Journal of Psychiatric Research 143 (2021) 155–162

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Neurophysiological predictors of gaze-contingent music reward therapy among adults with social anxiety disorder

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ARTICLE INFO

Keywords:
Error monitoring
Attention bias modification treatment
ERN
Pe
Frontal midline theta
Delta

ABSTRACT

Social anxiety disorder (SAD) is associated with fear of negative evaluation and heightened performance monitoring. The best-established treatments help only a subset of patients, and there are no well-established predictors of treatment response. The current study investigated whether individual differences in processing errors might predict response to gaze-contingent music reward therapy (GC-MRT). At baseline, healthy control subjects (HC; n = 20) and adults with SAD (n = 29), ages 19–43 years, completed the Flanker Task while electroencephalography (EEG) data were recorded. SAD participants then received up to 12 sessions over 8 weeks of GC-MRT, designed to train participants' attention away from threatening and toward neutral faces. Clinical assessments were completed 9- (post-treatment) and 20-weeks (follow-up) after initiating the treatment. At baseline, compared to HC, SAD performed the task more accurately and exhibited increased error-related negativity (ERN) and delta power to error commission. After controlling for age and baseline symptoms, more negative ERN and increased frontal midline theta (FMT) predicted reduced self-reported social anxiety symptoms at post-treatment, and FMT also predicted clinician-rated and self-reported symptom reduction at the follow-up assessment. Hypervigilance to error is characteristic of SAD and warrants further research as a predictor of treatment response for GC-MRT.

1. Introduction

Social anxiety disorder (SAD) is a debilitating psychiatric disorder characterized by excessive fear and avoidance of social or performance-related situations, fear of negative evaluation, and attention bias toward social threats (Harrewijn et al., 2017; Lazarov et al., 2016; Schneier, 2006). The best-established treatments, including cognitive-behavioral therapy (CBT) and serotonin reuptake inhibitor medications (SSRI) medications, as well as approaches such as attention bias modification therapy (ABMT), help only a subset of patients, highlighting a need for improved treatment and established predictors of response to specific treatments. We administered a novel ABMT, Gaze-Contingent Music Reward Therapy (GC-MRT), designed to reduce attention to threat in SAD (Lazarov et al., 2017, 2021), and we tested whether known neurophysiological indices of performance monitoring predicted treatment response.

1.1. Neurophysiological processes related to error monitoring

Error related processing holds promise as a biomarker in SAD. Consistent with the prominent fear of negative evaluation in SAD, several studies have found enhanced sensitivity to errors (Endrass et al., 2014; Kujawa et al., 2016; see also Barker et al., 2015; Judah et al., 2016). Different aspects of this error processing have been investigated through separate, but related, event-related brain potentials (ERPs). The error-related negativity (ERN) is elicited when individuals unexpectedly commit response errors (Falkenstein et al., 1991; Gehring et al., 1993), and is characterized by an early frontocentral negative deflection occurring within 75 ms of error commissions. By contrast, a correct-related negativity (CRN) is elicited following frequent correct responses within this same time window. Research has shown a more negative ERN among individuals with GAD (Weinberg et al., 2015), OCD (Endrass and Ullsperger, 2014; Riesel, 2019), SAD (Endrass et al., 2014;

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https://doi.org/10.1016/j.jpsychires.2021.09.022
Received 27 April 2021; Received in revised form 29 August 2021; Accepted 1 September 2021
Available online 2 September 2021

Kujawa et al., 2016) and adults with high social anxiety (Barker et al., 2015; Judah et al., 2016). Although ERN has been shown to be sensitive to individual differences in error salience (or aversion), few studies have also investigated its role in predicting treatment response (Klawohn et al., 2020; Kujawa et al., 2016).

1.2. Neural oscillations related to error monitoring

Error-related electrophysiological measures are also characterized by both frontal midline theta (FMT, 4–8 Hz) and delta power (1–3 Hz) (Luu et al., 2004; Yordanova et al., 2004). Although both FMT and delta show increased power following error commission compared to correct responses, they likely reflect separable processes (Yordanova et al., 2004). Evidence generally suggests that FMT stems from activity in the medial prefrontal cortex, including the dorsal anterior cingulate cortex (ACC) (Holroyd and Umemoto, 2016), reflecting cognitive control processes (Cavanagh and Frank, 2014), and is functionally related to ERN (Munneke et al., 2015). Increased FMT power is often associated with anxiety severity and anxiety disorders (Cavanagh et al., 2017; Cavanagh and Shackman, 2015), and electrical stimulation at the theta frequency within the ACC reduces anxiety-related symptoms in mice (Weible et al., 2017). Although the functional significance of delta power during error processing is less clear, it may be specific to error salience (Kolev et al., 2009; Yordanova et al., 2004). As past SAD studies have focused on ERPs, probing oscillatory activities could provide further insight about the mechanisms underlying impaired error processing in SAD.

1.3. Treatment for SAD

Established SAD treatment approaches, such as CBT and SSRI medications are not always effective (Davis et al., 2014; Loerinc et al., 2015). Alternative approaches include ABMT, which modifies attention away from threat-related stimuli. However, efficacy remains inconsistent across studies (Heeren et al., 2015). GC-MRT—a novel ABMT using eye tracking to trigger music reinforcement when participants allocate their attention to neutral faces over threatening faces (i.e., faces with disgust expressions)—has demonstrated clinical efficacy for SAD (Lazarov et al., 2017, 2021). Specifically, participants freely view face stimuli, as GC-MRT reinforces attending to neutral faces by playing rewarding music preselected by participants and discourages attending to threatening faces by silencing the music.

Several findings suggest that error-related processing has potential to predict GC-MRT outcome in SAD. First, abnormalities in error-related processing in SAD have been replicated. Making errors represents a highly salient performance threat for individuals with SAD, and thus, individual differences in processing threat of errors (i.e., more negative ERN) might relate to GC-MRT efficacy in reducing attention to social threats. Additionally, the GC-MRT method of training disengagement from threat may harness cognitive control, a process that has been linked to error monitoring (Yeung et al., 2004). Finally, another form of ABMT modulated hyperactive error monitoring in OCD (Klawohn et al., 2020) and reduced the ERN (i.e., less negative) in healthy young adults (Nelson et al, 2015, 2017).

1.4. Current study

Goals of this study were to characterize behavioral and electrophysiological markers related to performance on the Flanker Task, and to determine whether these components predicted GC-MRT response. First, we hypothesized that compared to HC, SAD participants would commit fewer errors given their fear of negative evaluation. Second, we hypothesized that error sensitivity in SAD would be reflected by a more negative ERN and increased FMT (Cavanagh et al., 2017; Cavanagh and Shackman, 2015). Given limited research probing delta power (Riesel et al., 2013; Sandre and Weinberg, 2019), we explored whether it would be enhanced in SAD. Consistent with precision medicine initiatives (Insel, 2014), we also hypothesized that greater hypersensitivity to errors in SAD (i.e., more negative ERN and increased FMT) would predict reductions in SAD symptoms following GC-MRT. Delta power also was explored as a predictor.

2. Material and methods

2.1. Participants

Adults with SAD (n = 29) as well as age- and sex-matched HC (n = 20), ages 18–60 years, were recruited online. Potential participants completed a brief phone screening by a research assistant followed by a clinical assessment. Diagnoses were confirmed with the Mini International Neuropsychiatric Interview (MINI v7.02) structured interview administered by a study psychiatrist. SAD participants met DSM-5 diagnostic criteria for current SAD as the principal diagnosis and scored ≥50 on the self-rated Liebowitz Social Anxiety Scale (*LSAS;* Liebowitz, 1987). Secondary diagnoses among SAD participants included GAD ($n = 1$) and major depressive disorder (MDD = 6). SAD participants were excluded if they reported a Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) >20 (severe depression was exclusionary to avoid delaying treatment), received any psychotherapy for SAD in the prior three months, or used any psychotropic medication in the prior four weeks other than an SSRI or serotonin-norepinephrine reuptake inhibitor at stable dose for at least three months (three were on such medication). HCs were excluded for any lifetime mental disorder. All participants were right-handed, fluent in English, and reported no history of seizure disorder or brain injury. Participant demographics are summarized in Table 1.

2.2. Procedure

Study procedures were approved by the Institutional Review Board at New York State Psychiatric Institute. After consent, a psychiatrist administered clinical interviews, and participants completed self-reports and then the Flanker Task while EEG data were recorded. SAD participants were randomized to receive either 4 weeks (8 sessions) or 8 weeks (12 sessions) of GC-MRT, with assessments at post-treatment (week 9) and follow-up (week 20). HC participants did not receive treatment.

2.3. Clinical measures

Psychiatrists administered the Mini International Neuropsychiatric Interview (*MINI;* Sheehan et al., 1998), a structured diagnostic interview and the LSAS (Liebowitz, 1987), a 24-item scale assessing severity of SAD over the past week, and the HAM-D (Hamilton, 1960). Internal consistency ranged from 0.97 to 0.98 across LSAS assessments. Participants also completed the Social Phobia Inventory (*SPIN;* Connor et al., 2000), a 17-item self-report of SAD symptoms over the past week. Item values range from 0 to 4, with higher scores indicating greater severity. Internal consistency ranged from 0.94 to 0.98. The LSAS and SPIN were re-administered at the post-treatment and follow-up assessments.

2.4. gaze-contingent music reward therapy

GC-MRT consisted of either eight 20-min sessions over four weeks, or 12 sessions over 8 weeks, as per randomization. (see Supplement for details; Fig. S1). Full clinical outcomes of this trial are being published separately.

2.5. Experimental task

Participants completed a standard Flanker Task (Eriksen and Eriksen, 1974). On each trial, four flanker arrows were presented in a horizontal line for 100 ms, all pointed the same direction with a space in the center (<< ≪ or ≫ >>). An arrow probe then appeared in the center

Table 1
Descriptive Statistics for Participants included in EEG Analyses Stratified by Group.

	HC	SAD			
	(*n* = 18)	(*n* = 26)	*t or χ2 (df)*	*p*	*d or Cramer's V*
Age *M* (*SD*)	28.44 (6.32)	26.96 (5.47)	.83 (42)	0.41	0.25
Years of Education *M* (*SD*)	15.83 (3.07)	15.62 (1.53)	.33 (42)	0.76	0.09
Gender *n (%)*			.38 (1)	0.54	0.09
Male	8 (44.44)	14 (53.85)			
Female	10 (55.56)	12 (46.15)			
Race *n* (%)			6.56 (4)	0.16	0.39
White	9 (50.00)	11 (42.31)			
Asian	3 (16.67)	7 (26.92)			
Black or African American	6 (33.33)	3 (11.54)			
More than one race	0 (0.00)	4 (15.38)			
Other race	0 (0.00)	1 (3.85)			
Hispanic *n (%)*			0.79 (2)	0.68	0.13
Yes	3 (16.67)	5 (19.23)			
No	15 (83.33)	20 (76.92)			
Prefer not to answer	0 (0.00)	1 (3.85)			
Family Income *n (%)*			2.91 (3)	0.41	0.26
$29,999 or less	5 (27.78)	8 (30.80)			
$30,000-$69,999	9 (50.00)	12 (46.20)			
$70,000 or more	4 (22.22)	3 (11.50)			
Unknown or Not Reported	0 (0.00)	3 (11.50)			
Clinical Interview *M* (*SD*)					
LSAS	6.06 (5.63)	83.62 (14.80)	−24.30 (34.34)	<.01	6.93
Range	0–20	57–121			
Self-report Questionnaires *M* (*SD*)					
SPIN	3.12 (4.15)	42.13 (8.94)	−18.41 (32.86)	<.01	5.60
Range	0–13	21–59			

Note. *d* = Cohen's *d*; LSAS = Liebowitz Social Anxiety Scale; SPIN = Social Phobia Inventory.
At baseline, 3 SAD and 1 HC participants did not complete the SPIN.

space for 50 ms under one of two conditions. On congruent trials, the central arrow pointed the same direction as the four flanker arrows (<or >), whereas on incongruent trials, the central arrow pointed the opposite direction of the four flanker arrows (>or <). Participants were instructed to respond to the direction of the central arrow probe with a right or left button press (RB-844 Response Pad, Cedrus, San Pedro, CA) quickly and accurately as possible. A blank screen jittered inter-trial interval of 1600–1800 ms before the next trial began. After 30 practice trials, the task consisted of 230 congruent and 120 incongruent trials (see Supplement for details).

2.6. EEG Acquisition and analysis

EEG data were acquired using a 32-channel ActiCap from Brain Products (Brain Products, Munich, Germany), digitized at 500 Hz, and recorded with a Cz reference. Impedances were kept below 20 kΩ. Analyses were performed offline using Brain Vision Analyzer 2.1 software (Brain Products, Munich, Germany) using established procedures (see Supplement). To isolate ERPs from overlapping components, the ERN difference wave (ΔERN) was created by subtracting the ERP on correct trials from the ERP on error trials for each electrode (Klawohn et al., 2020; Nelson et al., 2015, 2017). The peak of ΔERN was first identified by finding the maximum negativity between 0 and 100 ms in the grand average waveforms across participants where ΔERN typically reaches maximum amplitude. The ΔERN was measured at channel Cz by averaging the mean amplitude in the±25 ms window surrounding the peak of ΔERN, which corresponded to 16–68 ms following response. Importantly, the electrode montage did not include FCz, however, prior research also has used Cz to compute ERN (Riesel et al., 2013; Sandre et al., 2019). Additionally, both ERN (commission error trials) and correct response negativity (CRN; correct trials) also were computed at Cz during the same time-window. Prior research has also tested the Pe in relation to error monitoring (Endrass et al., 2014; Judah et al., 2016). We did not have specific hypotheses for this ERP component; however, processing and analyses are included in the Supplement.

Time frequency analysis was conducted to measure delta and FMT power (see Supplement for processing details). For each participant, delta (1.5–2.5 Hz) was extracted in a time window between 0 and 250 ms following response at electrode site Cz where it reached maximal power. The delta band had a mean frequency of 1.92 Hz (range = 1.57–2.30 Hz). FMT (4–7 Hz) was extracted in a time window between 0 and 150 ms following response at electrode site Cz where it reached maximal power. The FMT band had a mean frequency of 5.31 Hz (range = 4.35–6.37 Hz). Similar to the ERP analyses, difference scores also were calculated by subtracting the power on the correct response trials from the power on the commission error trials for both delta (ΔDelta) and FMT (ΔFMT). More positive ΔDelta and ΔFMT indicate more power on error relative to correct response trials. The time windows and electrodes for analyses were determined based on the grand average across both correct and commission error trials across all participants (Luck and Gaspelin, 2017).

2.7. Statistical analysis

Analyses utilized IBM SPSS Statistics 26 (IBM, Armonk, NY). The 4-week and 8-week GC-MRT groups did not differ in symptom severity at baseline, post-treatment, or follow-up (*ps* ≥ .25), and thus, SAD groups were combined for analyses. One HC was removed from analyses due to subsequently reporting clinically significant SAD symptoms. Two SAD participants were excluded from analyses due to poor task performance (dprime<0). As age significantly correlated with several EEG measures (*rs* ≥ -.36, *ps* < .02), it was included as a covariate in all of the analyses.

Spearman's rank-order correlation analyses were conducted across all participants and within the SAD group. To test behavioral effects related to the Flanker Task, the total sample was 19 HC and 27 SAD. A repeated measures ANOVA was conducted for error rates probing a *Group* (HC, SAD) x *Condition* (Congruent, Incongruent) interaction, controlling for age. Significant interaction effects were followed up with Bonferroni-corrected post-hoc tests. For EEG analyses, two additional participants were excluded due to poor data quality (1 SAD) or fewer than six commission error trials (1 HC). The total sample for the baseline EEG analysis was 18 HC and 26 SAD. Internal consistency of electrophysiological measures was computed by examining the correlation of odd- and even-numbered trials with a Spearman-Brown correction. Separate repeated measures ANOVAs were conducted on ERP amplitudes (CRN and ERN) and delta and FMT to test for *Group* (HC, SAD) x *Response Type* (Correct, Error) interaction collapsed across condition (Congruent, Incongruent) and controlling for age.

To examine GC-MRT treatment effects, we first tested whether, relative to baseline, SAD symptoms decreased at post-treatment (*n* = 19) and follow-up (*n* = 14). Retained participants had less clinician-rated anxiety at follow-up (no other differences emerged between the retained and lost SAD participants; see Supplement). Separate repeated measures ANOVAs were conducted on clinician-rated and self-reported SAD symptoms with *Time* (Baseline, Post-treatment, follow-up) as a

factor and a polynomial contrast. We then conducted separate linear regressions to test whether baseline error rate and electrophysiological measures predicted clinician-rated and self-reported SAD symptoms at post-treatment and follow-up, controlling for baseline symptoms and age. We used difference scores (i.e., ΔERN, ΔFMT, ΔDelta) to reduce the number of tests conducted.

3. Results

3.1. Baseline across-group analyses

Across both groups, clinician-rated and self-reported SAD symptoms were associated with lower error rates on incongruent trials (Spearman's *rhos* ≤ −.35, *ps* ≤ .03) as well as a larger (more negative) ERN (Spearman's *rhos* ≤ -.35, *ps* ≤ .03). Clinician-rated SAD symptoms showed a non-significant trend with a larger ΔERN (Spearman's *rho* = -.30, p = .051), while self-reported SAD symptoms showed a significant correlation with a larger ΔERN (Spearman's *rho* = -.36, p = .02). Clinician-rated SAD symptoms were associated with increased ΔDelta (Spearman's *rho*=.31, p = .04). Not surprisingly, a larger ERN correlated significantly with a lower error rate across conditions (Spearman's *rhos* ≥ .35, *ps* ≤ .02). These associations were not observed when analyses were restricted to the SAD group.

3.2. Baseline between-group behavioral markers

Error Rates. There were significant main effects of *Group*, F (1,43) = 10.12, p < .01, η_p^2=.19, and *Condition*, F (1,43) = 11.10, p < .01, η_p^2=.21. SAD made fewer errors (M = 9.61%, SE = 1.44) compared to HC (M = 16.79%, SE = 1.72), and across groups there were more errors on incongruent (M = 24.43%, SE = 2.12) than congruent trials (M = 1.98%, SE = 0.52). A *Group* × *Condition* interaction also emerged, F (1,43) = 5.24, p = .03, η_p^2=.11. Follow-up post-hoc tests revealed that relative to HC, SAD made fewer errors on incongruent trials (SAD: M = 18.36%, SE = 2.74, HC: M = 30.49%, SE = 3.27; p < .01) and congruent trials (SAD: M=.87%, SE=.67, HC: M = 3.09%, SE=.80; p = .04).

3.3. Baseline between-group neurophysiological markers

Internal Consistency. Internal consistency was acceptable-to-excellent across all ERP and time frequency indices: ERN (r = .84), CRN (r=.99), Pe (*rs*≥.81), Delta (*rs*≥.76), FMT (*rs* ≥ 0.88).

ERN and CRN. There was a main effect of *Group*, F (1,41) = 6.12, p = .02, η_p^2=.13, as SAD exhibited more negative ERN and CRN amplitudes (M = -.05, SE=.58) than HC (M = 2.21, SE=.70). There also was a main effect of *Response Type*, F (1,41) = 13.66, p < .01, η_p^2=.25; participants across groups exhibited more negative amplitudes for error (ERN: M = −1.66 μV, SE=.56) compared to correct trials (CRN: M = 3.82 μV, SE=.46). A marginally significant *Group* x *Response Type* interaction also emerged, F (1,41) = 4.05, p = .051, η_p^2=.09. On commission error trials, SAD (M = −3.27 μV, SE=.72) exhibited a more negative ERN compared to HC (M = -.04 μV, SE=.86), F (1,41) = 8.21, p < .01, η_p^2=.17, whereas there was no group difference on correct trials (p = .25; Fig. 1).

Delta. There were no main effects of *Group* (p = .32) or *Response Type* (p = .21). There was, however, a *Group* x *Response Type* interaction, F (1,41) = 4.15, p = .048, η_p^2=.09. SAD exhibited increased delta on error (M = 8.98 μV^2, SE = 1.40) compared to correct trials (M = 3.57 μV^2, SE=.72, p < .01), F (1,41) = 13.36, p < .01, η_p^2=.25, whereas for HC, delta did not differ as a function of error or correct trials (p = .71; Fig. 2).

Frontal Midline Theta. Although there was no main effect of *Group* (p = .64), there was a main effect of *Response Type*, F (1,41) = 13.36, p < .01, η_p^2=.25, as participants across groups exhibited increased FMT on error (M = 19.50 μV^2, SE = 2.90) compared to correct trials (M=.54 μV^2, SE=.56). The *Group* x *Response Type* interaction was not significant (p = .33; Fig. 2).

3.4. Predicting treatment response

Anxiety symptoms improved over time. LSAS decreased, F (2,28) = 5.59, p < .01, η_p^2=.29, which was a linear trend, F (1,14) = 6.83, p = .02, η_p^2=.33. SPIN scores showed a similar reduction, F (2,28) = 5.97, p = .01, η_p^2=.30, which also was linear, F (1,14) = 7.22, p = .02, η_p^2=.34.

After controlling for baseline symptoms and age, error rates did not predict SAD symptoms over time (Table 2). Similarly, the ΔERN did not predict clinician-rated SAD symptoms at post-treatment (p = .22) or at the follow-up (p = .20). However, ΔERN predicted reduced self-reported SAD symptoms at post-treatment, β=.56, SE=.80, p < .01 (Fig. 3B), but not at follow-up, (p = .16; Table 2).

For oscillations, ΔDelta did not predict clinician-rated or self-reported symptoms over time (*ps* > .55). Increased ΔFMT (i.e., FMT power on error minus correct trials) showed a non-significant association with reduced clinician-rated SAD symptoms at post-treatment, β = -.40, SE=.22, p = .056, but did predict a significant reduction in the symptoms at the follow-up, β = -.47, SE=.19, p = .04 (Table 2, Fig. 3D). By contrast, increased ΔFMT predicted reduced self-reported SAD symptoms at post-treatment, β = -.67, SE=.10, p < .01 (Fig. 3A), and the follow-up, β = -.66, SE=.09, p < .01 (Table 2, Fig. 3C).[1]

4. Discussion

We characterized electrophysiological markers related to SAD and investigated whether these markers predicted response to GC-MRT. Relative to HC, adults with SAD made fewer errors and exhibited a more negative ERN. Although prior studies did not find group differences in error rates, we replicated a larger ERN reported in SAD (Endrass et al., 2014; Kujawa et al., 2016). Prior research in SAD had focused on ERPs, and a novel contribution of our study is the exploration of neural oscillations related to impaired error processing in SAD. No baseline group differences emerged for FMT. However, exploratory analyses found increased delta following error commission compared to correct responses among SAD participants, whereas there was no difference among HC. Regarding treatment predictors, a more negative ΔERN predicted reduced self-reported anxiety symptoms at post-treatment but not the follow-up. Additionally, ΔFMT predicted reduced self-reported SAD symptoms at post-treatment as well as self-reported and clinician rated symptoms at the follow-up. Collectively, these findings highlight neurophysiological markers associated with SAD, some of which may predict GC-MRT response.

Consistent with prior research on ERN (Endrass et al., 2014; Kujawa et al., 2016), our findings show that SAD is characterized by heightened error monitoring, possibly reflecting reactivity to and/or threat value of error commission (ERN and delta). Further, the group differences on ERN but not on Pe (see Supplement) may suggest relatively more automatic error detection versus conscious elaboration of error commission. These results are also consistent with a broader literature suggesting heightened error monitoring across anxiety-related disorders (e.g., SAD: Endrass et al., 2014, GAD: Weinberg et al., 2015) and OCD (Endrass and Ullsperger, 2014). Specific disorders, however, may be characterized by slightly different impairments within the error monitoring system. For example, although ERN and FMT may underlie action-related regulation of cognitive control process involving error commission (i.e., response inhibition), delta power may reflect motivational saliency (or threat value) of error irrespective of response production. Given that SAD is characterized by excessive fear of social or

[1] Given the small sample size, we included one participant whose ΔFMT power was an outlier (>3SD). When this participant was removed from the analysis, increased ΔFMT at baseline predicted a reduction in self-reported social anxiety symptoms at the follow up (β = -.48, *SE*=.14, p = .04), but not at post-treatment (p > .12) or with the clinician-rated symptoms at post-treatment (p > .23) and the follow-up (p > .14).

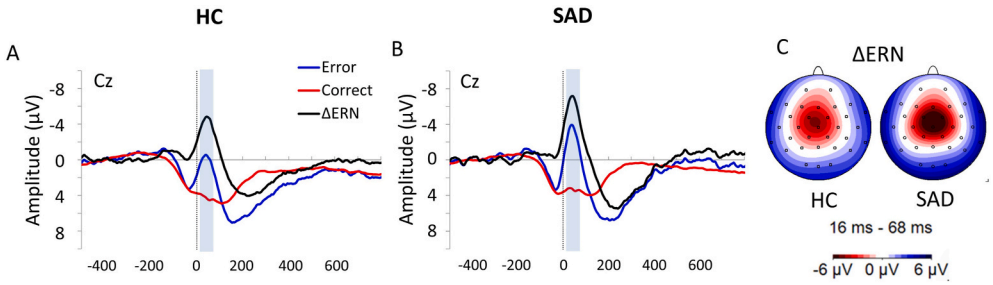

Fig. 1. Event-Related Potentials Elicited by Commission Errors (Error) and Correct Responses (Correct), their Difference Waves (Difference), and Associated Scalp Voltage Maps, Separately for Healthy Controls (HC) and Participants with Social Anxiety Disorder (SAD). ERPs are measured at channel Cz and response onset occurs at 0 ms. Negative is plotted up. (**A**) Error-related negativity (ERN) elicited by commission errors (blue line), and correct-related negativity (CRN) elicited by correct responses (red line), and their difference waves (black line) for HC and (**B**) SAD participants. Light blue highlights indicate where ERN/CRN are measured. (**C**) Scalp voltage map of the difference wave in ERN/CRN (ΔERN) for HC and SAD. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

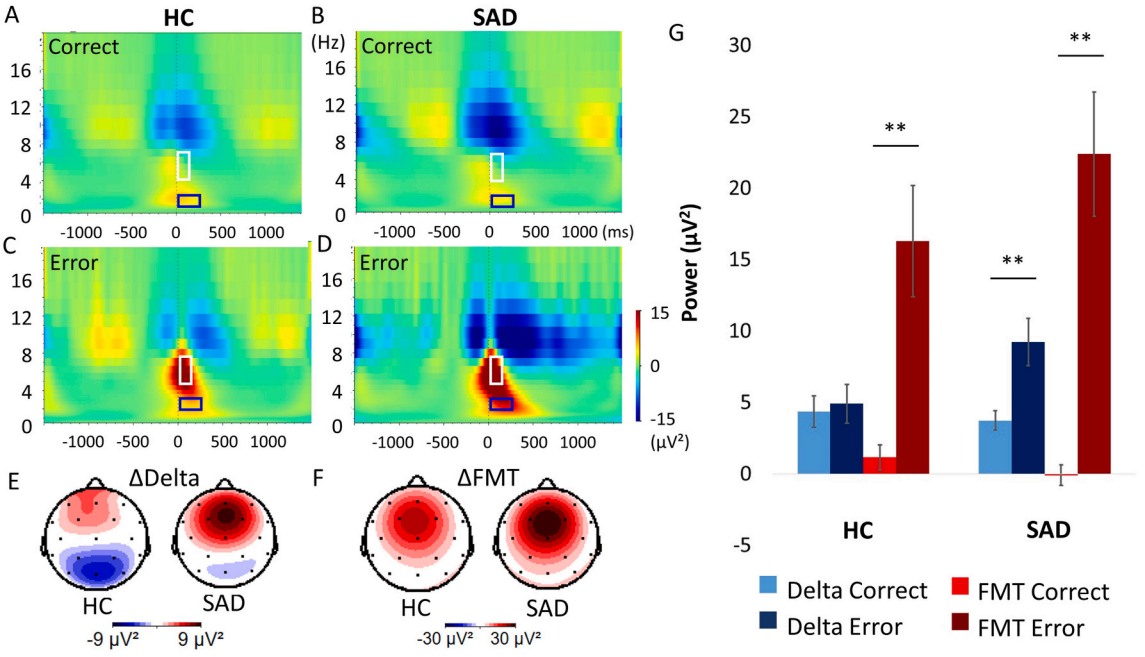

Fig. 2. Time-Frequency Plots for Delta Power (1.5–2.5 Hz) and Frontal Midline Theta (FMT) Power (4–7 Hz) Elicited by Correct Responses (Correct) and Commission Errors (Error), and Associated Scalp Maps in Difference scores, Separately for Healthy Controls (HC) and Participants with Social Anxiety Disorder (SAD). Power is measured at channel Cz and response onset occurs at 0 ms. The window of measurement is highlighted for delta power (blue square) and for frontal midline theta (FMT) power (white square) following correct responses among (**A**) HC and (**B**) SAD as well as commission errors among (**C**) HC and (**D**) SAD. Scalp map for the difference score (Error minus Correct) in (**E**) delta power (ΔDelta) and (**F**) FMT power (ΔFMT: error minus correct FMT power) is shown for HC and SAD. (**G**) Differences among Delta (Correct = Light Blue; Error = Dark Blue) and FMT (Correct = Light Red; Error = Dark Red) power are shown in the bar graphs. Error bars represent standard errors of the mean. The significant effects (**p < .01) reflect the main effect of Response Type for FMT, and the effect of Response Type only for SAD for delta power based on the Group x Response Type interaction. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

performance-related evaluation, delta to performance error may be enhanced for individuals with SAD, whereas more action-related processes (ERN and FMT) may relate more to disorders such as OCD, in which impairment may stem from general response monitoring (Endrass and Ullsperger, 2014). Identifying markers related to hypervigilance is important, as this may clarify neurophysiological processes that contribute to SAD onset (c.f., Kujawa et al., 2016) and persistence, which may provide an inroad for novel prevention and treatment approaches.

Both ERN and FMT predicted reduction in SAD symptoms following GC-MRT. Previous research has shown that other forms of ABMT lead to reductions in ERN amplitude following ABMT (Klawohn et al., 2020; Nelson et al., 2015, 2017). Additionally, greater attentional disengagement from negative stimuli during ABMT was associated with a reduced ERN (Nelson et al., 2015). SAD is characterized by excessive attention to social threat, and GC-MRT may specifically reduce aversion to social threat by training attention away from threatening faces (Lazarov et al., 2017, 2021). As heightened processing of threat of errors is a salient performance threat for individuals with SAD, it also may characterize individuals more likely to benefit from GC-MRT reducing attention to social threats. These neural markers are known to be associated with the function of dorsal ACC, which plays a critical role for regulation of cognitive control (Cavanagh and Shackman, 2015). GC-MRT may modulate ACC activity in SAD, leading to improved regulation of attentional disengagement from negative stimuli, helping those with heightened error monitoring to down-regulate their thoughts and behavior in response to socially threatening stimuli, and improving social anxiety symptoms. Indeed, direct electrical stimulation to induce oscillations at a theta band frequency in rodent dorsal ACC has shown to reduce anxiety-related behaviors (Weible et al., 2017). Given the ACC's

Table 2
Behavioral and electrophysiological measures predicting social anxiety symptoms at post-treatment and the follow-up assessment.

	SAD Symptoms	Predictor	Std. Beta	SE	Part-R	Overall Model	R^2
Post-Treatment	Clinician-rated	Total Error %	0.01	1.47	0.01	F (3,16) = 2.30	0.30
		ΔERN	0.25	1.87	0.31	F (3.15) = 4.55**	0.48
		ΔFMT	**−0.40***	0.22	−0.47	F (3,15) = 6.08***	0.55
		ΔDelta	0.12	0.63	0.16	F (3,15) = 3.84**	0.43
	Self-reported	Total Error %	−0.03	0.73	−0.03	F (3,16) = 1.91	0.26
		ΔERN	**0.56*****	0.8	0.65	F (3,15) = 6.65***	0.57
		ΔFMT	**−0.67*****	0.1	−0.71	F (3,15) = 8.48***	0.63
		ΔDelta	0.08	0.36	0.09	F (3,15) = 1.77	0.26
Follow-Up	Clinician-rated	Total Error %	−0.19	1.44	−0.23	F (3,11) = 2.91	0.44
		ΔERN	0.29	1.7	0.40	F (3, 10) = 4.83**	0.59
		ΔFMT	**−0.48****	0.19	−0.60	F (3,10) = 7.29***	0.69
		ΔDelta	0.14	0.92	0.18	F (3,10) = 3.74**	0.53
	Self-reported	Total Error %	−0.14	0.8	−0.17	F (3,11) = 2.83	0.44
		ΔERN	0.32	0.99	0.43	F (3,10) = 4.22**	0.56
		ΔFMT	**−0.66*****	0.09	−0.78	F (3,10) = 12.21***	0.79
		ΔDelta	−0.08	0.57	−0.09	F (3,10) = 2.85	0.46

Note: $p < .01$***, $p < .05$**, $p < .06$*; Bold text reflects significant predictors of treatment response; Clinician-rated = Clinician-rated Liebowitz Social Anxiety Scale. Self-reported = Social Phobia Inventory; Total Error % = Error % across the congruent and incongruent conditions. Overall Model includes baseline symptoms and age. The significance of each predictor is indicted in the column for standardized beta (Std. Beta). Part-R reflects the partial correlation of a given predictor, whereas R^2 reflects the effect size of the overall model.

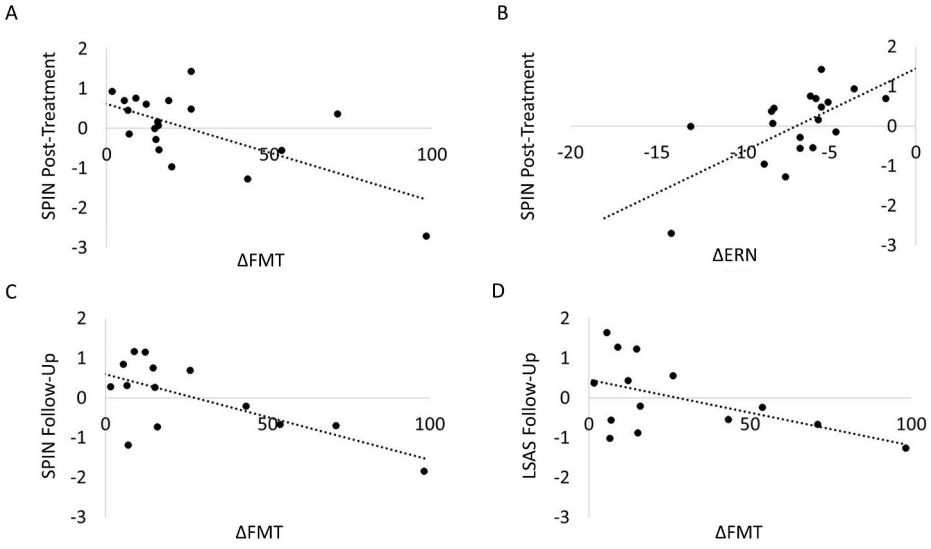

Fig. 3. Relations between Symptom Changes and Electrophysiology. Relation between self-reported social anxiety symptoms (i.e., SPIN) at post-treatment and (**A**) ΔFMT (error minus correct FMT power), and (**B**) ΔERN (error minus correct trials). Relation between self-reported social anxiety symptoms (i.e., SPIN) at follow-up and (**C**) ΔFMT. Relation between clinician-rated social anxiety symptoms (i.e., LSAS) at follow-up and (**D**) ΔFMT. Note that social anxiety symptoms (both SPIN and LSAS) are standardized residual scores after controlling for age and associated baseline symptoms.

role in goal-directed behavior and dysfunction across multiple psychiatric disorders (Holroyd and Umemoto, 2016), investigating the specific cognitive control processes related to ACC that predict GC-MRT response would be a promising future avenue; particularly, in a study that longitudinally monitors how neural change covaries with symptoms during treatment (Webb et al., 2021). Notably, delta power did not predict treatment response, even though error sensitivity in delta differentiated SAD from HC individuals. Although speculative, this finding again highlights that delta and FMT may reflect separable aspects of cognitive processes. That is, delta may index motivational salience of socially threatening stimuli that contributes to symptom differences but may not be sufficiently targeted in the attention bias modification treatment.

4.1. Limitations

There are several limitations of the present study. First, our findings must be interpreted with caution as the sample size was small. Future replication with sufficiently powered samples is essential. Second, although a previous randomized controlled trial demonstrated efficacy of GC-MRT (Lazarov et al., 2017, 2021), this study included no control treatment condition within the SAD group. Therefore, improvement in SAD symptoms may have been due to nonspecific factors. Third, and relatedly, it is not clear if the neurophysiological processes changed during treatment, and whether GC-MRT specifically modulated them. Future studies should examine these processes at multiple time points throughout a controlled treatment (Webb et al., 2021).

5. Conclusion

Our findings revealed that adults with SAD exhibited an aberrant error monitoring system, whereby baseline hypersensitivity to error commission also predicted treatment response to a novel reward-based attention modification treatment. Elucidating the neural indices underlying SAD will advance understanding of individual differences in pathophysiology and may help determine which individuals would likely benefit from available treatments. Ultimately, clarifying neural signatures may provide promising new targets for different types of treatments and perhaps, lead to improved long-term outcomes.

Data sharing

The data that support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

Dr. Auerbach is an unpaid scientific advisor for Ksana Health. Dr. Schneier has research support from Otsuka Pharmaceuticals and Compass Pathways. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. None of the other authors have any conflict of interest or disclosures with regard to the work presented in this manuscript.

Acknowledgement

This research was supported through funding from the NIMH (R61MH116089-01) and New York State Psychiatric Institute EEG Core Pilot Grant to Dr. Schneier. Dr. Lazarov was supported through NIMH funding (R61MH116089-01) and the Israel Science Foundation (374/20). Dr. Umemoto received partial support through the Sackler Award, and Dr. Auerbach was partially supported through NIMH funding (R01MH119771) and the Tommy Fuss Fund. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.09.022.

Author statement

Akina Umemoto: Data analysis, literature search, writing; **Sally L. Cole**: Data processing/analysis, literature search, writing-original draft; **Grace O. Allison**: Data processing/analysis, literature search, writing-original draft; **Sarah Dolan**: Data collection, resources; **Amit Lazarov**: Conceptualization, methodology, investigation, writing-editing; **Randy P. Auerbach**: Conceptualization, methodology, supervision, writing; **Franklin Schneier**: Conceptualization, methodology, supervision, writing-editing.

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