Original Article

CHRONIC STRESS

Chronic Stress
Volume 3: 1–12

DOI: 10.1177/2470547019848648
journals.sagepub.com/home/css
SAGE

Social Feedback Modulates Neural Response Associated With Cognitive Bias in Individuals Expressing Anxious Symptoms

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Abstract

Background: Social anxiety is characterized by a tendency to overestimate the likelihood of negative outcomes and consequences before, during, and after interpersonal interactions with social partners. Recent evidence suggests that a network of brain regions critical for perspective-taking, threat appraisal, and uncertainty resolution may function atypically in those prone to social anxiety. In this study, we used functional magnetic resonance imaging to examine neural activity in specific regions of interest in a sample of young adults who endorsed high or low levels of social anxiety.

Methods: We recruited 31 college student volunteers (age: 18–28 years), categorized as having high or low anxiety based on their Liebowitz Social Anxiety Scale-Self Report scores. These participants were each scanned while playing the iterated Prisoner's Dilemma game with three computerized confederates, two of whom they were deceived to believe were human co-players. This study focuses on data collected during play with the presumed humans. Regions of interest were defined for the temporoparietal junction, anterior midcingulate, and dorsomedial prefrontal cortex. Average weighted mean blood-oxygen-level-dependent signals for each subject were extracted and analyzed using mixed design analyses of variance to detect group differences in activation during decision-making, anticipation, and appraisal of round outcomes during the game.

Results: Behavior analysis revealed that the high-anxiety group was more likely to defect than the low-anxiety group. Neuroimaging analysis showed that the high-anxiety group exhibited elevated blood-oxygen-level-dependent activity relative to the low-anxiety group in all three regions during the social feedback appraisal phase but not during decision-making or the anticipation of interaction outcomes.

Conclusions: These findings provide evidence that some behaviors linked to cognitive biases associated with social anxiety may be mediated by a network of regions involved in recognizing and processing directed social information. Future investigation of the neural basis of cognition and bias in social anxiety using the prisoner's dilemma and other economic-exchange tasks is warranted. These tasks appear to be highly effective, functional magnetic resonance imaging-compatible methods of probing altered cognition and behavior associated with anxiety and related conditions.

Keywords

social anxiety, functional magnetic resonance imaging, Prisoner's Dilemma, temporoparietal junction, dorsomedial prefrontal cortex, anterior midcingulate

Received 16 October 2018; Accepted 9 April 2019

Introduction

Social anxiety (SA) is characterized by fear of embarrassment, criticism, humiliation, or rejection in social or performance situations.[1] It is common and often impairing; in a given year, roughly 6.8% of the United States population meets diagnostic criteria for social anxiety disorder (SAD), a severe manifestation of SA. In addition, over 40% of people who do not meet Diagnostic and

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Statistical Manual diagnostic criteria report considerable SA symptoms.[2]

Historically, SA has been defined and understood as a categorical construct[2] (i.e., one either has it or does not). Researchers and clinicians, however, have expressed concern that diagnostic cutoff points may be arbitrary.[3,4] Thus, many have embraced the notion that SA exists on a dimensional spectrum that also spans undiagnosed and subclinical populations.[5,6] SA, even at subclinical levels, has distinct cognitive, behavioral, and emotional correlates.[7–9] These include increased reactivity to social stress and negative social evaluation, negative automatic thoughts, negative observer-perspective images, and maladaptive coping strategies. These findings suggest that normal range SA is associated with changes in emotional experience, cognitive appraisals, and behaviors that parallel those found in SAD. However, less is known about whether the neural correlates of SA are comparable between those whose symptoms exceed diagnostic thresholds and those whose symptoms do not.

Prominent cognitive-behavioral theories of SA[10–12] identify maladaptive cognitive biases as central to the condition. Neuroimaging research on SA, however, has focused more heavily on the neural basis of emotional hyper-reactivity and fear response than on the neural correlates of these cognitions and their behavioral manifestations.[13] Interest has surged in looking beyond exaggerated emotional responses and examining complex, distributed patterns of atypical neural activity.[13,14] This shift has led researchers to identify a broader set of brain regions that may engage atypically in association with SA-related cognitive biases.

Inherent in interpersonal interaction is the need to determine what others might be thinking or feeling.[15,16] This process, commonly termed Theory of Mind (ToM),[17,18] involves discerning another person's perspective and attributing meaning to the perspective. Given that the cognitive biases associated with SA include a tendency to assume that others will criticize one's behavior, regions of the brain that facilitate ToM reasoning warrant attention as possible seats of atypical activation in SA.

In three recent studies that compared performance on ToM reasoning and decoding tasks between adults with and without SAD, individuals with SAD made more errors in interpreting socially relevant information than did diagnosis-free subjects.[19–21] These findings raise the possibility that individuals with SAD "over-mentalize" or attribute more intense emotion and meaning to social and emotional stimuli than is appropriate, given the contexts in which the stimuli appear. Abnormal ToM reasoning may thus contribute to the emergence of symptoms associated with negative interpretation bias and fear of negative evaluation.

The temporoparietal junction (TPJ) plays an important role in the ToM reasoning.[22,23] Elevated TPJ activity is associated with heightened sensitivity to social signaling and evaluation by others in individuals with SAD and related conditions.[24–26] These converging lines of research raise the possibility that abnormal TPJ activity is a critical neural biomarker underlying altered socio-cognitive capabilities in SA.

In addition to evaluating others' mental states atypically, people with SA also consciously appraise social situations in a distinctive, often biased manner. Consistent with general appraisal theories of anxiety disorders, exaggerated evaluations of perceived threat mediate the tendency for people experiencing SA to overestimate the likelihood that a catastrophic consequence will occur.[27,28,29] The dorsomedial prefrontal cortex (dmPFC) plays a significant role in conscious threat appraisal and the resolution of contextual fear.[27,28,29] Moreover, several studies suggest that in those experiencing SA, a complex network that includes the dmPFC as a hub[30] exhibits altered activity during the appraisal of negative faces,[31,32] social criticism and self-beliefs,[33] and SAD-related visual scenes.[34] The dmPFC is also consistently identified as a core node of the ToM network,[22,23] suggesting that its function generalizes to multiple cognitive domains and contexts.

Finally, people experiencing SA show distress in situations that do not offer certainty about what will happen next or what action they need to take to ensure innocuous outcomes.[35,36] The anterior midcingulate cortex (aMCC), appears to function as an integrational hub that mediates the cognitive processing of uncertainty.[37] A number of distinct adaptive response functions such as novelty identification, evaluation of reward and error, and the anticipation of emotionally salient information in the environment appear to be linked to the aMCC and to facilitate flexible response to uncertain situations.[38] Neural activity in the aMCC is particularly exaggerated during the anticipation of aversive stimuli and circumstances.[37,39–41] Furthermore, it has become increasingly evident that, as adjacent neural structures, the dmPFC and the aMCC function as an integrated unit in threat appraisal and cognitive conflict resolution.[40,42,44]

This study used the iterated Prisoner's Dilemma (iPD) task, a game that has been widely used to demonstrate how people may achieve stable cooperation over the course of prolonged interpersonal interactions.[43] During this task, players must make independent decisions about whether to cooperate or not cooperate (defect) with another player in order to win monetary rewards that are tallied based on the conjunction of their decisions. Each round in the task progresses through *three* phases (decision-making, anticipation of outcome, and feedback of outcome) that form a "social decision cascade"[45] that characterizes a typical reciprocal-exchange based

interaction.[46] The systematic structure of the iPD paradigm and its elicitation of varying responses to incentivized outcomes allow for examination of the complex cognitive processes that underlie social interaction in a cohesive and organized manner.[47,48]

The objective of this paper was to elucidate neural correlates of maladaptive social cognitive bias in individuals with high self-reported SA. Specific regions of interest (ROIs) were selected and cited based on the cognitive processes we expected to be tied to SA. We hypothesized that a network of regions involved in ToM reasoning (TPJ), conscious threat appraisal (dmPFC), and the processing and resolution of conflict and uncertainty (aMCC) would be recruited consistently during all three (decision, anticipation, and feedback) iPD game phases. Additionally, we predicted that individuals with high self-reported SA would exhibit more blood-oxygen-level-dependent (BOLD) activity within these regions during each phase than individuals with low self-reported SA.

Methods

Procedure

Institutional Review Board Approval. This project focuses on functional magnetic resonance imaging (fMRI) data collected during two time periods. The first dataset was acquired in 2008 using a 3-T magnet at the Emory University Biomedical Technology Center. The second dataset was gathered in 2016–2017 using a 3-T magnet at the Georgia State/Georgia Tech Center for Advanced Brain Imaging (CABI). Procedures were approved by the relevant institutional review boards.

Participants. For the 2008 dataset, we recruited 19 subjects from an undergraduate Psychology Department research pool via the SONA Systems Software online recruitment system. Researchers contacted interested individuals via telephone and invited them to participate. Four participants' data were excluded from analysis due to excessive head motion (framewise displacement mean of 1 mm or above) and 1 participant was removed from the scanner due to general discomfort, leaving data from 14 subjects, with a mean age of 20.6 (standard deviation (SD) = ±4.5 years), available for analysis.

For the 2016/2017 dataset, 20 adults were recruited from a Psychology Department undergraduate student pool. Two participants' data were excluded due to excessive motion in the scanner and one participant's age exceeded the threshold approved by the institutional review board, yielding a final sample of 17 subjects. The combined dataset comprised 26 females and 5 males, with a mean age of 20.5 years (SD = ±3.5 years). See Table 1 for an overview of participants' demographic information.

All participants completed the Liebowitz Social Anxiety Scale-Self Report Version[49] (LSAS-SR). We limited recruitment to participants with extreme high or low scores on the LSAS-SR. Participants in the sample pool who scored at or above the 75th percentile were identified as high SA (range of scores between 67 and 107). Participants who scored at the 25th percentile or lower were identified as low SA (range of scores between 3 and 27). LSAS-SR scores were within a range consistent with "marked" or "severe" SAD in the high SA group and asymptomatic presentation in the low SA group.[50] In total, 17 subjects comprised the high SA group and 14 subjects comprised the low SA group. For details of the LSAS-SR, see Supplemental Materials Section 4.

Exclusion criteria for both studies, which were screened for during a phone interview, included the presence of metals permanently embedded or implanted in the body, preexisting major medical conditions or traumatic brain injury, major psychiatric disorders including SAD, pregnancy, and current use of psychotropic medication.

Task Description

Each participant played three 20-round iPD games;[51] rounds proceeded as shown in Figure 1. In each round, the participant chose to cooperate or not cooperate (defect), and then waited for a "co-player," who independently decided to cooperate or to defect. The participant and co-player were equally rewarded ($2) if both cooperated; if one player cooperated but the other did not, the defecting player received a reward ($3) and the cooperating player received nothing ($0). If both chose to defect, both received a small reward ($1). Participants played the three PD games in a randomized order—in two, they were deceived into believing that they were playing with a confederate (but actually played a computer algorithm) and in one they were told that they were playing the computer (see Supplemental Materials Section 3 for algorithm configuration). After all three games had ended, participants were paid an average of the amount that they earned over the three games.

Participants had 6 s to make a decision during each round but could respond at any point during this window. The decision period was followed by an interstimulus interval (ISI) jittered in duration to be 3, 6, or 9 s. After the ISI, feedback regarding the round's outcome (participant and co-player's decision) was presented for 6 s.

Scanning

2008 Data. The 2008 dataset was acquired using a Siemens TIM Trio 3-T MRI scanner equipped with a 12-channel head coil. E-Prime 1.1 was used to present task stimuli (Psychology Software Tools, Inc.).

Table 1. Demographics data for the high- and low-anxiety groups.

	High anxiety			Low anxiety		
	All (N = 17) Mean (SD)	Female (N = 14) Mean (SD)	Male (N = 3) Mean (SD)	All (N = 14) Mean (SD)	Female (N = 12) Mean (SD)	Male (N = 2) Mean (SD)
Age	19.8 (2.0)	19.6 (1.6)	20.7 (3.8)	21.3 (4.7)	20.7 (4.6)	25.0 (4.2)
LSAS scores	80.5 (12.3)	82.7 (12.4)	70.0 (2.6)	15.5 (8.1)	17.3 (7.4)	5.0 (2.8)
Head motion values	.15 (.07)	.12 (.04)	.31 (.21)	.20 (.15)	.14 (.06)	.38 (.22)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Site						
BITC	8 (47)	5 (36)	3 (100)	6 (43)	6 (50)	0 (0)
CABI	9 (53)	9 (64)	0 (0)	8 (57)	6 (50)	2 (100)
Ethnicity						
Caucasian	7 (41)	6 (43)	1 (33.3)	4 (29)	3 (25)	1 (50)
African-American	5 (29)	4 (29)	1 (33.3)	6 (43)	6 (50)	0 (0)
Hispanic	1 (6)	1 (7)	0 (0)	2 (14)	2 (17)	0 (0)
Asian	4 (24)	3 (21)	1 (33.3)	2 (14)	1 (8)	1 (50)

BITC: Biomedical Technology Center; CABI: Center for Advanced Brain Imaging.

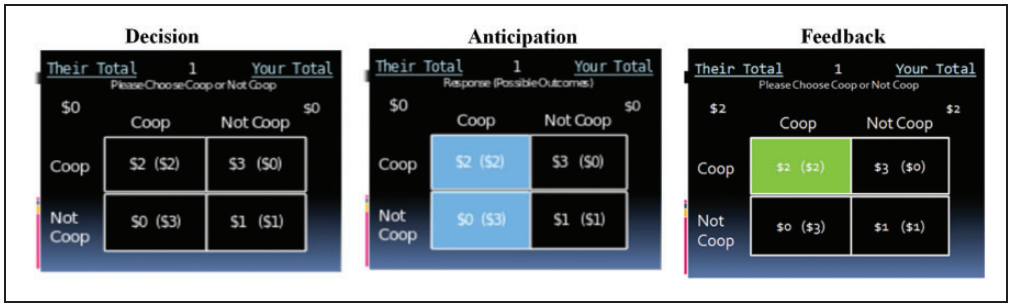

Figure 1. An example of a mutual cooperation round (CC) of the iterated Prisoner's Dilemma. Each round can be separated into decision, anticipation, and feedback phases.

Participants recorded decisions to cooperate or defect using a hand-held, four-button response box.

2016/2017 Data. The 2016 dataset was acquired at the CABI, which houses a Siemens TIM Trio 3-T MRI scanner equipped with a 12-channel head coil for rapid parallel imaging of the brain. E-Prime 2.0 was used to present task stimuli (Psychology Software Tools, Inc.). The procedures used for stimulus display and participant responses were consistent with the 2008 protocol. See Supplemental Materials Section 6 for details on the scanning parameters.

Preprocessing

We preprocessed the 2008 dataset using Statistical Parametric Mapping (SPM) 12 software. Functional data were corrected for slice timing and motion, realigned and registered to the mean echo-planar imaging image, spatially normalized to the MNI template of SPM and resliced into isotropic 2 mm voxels, and smoothed using an 8-mm full width at half maximum (FWHM) Gaussian kernel. For the 2016 dataset, we used Data Processing Assistant for Resting-State fMRI (DPARSF) software to follow the first steps described above (correction, co-registration, realignment/registration to the mean image). The images collected in 2016 needed to be resized to match the scale and dimensions of the 2008 dataset. After resizing was complete, the data were spatially normalized to the Montreal Neurological Institute (MNI) template of SPM and resliced into isotropic 2 mm voxels, and then smoothed using an 8-mm FWHM Gaussian kernel. Following these preprocessing steps, blinded reviewers evaluated the quality of the co-registration procedure by visually inspecting the fMRI images for inconsistencies; no corrections needed to be made.

Analysis

Behavioral Analysis. For all participants, across the 40 rounds played with the "human" confederate, an average

of 12 rounds resulted in mutual cooperation (CC); 6 resulted in unreciprocated cooperation (CD); 9 in unreciprocated defection (DC); and 13 resulted in mutual defection (DD). We conducted a one-way analysis of variance (ANOVA) to test the interaction between anxiety level and average cooperation rate. We also conducted a within-subject logistic regression with the decision of the subject as the binary outcome and the prior decision of the subject and co-player along with anxiety level as binary regressors of interest.

Event-Related Regressors. To analyze the fMRI data, we used a general linear modelling procedure in SPM12 to estimate event-related average BOLD response amplitudes across predefined ROIs at the individual subject and group levels. Primary event-related regressors comprised two regressors for the decision phase, two regressors for the anticipation phase (period of time between when the decision was made and the presentation of the outcome), and four regressors for the feedback phase (presentation of outcome consisting of conjunction of participant and co-player decision). The two decision and two anticipation regressors were specified according to whether the participant cooperated or defected. The four feedback regressors comprised a CC condition (mutual cooperation—both players cooperated); a CD condition (unreciprocated response—the subject cooperated while the co-player defected); a DC condition (another type of unreciprocated response—the subject defected while the co-player cooperated); and a DD condition (mutual defection—both players did not cooperate).

Additionally, all regressors distinguished between rounds played with human or computer co-players, doubling the total number of regressors to 16 for each individual subject. Finally, a framewise displacement regressor was included in the single subject analyses as a motion regressor. In the group-level analysis, the site at which data were collected was included as a covariate. Only data from the ''human co-player'' games were included in the subsequent two-group comparison analysis between high and low SA, as interactions of social exchange with a ''human'' were the primary interest.

Neuroimaging: ROI Analysis. ROIs were defined for the TPJ, the dmPFC, and the aMCC using PickAtlas.[52] For more details, see Supplemental Section 5.

We specified two decision contrasts in SPM (decision to cooperate (C) and decision to defect (D)), as well as two anticipation contrasts (anticipation after cooperation (C) and anticipation after defection (D)) and four feedback contrasts (reciprocated feedback (CC+DD), unreciprocated feedback (CD+DC), co-player cooperation (CC+DC), and co-player defection (CD+DD)). We took this approach to increase the power of the analysis and to allow distinct evaluation of responses to social and monetary contexts of feedback, consistent with previous PD research.[25,51,53]

We conducted one-sample t-tests to contrast BOLD activity during each phase against baseline (periods of non-activity) for each individual subject. We then extracted the average weighted mean of the BOLD signal within the ROI as a principal eigenvariate value (PEV). The PEV summarizes group data across voxels, yielding a singular value decomposition of the time series. This strategy is optimal for interpreting condition-related response amplitudes without assuming homogeneous responses within the ROI.[54] Finally, we compared the PEVs across the ROIs in a collection of group analyses modelled using 2×2 mixed-design analyses of covariance (ANCOVAs) in SPSS 25. In these analyses, we included anxiety group as a between-subject factor and phase as the within-subjects factor (e.g., co-player cooperation/defection, decision to cooperate/decision to defect, etc.). Site was included as the covariate.

Results

Behavioral Analysis

We conducted a one-way ANOVA to examine the interaction between anxiety level and average cooperation rates across both ''human'' co-player PD games. We found that while cooperation rates in the high-anxiety group ($M = 41.79$, $SD = 16.03$) trended lower than in the low-anxiety group ($M = 50.85$, $SD = 19.14$), this relationship was not significant, $F(1, 29) = 2.06$, $p = .16$.

A generalized linear mixed logistic regression (SPSS25) was conducted using the current decision of the subject as the binary outcome, and the prior decisions of the subject and the co-player as the binary regressors. Anxiety level was included as a fixed factor to test the interaction between these variables. The prior decision of the subject, $F(1, 812) = 18.55$, $p < .001$, and the prior decision of the partner, $F(1, 812) = 73.75$, $p < .001$, both significantly predicted the subsequent response of the subject: If the prior decision of the subject or the partner was to cooperate, this significantly increased the chance of cooperation by the subject in the subsequent round. However, there was no significant effect of the interaction between anxiety level and the prior decision of the subject on the current decision, $F(1, 812) = 0.071$, $p = .79$. Additionally, there was no significant interaction between anxiety level and the prior decision of the partner, $F(1, 812) = 0.882$, $p = .35$.

Neuroimaging Analysis

Decision-Making. For this analysis and all subsequent 2×2 mixed ANCOVAs, anxiety group (high, low) served as the between-subject factor, phase served as the within-subject factor (e.g., decision-making: decision to

cooperate vs. decision to defect), site of collection (CABI, Emory) was included as a covariate, and the dependent variable was the average weighted mean BOLD signal collected from our ROIs (TPJ, dmPFC, and aMCC). Our objective was to compare ROI BOLD responses between high and low SA subjects. For the results of a post hoc whole-brain analysis between both groups, see Supplemental Materials Section 1.

Main effects analysis revealed that decision-making was not significantly associated with BOLD response in the TPJ, $F(1, 28) = 2.05$, $p = .16$, the dmPFC, $F(1, 28) = 1.71$, $p = .20$, or the aMCC, $F(1, 28) = 1.43$, $p = .24$. Interactions between SA group and decision-making condition also did not significantly predict activation in the TPJ, $F(1, 28) = 1.04$, $p = .32$, the dmPFC, $F(1, 28) = .36$, $p = .55$, or the aMCC, $F(1, 28) = .20$, $p = .66$.

Anticipation of Outcome. Anticipation of outcome did not relate significantly to BOLD response in the TPJ, $F(1, 28) = .19$, $p = .67$, in the dmPFC, $F(1, 28) = .44$, $p = .51$, or the aMCC, $F(1, 28) = 2.06$, $p = .16$. The interaction between SA group and anticipation condition also did not significantly predict activation in the TPJ, $F(1, 28) = 0.002$, $p = .97$, in the dmPFC, $F(1, 28) = .40$, $p = .53$, or the aMCC, $F(1, 28) = 0.09$, $p = .77$.

Reciprocated and Unreciprocated Feedback. The main effect of feedback did not significantly predict BOLD response in the TPJ, $F(1, 28) = 0.66$, $p = .42$, the dmPFC, $F(1, 28) = .47$, $p = .50$, or the aMCC, $F(1, 28) = 2.80$, $p = .11$. However, the interaction between SA group and feedback condition did significantly predict BOLD activity in the TPJ, $F(1, 28) = 4.35$, $p < .05$, the dmPFC, $F(1, 28) = 12.63$, $p < .001$, and the aMCC, $F(1, 28) = 7.28$, $p < .01$. Although both groups exhibited similar BOLD responses during the processing of reciprocated feedback, high SA subjects exhibited significantly greater BOLD responses than did low SA subjects in each ROI during the processing of unreciprocated feedback (see Tables 2 to 4 for statistical analysis and Figures 2 to 7 for illustration of significant differences). Additionally, patterns of activity were similar for both types of unreciprocated responses (CD and DC).

Co-Player Feedback. Co-player feedback did not significantly predict BOLD response in the TPJ, $F(1, 28) = 2.80$, $p = .11$, or the dmPFC, $F(1, 28) = 2.12$, $p = .16$. However, co-player feedback did significantly predict BOLD response in the aMCC, $F(1, 28) = 4.93$, $p < .05$. Activity in the aMCC was more elevated during the processing of co-player defection than during co-player cooperation, regardless of participant anxiety level (see Table 5 for statistical analysis and Figure 8 for illustration of the difference). The interaction between SA group and feedback condition did not significantly predict BOLD activity in the TPJ, $F(1, 28) = 0.34$, $p = .57$, the dmPFC, $F(1, 28) = 0.01$, $p = .92$, or the aMCC, $F(1, 28) = 0.15$, $p = .71$.

Table 2. Mixed ANCOVA results regarding differences in response to reciprocated versus unreciprocated feedback in the TPJ.

Variables of interest	Degrees of freedom	Mean square	*F*	Significance
Feedback	1	.36	.66	.42
Feedback × Site	1	.79	1.45	.24
Feedback × Anxiety Level	1	2.38	4.35	.05*
Error	28	.55		

ANCOVA: analysis of covariance; TPJ: temporoparietal junction.
*=p<.05.

Table 3. Mixed ANCOVA results regarding differences in response to reciprocated versus unreciprocated feedback in the dmPFC.

Variables of interest	Degrees of freedom	Mean square	*F*	Significance
Feedback	1	.14	.47	.50
Feedback × Site	1	.007	.02	.88
Feedback × Anxiety Level	1	3.73	12.63	.001*
Error	28	.30		

ANCOVA: analysis of covariance; dmPFC: dorsomedial prefrontal cortex.
*=p<.05.

Table 4. Mixed ANCOVA results regarding differences in response to reciprocated versus unreciprocated feedback in the aMCC.

Variables of interest	Degrees of freedom	Mean square	*F*	Significance
Feedback	1	.006	.01	.91
Feedback × Site	1	.09	.20	.66
Feedback × Anxiety Level	1	3.15	7.28	.01*
Error	28	.43		

ANCOVA: analysis of covariance; aMCC: anterior midcingulate.
*=p<.05.

Discussion

Our objective was to identify neural mechanisms of maladaptive cognitive biases that individuals with SA exhibit

during social interactions. Our findings, in college students who self-reported high or low levels of SA, provided only partial support for hypotheses regarding group differences in BOLD response during decision-making, anticipation, and processing of feedback regarding choice outcome in the iPD game.

We had predicted that groups would differ significantly in activation in the TPJ, aMCC, and dmPFC during all three phases of play. BOLD activity within these neural regions did not differ between high and low SA individuals during decision-making and anticipation of outcome; however, we detected a significant group difference during processing of unreciprocated versus reciprocated feedback. Additionally, regardless of anxiety level, processing of co-player defection was associated with significantly stronger aMCC activity than was processing of co-player cooperation. These findings provide tentative evidence that key neural regions engaged during social interaction exhibit at least limited functional differences in individuals who self-report marked to severe levels of SA.

We speculate that responses to co-player cooperation and defection may be a function of monetary feedback (partner cooperation→max reward; partner defection→diminished reward), while responses to reciprocated and unreciprocated feedback are a function of

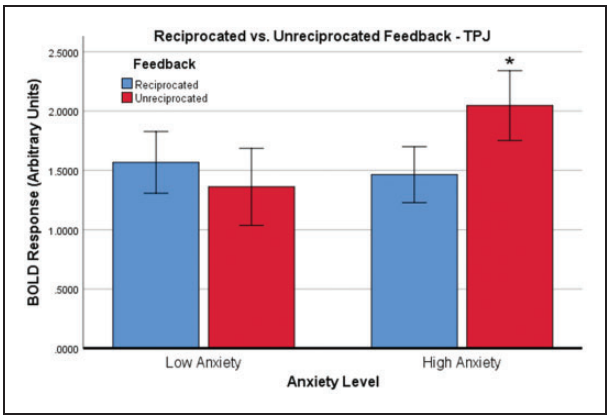

Figure 2. Mean BOLD response in TPJ during processing of reciprocated and unreciprocated feedback. BOLD: blood-oxygen-level-dependent.

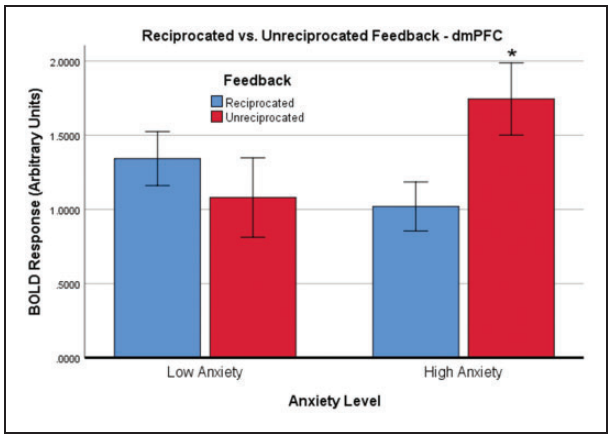

Figure 4. Mean BOLD response in dmPFC during processing of reciprocated and unreciprocated feedback. BOLD: blood-oxygen-level-dependent; dmPFC: dorsomedial prefrontal cortex.

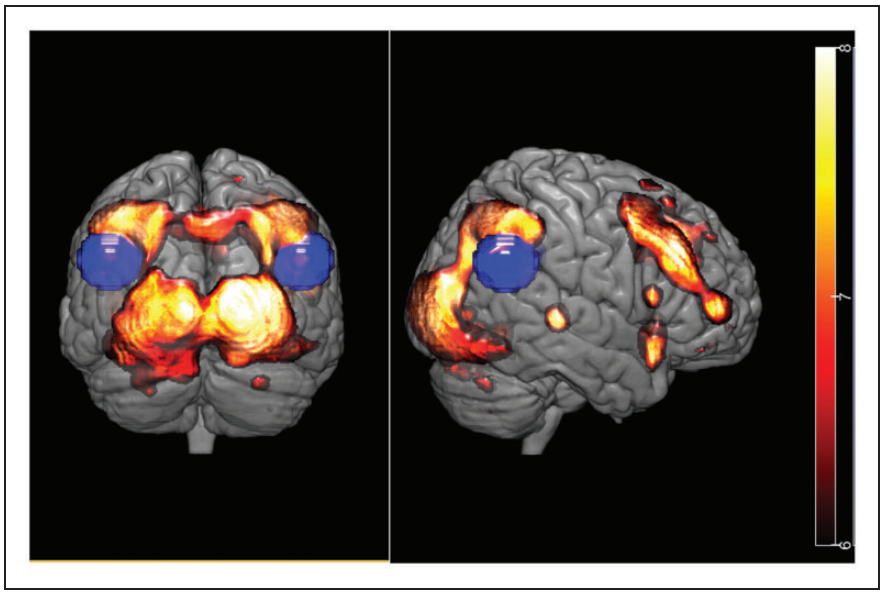

Figure 3. BOLD response during processing of unreciprocated feedback. A whole brain SPM map is displayed with the TPJ ROI highlighted in blue.

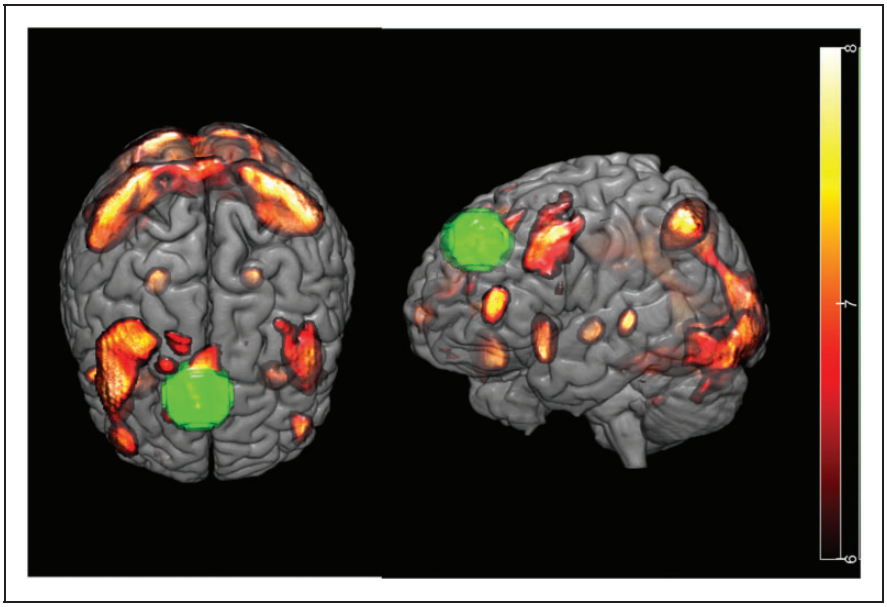

Figure 5. BOLD response during processing of unreciprocated feedback. A whole brain SPM map is displayed with the dmPFC ROI highlighted in green.

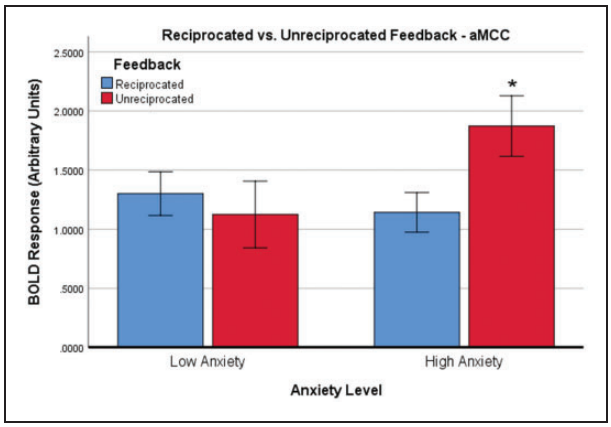

Figure 6. Mean BOLD response in aMCC during processing of reciprocated and unreciprocated feedback. aMCC: anterior midcingulate cortex; BOLD: blood-oxygen-level-dependent.

social feedback (reciprocated→fair and balanced; unreciprocated→unfair and unbalanced). Individuals with high levels of SA exhibited heightened sensitivity to social feedback in comparison to monetary feedback, an observation that substantiates recent neural evidence in child and adult clinical populations which report a heightened sensitivity to social feedback and a normal sensitivity to monetary feedback that does not differ from the healthy population.[55,56] These results could help explain our finding of elevated aMCC activity during co-player defection regardless of anxiety level. Although both groups might share similar sensitivities to monetary feedback, the high SA group exhibited a specific sensitivity to the social features and implications of the interaction particularly when they indicated conflict or discord (unreciprocated feedback). However, contrasting behavioral and neuroimaging studies in adolescent and adult populations suggest that SA may be linked to enhanced monetary reward anticipation in comparison to the healthy population irrespective of gain or loss contexts.[57,58] Future work will need to clarify the neural basis of reward processing in nonclinical and clinical populations.

Researchers lack consensus about whether to prioritize contrasting social feedback outcomes based on reciprocated/unreciprocated response[51,59] or partner choice[25,60,61] during the PD task. Furthermore, few researchers justify their decisions regarding how to categorize feedback outcomes. Given these lingering questions, it is imperative that future research test for differences in the processing of situational contexts (e.g. monetary vs. social) during interpersonal interactions in SA and determine whether such differences affect how players behave during economic exchange games. Neuroimaging paradigms utilizing this "monetary vs. social context" framework have already been applied to both neurotypical[62,63] and neuropsychiatric[64,65] populations, providing a solid foundation for addressing these questions.

Our results align only moderately with prior studies of SA that have used game-theory-based paradigms.[75–78] Our behavioral results, for example, lend only partial support to Rodebaugh and colleagues' recent findings using an iPD variant.[79] Notably, they found

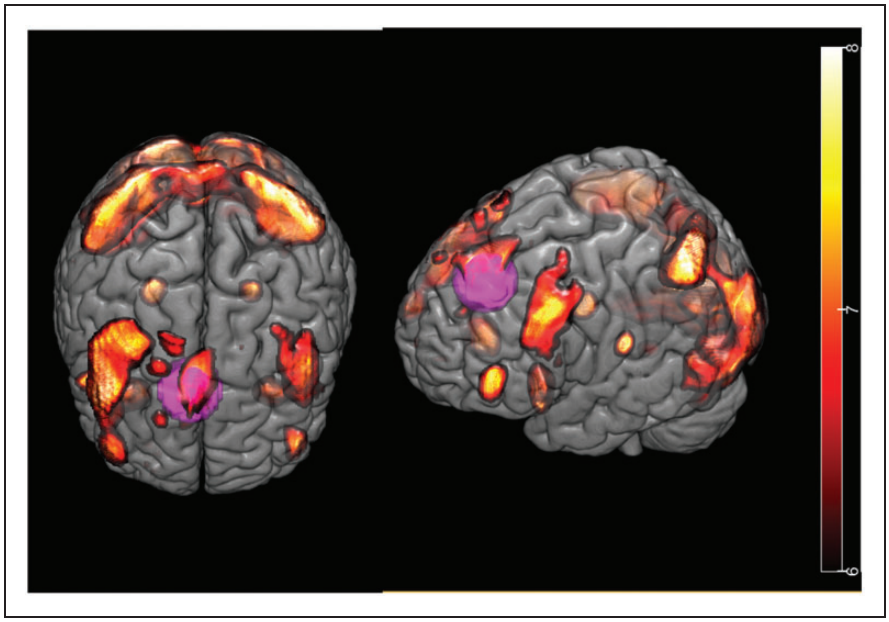

Figure 7. BOLD response during processing of unreciprocated feedback. A whole brain SPM map is displayed with the aMCC ROI highlighted in violet.

Table 5. Mixed ANCOVA results regarding differences in response to co-player feedback in the aMCC.

Variables of interest	Degrees of freedom	Mean square	*F*	Significance
Feedback	1	2.64	4.93	.04*
Feedback × Site	1	2.08	3.88	.06
Feedback × Anxiety Level	1	.08	.15	.71
Error	28	.54		

ANCOVA: analysis of covariance; aMCC: anterior midcingulate.
*=p<.05.

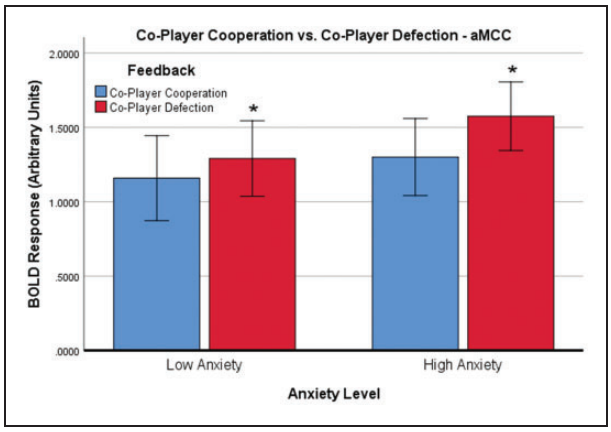

Figure 8. Mean BOLD response in aMCC during processing of co-player cooperation and co-player defection. aMCC: anterior midcingulate cortex; BOLD: blood-oxygen-level-dependent.

that self-reported vindictiveness was associated with heightened defection in SA individuals; we did not assess this personality trait, and thus its impact on our findings is unclear. Anderl et al.[76] reported associations between SA and reduction in reciprocation as trustee in the Trust Game but found no difference in investing/giving behavior as investor between groups. If we infer that the investor is player 1 than this result differs from what we see in PD game, with a greater trend toward defection in our sample coinciding with the Rodebaugh's paper.

Our findings also map only partially onto those of earlier neuroimaging studies using economic exchange tasks in SA samples. Sripada et al.[77] found reduced activity in the mPFC and a generalized response in the ventral striatum to both cooperative and competitive partners during the Ultimatum Game in adults with SAD. These results contrast with our whole brain findings of indicated elevated mPFC activity and elevated activity in the dorsal striatum (see Supplemental Materials Section 1) in response to co-player cooperation. This difference may reflect our use of the iPD game and a non-clinical sample.

Given the wealth of evidence indicating that the TPJ, aMCC, and dmPFC are relevant ROIs for SA, it was unexpected that they only exhibited significant differential activity at a group level during feedback. Substantial evidence implicates all three regions in aspects of social cognition that are modelled in the iPD game, including decision-making[40,66–68] and anticipation of social feedback.[41,69,70] One potential reason that we failed to detect significant group differences within these phases is that we

restricted our focus to participants without formally diagnosed anxiety disorders, whose symptoms ranged in severity. Evidence from a small body of fMRI research suggests that there may be salient differences in brain activity between subclinically and clinically anxious adults during tasks that involve processing emotional facial expressions[71,72] and self-referential/anxiety-relevant information.[73] It may thus be that participants in our study did not exceed a critical threshold of anxiety, at which distinguishable patterns of brain activity could be detected.

A few other limitations of this study are worth noting. Some relate to our study design and methodology. First, our study was underpowered in comparison to past studies that used similar methodology. Second, we collected our data at two independent sites, with several years separating times of collection. Diverging scanner protocols were used to collect the data; we thus needed to correct some images during preprocessing to ensure that parameters were consistent. To minimize the effects of any remaining differences, we also included site as a regressor in all analyses.

Other limitations include participant biases affecting gameplay strategy. For example, a number of participants used strategies that favored defection over cooperation, which limited the number of CD rounds that could be sampled from those subjects. These contrast images were still included in the subsequent group analysis and may have reduced the overall power of the analysis by introducing noise associated with the lack of variability in those trials. Additionally, we only explored a small number of possible ROIs previously implicated the cognitive symptomology of SA. There may be other potential differences between our low and high SA groups that were not accounted for in this study.

Conclusion

The significance of the context of decision outcomes in the iPD game is the most critical takeaway from this study. Future studies using the iPD paradigm should prioritize analyzing neural activity associated with both partner choice (monetary context) and reciprocation (social context) instead of selecting one form of feedback without rationale. Resources should also be directed toward testing neural variability across the SA spectrum using economic-exchange tasks. This would help researchers determine which paradigms most effectively model subtle variations in a heterogeneous SA population. Finally, it may be helpful to provide more direct feedback to participants in such studies. One could, for instance, display images of facial expressions matching the outcome of the round or provide a real-time video feed of their partner. To the best of our knowledge, no published work has used this approach and its application would increase the ecological validity of economic-exchange tasks as models of social interaction that are fMRI-compatible. Our study is the first to use the PD game paradigm to examine the neurocognitive correlates of SA-related social cognitive biases during interpersonal interaction.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by: a National Science Foundation Graduate Research Fellowship [DGE-1550139] to KT, a GSU Brains & Behavior seed grant to EBT & EN, the GSU/GA Tech Center for Advanced Brain Imaging grant to EBT & JT, and a 2CI Fellowship for Neuroimaging from GSU awarded to KT.

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Supplemental Material

Supplemental material for this article is available online.

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