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Investigating Steady State Visually Evoked Potentials as a Novel Biosignature for Anxiety-Related Attention Bias

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INVESTIGATING STEADY STATE VISUALLY EVOKED POTENTIALS AS A NOVEL BIOSIGNATURE FOR ANXIETY-RELATED ATTENTION BIAS

by

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Abstract

Investigating Steady State Visually Evoked Potentials As A Novel Biosignature For Anxiety-Related Attention Bias

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Anxiety-related attention bias (AB), a type of cognitive bias underlying the development and maintenance of anxiety disorders, is typically defined as exaggerated attention towards threat; however, some individuals also demonstrate AB away from threat and in some instances, no detectable AB at all. Debate about the reliability and validity of AB behavioral measures has prompted examination of additional assessment methods. Neurophysiological methods, such electroencephalography (EEG), have yielded encouraging early findings. The steady-state visually evoked potential (SSVEP), a measure of selective visual attention derived from EEG, holds promise as a biosignature for AB. Research documents heightened SSVEP power to emotionally salient stimuli such as threat faces among those with social anxiety; however, less is known about the association between SSVEP to threat and neutral stimuli among those with varying anxiety severity and subtypes. This study explored these questions, hypothesizing that those with severe anxiety as well as those with an anxiety diagnosis would show the greatest magnitude SSVEP power to threat faces relative to neutral faces. SSVEP power was extracted from EEG recordings generated while 95 adults completed a modified dot probe task in which angry and neutral face pairs flickered at unique frequencies. Contrary to our hypotheses, results showed that SSVEP to threat was not heightened among those with severe anxiety relative to those with mild or moderate anxiety; however, a significant interaction among emotion, hemisphere, and frequency emerged for those with an anxiety diagnosis showing differential magnitude of the SSVEP for neutral stimuli: 12Hz, but not 15Hz, SSVEP power in the right hemisphere to neutral stimuli was marginally greater than in the left hemisphere. This unique pattern of electrocortical facilitation to non-arousing stimuli is consistent with the idea that anxious individuals may process and attend to neutral or ambiguous stimuli differently than non-anxious individuals.

Keywords: Anxiety, attention bias, steady-state visually evoked potentials, SSVEP, EEG

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Introduction

Anxiety disorders are one of the most common mental health disorders in the United States, as an estimated one third of adults experience an anxiety disorder within their lifetime (Kessler et al., 2005). While individuals with anxiety may seek empirically validated therapies such as cognitive-behavioral therapy (CBT), anxiety remission rates after CBT treatment can be as high as 51% (Springer et al., 2018), highlighting the need for additional research to deepen both scientific and therapeutic understanding of the mechanisms underlying anxiety disorder development and maintenance. One such under-examined mechanism underlying anxiety disorder etiology and maintenance is the anxiety-related attention bias (AB).

AB is defined as selective and exaggerated attention towards threat (Bar-Haim et al., 2007; Cisler & Koster, 2010; Mathews & MacLeod, 2002). Interestingly, some individuals with heightened anxiety also demonstrate AB away from threat and in some instances, no detectable AB at all. Yet, because AB is typically assessed via behavioral tasks such as the Dot Probe (DP) task, these distinct patterns of AB cannot be verified due to debate about the reliability and validity of the DP task. Thus, there is a pressing need for additional AB assessment tools.

Neurophysiological metrics of AB using electroencephalography (EEG) have yielded promising findings. In particular, the steady-state visually evoked potential (SSVEP), a measure of selective visual attention, holds promise as a reliable and valid biosignature of AB. The SSVEP is enhanced in response to the presentation of emotionally salient visual stimuli, such as the threat faces presented in a typical DP task, among those with high social anxiety or a diagnosis of social anxiety disorder (SAD) (McTeague et al., 2018); however, less is known about SSVEP modulation by affective stimuli among those with varying anxiety severity and anxiety diagnoses. This study explored the phenomenon of SSVEP modulation by threat relative to neutral stimuli (angry versus neutral faces) among adults showing a range of anxiety symptoms and severity to examine whether, like behavioral metrics of AB, the SSVEP is selectively enhanced to threat.

First, we hypothesized that SSVEP power to threat faces - indicating enhanced selective attention - in comparison to neutral faces would be heightened across the entire anxious sample. Next, we hypothesized that individuals with severe anxiety relative to those with mild and moderate anxiety would show the greatest magnitude SSVEP power to threat faces relative to neutral faces. Similarly, we hypothesized that individuals with an anxiety diagnosis, in contrast to those without an anxiety diagnosis, would show the greatest magnitude SSVEP to threat faces relative to neutral faces.

Attention Bias

AB towards threat is detected in both clinically and non-clinically anxious individuals, in both children (Brown et al., 2013) and adults (Zvielli, Bernstein, & E. H. Koster, 2014), and among individuals with varying anxiety diagnoses, such as generalized anxiety disorder (GAD) (Waters et al., 2014) and panic disorder, specific and social phobias, post-traumatic stress disorder (PTSD), and obsessive compulsive disorder (OCD) (Bar-Haim et al., 2007; Dennis et al., 2019). Emerging evidence, however, also documents heightened AB *away* from threat, suggesting that anxious individuals show heterogeneous patterns of disrupted attention to threat, including patterns of attentional avoidance (Brown et al., 2013; Koster, Crombez, Verschuere, & De Houwer, 2006; Dennis et al., 2019).

Taken togther, this robust body of evidence suggests the conclusion that AB is an etiological mechanism in anxiety. When investigating AB among anxious samples, and AB heterogeneity, it is crucial to consider anxiety disorder subtype. Anxiety disorders may be classified into two groups: distress (e.g. GAD) versus fear-based (e.g. specific or social phobia) and these classes demonstrate unique patterns of AB, such that those with GAD show heighted AB towards threat while those with fear-based pathologies have been shown to evidence AB away from threat (Dennis-Tiwary et al., 2019; Waters et al., 2014). Adding to this complexity, studies employing neurophysiological methods such as event-related potentials (ERPs), have shown that those with distress-based anxiety disorders such as GAD may show impaired threat-safety discrimination, which may manifest as overgeneralized threat sensitivity and heightened arousal by neutral stimuli, as those neutral stimuli have been conceptualized as ambiguous and therefore potentially threat-relevant stimuli, for those with heightened AB to threat (Denefrio et al., 2018; Dennis-Tiwary et al., 2019; Jovanovic et al., 2014).

Neuroimaging evidence further supports the link between anxiety subtype and distinct patterns of AB. Evans et al. (2020), for example, found evidence of AB heterogeneity associated with unique neural activation patterns, such that avoidant and slow disengagement AB were associated with reduced default mode network activation. Additionally, heightened neural connectivity between the right amygdala, right middle occipital cortex, and right superior temporal sulcus were associated with avoidant AB as well as slow disengagement, relative to vigilance and fast disengagement.

Assessment of Attention Bias Via the Dot Probe (DP) Task

The DP task, a reaction time (RT) based task, is commonly used to assess and quantify the anxiety-related AB to threat. In the DP task, two visual stimuli appear concurrently on a computer screen - e.g. either a neutral and threat stimuli pair or a neutral and neutral stimuli pair. After stimuli offset, an arrow appears in the place of one of the stimuli previously on the screen, and participants are instructed to respond by indicating the direction of the arrow. RTs to the arrows replacing the threat (threat trials) or neutral (neutral trials) stimuli are generated and used to calculate AB scores.

Mean AB scores, calculated by subtracting the average RT to threat trials from the average RT to neutral trials in the DP task, allow researchers to quantify the overall pattern of attention bias across multiple trials. Threat bias scores calculated in this manner allow for quantification of both AB towards threat as well as AB away from theat, in that faster reaction times to threat trials, relative to neutral trials lead to positive scores, indicating facilitated attention towards threat, whereas slower responses to threat stimuli relative to neutral stimuli lead to negative scores that represent AB away from threat. This approach does not allow for exploration of variations in AB patterns that a participant may demonstrate throughout the course of the task. For example, during a single DP assessment an individual may initially demonstrate vigilance, fast RTs to threat stimuli but may later display avoidance, slower RTs to threat stimuli. Averaging the RTs to threat stimuli across all threat trials would obscure this variability in attention towards threat stimuli. Quantification of AB via Trial Level Bias Scores (TLBS) offsets the complexities of mean AB scores.

TLBS scores quantify AB for temporally contiguous DP task trial pairs, which facilitates investigation of temporal AB patterns that emerge throughout the course of a single DP assessment, and would reflect complex AB patterns such as early vigilance and later avoidance (Egan & Dennis-Tiwary, 2018; Zvielli et al., 2015). AB measures able to capture the temporal dynamics of AB, magnitude and directionality over time, will be crucial for elucidating the patterns and boundaries among individuals with varied anxiety subtypes, as evidence suggests that unique AB patterns emerge among individuals with varying anxiety severity and subtype.

Investigation of AB via neurophysiological methods such as electroencephalography (EEG), have yielded promising findings as well as broadened understanding of the cognitive and affective processing underlyingAB. In particular, the steady-state visually evoked potential (SSVEP) is well positioned to explore the complexities of AB as prior research indicates that it is a measure of selective visual attention and is modulated by affective stimuli.

Steady State Visually Evoked Potentials (SSVEP)

SSVEPs are neural oscillations that are naturally evoked by the allocation of covert or overt visual attention to stimuli flickering at a consistent rate. SSVEPs are derived from the magnocellular, parvocellular, and koniocellular pathways of the visual system and are modulated by selective visual attention to consistently flickering visual stimuli indicating that SSVEP power may serve as an objective and quantifiable metric of covert and overt attention; thus, the SSVEP is considered to be a continuous electrophysiological measure of selective visual attention (Norcia, Appelbaum, Ales, Cottereau, & Rossion, 2015; Thigpen et al., 2018; Vialatte et al., 2010).

SSVEP power is extracted from electroencephalography (EEG) recordings at the flicker frequency of the visual stimuli, allowing researchers to investigate the power of the neural oscillation at the exact frequency of the flickering stimulus (Thigpen et al., 2018). Greater SSVEP power at the flicker frequency of the visual stimuli indicates heightened sensory processing and visual-cortical facilitation of the attended stimuli (Andersen & Müller, 2010; McTeague et al., 2011). In addition to providing an objective and quantifiable metric of selective visual attention for discrete stimuli, the methodological power of the SSVEP is further enhanced as frequency-tagging allows researchers to concurrently present two non-overlapping visual stimuli that flicker at distinct rates and subsequently extract the oscillatory response to each individual stimulus at its unique frequency.

An additional methodological strength of the SSVEP is its sensitivity to both covert and overt attention. Unlike other measures of selective visual attention, such as eye tracking that assess overt attention allocation via the quantification of eye gaze and saccadic eye movements and thus may not be tailored for quantifying nuanced covert attention allocation, the SSVEP does not rely on eye gaze or eye movements to quantify attention, and thus is not constrained by them. This allows researchers to investigate and quantify both overt and covert attention allocation to a single stimulus, during tasks in which multiple visual stimuli are presented at once, such as during the DP task, conferring distinct benefits for the exploration of selective visual attention and the neural processes underlying attention to emotionally salient visual stimuli.

Research employing the SSVEP to investigate attention patterns to affective stimuli suggests that the SSVEP may be an effective tool for investigating anxiety-related AB towards threatening stimuli (McTeague et al., 2011; Norcia et al., 2015; Thigpen et al., 2018; Vialatte et al., 2010). For example, research exploring the sensitivity of the SSVEP to valenced stimuli reveals that SSVEP power varies for emotionally versus non-emotionally salient visual stimuli. One study, for example, showed that SSVEP power to emotional (e.g. angry and happy) versus neutral faces was heightened for high socially anxious individuals, but not for low socially anxious individuals, suggesting that SSVEP may serve as an index of sensitivity to affective stimuli and a novel measure of attention bias among the socially anxious (Wieser et al., 2016).

Among another sample of low and high socially anxious participants, McTeague et al. (2011) also documented electrocortical facilitation towards several types of emotional faces (angry, fearful, and happy), as compared to neutral faces, among those with high anxiety. Yet, studies conducted by Wieser et al. (2011) provided evidence of more constrained electrocortical facilitation, indicating enhanced SSVEP power to angry faces only, as compared to happy and neutral. Additional studies further documented that the SSVEP was specifically enhanced to angry and fearful face stimuli among the socially anxious (McTeague et al. 2018).

In addition to the socially anxious, evidence of SSVEP modulation has also been documented among healthy individuals. While much SSVEP literature exploring electrocortical responses to emotionally salient versus neutral stimuli has focused on the socially anxious, some researchers have explored SSVEP sensitivity to affective stimuli in healthy adults. Wieser et al. (2014), for example, found that healthy adults evidenced a greater SSVEP power to threatening faces in combination with threatening scenes compared to neutral faces and scenes. Interestingly, Schubring & Schupp (2019) found that SSVEP power to arousing (e.g. erotic images) versus non-arousing (e.g. romantic) images was significantly reduced in the alpha and lower beta frequency, indicating that SSVEP power may be modulated by stimulus saliency within particular frequency bands. Further highlighting the complexities of the association between SSVEP and emotionally salient stimuli, Thigpen et al. (2018) found no evidence of SSVEP power modulation in response to neutral or threat stimuli among a sample of low trait anxious adults. While the literature has extensively explored the association between SSVEP and emotionally salient face stimuli among the socially anxious, additional research is necessary to clarify the association between SSVEP and emotionally salient stimuli in both healthy individuals as well as those with anxiety diagnoses other than social anxiety disorder.

Additional research is also needed to clarify some methodological features of the SSVEP: some research indicates that (1) the degree of neural entrainment of the flicker frequency may vary based upon the flicker frequency employed in the experimental paradigm as well as (2) the degree of neural entrainment may also vary by hemisphere, such that the SSVEP may be more pronounced in one hemisphere than the other. During a covert spatial attention task, Keil et al. (2004) found that the SSVEP power was most pronounced in the right hemisphere and posited that this may be due to heightened sensitivity of the visual pathways in the right hemisphere to emotionally salient visual stimuli, alluding to automatic attention capture by threatening stimuli as in anxiety-related AB. Other studies have also documented differing patterns of SSVEP entrainment depending upon the flicker frequency of the visual stimuli (Bridwell & Srinivasan, 2012; Wu & Yao, 2007).

Exploration of the impact of different flicker frequencies on neural entrainment also revealed that the flicker frequency of the visual stimuli may impact the attentional network activated by the stimuli. Ding et al., 2005 found that delta (2-4Hz) and upper alpha (10-11Hz) frequencies activated an occipital-frontal network, while lower alpha (8-10Hz) frequencies activated parietal and posterior frontal cortex regions. Additionally, they found that flicker frequency was not only associated with a particular cortical network but that this also impacted whether or not the SSVEP power increased or decreased in response to the visual stimuli. It is worth noting that the stimuli used in this study were non-naturalistic stimuli (e.g. concentric circles), as the features of the stimuli also impact SSVEP entrainment. In another study, Bekhtereva & Müller (2015) found a significant difference in the SSVEP power between emotionally salient and neutral images for stimuli presented at 6Hz but did not find such an effect for stimuli presented at 15Hz.

Consideration of the robust research indicating the modulatory effect of affective stimuli on SSVEP power in the occipito-temporal brain regions (Keil et al., 2004; McTeague et al., 2011; Schubring & Schupp, 2019; Wieser et al., 2011; Wieser et al., 2016) points towards the

SSVEP as a promising tool to further investigate the neural mechanisms underlying AB phenotypes and a potential biosignature of anxiety-related AB to threat. Furthermore, given the complex findings indicating heighted electrocortical facilitation towards threat stimuli among varying groups, additional research is needed to clarify for whom the SSVEP modulatory effect is most pronounced.

As prior research has primarily investigated SSVEP modulation by emotionally salient stimuli among those with social anxiety, this project will explore the association between SSVEP and AB, SSVEP and anxiety severity, as well as SSVEP and other anxiety disorders. Identification of unique neurophysiological markers of AB would provide researchers and clinicians with quantifiable neurocognitive measures that could be used to identify individual differences in anxiety subtype and that future interventions could target to assess anxiety severity and treatment efficacy.

Specific Aims

This project investigated six specific aims, three main and three exploratory. Using data previously collected as a part of a randomized controlled trial exploring the efficacy of attention bias modification training (ABMT), we examined the following aims and hypotheses using data from the baseline session of this study, before participants completed the ABMT intervention. The three main aims investigate differences in SSVEP power based on emotion, anxiety severity and anxiety diagnosis. First, this study examined whether SSVEP power varied for threat versus neutral face stimuli and tested the hypothesis that SSVEP power to threat would be greater than SSVEP power to neutral faces. Second, we examined whether SSVEP power differed by anxiety severity by testing the hypothesis that those with severe anxiety would have the greatest magnitude SSVEP power to threat relative to neutral faces as compared to those with mild to moderate anxiety. Third, we examined if SSVEP power to threat as opposed to neutral stimuli was greater among those with a diagnosed anxiety disorder relative to those without an anxiety diagnosis and tested the hypothesis that those with an anxiety disorder diagnosis would exhibit the greatest magnitude SSVEP power to threat relative to neutral faces as compared to those without an anxiety disorder diagnosis.

This project also investigated three exploratory aims that examined SSVEP power frequency and hemisphere differences as well as the relationship between SSVEP power and AB. The first exploratory aim examined if SSVEP power varied by frequency and tested the hypothesis that 15Hz SSVEP power would be greater than 12Hz SSVEP power. The second exploratory aim examined if SSVEP power varied by hemisphere and tested the hypothesis that SSVEP power would be greater in the right occipital cortex than in the left occipital cortex. The third and final exploratory aim examined the relationship between SSVEP and AB measures. We tested the hypothesis that SSVEP to threat would be correlated with AB measures that indicate exaggerated attention towards threat, such as threat bias, peak positive, and mean positive.

Methods

Study Structure

The present study involved analysis of data collected during Time 1 of a longitudinal randomized controlled trial investigating the effect of Attention bias Modification Training (ABMT) on attention bias and anxiety in a sample of clinically anxious adults. Analyses conducted on Time 1 data, before administration of the ABMT intervention, explore the association between SSVEP, anxiety, and attention bias.

Participants

One hundred and twenty-six participants, whose age ranged from 18-41 (M = 25.43, SD = 6.37), were recruited from the City University of New York Hunter College Psychology Department participant pool. Of these 126 participants, 72 were females (57%).

Participants were pre-screened for moderate anxiety using the 21-Item Depression, Anxiety, and Stress Scale (DASS-21) prior to study enrollment, such that only those presenting with at least moderate to severe anxiety were deemed eligible. As such, only participants who scored 6 or higher on the anxiety subscale or 10 or higher on the stress subscale of the DASS-21 prescreen were recruited to participate ($M_{anxiety}$ = 9.35, $SD_{anxiety}$ = 3.49; M_{stress} = 12.76, SD_{stress} = 3.80).

During the Time 1 session, enrolled participants completed the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) as well as a brief Medication and Therapy History Questionnaire. Administration of the MINI facilitated identification of those individuals who met diagnostic criteria for disorders that were deemed exclusionary criteria (e.g. Substance Dependence/Abuse, Psychotic Disorders, Mood Disorders with Psychotic Features, or High Suicidality per the DSM-IV-R). Additionally, those individuals who started a new prescription medication or a new dosage of a current prescription medication within less than 6 months of their session 1 date as well as those who began therapy less than 4-6 weeks from the date of their first session were deemed ineligible. Sixteen individuals were deemed ineligible for further participation in the study based on their diagnostic status as well as their responses to Medication and Therapy History, as determined via the MINI and History of Medication and Therapy Questionnaire.

Of the remaining 110 participants, an additional 15 were excluded from the final analyses due to lack of usable SSVEP data, for a final sample of 95 participants for Time 1 analyses. Among this final sample of N=95, age ranged from 18 to 41 (*M* = 25.43, *SD* = 6.37), 65 were female, while 30 were male. The racial and ethnic demographics of these participants were as follows: 16 (16.8%) Hispanic/Latina and 61 (64.2%) Non-Hispanic/Latina, 47 (49.5%) Caucasian, 19 (20%) Asian, 12 (12.6%) Black or African American, 6 (6.3%) more than one race, and 1 (1.1%) American-Indian.

Materials and Procedures

During the Time 1 session, after completing the consent procedures, participants proceeded to the experimental booth for EEG setup. Upon completion of EEG setup, participants were positioned approximately 65cm away from the 17-inch computer monitor in preparation for data acquisition. Participants then completed the SSVEP computer task and the Dot Probe computer task. After completion of the computer tasks and EEG removal, research assistants administered the History of Medication and Therapy Questionnaire as well as the MINI, after which participants then completed the Hamilton Anxiety Rating Scale (HAM-A), a self-report anxiety questionnaire.

Measures: Interview & Self-Report Questionnaires

One diagnostic interview and two questionnaires were administered to identify those participants with anxiety disorders and symptoms.

Diagnostic Interview

Mini-International Neuropsychiatric Interview (MINI): Administration of the Mini-International Neuropsychiatric Interview (MINI) served a two-fold purpose; first, to identify those meeting diagnostic criteria for disorders that were exclusionary, such as Substance Use

Disorder; and second, to identify those individuals who met the diagnostic criteria for anxiety and depressive disorders.

Self-Report Questionnaires for Anxiety

The Hamilton Anxiety Rating Scale (HAM-A, Hamilton, 1959) is a 14-item self-report measure that assesses an individual's level of anxiety over the past week. Participants review a series of statements related to mental agitation, psychological distress, as well as somatic anxiety and rank each item from 0 to 4, where "0" indicates that symptoms are "not present" and "4" indicates that symptoms are "very severe." Possible total scores range from 0 to 56, where higher total scores indicate more severe anxiety. We confirmed that there were no significant outliers and that the HAM-A total scores were within +/- 3 SDs of the group mean. The HAM-A total score was used in project analyses.

The Depression, Anxiety, and Stress Scale (DASS-21; Henry & Crawford, 2005) is a 21-item self-report questionnaire that distinguishes between dimensions of depression, anxiety, and stress. Participants indicate how much each statement applied to them over the past week and rate each item from 0 to 3, where "0" indicates that the statement "did not apply to me at all" and "3" indicates that the statement "applied to me very much or most of the time." The DASS-21 allows for the generation of 4 scores: a total score as well as depression, anxiety, and stress subscores. All items are added together to generate the total score, while select items are summed to generate the subscores. The values from the total and subscores are then doubled, to allow classification of normal to severe levels of depression, anxiety, and stress according to the score cutoffs for the 42-Item DASS. Scores of 8-9 indicate mild anxiety, 10-14 indicates moderate anxiety, 15-19 indicates severe anxiety, and 20 or more indicates extremely severe anxiety. DASS-21 anxiety subscores that were greater than +/- 3 SDs from the group mean were deemed outliers and winsorized, such that those values above +/- 3SDs were replaced with the value closest to the outlier and within +/- 3 SDs. This corrected DASS-21 anxiety subscore was used in subsequent analyses.

Measures: Computer Tasks

Dot Probe Task

Dot Probe (DP) Task was administered to assess and facilitate quantification of attention bias. DP task stimuli included color pictures of 20 different individuals (10 males, 10 females) selected from the NimStim stimulus set (Tottenham et al., 2009) with one female taken from the Matsumoto and Ekman (Matsumoto and Ekman, 1989) stimulus set and was programmed using E-Prime version 2.0 (Schneider et al., 2002). The task consisted of 120 individual trials in which a fixation cross would appear on the computer screen for 500ms, followed by a pair of faces, either angry-neutral or neutral-neutral, that would remain on the screen for another 500ms. Each pair of faces, depicting the same individual, were shown above and below a fixation cross, with 14 mm between them.

Next, the pair of faces would disappear and an arrow, the target, would appear in the location of one of the images previously on the screen, at which time, in accordance with the instructions, the participant would click the computer mouse to indicate the direction of the arrow, where a left click indicated that the target had pointed to the left and a right click indicated that the target had pointed to the right. The task was designed such that a trial would remain on screen until the participant provided a response via mouse-click. A brief 500ms intertrial interval followed the participant response, and then the sequence repeated with the next randomized pair of faces. Of the 120 trials included in the task, there were 80 angry-neutral face pairs and 40 neutral-neutral face pairs. The targets were equally likely to appear on the top or bottom, behind an angry or neutral face cues, as well as pointing to the left or the right. Attention bias scores were generated using the reaction time data extracted from this Dot Probe Task. Figure 1 provides a visualization of a single DP task trial.

DP Task: Attention Bias Score Generation

DP Task data for each participant was reviewed for accuracy and completeness. Data for participants who completed the DP Task with 85% accuracy or higher were included in analyses. Reaction times that exceeded +/- 3 SD from an individual's mean were excluded. We then generated two sets of AB scores, traditional average AB scores as well as trial-level bias scores (TLBS).

Traditional Average AB Scores. We created three AB average reaction time (RT) scores – threat bias, vigilance, and disengagement – using RT data from the threat-neutral (TN) face pairs as well as neutral-neutral (NN) face pairs that appeared in each trial of the DP Task.

Threat bias scores were calculated as the average RT to neutral faces within TN pairs minus the average RT to threat faces within TN pairs [(RT_TN_neutral) - (RT_TN_threat)]. Threat bias scores assess the degree of attention captured by threat stimuli relative to neutral stimuli within a mixed TN pair, such that positive threat bias scores indicate facilitated attention towards threat while negative scores indicate relative threat avoidance.

Vigilance was computed as RT to neutral faces within NN pairs minus RT to threat faces within TN pairs [(RT_NN) - (RT_TN_threat)]. Vigilance assesses automatic attention to threat relative to a neutral condition, such that positive scores indicate low vigilance to threat and negative scores indicate high vigilance to threat.

Disengagement, calculated as RT to neutral faces within NN trials minus RT to neutral faces with TN trials [(RT_NN) - (RT_TN_neutral)], assesses difficulty disengaging from threat via exploration of the difference in RTs to neutral faces within mixed TN trials as compared to NN trials. High disengagement scores indicate difficulty disengaging from threat.

Trial-Level Bias Score Generation. In addition to average AB scores, we also generated TLBS scores. As the traditional AB scores investigate average RTs within a particular condition type relative to another, potentially meaningful variation within an individual's attention pattern is masked by averaging RTs across trials. TLBS scores offset this complexity by allowing one to explore the degree to which an individual's attention to threat and neutral stimuli varied throughout the duration of the DP task. TLBS scores were generated by examining RTs to neutral and threat faces during temporally contiguous matched pairs of TN_Neutral and TN-Threat trials as well as matched pairs of TN_Threat and TN_Neutral trials. For each individual pair of matched trials, scores were calculated as follows: (RT_TN_neutral) - (RT_TN_threat) (Egan & Dennis-Tiwary, 2018). This method generates an RT score for each temporally contiguous pair of matched trials within a single dot probe assessment, facilitating the exploration of potentially changing patterns of AB throughout the task. These RTs were then used to generate five TLBS scores: mean positive, mean negative, peak positive, peak negative, and variability. Mean positive was calculated as the average of all TLBS above zero. Mean negative is the average of all TLBS below zero. Peak positive is the highest TLBS score above zero. Peak negative is the lowest TLBS score below zero. Positive mean and peak TLBS indicate AB towards threat, while negative TLBS indicate bias away from threat. Variability was computed as the sum of the distance between sequential TLBS divided by the number of pairs (Egan & Dennis-Tiwary, 2018).

SSVEP Task

The SSVEP Task was a modified Dot Probe (DP) task that used the same face stimuli as the DP and incorporated frequency-tagging using 12Hz and 15Hz flicker frequencies for 128 pairs of angry and neutral faces, to investigate if SSVEP power was modulated by the emotional valence of the faces. The task was designed and administered using Presentation 20.0 (Neurobehavioral Systems, Inc., Albany, CA). All the stimuli in the task appeared on a gray background. The SSVEP task was structured as follows.

SSVEP Task Structure. At the beginning of the task, the following prompt would appear on the screen: "Ready…". Next, the participant received the following verbal instructions from a research assistant, "In each trial, a dot will appear in the center of the screen, followed by a pair of faces, and then by a target: pointing to the left < or pointing to the right >. Respond as quickly as you can without making mistakes using the '1' and '2' keys. That is, if the target is pointing to the left, hit the '1' key & if the target is pointing to the right, hit the '2' key. Press the '1' or '2' keys to start." After pressing the "1" or "2" button to start, the task proceeded through a series of 128 trials of face pairs. Each of the 128 trials was composed of three phases. First, a fixation dot would appear at the center of the computer screen. Next, a pair of flickering face images would appear on either side of the fixation dot for 2750 ms. The face stimuli had dimensions of 7cm (191 pixels) long by 5.5 cm (143 pixels) wide. The center of each face was positioned 6cm to the left and right of the fixation dot. After the faces disappeared, a unidirectional arrow, referred to as a "probe," would appear to the left or right of the fixation dot, in the same location as one of the faces that had previously been on the screen. This probe remained on the screen until the participant provided a response. Lastly, each trial concluded with an inter-trial interval that varied in length from 750 to 1000 ms. Figure 2 provides a visualization of a single SSVEP task trial.

All 128 SSVEP task trials were counterbalanced by frequency (12Hz or 15Hz), emotion (neutral or threat), and location (left or right), creating four cue conditions consisting of 32 trials each. In one such condition, a neutral face would appear on the left side of the fixation cross and flicker at 12Hz while a threat face would appear on the right and flicker at 15Hz, e.g [Left: 12Hz Neutral & Right: 15Hz Threat]. The remaining three pairs of cue conditions were as follows: [Left: 15Hz Neutral & Right: 12Hz Threat], [Left: 12Hz Threat & Right: 15Hz Neutral], and [Left: 15Hz Threat & Right: 12Hz Neutral]. SSVEP power was extracted for the 12Hz and 15Hz frequency bands separately from EEG recordings for each of the four cue conditions. As prior research indicates that SSVEP power is maximal in the parieto-occipital region of the cortex, 12Hz and 15Hz analyses of SSVEP power focused on parieto-occipital EEG channels. SSVEP power in the left occipital cortex was quantified using channels PO3, PO7, O1, Oz, and POz, while SSVEP power for the right occipital cortex was quantified using channels PO4,PO8, O2, Oz, and POz (Thigpen et al., 2018, Wieser et al., 2012).

SSVEP Task: Score Generation. SSVEP scores were created to allow exploration of differences in frequency, emotion, and hemispheric activity. Additional SSVEP average scores combined frequencies, visual field, as well as frequency & visual field. Finally, a ratio score comparing average SSVEP to neutral versus threat faces, combined across both frequencies & visual fields, was also generated.

Using the SSVEP power exported from channels PO3, PO7, O1, Oz, and POz for the left occipital cortex (LOC) and channels PO4,PO8, O2, Oz, and POz for the right occipital cortex (ROC), several SSVEP scores were generated: eight individual scores, ten mean scores, and one ratio score. The individual scores represent SSVEP power of a single frequency (e.g. 12Hz or 15Hz) to a particular face type (e.g. threat or neutral), in either the left visual field (LVF) or the right visual field (RVF). As visual stimuli presented to a visual field are passed to the contralateral occipital cortex, scores were generated accordingly and indicate that stimuli presented to the LVF are passed to the ROC. One such individual SSVEP score is 12Hz SSVEP power to neutral stimuli presented to the left visual field and passed to the right occipital cortex. Seven additional scores, structured in this same manner, were also generated: 12Hz SSVEP power to threat stimuli in the ROC, 12Hz SSVEP power to neutral stimuli in the LOC, 12Hz SSVEP power to threat stimuli in the LOC, 15Hz SSVEP power to neutral stimuli in the ROC, 15Hz SSVEP power to threat stimuli in the ROC, 15Hz SSVEP power to neutral stimuli in the LOC, and 15Hz SSVEP power to threat stimuli in the LOC.

These eight individual scores were then used to generate mean scores that combined LOC and ROC activity for each frequency and stimulus type, as follows: average 12Hz SSVEP power combined for the LOC and ROC to threat faces, average 12Hz SSVEP power combined for the LOC and ROC to neutral stimuli, average 15Hz SSVEP power combined for the LOC and ROC to threat faces, and average 15Hz SSVEP power combined for the LOC and ROC to neutral stimuli,

In addition to SSVEP power scores that combined across hemispheres, separate SSVEP scores that combined frequencies were also created: average of 12Hz and 15Hz SSVEP power to neutral stimuli in the ROC, average of 12Hz and 15Hz SSVEP power to neutral stimuli in the LOC, average of 12Hz and 15Hz SSVEP power to threat stimuli in the ROC, and average of 12Hz and 15Hz SSVEP power to threat stimuli in the LOC.

Next, two average scores that combined across both frequencies and hemisphere were created: the average of 12Hz and 15Hz SSVEP power in both the LOC and ROC for neutral stimuli (SSVEP Neutral) as well as the average of 12Hz and 15Hz SSVEP power in both the LOC and ROC for threat stimuli (SSVEP Threat). Lastly, a ratio score was generated, which was calculated as SSVEP Neutral divided by SSVEP Threat.

A LN transformation was performed on all SSVEP scores to address skewness and kurtosis in the data. All SSVEP scores used in analyses were LN transformed. Next, we performed winsorization such that for all SSVEP scores, extreme values of +/- 3 standard deviations (SDs) from the mean were replaced with the next highest value within +/- 3 SDs from the mean.

The SSVEP scores used in the analyses combined SSVEP power for both 12Hz and 15Hz stimuli as well as SSVEP power in both hemispheres; thus, unless otherwise noted, "SSVEP Neutral" refers to SSVEP power for both 12Hz and 15Hz neutral stimuli in both the left and right hemispheres. Similarly, unless otherwise noted, "SSVEP Threat" refers to SSVEP power for both 12Hz and 15Hz threat stimuli in both the left and right hemispheres. The "SSVEP Ratio" refers to the above referenced SSVEP ratio score, which was calculated as SSVEP Neutral divided by SSVEP Threat.

EEG Recording and Data Reduction

Participants were fit with a 64-channel nylon EEG cap, on which the channels were arranged in accordance with the International 10-20 system. Highly conductive, water soluble gel was inserted into each of the channels to provide contact between the scalp and each electrode to reduce impedance and improve signal quality. Continuous EEG was recorded during the SSVEP task via the BioSemi system (Biosemi; Amsterdam, Netherlands) using 64 sinstered, active, pintype Ag/AgCl scalp electrodes, sampled at 1024 Hz. A dedicated mastoid electrode was positioned behind each ear, and eye movements were monitored via electrooculogram (EOG). Two facial electrodes were positioned approximately 1 cm from the outer corner of each eye to facilitate measurement of the horizontal eye movements. An additional two facial electrodes were positioned approximately 1cm above and below the left eye to capture vertical eye movements.

During EEG acquisition, the Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode served as the ground electrodes. EEG data reference and filtering was conducted offline using Brain Vision Analyzer. The acquired EEG data was referenced offline to the mastoid electrodes. A Butterworth Zero Phase Filter was applied with a low cutoff value of 0.1Hz and a high cutoff value of 50 Hz. The data were then segmented based on trial type into 2000ms segments to which baseline correction was applied. Ocular correction was then performed on all 64 scalp electrodes using the four electrooculogram electrodes as a reference. Artifacts were then automatically identified such that voltage steps greater than 150 microvolts were removed. The data was subsequently visually inspected trial-by-trial for any additional eye movement artifacts. Finally, a Fast Fourier Transformation was applied to the segmented data to allow extraction of SSVEP power in the 12Hz and 15Hz frequency bands for each trial type.

Results

Demographic data – age, race and ethnicity – for all participants are reported in Table 1. Additionally, mean anxiety symptoms as quantified via the HAM-A and DASS-21 Anxiety subscores as well as attention bias scores are summarized in Table 2.

Split-half reliability of AB scores

Split-half reliability was examined for the dot probe task by creating mean RTs by experimental condition (neutral probes in TN trials, angry probes in TN trials, neutral probes in NN trials) and mean AB scores (threat bias, vigilance, and disengagement), separately for even and odd trial for every session of dot probe task. In addition, split-half reliability of trial-level bias scores (TLBS) was computed to examine the reliability of variability indices and peaks. To quantify reliability of these AB measures, Pearson correlations were conducted between even and odd trials used to generate mean RT and mean AB scores, and between the first and second half of trials for TLBS scores.

Although mean RTs for the dot probe were highly significantly correlated between even and odd trials (*r*'s > .81, all *p*'s < .001), mean AB scores showed non-significant split-half reliability (all *p*'s > .08) with the exception of the Time 1 dot probe (disengagement; $r = .24$, $p = .008$). The overall non-significant split-half reliability for mean AB measures is consistent with the previous literature (Kappenman, Farrens, Luck, & Proudfit, 2014; Rodebaugh et al., 2016; Schmukle, 2005). In contrast, split-half reliability for the four TLBS metrics (mean positive, mean negative, peak difference, and variability) were significant at Time 1 (*r*'s > .28, all *p*'s < .01).

SSVEP Power to Threat and Neutral Stimuli for the Entire Sample

To test the hypothesis that SSVEP power to threatening faces would be greater than SSVEP power to neutral faces for all participants in the sample, regardless of anxiety level or anxiety subtype, we conducted a paired t-test using the SSVEP Neutral and SSVEP Threat scores. Contrary to the hypothesis, the test revealed that there was no significant difference between SSVEP power to threat faces (*M* = .759, *SD* = .720) and neutral faces (*M* = .787, *SD* = .757); $t(94) = .567$, $p = .572$.

Subsequently, we conducted partial correlations, controlling for HAM-A and the DASS-21 Anxiety separately. The partial correlation analyses revealed no significant correlations between the SSVEP and AB scores, and the results are reported in Tables 3 and 4.

SSVEP Power to Threat and Neutral Stimuli Based on Anxiety Level

We conducted bivariate correlations to explore the association between SSVEP, self-report measures of anxiety, and attention bias. These analyses revealed no significant correlations and are reported in Table 5. Figures 3-5 provide visualizations of the correlations between anxiety and SSVEP.

To test the hypothesis that individuals with severe anxiety would show the greatest SSVEP to threat stimuli relative to neutral stimuli as compared to those with mild or moderate anxiety and to explore if SSVEP power varied by frequency and hemisphere among those with varying anxiety severity, we conducted a 2 (Emotion: Threat & Neutral) x 2 (Hemisphere: Left Occipital Cortex & Right Occipital Cortex) x 2 (Frequency: 12Hz & 15Hz) x 3 (Anxiety Severity: Mild, Moderate, Severe) repeated measures ANOVA, where emotion, hemisphere, and frequency were the within-subjects variables and anxiety severity was the between-subjects variable. The ANOVA revealed that the only statistically significant difference among the groups was due to the within-subjects effect of frequency $F(1,92) = 28.000$, Wilks' $\lambda = .767$, $p = .001$, $\eta^2 = .233$, such that 12Hz SSVEP power was greater than 15Hz SSVEP power.

SSVEP Power to Threat and Neutral Stimuli Based on Anxiety Disorder Diagnosis

To investigate the hypothesis that those with an anxiety disorder diagnosis, relative to those without, would show the greatest SSVEP to threat stimuli relative to neutral stimuli as compared to those with no anxiety diagnosis and to explore if SSVEP power varied by frequency and hemisphere based on the presence of an anxiety disorder diagnosis, we conducted a 2 (Emotion: Threat & Neutral) x 2 (Hemisphere: Left Occipital Cortex & Right Occipital Cortex) x 2 (Frequency: 12Hz & 15Hz) x 2 (Anxiety Disorder Diagnosis: Present & Not Present) repeated measures ANOVA, where emotion, hemisphere, and frequency were the within-subjects variables and anxiety disorder diagnosis was the between-subjects variable. The ANOVA revealed that there was a statistically significant interaction among emotion, hemisphere, frequency, and anxiety diagnosis, $F(1,93) = 4.909$, $p = .029$, $\eta^2 = .050$. Bonferroni adjusted post-hoc analyses exploring this interaction revealed a marginally statistically significant simple effect of hemisphere, $F(1,93) = 3.366$, Wilks' $\lambda = .965$, $p = .070$, $\eta^2 = .035$, such that 12Hz SSVEP power to neutral stimuli in the right hemisphere ($M = .943$, $SE = .140$) was greater than SSVEP power to neutral stimuli in the left hemisphere ($M = .626$, $SE = .174$) for those with an anxiety diagnosis. Further, Bonferroni adjusted post-hoc analyses also revealed a significant difference between 12Hz and 15Hz SSVEP power for each level combination of the pairwise comparisons except SSVEP to neutral stimuli in the left hemisphere among those with an anxiety diagnosis. These results are visualized in Figure 6. The main effect of frequency was significant, $F(1,93) = 30.547$, Wilks' $\lambda = .753$, $p = .001$, $\eta^2 = .247$, such that 12Hz SSVEP power was greater ($M = .746$, $SE = .077$) than 15Hz SSVEP power ($M = .368$, $SE = .087$). In contrast, the main effect of anxiety diagnosis was not significant, $F(1,93) = .454$, $p = .502$, nor was emotion, $F(1,93) = .007$, $p = .935$, or hemisphere $F(1,93) = .076$, $p = .783$.

SSVEP Power and Attention Bias

To test the hypothesis that SSVEP to threat would be correlated with AB measures that indicate exaggerated attention towards threat, such as threat bias, peak positive, and mean positive, we conducted bivariate correlations to explore the association between SSVEP, self-report measures of anxiety, and attention bias. The SSVEP scores used in the bivariate correlations included the SSVEP ratio score, SSVEP threat, SSVEP neutral, the frequency combined SSVEP scores, as well as the hemisphere combined SSVEP scores. These analyses revealed no significant correlations and are reported in Table 5.

To further clarify the nature of the relationship between the heightened 12Hz SSVEP power to neutral stimuli in the right hemisphere identified among anxious individuals in prior analyses, we conducted a series of linear multiple regression analyses to test the moderating effect of anxiety severity, quantified via the HAM-A self report questionnaire, on the association between 12Hz SSVEP power to neutral stimuli in the right hemisphere and anxiety-related AB. The predictor variable was 12Hz SSVEP power to neutral stimuli in the right hemisphere, the moderator was self-reported anxiety, and the outcome variables tested were the following TLBS AB scores: mean positive, mean negative, peak positive, and peak negative. The regression analyses revealed no significant moderating effects of anxiety on the association between 12Hz SSVEP power to neutral stimuli in the right hemisphere and anxiety-related AB TLBS. Table 6 presents a summary of the results for these moderation analyses.

Discussion

The goal of this study was to assess the potential of the SSVEP to serve as a novel biosignature for anxiety-related AB. We explored this via two approaches; first, by investigating SSVEP power differences based on anxiety severity and diagnosis and second, by exploring the association between SSVEP, AB, and anxiety. Additionally, we integrated exploratory analyses investigating frequency and hemispheric differences. These findings have the potential to inform the SSVEP literature as well as AB heterogeneity literature by interrogating potential disruptions in threat monitoring among anxious individuals. Findings from this study suggest that the SSVEP may be sensitive to overgeneralized threat processing - i.e., disruption of processing of ambiguous stimuli - among those with anxiety diagnoses.

Association Between SSVEP Power and Anxiety

First, we tested the hypothesis that SSVEP power to threat stimuli would be significantly greater than SSVEP to neutral stimuli among the entire sample, including individuals with varying levels of anxiety severity and anxiety diagnoses. Analyses revealed no significant differences in SSVEP to threat versus neutral across the entire sample. These null findings are consistent with Thigpen et al., 2018, who employed the DP task that found no significant differences in SSVEP to threat versus neutral stimuli in a sample of participants with low trait anxiety. Additionally, it is possible that analyses exploring differences in SSVEP power to threat versus neutral did not reveal any significant differences, as this sample contained only 19 individuals with a diagnosis of social phobia, indicating that the majority of the individuals in this sample may not have heightened social phobia symptoms, in contrast with the prior literature in which heightened SSVEP was documented among individuals with high social anxiety symptoms (McTeague et al., 2011; Wieser et al., 2011, Wieser et al., 2016). Considering that this sample contains only a small subset of individuals with social anxiety symptoms and considering the heightened SSVEP to threat has primarily been documented among individuals with social anxiety symptoms, these results suggest that heightened SSVEP to threat stimuli may be a phenomenon unique to individuals with sensitivity to social cues, such as threatening faces.

Second, we tested the hypothesis that SSVEP power to threat stimuli relative to neutral stimuli would be most enhanced for those with severe anxiety relative to those with mild or moderate anxiety, and found that there was no significant difference. In contrast to these findings, other work comparing the cortical facilitation to threat versus safety cues among a sample of low and high anxious individuals revealed that those with low anxiety showed heightened neural activity towards threat contexts compared to a safety contexts, while high anxiety individuals showed no such differences, suggesting that those with high anxiety may have impaired threat-safety discrimination, potentially due to amygdalar hyperactivity leading to an overgeneralized fear response (Stegmann et al., 2019). A similar finding of impaired discrimination between aversive and non-aversive social stimuli was documented by Ahrens et al. (2014) among a sample of individuals with high social anxiety as compared to those with low social anxiety, where the low socially anxious groups displayed heightened cortical activity to threat stimuli, while the high social anxiety group did not. It is possible that our analyses did not reveal significant differences in SSVEP power to threat versus neutral based on anxiety severity (mild, moderate, or severe) as this study quantified anxiety using the HAM-A, which provides a broad state measure of anxiety, including items meant to assess recent experiences of psychological distress as well as somatic anxiety. In contrast, the Stegmann et al. 2019 study quantified anxiety using the trait segment of the State-Trait Anxiety Inventory, which assesses one's disposition towards anxious thinking and does not include items assessing somatic anxiety symptoms. Additionally, the Ahrens et al. 2014 study explored SSVEP power difference among individuals with varying levels of social anxiety; in contrast to our study, which did not contain measures to assess social anxiety severity.

Third, we tested the hypothesis that SSVEP to threat relative to neutral would be most heightened among those with an anxiety diagnosis relative to those without. No significant differences based on only anxiety diagnosis emerged. SSVEP literature presents conflicting evidence regarding which groups of individuals demonstrate enhanced electrocortical facilitation towards threatening stimuli. Heightened SSVEP to threat relative to neutral has been documented among those with high social anxiety symptoms or a diagnosis of social anxiety disorder or social phobia (McTeague et al., 2011; McTeague et al., 2008; Wieser et al., 2011; Wieser et al., 2016)l however, other studies have documented heightened SSVEP to threat relative to neutral among those with low anxiety rather than high anxiety (Ahrens et al., 2014; Stegmann et al., 2019). Additional research will be necessary to clarify the cognitive and affective factors underlying for whom SSVEP power to threat is facilitated versus depressed and under what conditions. While the SSVEP effect needs additional research, many studies cite these effects among the socially anxious, suggesting that specific anxiety symptom clusters may be a crucial contributing factor underlying SSVEP facilitation or the lack thereof. This consideration in mind, of the participants included in this study, only 19 individuals had a diagnosis of social phobia (the DSM-IV R version of social anxiety disorder). While this presented an opportunity to explore the phenomenon of enhanced SSVEP to emotionally salient stimuli among a sample with anxiety symptoms unique from prior studies, our sample does not reflect the anxiety symptom clusters typically seen of participants in studies where heighted cortical facilitation towards threat stimuli is observed. It is possible that cortical facilitation towards threat stimuli relevant to social signals and processing- i.e., emotional faces used in the present and prior studies - is a phenomenon most commonly observed among those with impaired threat-safety discrimination, heightened social anxiety symptoms, or a social anxiety disorder diagnosis.

Finally, we tested the hypothesis that SSVEP to threat relative to neutral would be greatest among those with an anxiety diagnosis as opposed to those without an anxiety diagnosis. We also investigated the exploratory hypotheses that 15Hz SSVEP power would be greater than

12Hz SSVEP power as well as that SSVEP power in the right hemisphere would be heighted relative to the left hemisphere. We found a marginally significant interaction effect such that 12Hz SSVEP power to neutral stimuli was enhanced in the right hemisphere for those with an anxiety diagnosis. Analyses revealing that 12Hz SSVEP power to neutral stimuli in the right hemisphere was greater than 12Hz SSVEP power to neutral stimuli in the left hemisphere with marginal significance indicates differential processing of neutral stimuli among individuals with an anxiety diagnosis.

In consideration of the observed hemispheric difference, prior studies exploring threat bias in a sample of low and high socially anxious college students found evidence of vigilance toward threat stimuli among the highly socially anxious and that this effect was particularly pronounced for stimuli presented to the left visual field, suggesting the role of the right hemisphere in processing emotionally salient visual stimuli (Mogg & Bradley, 2002). While our sample only included 19 individuals with a diagnosis of Social Phobia, it did include 35 individuals with a diagnosis of GAD. Heightened right hemispheric cortical activity has also been found among those with a diagnosis of GAD.

Further evidence of right lateralized neural activation in response to affective stimuli among those with GAD has been documented in magnetic resonance imaging (MRI) studies. Structural MRI research conducted by Molent et al. (2017) revealed evidence of structural differences in the right hemisphere of individuals with a diagnosis of GAD relative to healthy controls; specifically, reduced cortical thickness in the right hemisphere as well as right hemisphere hyper-gyrification in the superior parietal cortex. They propose that the alterations in cortical thickness may underlie GAD features such as emotion dysregulation. Additionally, the frontal and parietal hyper-gyrification observed was reported to potentially indicate differential neurodevelopment contributing to the abnormal emotional processing present among those with GAD.

Echoing evidence of affective sensitivity lateralized to the right hemisphere, a functional MRI study led by Buff et al. (2017) found elevated activity in the right bed nucleus of the stria terminalis (BNST) and right amygdala to threat anticipation among those with a diagnosis of GAD relative to healthy controls, suggesting the role of the right amygdala and BNST in threat anticipation and response among those with GAD. Further, the authors indicate that BNST activity among those with GAD may serve as a biosignature for information-processing biases, a contributing factor to anxiety-related threat sensitivity. These findings bolster the theory of an enhanced role of the right hemisphere (Lee et al., 2004; Madonna et al., 2019) in the processing of emotionally salient, aversive stimuli as well as provide evidence in support of the neuroanatomical and neurofunctional basis for anxiety disorders, such as GAD, as well as anxiety-related attention bias to threat (Buff et al., 2017; Molent et al., 2017).

Finally, the observed differential pattern of neural activity – heightened SSVEP for neutral stimuli in the right hemisphere as compared to the left hemisphere among those with an anxiety diagnosis – suggests the involvement of the right hemisphere in the processing of affective stimuli, which in this instance would be neutral stimuli. These findings suggest that these individuals may interpret ambiguous, neutral stimuli as threatening, a feature of anxiety-related AB among those with GAD and hint at prior literature indicating impaired threat discrimination among those with distress-based anxiety disorders such as GAD (Denefrio et al., 2018; Mennin et al., 2002; Salters-Pedneault et al., 2006).

Association Between SSVEP Power and Attention Bias

In the second approach to explore if SSVEP power could serve as a biosignature for AB, we tested the hypothesis that SSVEP to threat would be correlated with AB measures that indicate exaggerated attention towards threat, such as threat bias, peak positive, and mean positive. We conducted bivariate correlations between SSVEP, anxiety, as well as both mean and TLBS AB scores which revealed no significant correlations. As the mean AB scores, such as threat bias and vigilance, are generated by subtracting average RTs across DP task trial types, potentially meaningful temporal variations in AB patterns that emerge during the course of the task would be masked. Additionally, while the TLBS scores provide more granular measures of AB, including both peak and mean negative as well as positive, in addition to a variability score, similar to the average AB score, the TLBS AB scores are measures of bottom-up automatic attention processes. In contrast, as the SSVEP is elicited over the course of 2750ms, and is thus a continuous measure of visual attention. These temporal variations in the stage of visual information processing may underlie the lack of correlation between SSVEP measures of visual attention to threat stimuli and behavioral AB measures.

Finally, to further explore the finding that those with an anxiety diagnosis display enhanced SSVEP power to neutral stimuli in the right hemisphere, we conducted a series of targeted hierarchical multiple regressions to explore if self-report anxiety moderated the relationship between SSVEP and TLBS measures of AB. These regression analyses yielded no significant findings. As the TLBS AB scores – peak positive, peak negative, mean positive, mean negative – represent bottom-up attention capture by threat stimuli during early stages of attention processing and considering that the the SSVEP is a continuous measure of selective visual attention, these results provide evidence in support of the conceptualization of the SSVEP as a cognitive phenomenon that may represent later elaborative stages of attention processing, perhaps more akin to top-down attention processing (Cisler & Koster, 2010; Hajcak et al., 2013).

The SSVEP may be similar to event-related potentials (ERPs) such as the late positive potential (LPP), which is sensitive to emotionally salient visual stimuli such as the threat faces presented in the SSVEP task and reflects late stage attentional processes, during which more elaborative top-down attention is engaged (Hajcak et al., 2013; Myruski et al. 2019). Models of AB heterogeneity posit that the interaction between early-stage threat sensitivity and later stage elaborative processing underlie attention bias heterogeneity (Gupta et al., 2019). While threat sensitivity may be quantified via early-emerging ERPs such as the N170 and thus provides a measure of early attention capture by threat related stimuli (Zhang et al., 2018), elaborative processing may be conceptualized as a late stage attentional processing reflective of more top-down attention. As the SSVEP is a measure of continuous visual attention, associated with ERPs that quantify late-stage affect sensitivity, it is possible that the SSVEP may reflect late emerging threat sensitivity, during elaborative stages of attention processing, when top-down cognitive control is engaged or it may reflect a combination of bottom-up attention capture by threat stimuli as well as recruitment of top-down cognitive control (Hajcak et al., 2013; Myruski et al. 2019).

Conclusion

Study Limitations

The following study limitations should be noted. As the SSVEP is equipped to assess both overt and covert attention, it is important to note that the SSVEP task did not require that the participant's gaze be directed towards the fixation dot between the face stimuli presented during the task. Future studies should integrate eye-tracking with the SSVEP task to (1) require participant gaze fixation on the fixation dot during task trials, (2) support identification of, controlling for, and analysis of any eye movements, as well as (3) to allow researchers to more reliability distinguish between SSVEP elicited by overt versus covert attention.

Additionally, this study employed the DASS-21and HAM-A to quantify self-report anxiety as well as the MINI to identify anxiety diagnoses. To facilitate comparison of study findings with extant research, future studies investigating SSVEP and anxiety should incorporate the self-report anxiety measures used in prior studies to support efforts to duplicate as well as build upon prior evidence documenting SSVEP modulation by affective stimuli.

Future Directions

As much of the prior literature exploring the association between SSVEP power and emotionally salient stimuli has been conducted among individuals with social anxiety symptoms and diagnoses, future studies should aim to recruit a substantial sample of individuals with low and high social anxiety symptoms as well as individuals with low and high generalized anxiety symptoms. Conducting a study in the manner would (1) facilitate comparison of the study results to prior literature exploring SSVEP among those with social anxiety symptoms, (2) present an opportunity to duplicate those findings, and (3) allow researchers to investigate if the pattern of SSVEP modulation by affective stimuli demonstrated by those with social anxiety symptoms differs from individuals with other anxiety symptoms types, such as generalized anxiety symptoms. Furthermore, this would build upon the findings from this study – namely, that those with an anxiety disorder diagnosis demonstrate a differential pattern of electrocortical facilitation in the right hemisphere for neutral stimuli. Such research would further inform existing literature indicating that sensitivity to neutral stimuli may not be ubiquitous, but rather may be unique to individuals with certain anxiety subtypes, such as GAD (Denefrio et al., 2018; Dennis-Tiwary et al., 2019; Jovanovic et al., 2014). Lastly, future studies should incorporate single trial SSVEP analyses to allow exploration of the temporal dynamics of SSVEP modulation during the course of a single SSVEP task assessment as well as to facilitate quantification of variability in attention capture by affective stimuli at different temporal stages during the task (Keil et al. 2008; Wieser et al. 2014).

In summary, the present study identified preliminary evidence of lateralized electrocortical facilitation in the right hemisphere, relative to the left, for neutral stimuli among those with an anxiety disorder, contributing to the SSVEP anxiety-related AB literature. Further research is needed to identify the anxiety symptom, severity, and diagnosis profile of the individuals who display this right lateralized electrocortical activity. Clarifying the association between SSVEP and different anxiety subtypes will not only inform AB literature but will also inform efforts to develop targeted and effective anxiety treatments based upon an individual anxiety symptom and AB profiles via the identification of anxiety-related AB biosignatures.

Figures

Figure 1
Dot Probe Task Trial

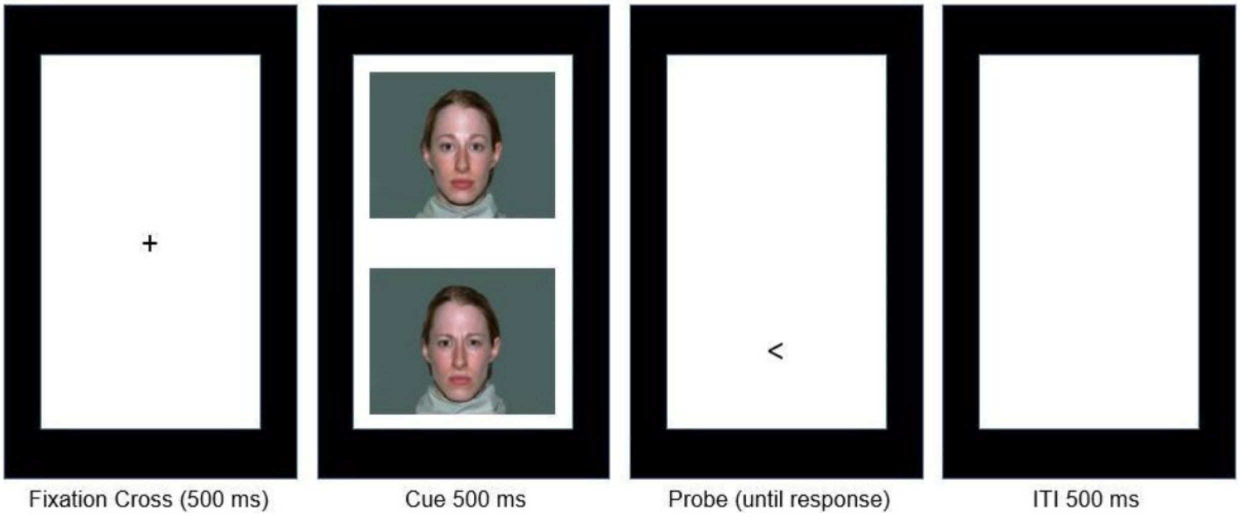


Figure 2
SSVEP Task Trial

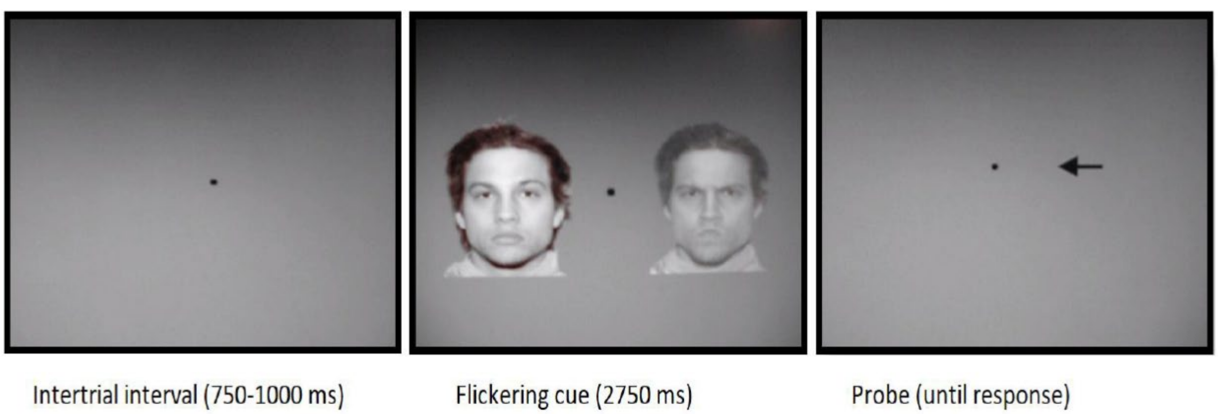


Figure 3

Association Between Anxiety and SSVEP Neutral

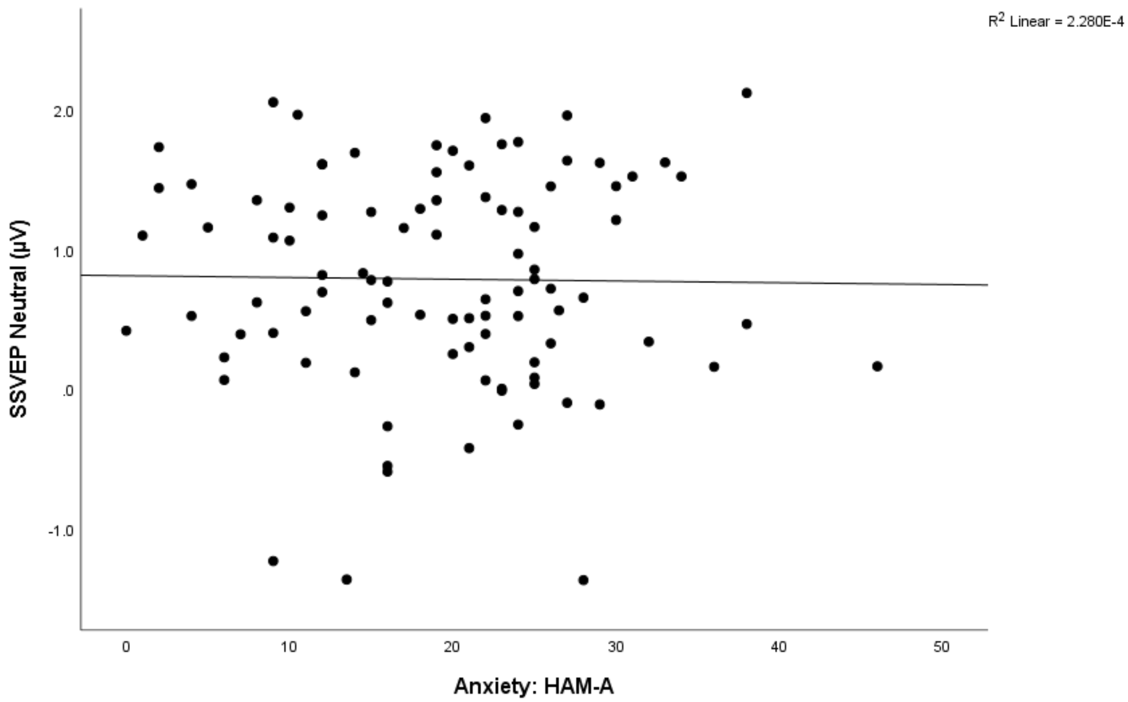


Figure 4

Association Between Anxiety and SSVEP Threat

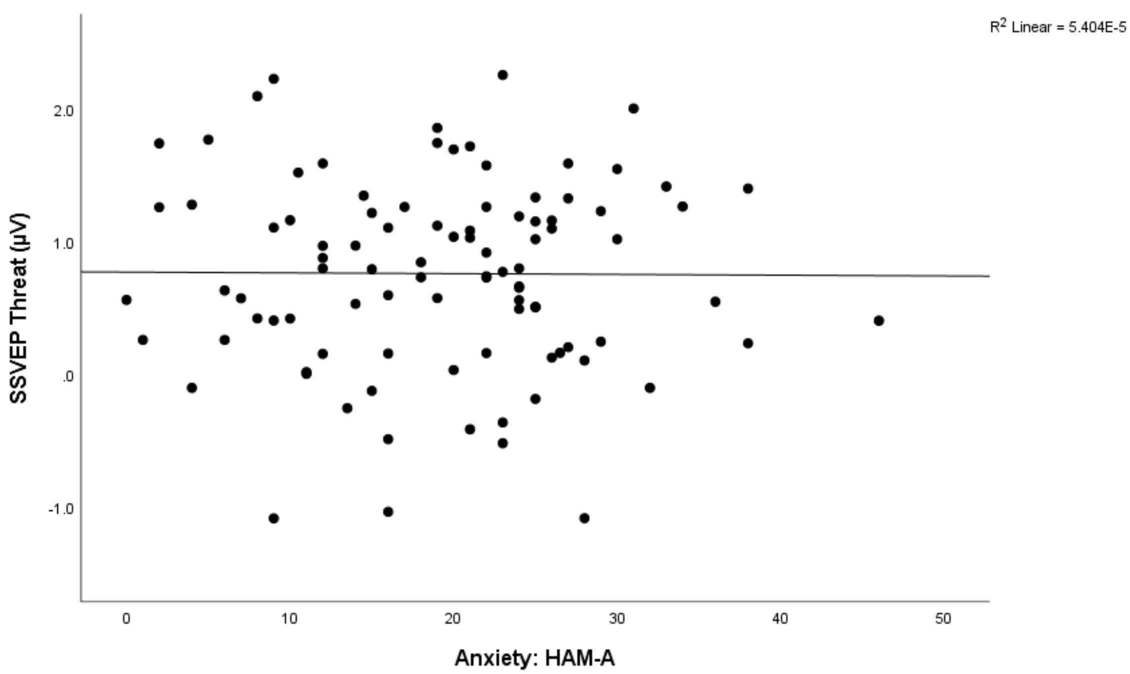


Figure 5

Association Between Anxiety and SSVEP Ratio

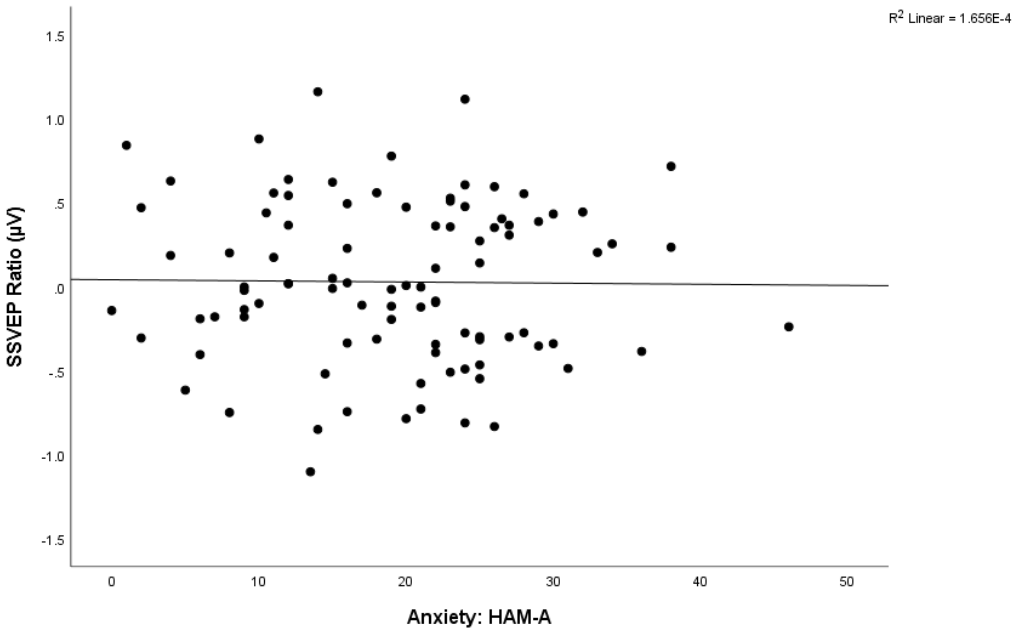
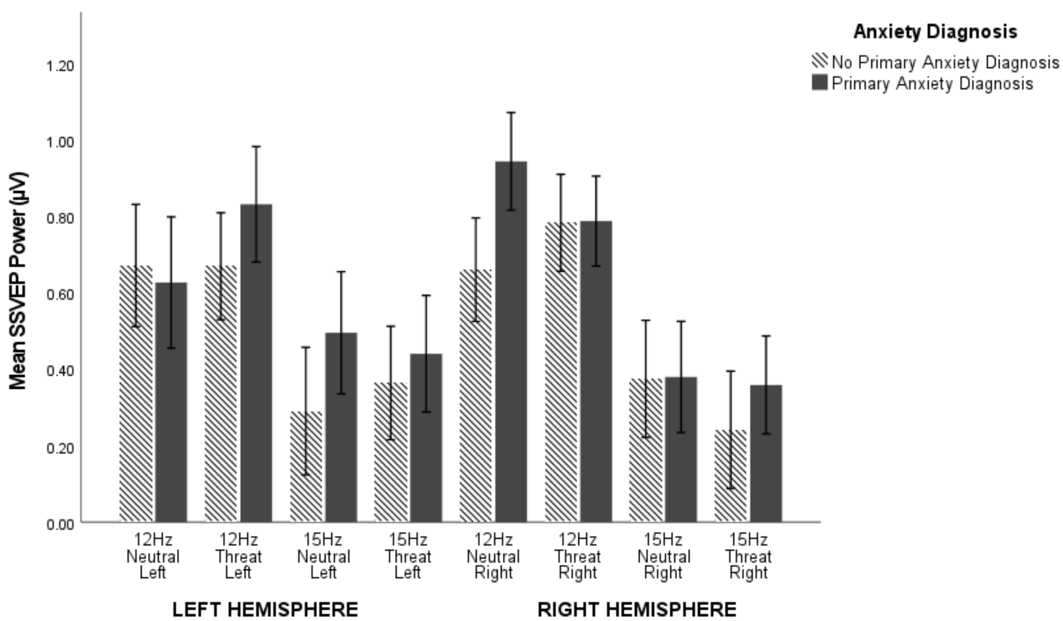


Figure 6

Hemispheric and Frequency Differences in SSVEP Power



Tables

Table 1
Demographics: Age, Race & Ethnicity

	Female (N = 65)	Male (N = 30)
Participant Age	**Mean (SD)**	
Age in Years	25.12 (6.39)	26.07 (6.38)
Ethnicity & Race	**Frequency**	
Ethnicity		
Hispanic or Latino	12	4
Not Hispanic or Latino	42	19
Race		
American-Indian	1	0
Asian	12	7
Black or African American	9	3
White	31	16
More than one race	5	1

Table 2
Anxiety and AB Descriptive Statistics by Sex

	Female		Male	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Self Report Measures of Anxiety				
HAM-A	65	18.99 (9.32)	30	19.55 (8.81)
DASS-21 Anxiety	61	6.13 (4.49)	29	6.97 (5.12)
Attention Bias Scores				
Threat Bias	65	1.01 (24.79)	30	-4.02 (18.96)
Vigilance	65	-0.52 (27.86)	30	-1.48 (19.03)
Disengagement	65	1.41 (26.9)	30	-5.09 (23.56)
Mean Positive	65	105.67 (41.68)	30	85.7 (32.16)
Mean Negative	65	-101.11 (43.32)	30	-94.22 (43.23)
Peak Positive	65	355.26 (183.47)	30	334.8 (216.76)
Peak Negative	65	-351.29 (192.19)	30	-355.2 (192.02)
Variability	65	2.01 (0.84)	30	1.81 (0.78)

Table 3

Partial Correlations Between SSVEP & AB Scores, Controlling for HAM-A

Variables	1	2	3	4	5	6	7	8	9	10	11
1. SSVEP Neutral											
2. SSVEP Threat	0.765										
3. SSVEP Ratio	0.394	-0.29									
4. DASS-21 Anxiety	-0.016	0.046	-0.09								
5. Threat Bias	-0.045	-0.036	-0.016	-0.17							
6. Vigilance	-0.003	-0.096	0.133	-0.144	0.43						
7. Disengagement	-0.008	0.076	-0.12	0.031	0.53	-0.509					
8. Mean Positive	0.124	0.085	0.063	-0.063	0.152	-0.343	0.426				
9. Mean Negative	-0.125	-0.054	-0.11	-0.072	0.379	0.501	-0.076	-0.729			
10. Peak Positive	0.115	0.055	0.093	-0.126	0.313	-0.178	0.437	0.79	-0.443		
11. Peak Negative	-0.014	0.033	-0.069	0.021	0.316	0.485	-0.11	-0.649	0.844	-0.433	
12. Variability	0.074	0.02	0.082	-0.034	-0.113	-0.423	0.22	0.858	-0.885	0.57	-0.811

Note: None of the correlations were statistically significant.

Table 4

Partial Correlations Between SSVEP & AB Scores, Controlling for DASS-21

Variables	1	2	3	4	5	6	7	8	9	10	11
1. SSVEP Neutral											
2. SSVEP Threat	0.766										
3. SSVEP Ratio	0.396	-0.287									
4. HAM-A	0.039	-0.005	0.066								
5. Threat Bias	-0.043	-0.029	-0.022	0.139							
6. Vigilance	0.001	-0.09	0.131	0.16	0.429						
7. Disengagement	-0.01	0.074	-0.122	-0.073	0.527	-0.514					
8. Mean Positive	0.124	0.088	0.059	0.025	0.146	-0.347	0.426				
9. Mean Negative	-0.12	-0.051	-0.106	0.14	0.385	0.508	-0.083	-0.726			
10. Peak Positive	0.117	0.061	0.087	0.072	0.305	-0.186	0.437	0.789	-0.441		
11. Peak Negative	-0.012	0.032	-0.064	0.051	0.328	0.494	-0.114	-0.647	0.845	-0.429	
12. Variability	0.073	0.021	0.079	-0.001	-0.12	-0.427	0.221	0.858	-0.882	0.57	-0.81

Note: None of the correlations were statistically significant.

Table 5

Bivariate Correlations Among SSVEP, Anxiety and AB

Variable	N	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11	12	13
1. SSVEP Neutral[a]	90	0.81	0.73	--												
2. SSVEP Threat[a]	90	0.78	0.70	.77**	--											
3. SSVEP Ratio[b]	90	0.03	0.49	.39**	-.29**	--										
4. HAM-A	90	19.34	9.14	0.04	0.04	0	--									
5. DASS-21 Anxiety	90	6.40	4.69	0.02	0.06	-0.06	.73**	--								
6. Threat Bias	90	-0.57	23.52	-0.04	-0.04	-0.02	0.02	-0.1	--							
7. Vigilance	90	-1.07	24.16	0	-0.09	0.13	0.08	-0.04	.431**	--						
8. Disengagement	90	-0.15	25.18	-0.01	0.07	-0.12	-0.07	-0.03	.53**	-.51**	--					
9. Mean Positive	90	96.83	38.28	0.12	0.08	0.06	-0.03	-0.07	0.15	-.34**	.43**	--				
10. Mean Negative	90	-96.45	41.99	-0.12	-0.05	-0.11	0.13	0.04	.38**	.51**	-0.08	-.73**	--			
11. Peak Positive	90	335.58	184.21	0.11	0.05	0.09	-0.03	-0.11	.31**	-0.18	.44**	.79**	-.44**	--		
12. Peak Negative	90	-341.87	187.67	-0.01	0.04	-0.07	0.10	0.08	.32**	.49**	-0.12	-.65**	.85**	-.43**	--	
13. Variability	90	1.89	0.78	0.07	0.02	0.08	-0.04	-0.05	-0.11	-.43**	.22*	.86**	-.88**	.57**	-.81**	--

[a] Combined SSVEP power for both 12Hz & 15Hz in both the left and right hemispheres

[b] SSVEP Neutral / SSVEP Threat

*p < .05. **p < .01.

Table 6

Multiple Linear Regression Analyses Investigating the Moderating Effect of Anxiety on the Association Between SSVEP Power to Neutral Stimuli and TLBS Scores Measures of AB

	b	***SE***	***t***	***p***	**95% Confidence Interval**	
MODELS					**Lower Bound**	**Upper Bound**
Outcome Variable: Mean Positive						
Constant	99.24	4.15	23.91	0.001	90.99	107.49
12Hz Right Hemisphere SSVEP to Neutral	-2.56	4.58	-0.56	0.577	-11.65	6.53
HAM-A	-0.13	0.46	-0.29	0.772	-1.05	0.78
HAM-A x 12Hz Right Hemisphere SSVEP to Neutral	-0.24	0.5	-0.49	0.628	-1.22	0.74
Outcome Variable: Mean Negative						
Constant	-98.63	4.43	-22.28	0.001	-107.42	-89.83
12Hz Right Hemisphere SSVEP to Neutral	5.43	4.88	1.11	0.269	-4.26	15.13
HAM-A	0.48	0.49	0.98	0.33	-0.5	1.46
HAM-A x 12Hz Right Hemisphere SSVEP to Neutral	0.63	0.53	1.19	0.239	-0.42	1.68
Outcome Variable: Peak Positive						
Constant	348.56	20.21	17.25	0.001	308.43	388.7
12Hz Right Hemisphere SSVEP to Neutral	-9.48	22.28	-0.43	0.671	-53.73	34.76
HAM-A	-0.26	2.24	-0.11	0.909	-4.72	4.2
HAM-A x 12Hz Right Hemisphere SSVEP to Neutral	-0.48	2.41	-0.2	0.842	-5.27	4.31
Outcome Variable: Peak Negative						
Constant	-351.07	19.32	-18.17	0.001	-389.44	-312.69
12Hz Right Hemisphere SSVEP to Neutral	45.05	21.3	2.12	0.037	2.75	87.36
HAM-A	1.69	2.15	0.79	0.434	-2.58	5.95
HAM-A x 12Hz Right Hemisphere SSVEP to Neutral	2.98	2.3	1.29	0.199	-1.6	7.56

Note: For all regression analyses in this table, SSVEP is the independent variable, HAM-A is the moderator, and AB is the outcome variable.

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