mixed-effects modelling (LMEM) to examine whether the within-person effect of one stress response measure (e.g., anxiety) on the other stress response measure (e.g., salivary cortisol) is moderated by an individual-differences variable (e.g., SAD vs. controls). The LMEM approach is statistically preferable (Hox, Moerbeek, & Van de Schoot, 2018), although it can be less intuitive to interpret (Sommerfeldt et al., 2019). We, therefore, conducted both forms of analysis. To account for the different temporal dynamics of the slow-acting HPA axis response (i.e., in the salivary cortisol) and the faster-acting subjective experience, our analyses included a phase shift to align the expected peak responses of the two systems (Schlotz et al., 2008). Self-reported anxiety was expected to begin to increase between baseline (sample 1) and task introduction (sample 2) and to decline following task cessation and debriefing (between samples 4–5), whereas peak salivary cortisol typically occurs between sample 5 to sample 8 (Grace et al., 2019). Therefore, a phase shift was applied to align the expected anxiety peaks with expected cortisol peaks, shifting the anxiety time points forward by four time points, resulting in five time points included in the concordance analyses.

3. Results

3.1. Responders vs. non-responders on salivary cortisol

Using the threshold of baseline-to-peak cortisol increases of 1nmol/l (0.036245 μg/dL; Miller et al., 2013), 17 of the 80 participants who had saliva samples and completed the TSST protocol were classified as non-responders (21.25%). The proportion of non-responders did not differ between SAD and healthy control groups (Table 1). Fig. 2 depicts the median salivary cortisol concentration across time for groups and responder status.

3.2. Salivary cortisol

For group comparisons, we report on the Bayesian group comparisons (SAD vs. controls) for baseline and AUC salivary cortisol concentrations that include the cortisol non-responders; the results did not change after re-running the analyses excluding the cortisol non-responders; see Supplementary Material Table S3. Supplementary Table S2 reports median salivary cortisol baseline for the four subgroups and baseline differences, with results indicating no baseline differences between the four groups. Supplementary Figure S1 and Table S3 provide the medians, confidence intervals, and interquartile range for the results we report next. See Supplementary Material for Bayes factor interpretation guidelines.

Comparing groups (SAD vs. controls) in baseline cortisol concentration, a Bayesian Mann-Whitney *U* test yielded a Bayes factor of BF01 = 2.392, indicating that the H0 is only 2.392 times more likely to occur (than the H1), thereby reflecting anecdotal (inconclusive) evidence of the groups having comparable baseline levels (Lee & Wagenmakers, 2014). Comparing groups (SAD vs. controls) in response to the TSST, we first report on AUCi and then AUCg. For salivary cortisol AUCi (rate of change), a Bayesian Mann-Whitney U test yielded a Bayes factor of BF01 = 2.304, indicating that the H0 is 2.304 times more likely to occur (than the H1) and providing anecdotal (inconclusive) evidence for the groups having comparable salivary cortisol AUCi to the TSST. For salivary cortisol AUCg (systemic output), a Bayesian Mann-Whitney U test yielded a Bayes factor of BF01 = 4.020, indicating that the H0 is 4.020 times more likely to occur (than the H1) and providing substantial evidence for the groups having comparable salivary cortisol AUCg to the TSST.

3.3. Self-reported affect

Table 2 presents the frequentist statistics for the affect ratings for baseline and AUC analyses. For baseline, a series of Mann-Whitney *U* tests revealed that the SAD group (vs. controls) had significantly higher ratings on all negative affect items and significantly lower ratings on happiness.

In response to the TSST and for measures of AUC_i, Mann-Whitney *U* tests revealed that participants in the SAD group (vs. controls) self-reported significantly higher levels of anxiety and sadness, and significantly different AUCi measures, indicating greater time-dependent (change) reactivity in anxiety and sadness in the SAD than in the control group. However, we found no reliable evidence of group differences in happiness, tiredness, or withdrawal. For AUC_g, the SAD group (vs. controls) self-reported significantly higher negative affect (all items) and significantly lower happiness. We note here that for AUCi, the negative values in the SAD group resulted from a bigger change in values with more values below the baseline level than above, as reflected in a steeper decline and recovery immediately after the stressor in the SAD group.

3.4. Concordance between salivary cortisol and anxiety

Given our specific focus on comparing expected physiological reactivity to subjective reactivity of the TSST, the concordance analyses were conducted using data from the cortisol responders only (n = 30 SAD and *n* = 33 control participants). Using within-person correlation coefficient analyses, we first plotted the median cortisol levels and self-reported anxiety levels across time for SAD and control responders separately (Fig. 3).

Visual inspection of the data showed the expected early self-reported peak response relative to a delayed peak salivary cortisol response. This is consistent with the recommended time window to capture the peak salivary cortisol stress response (between 30 and 45 min post-task onset (see Grace et al., 2019). We, therefore, implemented a phase-shift in the

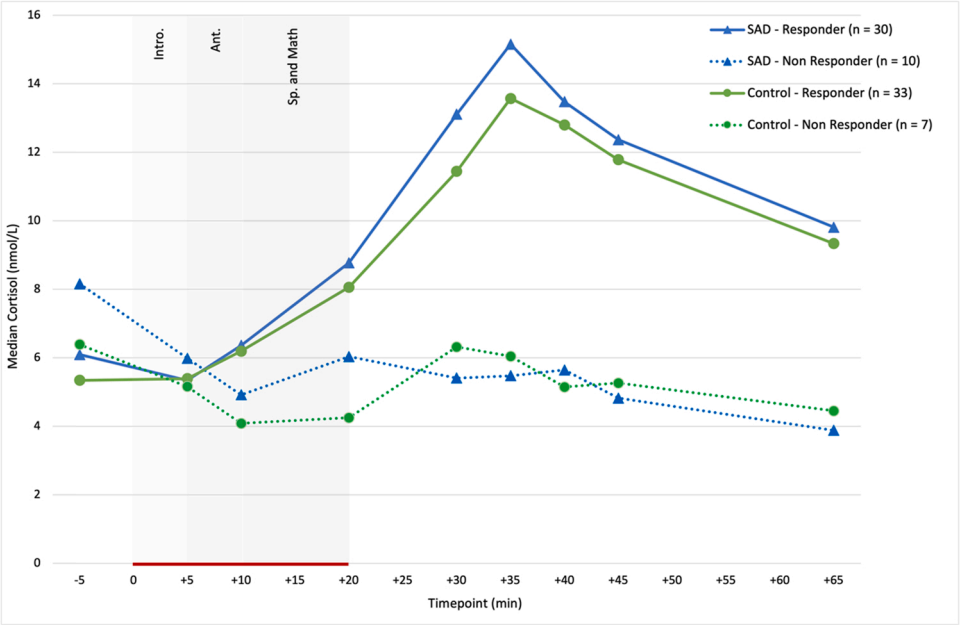

Fig. 2. Median salivary cortisol concentration (nmol/L) across the nine points in time of the Trier Social Stress Test for the SAD compared to control groups, separated by responders (R) vs. non-responders (NR); N = 80. The red line demonstrates active component of the TSST (intro. = task introduction; ant. = anticipation phase; sp. and math. = speech and arithmetic task).

Table 2
Group comparisons on self-reported affect ratings and salivary cortisol (responders and non-responders included) for baseline and areas under the curve for SAD and healthy control participants.

	SAD	Controls				
Self-report Affect Ratings			*U*	*z*	*p*	*r*
N	40	41				
Baseline:						
Anxiety	67.50 (48.25–83.00)	15.00 (3.00–36.50)	149.00	-6.34	< 0.001	0.70
Happiness	50.00 (21.50–63.50)	77.00 (67.00–84.00)	230.00	-5.58	< 0.001	0.62
Tiredness	61.50 (25.50–81.25)	31.00 (17.00–52.00)	527.00	-2.77	0.006	0.31
Sadness	22.50 (8.00–50.75)	2.00 (0.00–4.00)	252.50	-5.39	< 0.001	0.60
Withdrawal	38.50 (22.00–58.0)	5.00 (1.00–17.00)	260.00	-5.30	< 0.001	0.59
AUCi:						
Anxiety	-712.50 (−1321.25 to 184.38)	95.00 (−451.25 to 556.25)	504.50	-2.98	0.003	0.33
Happiness	-653.75 (−1201.41 to 314.38)	-385.00 (−1097.50 to −32.50)	809.00	-0.10	0.917	0.01
Tiredness	-75.00 (−858.13 to 335.00)	-262.50 (−995.00 to 83.75)	758.50	-0.58	0.561	0.06
Sadness	-331.25 (−800.00 to 96.88)	0.00 (−28.75 to 137.50)	526.50	-2.78	0.006	0.31
Withdrawal	-410.94 (−945.62 to 721.25)	0.00 (−227.50 to 80.00)	681.00	-1.31	0.189	0.15
AUCg:						
Anxiety	4078.75 (2695.00–4756.88)	1220.00 (747.50–2265.66)	136.00	-6.46	< 0.001	0.72
Happiness	2620.00 (1601.88–3410.00)	4902.50 (4390.00–5557.50)	208.00	-5.78	< 0.001	0.64
Tiredness	3746.25 (1835.00–5414.38)	1822.50 (1110.00–3390.00)	475.00	-3.26	0.001	0.36
Sadness	1393.75 (538.13–2551.25)	197.50 (13.75–687.50)	253.50	-5.36	< 0.001	0.60
Withdrawal	2377.50 (1365.00–3931.25)	540.00 (93.75–1023.75)	210.50	-5.76	< 0.001	0.64
Salivary Cortisol			**BF10**	**BF01**	**95% CI**	
N	40	40				
Baseline:	6.67 (4.48–9.90)	5.33 (4.12–6.70)	0.418	2.392	-.662 to.172	
AUCi:	184.68 (−1.03 to 331.17)	210.08 (54.01–323.20)	0.434	2.304	-.183 to.671	
AUCg:	621.66 (448.62–813.77)	634.15 (486.84–774.44)	0.249	4.020	-.405 to.428	

Note. Median (interquartile range Q1 to Q3); SAD = social anxiety disorder; AUCi = area under curve with respect to increase/change; AUCg = area under curve with respect to ground; *N* = sample size. *U* = Mann-Whitney U test; z = z test statistic; *r* = effect size, *p* = *p*-value significant at $p < .05$ level, * $p < .05$. * * $p < .01$. * ** $p < .001$.

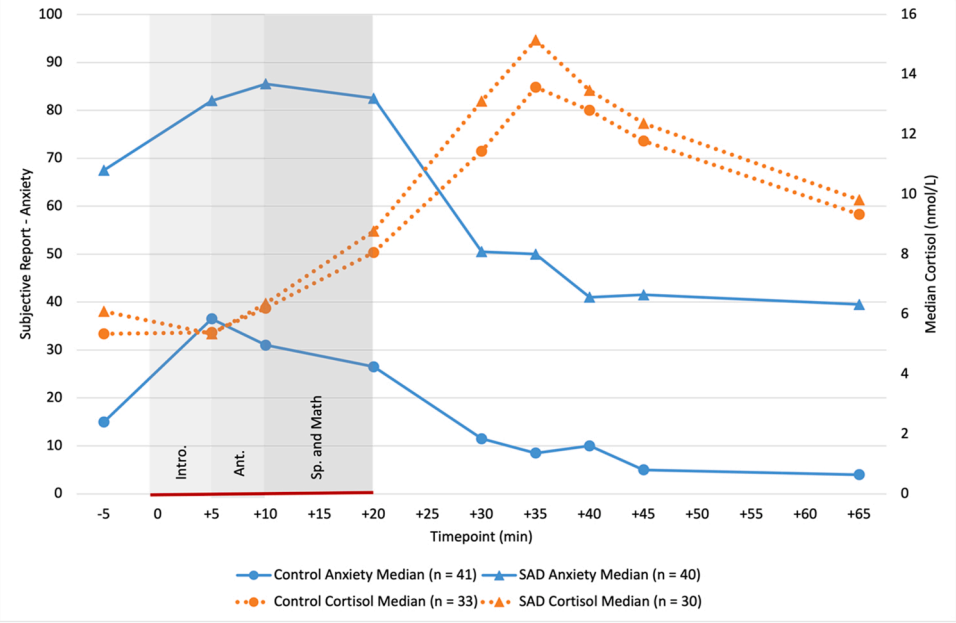

Fig. 3. Median subjective anxiety and salivary cortisol concentration (nmol/L; cortisol responders only) across the nine points in time of the Trier Social Stress Test for the SAD compared to control groups; N = 81. The red line demonstrates active component of the TSST (intro. = task introduction; ant. = anticipation phase; sp. and math. = speech and arithmetic task).

self-reported anxiety responses from time-point 1 (−5 min) to time-point 5 (30 + min; 10 min post-cessation of active TSST), such that time-points 5–9 (inclusive) were used for concordance analyses (see Supplementary Fig. S2). The within-person cortisol-anxiety correlation coefficients ranged between − 1 to + 1 and show an overall moderate negative association (for the original data) for both the SAD and control groups with median (Q1 to Q3) values being − 0.603 (−0.773 to −0.385) for the SAD group and − 0.544 (−0.683 to −0.350) for controls (p = .229), and a moderate-to-strong positive association for the phase-shifted data with median (Q1 to Q3) of.405 (−.207 to.800) for SAD and.400 (.052–.–0.600for controls (p =[T 0.907suggesting a similar level of concordance in the two response systems across groups. To check the robustness of our within-person correlation analyses, we re-ran the above analyses using linear mixed-effects models (LMEM). In these models, we tested whether the effect of anxiety on salivary cortisol (modelled at level-1) was moderated by the clinical group (SAD vs.

controls; modelled at level-2) accounting for a phase shift. Those results resembled the two-step within-person correlation approach reported above (data not shown).

4. Discussion

This study examined the subjective and physiological (salivary cortisol) responses to acute social stress in SAD compared to healthy control participants. As predicted (H1), there were no group differences in salivary cortisol levels at baseline, however, there were both substantial (AUCg) and inconclusive (AUCi) evidence for salivary cortisol group differences in response to acute social stress. Moreover, as predicted (H2), SAD individuals (vs. controls) reported significantly higher subjective experiences of anxiety, sadness, tiredness, and withdrawal, and lower levels of happiness at baseline and overall during the stress task (captured by AUCg, with a significant change in anxiety and sadness additionally being captured by AUCi). Then, after accounting for the different temporal dynamics of cortisol and subjective responses, we found unique evidence of within-person concordance from a moderately positive association between anxiety and salivary cortisol that was comparable between the SAD and control groups (H3).

4.1. Heightened anxiety despite normal salivary cortisol to social stress in SAD

Our main findings imply that individuals with SAD differ from their healthy peers primarily in terms of self-reported psychological responses rather than in their physiological (salivary cortisol) responses to social stress. These findings of normal cortisol response despite heightened psychological response to social stress are consistent with reports in clinical (Klumbies et al., 2014; Krämer et al., 2012; Martel et al., 1999) and socially anxious groups (von Dawans et al., 2018) but are inconsistent with studies reporting significantly larger salivary cortisol reactivity to social stress for those with SAD (see Furlan et al., 2001; Roelofs et al., 2009; van West et al., 2008).

Despite generally elevated levels of psychological stress, i.e., anxiety, to the stressor (AUCg), those with SAD also showed a much greater change in their levels of anxiety (AUCi), evident in a steep reduction in anxiety immediately post the stressor, compared to controls. This highlights the need for testing over multiple time points during the stressor to capture the pattern of stress response rather than only testing pre- and post-stressor (Klumbies et al., 2014). Quicker recovery from acute stress following heightened stress is likely because those with SAD are experienced in using coping strategies (e.g., safety behaviours) to adapt and overcome daily exposures to acute stress (Piccirillo, Taylor Dryman, & Heimberg, 2016). Alternatively, depressive symptoms have been linked to steep reactivity and recovery slopes to the TSST among cortisol responders (Fiksdal et al., 2019) and our cohort of SAD participants had significantly higher depressive (and anxiety and stress) symptoms as measured on the DASS-21 compared to controls. More research into the psychological and physiological recovery from acute stress in those with SAD compared to controls is needed.

We cannot fully determine why our study results differ from those who report heightened cortisol responding in those with SAD (vs. healthy controls) during acute social stress (see Furlan et al., 2001; Roelofs et al., 2009; van West et al., 2008). However, there are various methodological differences among the studies. At first, our sample of SAD patients was two-fold (n = 40) that of the studies with inconsistent outcomes (n = 18–25) (Furlan et al., 2001; Roelofs et al., 2009; van West et al., 2008), whereas our sample size was more in line with studies of similar and even larger sample sizes of SAD (n = 41–88) (Klumbies et al., 2014; Krämer et al., 2012). We also employed a newly standardized optimal version of the TSST (see Grace et al., 2019) for logistical ease and to reduce participant burden. Other studies administered either the standard TSST (Roelofs et al., 2009) and an adapted (shortened) version of the TSST to suit children (van West et al., 2008) or used a speech task other than the TSST (Furlan et al., 2001). We also strictly matched our groups on age, gender, and level of education, and our clinical SAD group had no comorbidities and was not using medication for their symptoms. Other studies included young children (van West et al., 2008) or the clinical group who had comorbid disorders and used medication such as antidepressants (Roelofs et al., 2009; van West et al., 2008). One study showed that the SAD with comorbid MDD group did not differ in salivary cortisol responding to social stress whereas the SAD-only group showed cortisol differences when compared to controls (Yoon & Joormann, 2012). We recognise that our assessment for comorbid disorders (using the MINI 7.0.2) may not have been sensitive enough to detect comorbid disorders such as MDD. Medication use can contribute to variability in cortisol stress response, such as reduced cortisol secretion in response to acute stress in individuals with GAD treated with escitalopram and/or diazepam (Plag, Schumacher, Schmid, & Ströhle, 2013). As such, sample size, the type of stressor employed, age, and the presence of comorbidities and medication use may have contributed to the inconsistency in findings.

4.2. Concordance in self-reported anxiety and salivary cortisol

Our concordance findings provide novel evidence for moderate psycho-endocrine covariance or coupling in our cohort, regardless of clinical status, and suggest that the more heightened self-reported responding observed among SAD participants (relative to healthy controls) was not due to a decoupling of self-reported and physiological responding. The direct statistical approach used in the current study was not conducted in any of the aforementioned studies and was inconsistent with specific conclusions made by others of such findings providing evidence for discordance (Klumbies et al., 2014) or a lack of concordance (von Dawans et al., 2018) between self-reported and physiological reactions to social stress despite not testing this relationship directly.

Our findings are consistent with the evidence in healthy controls reporting covariance of the psychological and physiological stress response from measurements obtained during the stressor (Hellhammer & Schubert, 2012). In the current study, the TSST may have been sufficiently anxiety-provoking for healthy controls to render it difficult to observe differences between them and SAD individuals, at least in some measures of reactivity such as salivary cortisol. Alternatively, the heightened self-reported anxiety may simply have been due to more intense self-reported experiential reactions to social stress observed in those with SAD. This is supported by evidence in healthy men showing that social anxiety modulated subjective response but not cortisol response to acute social stress (von Dawans et al., 2018).

To further interpret our results, we draw on theoretical models. Contemporary models of SAD emphasise that anxiety disorders are the result of cognitive biases and that negatively biased processing of social information and experience serves as a central mechanism in maintaining the disorder (Clark & Wells, 1995; Rapee & Heimberg, 1997). When faced with a social threat, socially anxious individuals shift their attention away from the social situation (missing most of the actual information) and direct their attention inward to engage with increased self-monitoring and examination of their current experience (Hirsch, Clark, Mathews, & Williams, 2003). Moreover, Barlow's (2002) model of anxiety suggests that social anxiety experiences can cause an unexpected burst of emotions that is perceived by individuals with SAD as their emotions and bodily reactions being out of their control. Therefore, a potential explanation for the pattern of results in our study could be that it is the perceived (heightened) negative interpretation of stressors and a perceived lack of internal control over the anxiety that leads to increased psychological distress in individuals with SAD. This heightened anxiety and biased interpretations could mean that individuals with SAD have an overreliance on their psychological response system because of their perceptions and is either not reflected in their physiological response or there is a misinterpretation of their normal

physiological responses to social stress. The latter is supported by evidence showing that individuals with SAD were significantly more aware of changes in physiological arousal (increases in heart rate and blood pressure), potentially over-interpreting these physiological signals, despite small or negligible differences compared to healthy controls (Anderson & Hope, 2009). Thus, individuals with SAD may be catastrophising about the normal changes in physiological arousal from social stress likely due to their higher levels of anxiety sensitivity that are fueled by their biased perceptions and increased internalization of a social stressor.

4.3. Baseline salivary cortisol and anxiety responding

Our finding of similar *baseline* salivary cortisol concentrations but heightened subjective anxiety in the SAD group at the same time point is consistent with previous studies (Furlan et al., 2001; Krämer et al., 2012; Roelofs et al., 2009; van West et al., 2008), and provides support for anxiety sensitivity (rather than abnormal physiological markers) playing a key role in explaining the current findings. Our lack of baseline salivary cortisol difference between the groups diverges from the trend observed by Klumbies et al. (2014) where the SAD group demonstrated higher baseline cortisol markers. However, the Klumbies et al. (2014) study included two-time points in the baseline measure, i.e., upon arrival (at −45 min) and 1 min before task introduction (at −1 min), compared to our baseline measure that was taken 5 min before the task introduction that followed a 15-minute acclimation period. Saliva collection at arrival and again just prior to the task introduction in the Klumbies et al. (2014) study may have enhanced the impact of extraneous factors (e.g., anticipatory anxiety due to meeting a stranger, and immediately being asked to provide saliva) compared to our study where participants had a chance to acclimatize before any formal procedures were conducted. Moreover, while often not explicitly reported, how participants are informed of the task and how close in proximity participants are made aware of the upcoming stress task may increase anticipatory anxiety, particularly among individuals with SAD. The current study was part of a larger study, and as such participants were already familiar with the lead researcher and the saliva sampling process prior to the TSST lab session.

4.4. Study strengths and limitations

We highlight here that the sample size observed in this study (SAD, n = 40, and healthy controls, n = 41) is one of the largest samples of psychosocial stress research in an adult diagnostic SAD group; only one other study of the TSST had a larger sample size of n = 88 although comorbidities and medication use were present (Klumbies et al., 2014) unlike the current study. Additionally, both groups were well matched on three key confounders including age, gender, and education level which leads to a more accurate estimation of between-group differences. Then, from a frequentist point of view, 40 participants per group are sufficient to detect moderate to large size differences between the two groups. Each participant was also assessed 10 times (baseline + 9 follow-up points) leading to 400–410 data points per group which is sufficient to run MEM and construct ROC and calculate AUC. Finally, this sample was more than sufficient for the Bayesian Mann-Whitney U test which allows for an accurate approximation from a relatively small sample (Chechile, 2020).

A major limitation of our study is that the participants with SAD were not representative of the typical SAD population due to the absence of comorbidities in the current cohort. We acknowledge that our use of the MINI may have lacked sensitivity to detect these comorbid disorders. Future research may seek to examine the acute stress response in SAD with and without comorbidities or in direct comparison with other relevant primary disorders (e.g., GAD) to better understand differences in physiological responses to stress among anxiety/mood disorders. Another limitation is that the limited number of non-responders (n = 17) precluded us from further exploring why some individuals show a cortisol response while others do not (Miller et al., 2013). This could have important implications for understanding the relationship between physiological and self-reported acute stress responses. It is however important that future studies report on cortisol non-responders including how this was dealt with in the main analyses. Further, our concordance analyses relied on a small number of time-points ($n = 5$), which may lead to unreliable estimates of within-person correlations. and assumed equal intervals between measurement occasions. Thus, future research would benefit from examining concordance between the self-reported and physiological stress response across a broader range of time points (e.g., at baseline, across the entire stress protocol, and recovery) with consistent time intervals between successive measurement occasions (e.g., 5-min intervals) or using a continuous-time modelling approach (Van Montfort, Oud, & Voelkle, 2018). We also note that we found substantial AUCg support for similar salivary cortisol levels between groups to social stress but AUCi failed to provide such supporting evidence. We acknowledge that AUCi could additionally reflect stress habituation and recovery and future research may want to incorporate these aspects in their study aims (Olivera-Figueroa, Juster, Morin-Major, Marin, & Lupien, 2015). Then, a final limitation of the current study is the focus on salivary cortisol reactivity, which does not necessarily occur with the same visible and potentially embarrassing signs compared to that of heart rate, sweating, and blood pressure. Nevertheless, SAD individuals likely interpret all physiological changes similarly. We acknowledge several additional biological markers (e.g., ACTH, norepinephrine, vasopressin) and bodily systems (e.g. SAM system, cardiovascular system) that may be of interest in experimental research of the acute stress response (Grace et al., 2019). Furthermore, recent evidence has shown that a history of childhood maltreatment may alter the with-in person associations between psychological and physiological markers of stress, as assessed using the TSST, at least in healthy controls (Kuhlman *et al.* 2021). The inclusion of additional biological or physiological markers of acute stress was beyond the scope of this study, however, we note the focus on salivary cortisol alone as a physiological marker of stress is considered a potential limitation of this study. Future research would benefit from the inclusion of physiological measures capturing both major components of the stress response, the HPA axis, and the SAM axis, as well as account for some form childhood maltreatment.

4.5. Conclusion

This study demonstrates that during acute psychosocial stress, self-reported stress reactivity convincingly differentiates the SAD group from the healthy control group at baseline and response to social stress. The groups had similar salivary cortisol levels at baseline, and, there was both substantial (AUCg) and inconclusive (AUCi) evidence for no group differences in the salivary cortisol response to social stress. Importantly, we provide evidence that self-reported anxiety is moderately concordant with salivary cortisol in response to psychosocial stress in all participants when accounting for the temporal dynamics in self-reported and physiological stress response systems. Thus, we provide unique evidence that the heightened self-reported stress is not due to a decoupling of self-reported and physiological responses but may instead be due to heightened 'anxiety sensitivity' as a result of prolonged biased perceptions, over-internalisation of social events, and reliance on coping strategies. These findings warrant further examination of the relationship between the self-reported and physiological response to acute social stress, including examining other physiological markers and non-social (physical) stress, in SAD. Further neuroimaging studies to fully understand the mechanisms implicated in these findings are needed, along with a more detailed exploration of the nature of recovery from social stress in SAD. These findings suggest current treatments may benefit from educating individuals about the nature of their psychological vs. physiological signals from the body during anxiety-provoking social

scenarios to enable them to better interpret these signals.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopsycho.2022.108444.

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