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Analyzing Brain Networks Associated with Social Evaluation and Uncertainty in Subclinical Social Anxiety

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ANALYZING BRAIN NETWORKS ASSOCIATED WITH SOCIAL EVALUATION AND UNCERTAINTY IN SUBCLINICAL SOCIAL ANXIETY

by

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Under the Direction of Erin Tone, Ph.D. and Jessica Turner, Ph.D.

ABSTRACT

In interpersonal interactions, socially anxious individuals continuously monitor for social threats and fear negative evaluation from their peers. We know little about whether these cognitive biases correlate with patterns of brain function in relevant regions that have been associated with evaluation of self and others. Recent evidence implicates neural structures critical to perspective-taking and the processing of uncertainty may function atypically in those who are anxious. In the present study, we examined neural activity in two such regions of the brain—the temporoparietal junction and the anterior midcingulate cortex — during Prisoner's Dilemma game play. There were no significant group differences in activation in both regions during the processing of partner choice and anticipation of outcome during gameplay. However, there were significant differences in the processing of social feedback. These findings provide evidence that Prisoner's Dilemma researchers should begin to consider how social and monetary context affects decision-making in diverse populations.

INDEX WORDS: fMRI, Social Anxiety, Social Evaluation, Uncertainty, Theory of Mind, Prisoner's Dilemma

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DEDICATION

I dedicate this thesis to my family and friends who have provided me with their unwavering support and immeasurable goodwill throughout this process.

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I would like to acknowledge and thank my committee co-chairs Professor Jessica Turner and Professor Erin Tone for bestowing upon me access into the vast and immense space that is their collective knowledge in the realm of not only neuroimaging but research and scholarship. Without their persistent help and steadfast patience my pursuit of this Master's degree would not have been possible. I could only hope that one day my accomplishments will scratch the surface of what these two women have accomplished in their careers and in their personal lives. I am forever grateful for the time they invested in my development and success.

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LIST OF ABBREVIATIONS

American Psychological Association=APA

Analysis of Covariance=ANCOVA

Analysis of Variance=ANOVA

Anterior Cingulate Cortex=ACC

Anterior Insula=AI

Anterior Midcingulate Cortex=aMCC

Arbitrary Units=A.U.

Blood Oxygen Level Dependent=BOLD

Center for Advanced Brain Imaging=CABI

Central Nervous System=CNS

Diagnostic and Statistics Manual of Mental Disorders=DSM

Dorsolateral Prefrontal Cortex=dlPFC

Dorsomedial Prefrontal Cortex=dmPFC

Field of View=FOV

Flip Angle=FA

Full Width Half Maximum=FWHM

Functional Magnetic Resonance Imaging=fMRI

Generalized Anxiety Disorder=GAD

Generalized Autocalibrating Partial Parallel Acquisition=GRAPPA

Georgia State University=GSU

Institutional Review Board=IRD

International Classification of Diseases=ICD

Interstimulus Interval=ISI

Intolerance of Uncertainty=IU

Iterated Prisoner's Dilemma=iPD

Liebowitz Social Anxiety Scale=LSAS

Magnetization-Prepared 180 degrees Radio-Frequency Pulses and Rapid Gradient-Echo=MPRAGE

Major Depressive Disorder=MDD

Mutual Cooperation=CC

Mutual Defection=DD

Mind in the Eyes=MIE

Movie for the Assessment of Social Cognition=MASC

Periaqueductal Grey Matter=PAG

Principal Eigenvariate Value=PEV

Prisoner's Dilemma=PD

Region of Interest=ROI

Singular Value Decomposition=SVD

Social Anxiety=SA

Social Anxiety Disorder=SAD

Statistical Parametric Mapping=SPM

Stria Terminalis=ST

Temporoparietal Junction=TPJ

Theory of Mind=ToM

Time Repitition=TR

Time Echo=TE

Uncertainty and Anticipation Model of Anxiety=UAMA

Unreciprocated Cooperation=CD

Unreciprocated Defection=DC

Ventral Striatum=VS

Ventral Tegmental Area=VTA

Ventromedial Prefrontal Cortex=vmPFC

1 INTRODUCTION

1.1 Social Anxiety

1.1.1 Prevalence and Phenomenology

Social anxiety (SA) is characterized by fear of embarrassment, criticism, humiliation, or rejection, as well as high levels of distress and avoidance in social or performance situations (American Psychiatric Association, 2013). Cognitive research has demonstrated that SA is also associated with sensitivity to social threat and uncertainty in ambiguous social situations (Clark & Wells, 1995; Grupe & Nitschke, 2013; Rapee & Heimberg, 1997). Although in a given year roughly 6.8% of the United States population meets diagnostic criteria for Social Anxiety Disorder (SAD), which is an extreme manifestation, SA more commonly occurs at subclinical levels, affecting up to 18.38% of people at a subclinical level and 23.07% at a symptomatic level (one DSM-IV criterion missing/two or more criteria missing, respectively) (Knappe, Fehm, & Wittchen, 2009).

People who are socially anxious often display negative interpretative biases, or a tendency to interpret neutral or ambiguous social information as unfavorable, leading them to ruminate about the possibility that social interactions will fail (Badra et al., 2016; Miers, Blöte, Bögels, & Westenberg, 2008; Walsh, McNally, Skariah, Butt, & Eysenck, 2015). Moreover, they often inaccurately attribute negative emotions and intentions to others based on their facial expressions or other visible cues (Button, Lewis, Penton-Voak, & Munafò, 2013; Hezel & McNally, 2014). Finally, individuals with SA exhibit a propensity to avoid uncertainty in socio-evaluative situations, presumably because they fear that they will be unable to respond competently in the face of uncertain events (Boelen & Reijntjes, 2009).

However, SA doesn't appear to be best defined as a categorical construct (i.e., one either has it or one does not), even though the Diagnostic and Statistics Manual of Mental Disorders (DSM) (American Psychological Association [APA], 2013) and International Classification of Diseases (ICD) (National Center for Health Statistics, 2015) diagnostic systems have traditionally conceptualized it in a categorical format. According to these diagnostic systems, decisions about whether treatment is warranted are based on the number of symptoms displayed and the degree to which they impair functioning. However, researchers and clinicians have expressed concern that diagnostic cut points may be arbitrarily determined, and thus many scholars have embraced the notion that the symptoms that characterize SA exist on a spectrum and can be analyzed dimensionally (Schneier, Blanco, Antia, & Liebowitz, 2002; Stein, Ono, Tajima, & Muller, 2004).

Recent evidence suggests that SA, even at subclinical levels, has distinct cognitive, behavioral, and emotional correlates. One study examining reactivity to social stress, for example, revealed associations between subclinical SA symptoms and increased state anxiety, biased appraisals associated with the probability and costs of negative social evaluations, changes in facial expression that signaled anxiety, and lower cortisol reactivity (Crișan, Vulturar, Miclea, & Miu, 2016). Another study examined the generation of automatic thoughts, imagery and safety behaviors in individuals with high self-reported social anxiety, people with clinician-diagnosed clinical/subclinical social phobia, and controls (Ranta, Tuomisto, Kaltiala-Heino, Rantanen, & Marttunen, 2014). Participants completed a thought-listing procedure in which they were given a target situation and told to list the kind of thoughts, perspective images, and coping strategies they would use in those situations. Individuals in both anxiety groups showed a significant elevation in reported negative automatic thoughts, observer-perspective images

(negative self-images seen from an observers perspective), and safety behaviors (e.g. stuttering, speaking quietly, avoiding eye gaze). Furthermore the frequency was comparable to that observed in previous studies of SAD samples (Alfano, Beidel, & Turner, 2006; Rheingold, Herbert, et al., 2003; Hignett & Cartwright-Hatton, 2008; Hodson, McManus, et al., 2008).

Considerable evidence thus suggests that subclinical SA is associated with significant changes in emotional experience, cognitive appraisals, and behaviors that parallel those found in samples with 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. Neuroimaging research on subclinical SA could help address this question; it could also provide information about the utility of a dimensional perspective as opposed to a Gaussian distribution framework, for understanding SA.

1.2 Anatomy and Physiology

1.2.1 Clinical Social Anxiety

Two recent literature reviews on clinical SA and its neurobiological correlates identified dysfunction in five key neural regions: the amygdala, the ventromedial prefrontal cortex (vmPFC), the insula, the hippocampus, and the dorsolateral prefrontal cortex (dlPFC) (Freitas-Ferrari et al., 2010; Pietrini et al., 2010). Those findings strongly suggest the presence of functional abnormalities in the neural systems involved in the manifestation of fear (Lang, McTeague, & Bradley, 2014), in the processing of emotional stimuli (Etkin & Wager, 2007), in awareness of self (Stein, 2015), and in the evaluation of others' intentions (Plana, Lavoie, Battaglia, & Achim, 2014). Of the brain regions that have been linked to SA, the amygdala is the most thoroughly studied (Etkin & Wager, 2007; Tovote, Fadok, & Lüthi, 2015); this focus

highlights the field's emphasis to date on aberrant emotional and fear processing as the primary indicators of SA.

Early research focused almost exclusively on the amygdala as a key player in human SAD, due to its well-documented role in fear and visceral emotional responses in other species (Berntson, Sarter, & Cacioppo, 2003; McDonald, 1998; Price, 2003). Birbaumer and colleagues (1998) were among the first to examine amygdala responses to stimuli that are relevant to SAD in a human population. Using functional magnetic resonance imaging (fMRI), they showed that the amygdala selectively activated when people were exposed to potentially fear-relevant face stimuli (Birbaumer et al., 1998). A large number of neuroimaging studies subsequently have found that people with SAD show more elevated amygdala activity in comparison to the neurotypical population when they view threatening faces (Beesdo et al., 2009; Cannistraro & Rauch, 2003; Kent & Rauch, 2003; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009). SAD has also been linked to atypical amygdala activity in response to ambiguous faces (Cooney, Atlas, Joormann, Eugène, & Gotlib, 2006; Evans et al., 2008; Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002), which suggests that affected individuals are sensitive not only to overt threat cues, but also to those that are vague or undefined in nature.

Another region of the brain commonly implicated in socially anxious people's atypical responses to social cues is the prefrontal cortex, which plays key roles in the regulation and modulation of initial emotional responses generated from the amygdala (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Lee, Heller, van Reekum, Nelson, & Davidson, 2012). The vmPFC also appears to play a critical role throughout prefrontal cortex development in mediating and organizing flexible social behaviors that include valuation, inhibition, and rule use (Nelson & Guyer, 2011). In addition, it is activated during self-referential processing and self-

awareness (Kim & Johnson, 2012, 2015) as well as decision-making (Hebscher & Gilboa, 2016; Kuss et al., 2015), all of which are cognitive domains in which individuals with SA consistently report varying degrees of abnormalities.

Findings of aberrant amygdala and vmPFC responses in the context of SA have been reinforced by evidence of reduced functional connectivity between the amygdala and the vmPFC, whether the individual being scanned is at rest or participating in a behavioral task (see Figure 1) (Kim, Gee, Loucks, Davis, & Whalen, 2011; Klumpp, Keutmann, Fitzgerald, Shankman, & Phan, 2014; Prater, Hosanagar, Klumpp, Angstadt, & Phan, 2013). Based on such studies, a widely acknowledged model of fear in SA has emerged, in which dissociation between the amygdala and vmPFC leads to dysfunctional processing of internal or external threats, as well as to exaggerated physiological and emotional responses to those cues (Freitas-Ferrari et al., 2010).

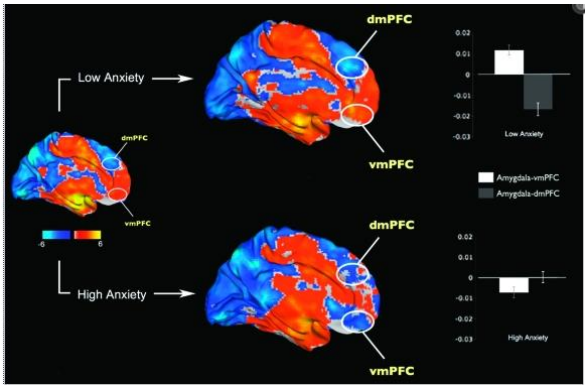

Figure 1 Kim et al. (2011) showing reduced functional connectivity between amygdala and vmPFC at rest in socially anxious individuals and increased connectivity between amygdala and dmPFC in low anxious subjects. Adapted from "Anxiety Dissociates Dorsal and Ventral Medial Prefrontal Cortex Functional Connectivity with the Amygdala at Rest" by M. J. Kim, D. Gee, etc., 2011, Cerebral Cortex, 21(7), p. 1667-73. Copyright 2010 by Oxford University Press.

1.2.2 Subclinical Social Anxiety

Subclinical SA also appears to be associated with atypical patterns of brain function, but these patterns vary across studies and differ in the degree to which they correspond with those observed in clinically diagnosed samples (Abraham et al., 2013; Carré et al., 2014; Duval et al., 2013). Specifically, the patterns of activation reported in subclinical SA samples diverge from the abnormalities in recruitment and connectivity seen in the literature that has focused on emotional expression and regulation in clinical SA.

A diverse array of tasks, including facial emotion processing paradigms, has been used to examine neural correlates of emotional response to social threat in subclinical populations. Although BOLD activity differed between participants with subclinical SA and controls in at least two studies, these differences were found in regions seldom implicated in prototypical models of clinical SA; these regions included the anterior insula, lateral prefrontal cortex, and the anterior cingulate (Carré et al., 2014; Duval et al., 2013). Other research has focused explicitly on brain activity associated with fear of negative evaluation in response to negative self-referential statements in adults with subclinical SA (Abraham et al., 2013). Although this study found evidence of elevated activation in the vmPFC and the amygdala within all participants, no group differences between subclinical SA and healthy controls were apparent. These findings differ notably from those of a similar study that compared activation in the same neural structures between adults with clinical SA and non-anxious controls (K. Blair et al., 2008). Taken together, these two studies raise the possibility that atypical fear circuit functioning, at least in response to negative self-referential statements, may only be detectable in the presence of severe SA symptoms like those that characterize individuals with SAD.

Due in part to the divergent findings seen in clinical and non-clinical samples, there has been a recent surge of interest in looking beyond exaggerated emotional response in the amygdala within clinical and subclinical SA and examining more complex, distributed patterns of atypical neural activity (Gentili et al., 2009, 2016). This shift has led researchers to identify a broader set of brain regions in which atypical activity may underlie the maladaptive cognitive biases apparent in socially anxious people. Of particular interest for this study are regions engaged while people are evaluating social cues and their meanings, as well as regions engaged during periods of anticipation and uncertainty during a social interaction.

Inherent in interpersonal interaction is the need to determine what others might be thinking or feeling (Gentili et al., 2009; Mitchell & Phillips, 2015). This process involves discerning the other person's perspective and attributing meaning to the perspective and is commonly termed Theory of Mind (ToM) (Bradford, Jentzsch, & Gomez, 2015; Mahy, Moses, & Pfeifer, 2014). Given that the cognitive biases associated with SA include a tendency to assume that others will be critical of one's behavior, regions of the brain that implement ToM warrant attention as possible seats of atypical activation in SA.

1.3 Social Evaluation in Anxiety

1.3.1 Theory and Cognitive Model

Clark and Wells (1995) and Rapee and Heimberg (1997) developed two widely-cited and highly-regarded cognitive models of SA that are distinct, but compatible, and that underscore the ways in which socially anxious people evaluate their social environment in dysfunctional ways. According to Clark and Wells' (1995) model, when anxious individuals enter social situations, previous emotionally salient experiences interact with cognitive and behavioral predispositions to negatively bias their perceptions of themselves and the perspectives

of people with whom they are interacting. Further, they tend to fixate on internal cues that could signal an anxious response, such as an accelerated heart rate. As a function of their biased perceptions and excessive internal focus, people with SA tend to assume that they will behave incompetently, that catastrophic consequences will ensue, and that they will thus lose worth and social standing.

Rapee and Heimberg (1997) contended that individuals with SA are inherently critical of themselves. They thus assume that others will hold them to similarly excessive standards and evaluate them negatively. Socially anxious people's negative internal representations of their appearance and behavior conflicts with the perfect image that they imagine that their "audience" should not only see, but also unequivocally expects from them. This leads them to be hypervigilant and attentive to the possibility of negative evaluation from their "audience", particularly from people whose opinions they value the most.

Thus, socially anxious people should be more likely than most to dwell on the thoughts and feelings that others may be having about them. Furthermore, as Hofmann's (2007) comprehensive cognitive model of social anxiety suggests, the implications of this thought process are likely to be uncomfortable and to bias how socially anxious people perceive the results of their interactions with others (see Figure 2). According to this model, in cases of potential social evaluation, vulnerable individuals overestimate not only the probability that a social situation will have a negative outcome, but also the likelihood that that outcome will come with heavy social costs and possible negative consequences that will influence future interactions with their peers. They also tend to underestimate the likelihood of engaging in positive exchanges with their peers that will have no bearing on their overall social standing.

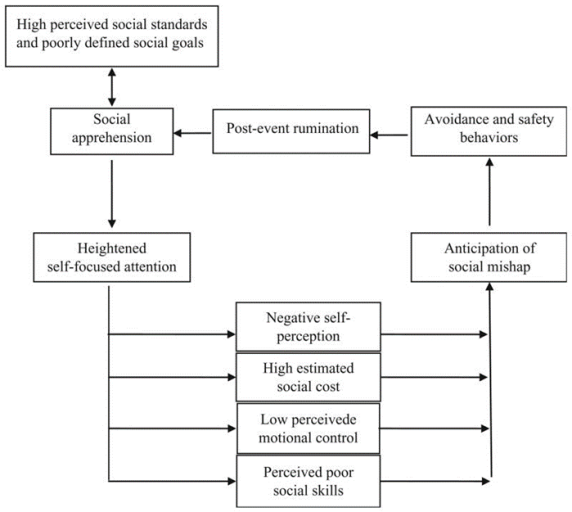

Figure 2 Hofmann's (2007) comprehensive cognitive model of social anxiety. Adapted from "Cognitive Factors that Maintain Social Anxiety Disorder: a Comprehensive Model and its Treatment Implications" By S. Hoffman, 2007, Cognitive Behavioral Therapy, 36(4), p. 193-209. Copyright 2007 by Taylor & Francis.

Together, the tendencies among socially anxious people to focus in a negatively biased manner on what others may think and feel about them and to assume that others' negative perceptions are highly likely to lead to catastrophic outcomes create a heightened risk that these individuals will misread or inaccurately anticipate others' thoughts and emotions in the context of social situations. In other words, they seem likely to show important and potentially problematic biases in a set of processes that have been termed "Theory of Mind" (Baron-Cohen, Leslie, & Frith, 1985; Frith, C. & Frith, 2005).

1.4 Theory of Mind

1.4.1 Definition and Theory

In a pivotal paper, Premack and Woodruff (1978) questioned whether chimpanzees can understand that others may see the world differently than they do. This paper provided an initial definition of theory of mind (ToM), or mentalizing, as the ability to attribute mental states such as beliefs, intents, desires, knowledge, and pretending to oneself and to others. This ability also

requires understanding that others have beliefs, desires, intentions, and objectives that diverge from one's own. Others have since expanded on this construct, noting, for example, that when explaining a person's behavior in terms of a goal, desire, or trait, we recognize that this mental representation does not necessarily correspond to our own interpretations of reality (Meltzoff, 1995).

1.4.2 ToM and Neural Correlates

A number of reviews and meta-analytic studies have attempted to uncover the neural correlates of ToM reasoning (Frith, C.D. & Frith, 2006; Gallagher & Frith, 2003; Mitchell, 2009; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). The diversity of processes implicated suggests that these structures comprise an integrated circuit with components that participate in both distinct and overlapping ways in varied aspects of ToM reasoning. However, it is not entirely clear which regions of the circuitry are recruited specifically for perspective-taking and belief reasoning, both of which could constitute potential mechanisms underlying the cognitive bias towards social threat in SA.

Recent meta-analyses implicate two regions—the temporoparietal junction (TPJ) and mPFC, as "core" nodal regions that underlie ToM reasoning (Mitchell, 2009; Schurz et al., 2014). Several lines of evidence converge to support the idea that the TPJ is a key player in this type of social cognition, which makes this structure a particularly good candidate as a mediator of the biases evident in SA. First, overwhelming evidence implicates the structure as an essential player in mentalizing, which is a general term that encompasses the cognitive processes involved in reasoning about the self and others (Frith, C.D. & Frith, 2006; Frith, U. & Frith, 2003). Findings from a meta-analysis of over 200 studies show that this region participates heavily in the representation of others' transient or temporary mental states from their perspectives (Van

Overwalle, 2009). These mental states include goals, intentions, and beliefs, which are represented even when they differ from or are incongruent with our own beliefs.

Second, the TPJ is responsible for integrating information from the thalamic and limbic systems with visual, auditory, and somatosensory cortical information to support social cognition (Carter & Huettel, 2013). The TPJ thus appears to serve as a hub, pulling together data across distinct cognitive domains (e.g., perception, attention, memory, and semantics) to facilitate social reasoning (see Figure 3). Inefficient or overly effective integration of sensory and contextual information in this region could have wide-ranging effects on overall mentalizing ability.

Third, visual perspective-taking that involves seeing objects or ideas from another person's viewpoint seems to recruit the bilateral TPJ in a variety of contexts (Santiesteban et al., 2012; Schurz et al., 2015; Schurz, Aichhorn, Martin, & Perner, 2013). For example, the TPJ seems to play a critical role in false-belief reasoning, or understanding when and why others may hold inaccurate beliefs about the world (Mitchell, 2009; Schurz et al., 2014). Recognizing that someone has different knowledge about the world than we do is essential if we are to understand and adapt to that person's moment by moment behavior in a social interaction.

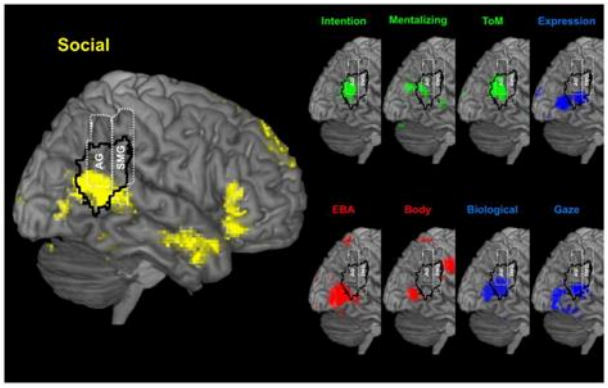

Figure 3 Meta-analytic evidence of social function encoding and processing in the TPJ (Carter & Huettel, 2013). Adapted from "A Nexus Model of the Temporoparietal Junction", by R. Carter & S. Huettel, 2013, Trends in Cognitive Science, 17(7), p. 328-336. Copyright 2013 by Elsevier.

In contrast to the TPJ, the other nodal region for ToM—the mPFC—appears to support inferences from a first-person perspective about persistent or enduring personality dispositions of the self as well as others (Van Overwalle, 2009). The mPFC also seems to play a critical role in anticipating what others will do in the future by supporting consideration of what we would do in the same situation (Frith, C.D. & Frith, 2006). Saxe and Powell (2006) suggested that the mPFC is generally involved in processing socially or emotionally relevant information about self and others, but that it does not participate specifically in belief-desire reasoning (Saxe & Powell, 2006) as the TPJ appears to do. Indeed, this distinction is one reason underlying suggestions that the TPJ is the integral component of a dedicated neural architecture for ToM reasoning that is domain-specific and adapted for perspective-taking and intention prediction (Mahy et al., 2014).

The mPFC does, however, exhibit a high degree of functional connectivity with the TPJ (Li, Mai, & Liu, 2014), which raises the possibility that the two structures operate in concert. Recent evidence indicates that sub-regions of the mPFC and TPJ play integrated functional roles in processing social emotion, as opposed to basic emotion (Burnett & Blakemore, 2009), and in making inferences about another person's emotions versus making inferences about their intentions and behavior (Atique, Erb, Gharabaghi, Grodd, & Anders, 2011). This information provides clarity to the findings of a recent meta-analysis that indicate that, while a number of regions have been implicated in ToM processing, the mPFC and the TPJ are the only candidates that are consistently recruited across all ToM tasks (Schurz et al., 2014).

The TPJ and mPFC play overlapping and reciprocal roles in supporting both self-referential processing and ToM reasoning (Mars et al., 2012). Each, however, appears to make distinct contributions to these socio-cognitive processes and more research is needed to clarify their relationship with each other. Broadly, however, the literature points to the TPJ as the

predominant player in perspective-taking and belief reasoning (Carter & Huettel, 2013; Krall et al., 2015; Van Overwalle, 2009) while the mPFC appears to support more introspective and contemplative processes.

1.4.3 TPJ Involvement in Anticipation and Feedback Appraisal

A small body of evidence implicates the TPJ in considering social context when anticipating negative outcomes. Past research suggests that the TPJ plays roles in the process of supplementing subjective evaluation of a person's decisions by attributing positive or negative intentions to them (Liljeholm, Dunne, & O'Doherty, 2014), in the down-regulation of positive emotional expression in anticipation of diminished monetary reward (Staudinger, Erk, & Walter, 2011), and in the anticipation of the experience of guilt following perceived commission of moral transgressions (Seara-Cardoso et al., 2016).

Evidence of the TPJ's involvement in appraising and processing feedback regarding one's own social decisions is more substantial. The TPJ has been implicated in the appraisal of social outcomes in a diverse array of research contexts, such as economic-exchange tasks (Archetti & Scheuring, 2011; Grecucci, Giorgetta, Bonini, & Sanfey, 2013; McClure-Tone et al., 2011), tasks involving exposure to socially contextualized first and third person statements (Pfeifer et al., 2017; Zaki, Hennigan, Weber, & Ochsner, 2010; Zhang & Mo, 2016), and tasks focused on presentation of conflicting visual and verbal social cues (Zaki, Kallman, Wimmer, Ochsner, & Shohamy, 2016). The tendency for socially anxious individuals to fixate on the social performance feedback they receive from their peers (Cody, Teachmen,et al. 2010; Nepon, Flett, et al. 2011; Smith, Sarason, et al. 1975) is possibly connected to atypical TPJ activity.

1.4.4 ToM and Social Anxiety

Only recently has research begun to consider the ways in which ToM may be relevant to SA. Most work to date on SA and ToM has focused on individuals who meet criteria for SAD. In two studies that compared performance on ToM tasks [Mind in the Eyes task (MIE; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) and Movie for the Assessment of Social Cognition (MASC; Dziobek et al., 2006)] between adults with and without SAD, individuals with SAD made more errors than did non-socially-anxious participants on both ToM tasks (Hezel & McNally, 2014; Washburn, Wilson, et al., 2016). Those with SAD also had difficulty decoding socially-relevant information. The authors interpreted these findings as indicating that individuals with SAD "over-mentalize" or attribute more meaning to social and emotional stimuli than is appropriate, given the contexts in which the stimuli appear.

Yoon and colleagues (Yoon et al., 2016) conducted one of the first fMRI studies to examine the neural correlates of ToM, as well as functional connectivity among relevant structures during task performance, in adults with and without SAD. Patients, compared to controls, exhibited increased memory for faces paired with negative self-referential comments. They also exhibited hyperactivation in the TPJ and a number of other relevant structures during encoding, but not retrieval. TPJ activity during encoding was positively correlated with scores on the Brief Fear of Negative Evaluation Scale (BFNE; Leary, 1983). The researchers speculated that the TPJ hyperactivity observed in the SAD group during encoding may have reflected heightened sensitivity to social evaluation by others, which is consistent with the idea that the TPJ plays a critical role in socio-evaluative processes.

1.5 Uncertainty in Social Anxiety

1.5.1 Cognitive Theory and Qualitative Evidence

People with SA appear to become distressed when they are in situations that do not offer certainty about what is going to happen next or what action they need to take to ensure positive outcomes (Boelen & Reijntjes, 2009; Carleton, Collimore, & Asmundson, 2010). Indeed, evidence from at least four studies (Boelen & Reijntjes, 2009; Carleton, Collimore, & Asmundson, 2010; Counsell et al., 2017; Teale Sapach, Carleton, Mulvogue, Weeks, & Heimberg, 2015) suggests that people with SA often exhibit intolerance of uncertainty (IU), or a tendency "to consider the possibility of a negative event occurring as unacceptable and threatening irrespective of the probability of its occurrence" (Carleton, Norton, & Asmundson, 2007, p. 106).

Elevated IU appears to relate to a number of problematic cognitive and behavioral outcomes. For example, it may impair problem-solving skills, decision-making, and overall executive functioning (Koerner & Dugas, 2007). Further, as socially anxious individuals begin to experience situations that feel threatening, their heightened IU has the potential to precipitate cognitive and behavioral avoidance of ambiguity that might signal additional risk (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). It remains unclear, however, whether and how the brains of socially anxious people respond in distinctive ways to this kind of contextual uncertainty. Anxiety neuroimaging research has primarily focused on emotional reactivity to threat in general, with limited attention to the mediators of cognitive processes required to execute adaptive behaviors in uncertain settings.

The construct of uncertainty can be parsed into at least four distinct categories [sensory uncertainty (am I perceiving stimuli accurately?), state uncertainty (what is going on right now?),

rule uncertainty (what rules should guide my behavior?), and outcome uncertainty (what will happen next?)] (Bach & Dolan, 2012). Outcome uncertainty is particularly relevant to the present study, because a primary fear for socially anxious people is that their own actions will provoke negative responses from others, who are more are less unpredictable. Using economic exchange paradigms, we can capture, quantify, and manipulate others' unpredictability in the experimental context by structuring social interactions according to probabilistic rules about the likelihood that a given action will lead to a rewarding or a punishing outcome. We can thus examine how people respond and what regions of the brain are recruited when they can predict with varying levels of confidence how likely an outcome is under changing interpersonal dynamics that model a real world social dilemma.

1.5.2 Neural Activity under Conditions of Uncertainty

Researchers have only recently begun to examine how conditions of uncertainty are processed in the brain. Although several brain regions have been implicated (Grupe & Nitschke, 2013), the anterior midcingulate cortex (aMCC), appears to function as a hub that is particularly relevant to uncertainty processing in the context of anxiety. According to Grupe and Nitschke's (2013) uncertainty and anticipation model of anxiety (UAMA; see Figure 4), anxious people's difficulties tolerating and responding to uncertain future threats stem from five dysfunctional cognitive and emotional processes: inflated estimates of threat cost and probability, increased threat attention and hypervigilance, deficient safety learning, behavioral and cognitive avoidance, and heightened reactivity to threat uncertainty.

The aMCC shares extensive reciprocal connections with multiple regions, including the amygdala, dlPFC and dmPFC, parietal cortex, and insula, with which it works to sustain these five processes and coordinate them in order to diminish uncertainty and facilitate the generation

of adaptive behavior in relevant situations (Mechias, Etkin, & Kalisch, 2010; Shackman et al., 2011; Vogt, 2016). Breakdowns in this network's structures and connecting pathways are likely to disrupt effective and efficient processing when circumstances are uncertain. A number of distinct functions such as novelty identification, evaluation of reward and error, and the anticipation of emotionally salient information in the environment are suggested to converge in the aMCC and facilitate response to uncertain situations (Vogt, 2016). This evidence provides support for the ideas that the aMCC figures prominently in feedback-mediated decision-making and that disruption of proper functioning affects the seamless flow of social decision-making when an interacting person is faced with ambiguity.

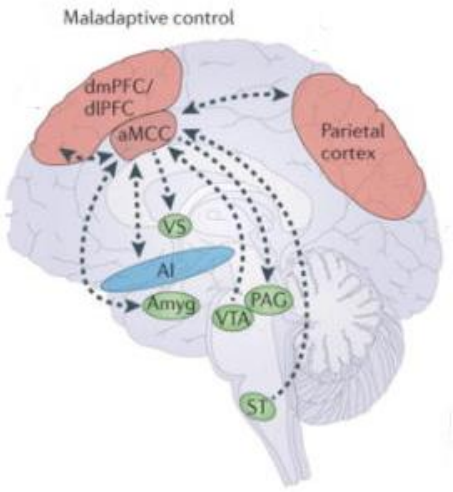

Figure 4 Based on the UAMA (Grupe & Nitschke, 2009), identifying and executing adaptive responses are associated with aMCC dysfunction and directly influence the five processes of the UAMA. Adapted from "Uncertainty and Anticipation in Anxiety: An Integrated Neurobiological and Psychological Perspective" by D. Grupe & J. Nitschke, 2013, Nature Reviews Neuroscience, 14(7), p.488-501, Copyright 2013 by Springer Nature.

1.5.3 aMCC Involvement in the Anticipation of Threat

A multitude of papers have been published suggesting that brain activity in the aMCC is particularly exaggerated during the anticipation of aversive stimuli and circumstances. There is

growing evidence, for instance, that the aMCC is activated during sustained anticipatory processing when participants are informed that they will be exposed to emotionally aversive images as opposed to neutral images (Grupe, Oathes, & Nitschke, 2013; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006). The aMCC's sensitivity to the expectancy of threat has also been observed in response to the anticipation of painful stimuli such as an unpredictable electric shock, in variety of contexts (Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011; Carlsson et al., 2006). Furthermore, evidence also indicates that anxious adults and adolescents who report diminished perceived cognitive control during the anticipation of aversive threats exhibit elevated aMCC activity in comparison to their healthy counterparts (Alvarez et al., 2015). Overall, the evidence to date indicates that the aMCC engages routinely in unpredictable circumstances, which socially anxious people may find particularly distressing (Boelen & Reijntjes, 2009; Carleton et al., 2010; Counsell et al., 2017).

1.6 Prisoner's Dilemma

1.6.1 Justification for the Use of the Prisoner's Dilemma Paradigm to Study Social Behavior

It is difficult to study socio-cognitive processes and their neurobiological correlates in a controlled lab setting because of the ambiguity and unpredictability of unstructured social interactions. To address these challenges, researchers have turned to interactive economic exchange tasks that have the advantage of closely simulating real-life social interactions, while also being capable of isolating and quantifying complex social behaviors (King-Casas & Chiu, 2012; Sanfey, 2007). These tasks consist of simple decision-making scenarios that are structured around game theory, a collection of robust models designed to help us understand and explain

situations in which decision-makers must interact with or bargain with one another (Neumann, 1947).

The Prisoner's Dilemma (PD) task is an economic exchange game that has been widely used to illustrate how people may achieve stable cooperation over the course of multiple interactions, even when they implicitly believe it is in their own best interests not to cooperate consistently (Kreps, Milgrom, Roberts, & Wilson, 1982). During this task, players must make independent decisions about whether to cooperate or not cooperate (defect) with another player in order to win money. The game can be played as a one-round single shot or as an iterated task comprising multiple rounds played between the same two players. The payoff for each round of the iterated version of the game is maximized for a player who defects when the co-player cooperates; the worst outcome occurs when the decisions are reversed. However, if both players mutually cooperate over the course of the game they can reach what has been termed “Nash’s equilibrium,” in which both players continually make the best response for both parties because the alternative is unfavorable (Neyman, 1985; Roth & Murnighan, 1978). This situation benefits both players, and a large number of studies utilizing the PD task have focused on comparisons between equilibrium responses and self-interested responses (situations in which the player attempts to maximize the payoff by defecting for the majority of the task) (Axelrod & Hamilton, 1981; Cooper, DeJong, Forsythe, & Ross, 1996; Kreps et al., 1982; Neyman, 1985; Nowak & Sigmund, 1993).

The iterated Prisoner’s Dilemma (iPD) task provides a structured context that effectively elicits quantifiable patterns of interaction (e.g., displays of pro-social, submissive, hostile or competitive behavior) that vary depending on how anxious a player is (McClure et al., 2007; Rodebaugh, Heimberg, Taylor, & Lenze, 2016). Each round in the iPD unfolds as a series of

phases that mirrors a typical conflict-resolution exchange. First, the participant makes a choice (cooperate or defect), then the participant waits in anticipation of the outcome (when the co-player's response is revealed), and finally, the participant receives feedback regarding the other person's decision.

The iPD game is a particularly useful paradigm for studying SA and its correlates for several reasons. First, the iPD task requires participants to make repeated predictions about others' behavior and to face painful or rewarding consequences based on their accuracy. Thus, for socially anxious people, who commonly lack confidence that they can anticipate or predict another person's behavior in a social setting (Whiting, Davis, & Reuther, 2012), this paradigm presents a realistic and stressful set of social challenges. Second, behavioral studies that use facial-cue processing or self-referential statement paradigms lack ecological validity, in that they may not effectively simulate the stressors encountered during a social interaction. Finally, unlike many other ecologically valid behavioral tasks, such as stress-provoking conversations with confederates or delivery of speeches under scrutiny, the iPD task is compatible with neuroimaging, which requires collection of data during multiple events involving salient behaviors.

1.6.2 Behavioral and Neural Correlates of Social Anxiety during iPD Gameplay

Research has already begun to illustrate how social exchange can activate the brain's reward system, how affective factors play an important role in bargaining and competitive games, and how the ability to assess another's current and past intentions relates to strategic play (Sanfey, 2007; Sripada, Angstadt, Liberzon, McCabe, & Phan, 2013). Recently, a few studies have been published that examine how anxiety in particular may influence patterns of behavior, emotional response, and brain activity during economic exchange tasks such as the iPD.

In one of the first behavioral studies to examine associations between iPD play and anxiety, McClure and colleagues (2007) found youths with anxiety disorders, particularly girls, to be particularly sensitive to defection and distress in the context of iPD game play. These youths nonetheless continue to cooperate, presumably in order to ensure positive affiliation and cohesion (McClure et al., 2007). Rodebaugh and colleagues have administered an iPD variant (the Flexible Iterated Prisoner's Dilemma) to socially anxious and non-anxious adults and have found that those with SAD show a pattern of interpersonal constraint, marked by atypical cooperative behavior, particularly if they are also prone to vindictiveness (Rodebaugh et al., 2013, 2016; Rodebaugh, Klein, Yarkoni, & Langer, 2011).

To date no published research has examined how SA relates to activity in neural regions that support social evaluation under conditions of certainty and uncertainty. In the only fMRI study conducted to characterize clinically anxious adolescents' neural, behavioral, and emotional responses during the iPD game, researchers found that anxious adolescents showed significant elevations in activation in the right TPJ, precuneus, and insula compared to controls in response to co-player defection while controls showed greater mPFC/ACC activation than patients (McClure-Tone et al., 2011). Groups also differed significantly in post-feedback behavior: anxious adolescents were more likely than controls to cooperate following trials when the co-player defected. Additionally, during receipt of feedback about co-player defection, anxious youth who showed stronger TPJ activity also reported more negative evaluations of the co-player.

The present study takes an initial step toward elucidating the neural regions involved in various cognitive biases in SA and suggests that ToM regions, such as the TPJ, could show distinctive patterns of activation linked to display of these biases. The iPD overall could be an

effective paradigm for eliciting neural responses that encompass more than the amygdala activation typically seen in SA studies. This study could also provide additional support for the assertion that economic-exchange tasks are useful models of social dilemmas and effective tools for research aimed at developing functional biomarkers for disorders characterized by impairments in interpersonal functioning.

1.7 Aims of Study

The literature reviewed thus far provides evidence that ToM reasoning and the generation of responses under conditions of uncertainty are each associated with distinct neurobiological structures integral to decision-making and navigating social interactions. These regions appear to function atypically in both clinical and subclinical SA. Both ToM as a whole and uncertainty remain understudied in the context of the iPD paradigm in the population. The iPD is a robust and valid research paradigm that is highly effective in simulating social interaction in comparison to previous paradigms that did not utilize economic-exchange tasks in a socially-relevant context. Therefore, the aims of this study are to investigate brain regions involved in perspective-taking and response to uncertainty and examine BOLD activity in these regions during various periods of the task in subclinical socially anxious adults. A region of interest (ROI) will also be defined in the TPJ to calculate BOLD response associated with perspective-taking and intention attribution. A ROI was defined in the aMCC to calculate BOLD response associated with response to uncertainty in the social context.

Aim 1. The first aim is to compare the BOLD response in a ToM-linked structure between people with high and low self-reported SA during the anticipation and feedback phases of iPD game trials.

Hypothesis 1. High-SA adults will exhibit an elevated BOLD response in the bilateral TPJ in comparison to low-SA adults. Furthermore, this difference will be evident during anticipation of outcomes of iPD game trials, as well as during feedback regarding trial outcomes based on the co-player's decisions. Additionally, the TPJ response will be more strongly elevated in instances of co-player defection, regardless of the participant's choice.

Aim 2. The second aim is to compare BOLD response in an uncertainty-linked structure between socially anxious participants and healthy controls during the anticipation phase of iPD game trials (regardless of whether the player cooperated with or betrayed the other player) compared to baseline.

Hypothesis 2. High-anxious subjects will exhibit an elevated BOLD response in the aMCC in comparison to low-anxious participants, regardless of whether the individual cooperated or betrayed the co-player. Furthermore, this response will be confined to periods of anticipation of the outcome of the trial.

2 METHODS

2.1 Procedure

2.1.1 IRB Approval

This project focused on fMRI and behavioral data collected during two time periods. The first dataset was gathered in 2008; scans were completed on a 3-T magnet at Emory University. 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 Georgia State University, CABI, and Emory University institutional review boards.

2.1.2 Participants

For the 2016/2017 dataset, 20 adults were recruited from the undergraduate psychology department student pool of Georgia State University via the SONA online participant recruitment system. SONA allows for the prescreening of undergraduate participants through the completion of demographic surveys and psychometric measures. Two participants' data were excluded due to excessive motion in the scanner and 1 participant's age exceeded the previously established threshold approved by the IRB, yielding a final sample of 17 subjects. The age range of the participants was 18-35 years.

To determine levels of fear and avoidance in social situations, all participants were administered the Liebowitz Social Anxiety Scale-Self Report Version (LSAS-SR; Baker, Heinrichs, Kim, & Hofmann, 2002). Participants in the sample pool who scored at or above the 75th percentile or higher were identified as high SA. Participants who scored at the 25th percentile or lower were identified as low SA/controls. Additionally, answers to the LSAS-SR were analyzed to determine the kinds of fears reported by both groups. The high SA group tended to report elevated performance-based and interaction-based fears while the low SA group reported minimal fears associated with performance and interaction.

Exclusion criteria, which were screened for during a phone interview, included the presence of any metals permanently embedded or implanted in the body, any preexisting major medical conditions, any major psychiatric disorders, and current use of any psychotropic medication.

For the 2008 dataset, 19 subjects were recruited from the undergraduate psychology department student pool of Georgia State University via the SONA online participant recruitment system. Participants were selected from a larger pool of students who had completed the LSAS-

SR. Individuals who reported high levels of SA or low levels of SA (defined identically as in the 2016/2017 sample) were contacted via telephone by researchers and invited to participate in the MRI study at the Center for MR Research at Emory University. Four participants' data were excluded from analysis due to excessive head motion and 1 participant was removed from the scanner due to general discomfort, leaving data from 14 subjects, aged 18-35 years, available for analysis. Overall, between datasets, 25 females and 6 males were recruited for the study, with a mean age of 20.6 years (SD=3.5 years).

Individuals older than 50 years were excluded from the study due to potential changes in brain metabolism that may be associated with aging (Angelie et al., 2001). Additional exclusion criteria included presence of any metals permanently embedded or implanted in the body, pregnancy or the use of contraceptives 48 hours prior to the MRI scan time, the presence of an identifiable Central Nervous System (CNS) disorder or a history of loss of consciousness due to a traumatic brain injury, and the presence of a visual or hearing disability that would prevent the participant from seeing and hearing the stimuli in the scanner.

2.1.3 Anxiety Measures

Severity of SA symptoms was assessed using the LSAS-SR. This short questionnaire is designed to assess the range of social interaction and performance situations feared by a patient in order to assist in the diagnosis of SAD consistent with the criteria established by the DSM-V. The scale's items each describe one of 24 social situations, 13 of which relate to performance anxiety and 11 of which concern social situations. For each of the 24 social situations, participants first rate on a Likert scale from 0 to 3 how much fear or apprehension they feel: 0) none, 1) mild, 2) moderate, and 3) severe. They then rate how likely they are to avoid each social situation: 0) never, 1) occasionally, 2) often, and 3) usually. Combining the total scores of the

Fear and Avoidance sub-sections of the questionnaire yields an overall score with a maximum of 144 possible points.

Heimberg et al. (1992) found that scores on an interviewer-administered version of the LSAS were significantly correlated with scores on the Social Phobia Scale, an observer measure of social phobic symptoms referred to as the Brief Social Phobia Scale, (Davidson et al., 1991) and the Social Interaction Anxiety Scale (Mattick & Clarke, 1998) . In another study (Heimberg et al., 1999), LSAS scores correlated strongly with scores on other scales, including the Hamilton Rating Scale for Depression, Beck's Depression Inventory and the Hamilton Anxiety Rating Scale. Scores on the LSAS and its subscales were normally distributed and demonstrated excellent internal consistency and convergent validity in this study.

This scale has been validated as a self-report measure (Fresco et al., 2001) and is often supplemented with the Structural Clinical Interview for DSM in a clinical setting (Rytwinski, 2009). Fresco and colleagues (2001) compared the clinician-administered and self-report measure of the LSAS and failed to find any significant differences on any scale or subscale score. Both forms were internally consistent and the subscale intercorrelations for the two forms were fundamentally identical. Correlations of each LSAS-SR index with its complement, the Liebowitz Social Anxiety Scale–Children and Adults were all significant. Finally, the convergent and discriminant validity of the two forms of the LSAS was shown to be robust. The LSAS-SR thus appears to be an accurate and cost-effective way to identify and sub-type subjects with SAD and subclinical SA.

2.2 Task Description

In both datasets, in each 20-trial iterated Prisoner's Dilemma (PD) game (Rilling, Gutman, Zeh, Pagnoni, Berns, & Kilts, 2002), trials proceeded as shown in Figure 5; the

participant chose to cooperate or betray, and then waited for a “co-player”, who independently decided to cooperate or to betray (defect). The participant and co-player were equally rewarded ($2) if both cooperated; if one player betrayed but the other cooperated, the betraying player received a reward ($3) and the cooperating player received nothing ($0). If both chose to betray, both received only a small reward ($1). Each participant played three PD games in a randomized order—in two, they were deceived to believe 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.

Participants had six seconds to make a decision during each trial; thus, there was variability in reaction times for each participant. The decision was followed by a 3, 6, or 9 second jittered interstimulus interval (ISI). After the jitter period, feedback regarding the trial outcome was presented for six seconds.

The 20-trial game was split into 5-trial blocks, with an additional blank trial included in each block. After every five trials, the participant was given as much time as needed to answer each of four emotional assessment questions before beginning the next 5-trial block. After the last 5-trial block of the 20-trial game, the participant answered four emotional assessment questions and then viewed both players’ total earnings for the game. After 12-20 seconds, participants then answered ten additional emotional assessment questions. Each game proceeded in this fashion. Participants were paid an average of the amount that they earned over the three games. If viewed as a series of interpersonal interactions, the Prisoner's Dilemma can provide a measure of willingness to work together or to work for one's own self-interest by counting the number of times a participant cooperates or defects while playing the game (Axelrod, 1980).

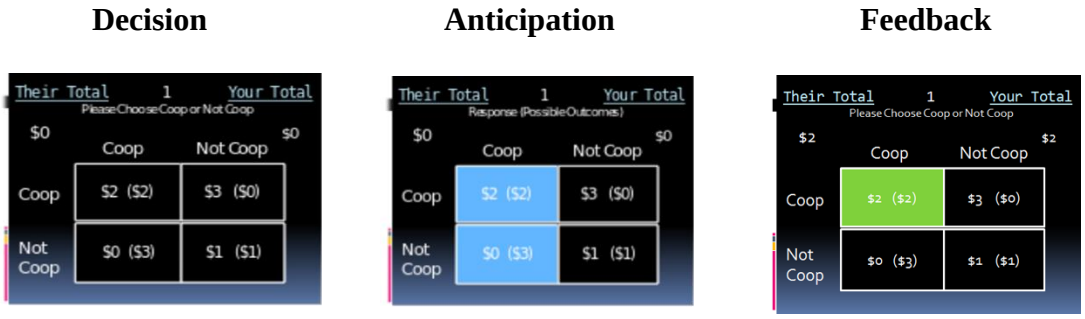

Figure 5 An example of a mutual cooperation trial (CC) of the Prisoner's Dilemma. Each trial can be separated into a decision, anticipation, and feedback phase.

2.3 Experimental Design

Following consent, an examiner informed participants that they would play a game with other study participants via a wireless computer network. The examiner provided no further information about the co-player and deferred responses to all questions about the co-player until the end of the task. Participants then underwent training on the game and completed practice rounds in a mock scanner. During each of the rounds that constitute a game, two players (the participant and a computerized co-player) independently and simultaneously chose to cooperate with or "defect from" (not cooperate with) the other player. The participant indicated his or her choice via trigger press (left="cooperate", right="not cooperate"). After both players submitted their choices, the outcome of the round appeared on the screen, along with a running total of each player's cumulative earnings for a game. Periodically during the game and after the game, participants were asked (via the computer screen) about their perceptions of and predictions about their co-player's intentions and goals, as well as about their own emotional responses during play and their levels of confidence in their predictions.

Subsequently, in accordance with guidelines for ethically appropriate authorized deception, participants were debriefed about the deception involved in the task and the motivation for its use. They were informed at consent that during the study protocol they would

be given misleading or inaccurate information, but they were not told when this would occur. During post-game debriefing, a research assistant read each participant a standardized statement that described how they had been deceived and explained that deception was necessary to ensure that they experienced the game as a "real" interaction with another person. After the researcher explained the deception process and rationale, participants were asked if they had believed the deception and encouraged to express any concerns that they had about being deceived. No participants expressed concerns and all participant data was retained for further analysis.

2.4 Scanning

2.4.1 2008 Data

The 2008 dataset was collected 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.). Participants recorded decisions to cooperate or defect using a hand-held, 4-button response box.

A localizer and a manual shim procedure preceded each functional scan. Functional task-related BOLD signal data was acquired with a ZSAGA functional protocol, a method for reducing the influence of magnetic susceptibility artifacts in echo planar imaging (Heberlein & Hu, 2004) (number of volumes vary depending on time spent on task; TR = 3,000 ms; TE 1 = 30 ms; TE 2=65.8 ms; matrix size = 64 x 64 mm; FA =90°; 3.3 x 3.3x 3.3 mm^3 voxels; 30 interleaved slices; FOV = 210 mm). A high resolution anatomical image was also acquired using a T1-weighted standardized magnetization gradient echo sequence to aid spatial normalization (MPRAGE; sagittal plane; TR =2300 ms; TE=3.02 ms; matrix size of 256x256 mm, 1 mm^3 isomorphic voxels, 176 interleaved slices; FOV = 256 mm; flip angle 8°).

2.4.2 2016/2017 Data

The 2016 dataset was collected at the Center for Advanced Brain Imaging (CABI), which houses a Siemens TIM Trio 3T MRI scanner equipped with a 12-channel head coil for rapid parallel imaging of the brain. The E-Prime 2.0 platform was used to present task stimuli (Psychology Software Tools, Inc.). The procedure used to display tasks stimuli and allow participants to make decisions on the stimuli was consistent with the Emory protocol.

A localizer and a manual shim procedure preceded each functional scan. A 40 minute functional task-related BOLD scan was acquired with a T2*-weighted echo-planar functional protocol (number of volumes vary depending time spent on task; TR = 2,000 ms; TE = 30 ms; matrix size = 64 x 64 mm; FA =77°; 3.4 x 3.4x 4.0 mm^3 voxels; 33 interleaved slices; FOV = 220 mm). A high resolution anatomical image was also acquired using a T1-weighted standardized magnetization spoiled gradient echo sequence to aid spatial normalization (MPRAGE; sagittal plane; TR =2250 ms; TE=4.18 ms; GRAPPA parallel imaging factor of 2; a matrix resolution size of 256x256 mm, 1 mm^3 isomorphic voxels, 176 interleaved slices; FOV = 256 mm; FA=9°).

2.5 Preprocessing

For the 2008 dataset, preprocessing was completed using SPM12. Functional data were corrected for slice timing and motion, realigned and registered to the mean image, spatially normalized to the MNI template of SPM and resliced into isotropic 2mm voxels, and smoothed using an 8mm FWHM Gaussian kernel. For the 2016 dataset, using DPARSF software, functional data were corrected for slice timing and motion, co-registered to the anatomical data, and realigned and registered 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 completed, the

data were spatially normalized to the MNI template of SPM and resliced into isotropic 2mm voxels, and smoothed using an 8mm FWHM Gaussian kernel. After completing these preprocessing steps, the quality of the co-registration procedure was evaluated by visually inspecting the fMRI images for any inconsistencies.

2.6 Analysis

2.6.1 Behavioral Analysis

Three independent chi-square tests were used to compare decision-making behavior between the high anxiety and low anxiety groups. This analysis was conducted to provide descriptive information about participants' tendency to cooperate or defect overall, tendency to cooperate or defect after co-player cooperation, and tendency to cooperate or defect after co-player defection.

2.6.2 Event-Related Regressors based on PD Paradigm

To analyze the fMRI data, general linear modelling was conducted using SPM12 to estimate event-related average BOLD response amplitudes across predefined regions of interest (ROI) at the individual subject level and the group level. Secondary exploratory analyses were conducted after testing the original hypotheses.

Primary event-related regressors were comprised of four regressors for the feedback component of each event type of interest and two regressors for the anticipation component. 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). The 2 anticipation regressors were specified according to whether the participant cooperated or defected.

Additionally, to account for other activity that could confound results, regressors were specified for the decision portion of the task, as well as for periods during which subjects answered emotional assessment questions. Two regressors accounted for whether a decision was made to cooperate or defect, and one regressor accounted for the emotional assessment questions. Furthermore, because we wanted to account for the fact that two out of the three games were played against a "human" and one game was played against a computer, all regressors distinguished between trials played against human or computer, doubling the total number of regressors to 18 for each individual subject. Finally, a framewise displacement regressor was included in the single subject analyses as an additional motion regressor. In the group-level analysis, the site at which data were collected was included as a covariate.

Overall, comparisons examined differences in activity within the TPJ and aMCC between high and low anxiety groups during different feedback conditions (e.g., CD+DD trials versus CC + DC trials).

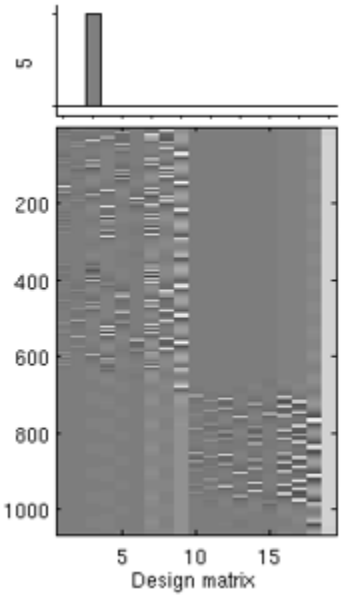

Figure 6 Sample design matrix of 18 condition task (Each column represents a condition of interest associated with the task that was included in the complete statistical model of analysis)

2.6.3 Neuroimaging: Region of Interest Analysis

Regions of interest (ROIs) were defined for the TPJ and the aMCC using PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). The ROI for the TPJ was generated based on the approach that McClure-Tone et al. (2011) used. This ROI consisted of a sphere with a radius of 15 mm, centered at coordinates 48, −54, 27. The ROI for the aMCC was generated based on the method that Grupe et al. (2013) used in a paper examining dissociable networks that process the anticipation of aversion. The peak voxel was centered at coordinates 3, 7, 33 with a radius of 10mm (Grupe, Oathes, & Nitschke, 2013). Because the aMCC is a large region, the radius was expanded to 15mm to more effectively capture activity comprehensively across the region.

Once the masks for the two ROIs were designed, the anticipation contrasts specified in SPM were anticipation after cooperation (C), anticipation after defection (D), and anticipation regardless of decision (C+D). The feedback contrasts specified were mutual cooperation (CC), unreciprocated cooperation (CD), unreciprocated defection (DC), and mutual defection (DD). To examine general responses to co-player cooperation, the CC and DC trials were combined (co-player Cooperation); to examine general responses to co-player defection the CD and DD trials were combined (co-player Defection).

***Hypothesis 1*.** To test the first hypothesis, we conducted one-sample t-tests to contrast BOLD activity during general anticipation (C+D) and the two feedback conditions (CC+DC/CD+DD) against baseline for each individual subject. The TPJ mask was applied individually after specifying each contrast, and the p-value was set at an uncorrected threshold of .05. The average weighted mean of the BOLD signal within the ROI was extracted as the

principal eigenvariate value (PEV). The PEV summarizes group data across voxels, yielding a singular value decomposition (SVD) of the time series. This strategy is optimal for interpreting condition-related response amplitudes without assuming homogenous responses within the ROI (Friston, Rothstein, Geng, Sterzer, & Henson, 2006).

Additionally, to test the hypothesis that activity during feedback regarding defection would be significantly greater than activity during feedback regarding cooperation, t-tests were conducted contrasting BOLD activity during feedback about defection (CD+DD) with activity during feedback regarding cooperation from the co-player (CC+DC). The PEVs across the ROI were then compared in a pair of group analyses modelled using a 2x2 mixed design ANOVA in SPSS. In the first analysis, anxiety group was included as the between groups variable (High/low) and feedback was included as the within-subjects variable (co-player cooperation/defection). In the second analysis, anticipation of co-player response following player choice was included as the within-subjects variable (anticipation following the decision to cooperate versus anticipation following the decision to defect).

The frequency of each trial type varied markedly across participants, with some generating equivalent numbers of each type and others generating no trials of a particular type (e.g., a participant defects for a whole game, and consequently no CC or CD trials occur for that individual). This affected our study's power; thus, to facilitate discussion and to inform future hypothesis generation, given the limited research in this area, we elected to report, but not to interpret, findings that were significant at uncorrected thresholds of $p < .01$ and $p < .05$.

Hypothesis 2. To test the second hypothesis, we followed the procedures specified for Hypothesis 1; the only difference was that we used the aMCC mask instead of the TPJ mask.

3 RESULTS

3.1 Behavioral Analysis

A Pearson chi-square test of independence was performed to examine the tendencies of high and low anxiety subjects to cooperate or defect. Results indicated that the relationship between these variables was statistically significant, $\chi 2$ (3, N=3122) = 23.355, $p < .001$. Although rates of cooperation were similar across groups, high anxiety subjects were more likely to defect than were low anxiety subjects.

We conducted a second Pearson chi-square test of independence to examine the association between high/low anxiety group membership and tendency to cooperate or defect after co-player cooperation. The relationship between these variables was significant, $\chi 2$ (1, N=667) = 10.918, $p < .001$. Low anxiety subjects were more likely to cooperate after co-player cooperation in comparison to high anxiety subjects. High anxiety subjects were more likely to defect after co-player defection in comparison to low anxiety subjects.

A final Pearson chi-square test of independence was performed to examine the tendency of high and low anxiety subjects to cooperate or defect after co-player defection. There was no significant relationship between these variables, $\chi 2$ (1, N=574) = 1.627, $p = .202$.

3.2 Neuroimaging Results

3.2.1 TPJ Activation during Co-Player Feedback

An independent samples t-test was conducted to compare TPJ response during receipt of feedback about co-player cooperation between high and low anxiety subjects. BOLD response in the TPJ did not differ significantly between high (M = 1.33, SD = 1.48) and low anxiety groups (M = 1.31, SD = 0.88) in response to co-player cooperation, $t(29) = -0.04$, $p = .97$. A separate independent samples t-test also showed a non-significant difference between high (M = 1.93, SD

= 1.55) and low anxiety groups (M = 1.68, SD = 1.17) in response to co-player defection, $t(29) = -0.50$, $p = .62$.

We then conducted a 2 x 2 mixed ANCOVA to compare BOLD response within the TPJ during feedback about co-player cooperation and feedback about co-player defection between high and low anxiety groups (see Figure 7). For this and all subsequent mixed ANCOVAs, anxiety group (high, low) was included as a between-subjects factor and site of collection (CABI, Emory) was included as a covariate. A main effects analysis revealed that co-player feedback did not significantly predict BOLD response in the TPJ, $F(1,28) = 2.80$, $p = .11$. The interaction between anxiety group and feedback condition also did not significantly predict BOLD activity in the TPJ, $F(1,28) = 0.34$, $p = .57$.

Table 1 Mixed ANCOVA results for examining differences in response to co-player feedback in the TPJ

Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
Feedback	1	2.01	2.80	.11
Feedback x Site	1	.70	.97	.33
Feedback x Anxiety Level	1	.24	.34	.57
Error	28	.72		

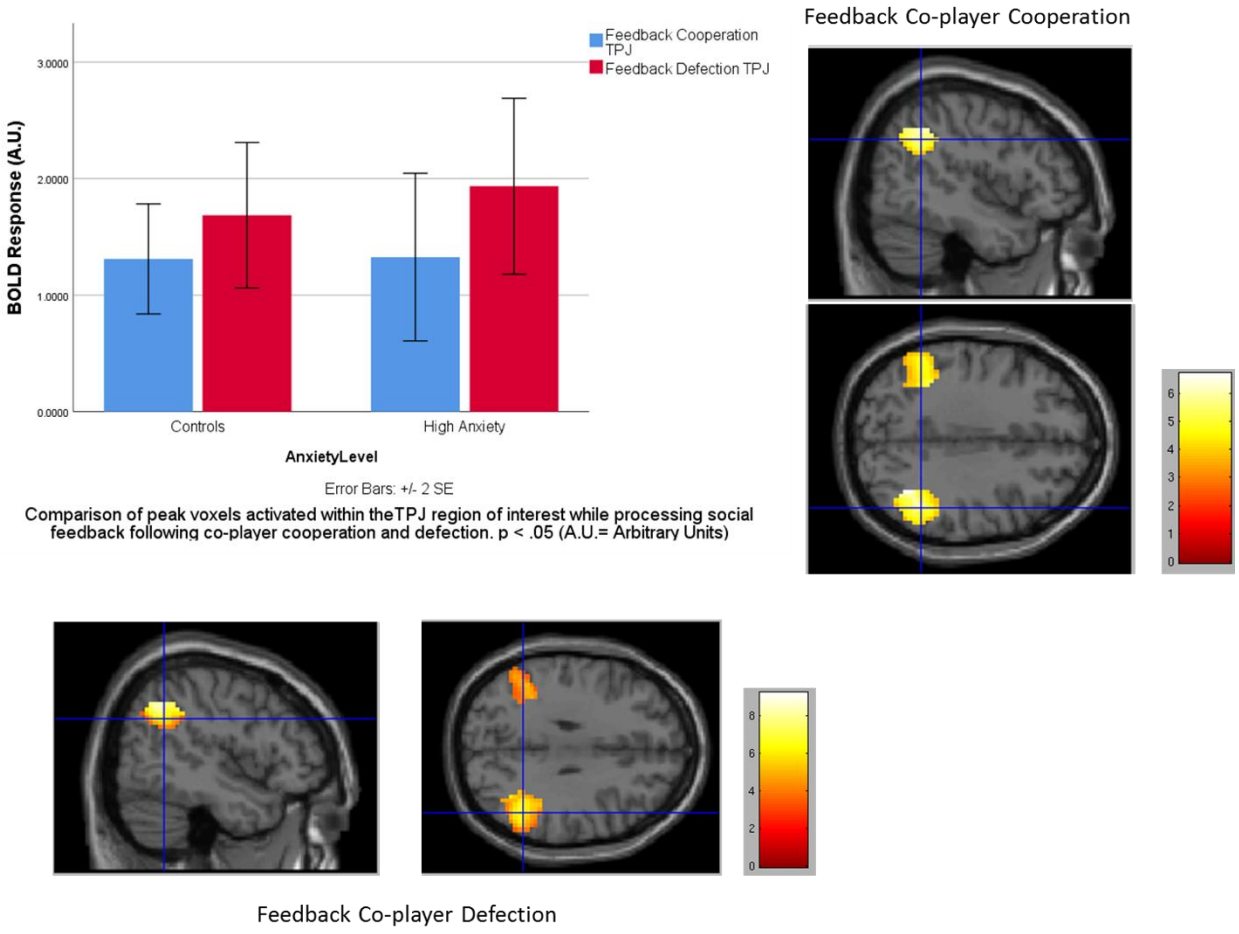

Figure 7 Mean BOLD response in the TPJ during processing of co-player feedback

3.2.2 TPJ Activation during Anticipation of Outcome

An independent samples t-test was conducted to compare the BOLD response within the TPJ during the periods of anticipation following the decision to cooperate and anticipation following the decision to defect between high and low anxiety subjects. High anxiety subjects (M = 0.85, SD = 1.18) and low anxiety subjects (M = 0.64, SD = 0.82) exhibited similar BOLD responses in the TPJ when anticipating outcomes following their own decision to cooperate $t(1,29) = -0.58$, $p = .57$. No significant differences in BOLD activity elicited during anticipation following the decision to defect were evident between high anxiety (M = .94, SD = 1.26) and low anxiety subjects (M = 0.75, SD = 0.78), $t(1,29) = -0.48$, $p = .64$.

A 2 x 2 mixed ANCOVA was conducted to compare BOLD response within the TPJ during anticipation following cooperation and during anticipation following defection between high and low anxiety subjects. A main effects analysis revealed that anticipation of outcome did not significantly predict BOLD response in the TPJ, $F(1,28) = .19$, $p = .67$. The interaction between anxiety group and anticipation condition also did not significantly predict activation in the TPJ, $F(1,28) = 0.002$, $p = .97$.

Table 2 Mixed ANCOVA results for examining differences of anticipatory processing in the TPJ

Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
Anticipation	1	.13	.19	.67
Anticipation x Site	1	.06	.09	.77
Anticipation x Anxiety Level	1	.001	.002	.97
Error	28	.69		

3.2.3 aMCC Activity during Co-Player Feedback

An independent samples t-test comparing aMCC response to co-player cooperation between high and low anxiety subjects did not yield evidence of significant differences between high anxiety subjects (M = 1.33, SD = 1.48) and low anxious individuals (M = 1.31, SD = 0.88), $t(1,29) = -0.24$, $p = .81$. An independent samples t-test comparing aMCC response to co-player defection between high anxiety (M = 1.93, SD = 1.55) and low anxiety subjects (M = 1.68, SD = 1.17) also yielded non-significant results, $t(1,29) = -0.5$, $p = .62$.

A 2 x 2 mixed ANCOVA was conducted to compare BOLD response in the aMCC during feedback about co-player cooperation and feedback about co-player defection in both high and low anxiety subjects. The main effects analysis revealed that co-player feedback did significantly predict BOLD activity within the aMCC, $F(1,28) = 4.93$, $p < .05$. aMCC activity was more elevated during the processing of co-player defection in comparison to co-player cooperation. However, the interaction between anxiety group and feedback condition did not significantly predict BOLD activity in the aMCC, $F(1,28) = 0.15$, $p = .71$.

Table 3 Mixed ANCOVA results for examining differences in response to co-player feedback in the aMCC

Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
Feedback	1	2.64	4.93	.04*
Feedback x Site	1	2.08	3.88	.06
Feedback x Anxiety Level	1	.08	.15	.71
Error	28	.54		

3.2.4 aMCC Activation during Anticipation of Outcome

An independent sample t-test was conducted to compare BOLD activation in the aMCC between high and low anxiety subjects during both anticipation of co-player response following the participant's decision to cooperate and anticipation of co-player response following the participant's decision to defect. BOLD responses did not differ significantly between high anxiety subjects (M = 0.81, SD = 0.66) and low anxiety subjects (M = 0.58, SD = 0.90) when they were anticipating outcomes following their own decisions to cooperate $t(1,29) = -0.81$, $p = .42$. BOLD activity was also similar between high anxiety (M = 0.99, SD = 1.46) and low anxiety subjects (M = 0.90, SD = 1.05) during anticipation following their own decisions to defect, $t(1,29) = -0.20$, $p = .84$.

We conducted 2 x 2 mixed ANCOVAs to compare BOLD responses within the aMCC between high and low anxiety subjects during both anticipation following cooperation and anticipation following defection. The main effects analysis revealed that anticipation of outcome did not predict significant BOLD response in the aMCC, $F(1,28) = 2.06$, $p = .16$. Anxiety group and anticipation condition did not interact to significantly predict activity in the TPJ, $F(1,28) = 0.09$, $p = .77$.

Table 4 Mixed ANCOVA results for examining differences in anticipatory processing in the aMCC

Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
Anticipation	1	1.28	2.06	.16
Anticipation x Site	1	.74	1.19	.28
Anticipation x Anxiety Level	1	.05	.09	.77
Error	28	.62		

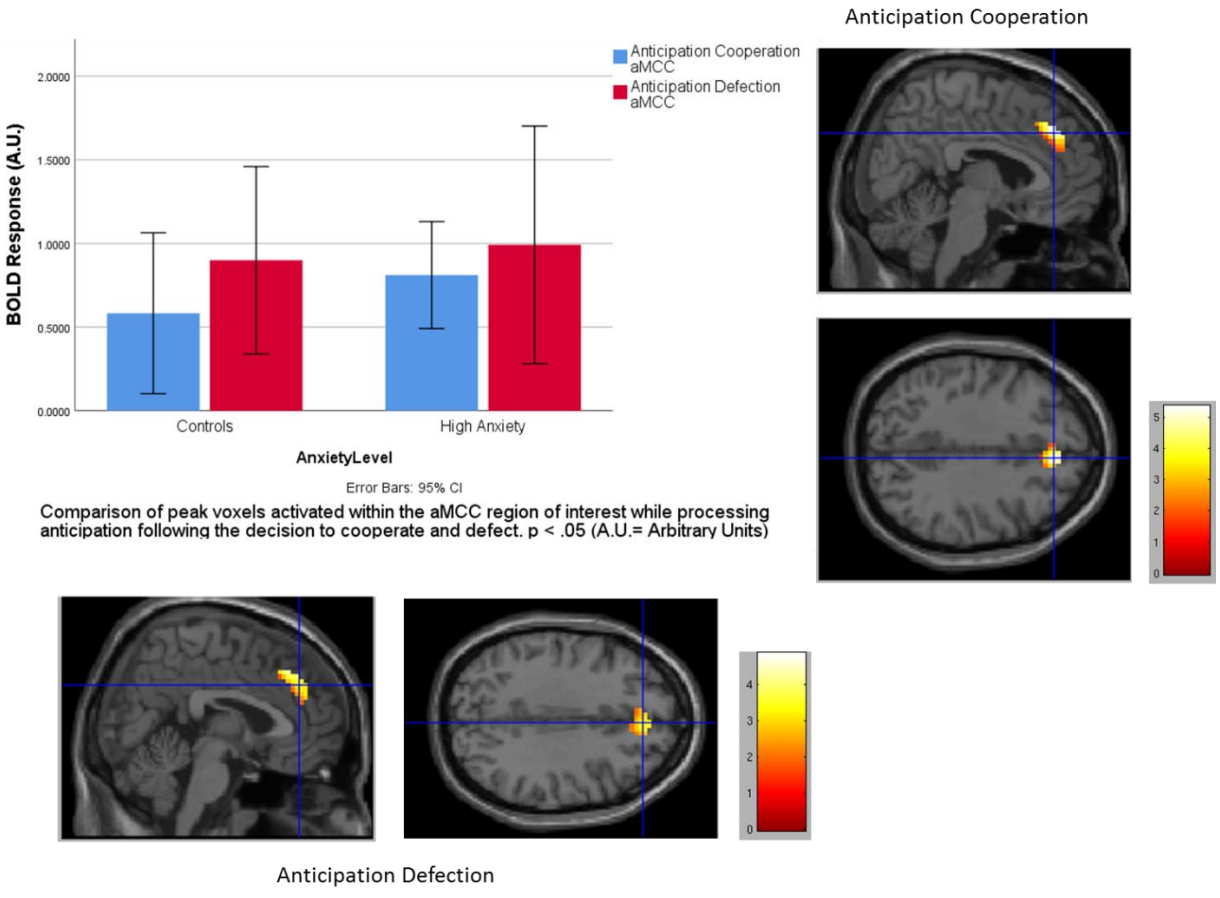

Figure 8 Mean BOLD Response in the aMCC during the anticipation of outcome

3.3 Exploratory Analyses

3.3.1 TPJ Activation during Reciprocated and Unreciprocated Feedback

Due to the lack of consensus within iPD literature concerning how outcome trials should be arranged and analyzed, we decided to run post-hoc tests examining group differences in both ROIs during periods in which participants received reciprocated (CC+DD) and unreciprocated (CD+DC) feedback. An independent samples t-test was conducted to compare TPJ response during receipt of reciprocated feedback between high and low anxiety subjects. BOLD response in the TPJ did not differ significantly between the high (M = 1.43, SD = 1.29) and low (M = 1.60, SD = 1.17) anxiety subjects in response to reciprocated feedback, $t(29) = .37$, $p = .71$. A separate independent samples t-test also showed a non-significant difference between high (M = 2.03, SD = 1.55) and low (M = 1.39, SD = .95) anxiety groups in response to unreciprocated feedback, $t(29) = -1.35$, $p = .19$.

We conducted a 2 x 2 mixed ANCOVA to compare BOLD response within the TPJ during reciprocated feedback and unreciprocated feedback between high and low anxiety subjects (see Figure 9). A main effects analysis showed that feedback did not significantly predict BOLD response in the TPJ, $F(1,28) = 0.66$, $p = .42$. However, the interaction between anxiety group and feedback condition did significantly predict BOLD activity in the TPJ, $F(1,28) = 4.35$, $p < .05$. While both groups exhibited a similar BOLD response during the processing of reciprocated feedback, high anxiety subjects exhibited significantly greater BOLD response during the processing of unreciprocated feedback in comparison to low anxiety subjects.

Table 5 Mixed ANCOVA results for examining differences in response to reciprocated & unreciprocated feedback in the TPJ

Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
Feedback	1	.36	.66	.42
Feedback x Site	1	.79	1.45	.24
Feedback x Anxiety Level	1	2.38	4.35	.05*
Error	28	.55		

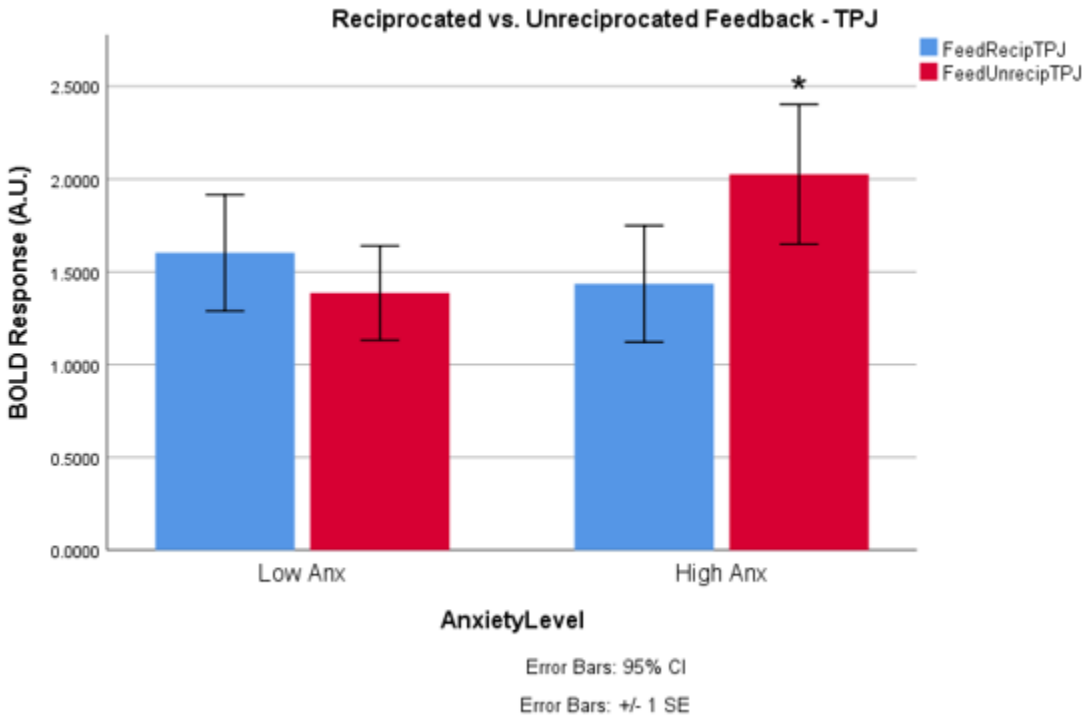

Figure 9 Mean BOLD response in TPJ during processing of reciprocated and unreciprocated feedback

3.3.2 aMCC Activation during Reciprocated and Unreciprocated Feedback

An independent samples t-test was conducted to compare aMCC response during reciprocated feedback between high and low anxiety subjects. BOLD response in the aMCC did not differ significantly between high (M = 1.11, SD = 1.12) and low anxiety individuals (M = 1.34, SD = 0.95) during processing of reciprocated feedback, $t(29) = .60$, $p = .56$. A separate independent samples t-test also showed a non-significant difference between high (M = 1.84, SD = 1.43) and low anxiety groups (M = 1.16, SD = 1.00) during processing of unreciprocated feedback, $t(29) = -1.52$, $p = .14$.

A 2 x 2 mixed ANCOVA was conducted to compare BOLD response within the aMCC during feedback about co-player cooperation and feedback about co-player defection between high and low anxiety subjects (see Figure 10). A main effects analysis showed that feedback did not significantly predict BOLD response in the aMCC, $F(1,28) = 2.80$, $p = .11$. However, the interaction between anxiety group and feedback condition did significantly predict BOLD activity in the aMCC, $F(1,28) = 0.34$, $p = .57$. While BOLD response to reciprocated feedback was similar between groups, aMCC was significantly elevated in high anxiety comparison to low anxiety subjects when processing unreciprocated feedback.

Table 6 Mixed ANCOVA results for examining differences in response to reciprocated & unreciprocated feedback in the aMCC

Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
Feedback	1	.006	.01	.91
Feedback x Site	1	.09	.20	.66
Feedback*Anxiety Level	1	3.15	7.28	.01**
Error	28	.43		

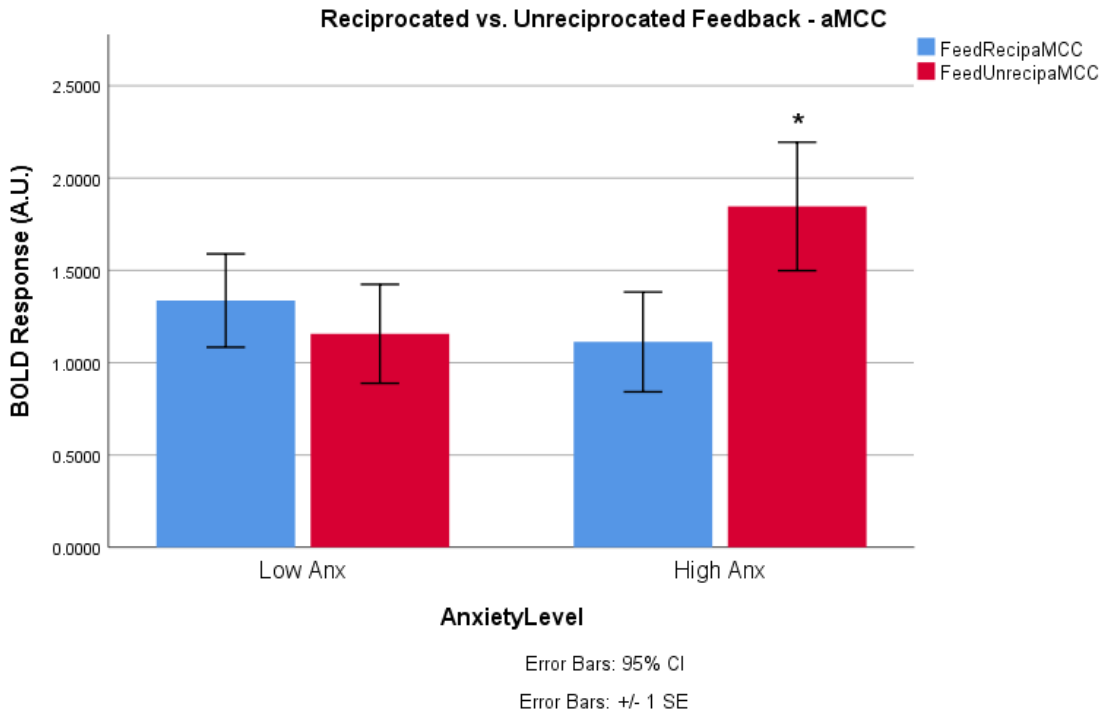

Figure 10 Mean BOLD response in the aMCC during the processing of reciprocated and unreciprocated feedback

3.3.3 Effect of Site on aMCC activity during Co-player Feedback

The mixed ANCOVA examining group differences in the aMCC during co-player cooperation and defection revealed an interaction that was on the verge of significance between feedback and site of collection, $F(1,29) = 3.88$, $p = .06$ (see Table 3). To tease apart the nature of this relationship, we conducted a post-hoc mixed ANOVA including site as the between-subjects factor predicting response to co-player feedback. There was a significant difference in BOLD response between sites at CABI, $F(1,29) = 71.86$, $p < .001$ and at Emory, $F(1,29) = 9.42$, $p < .01$. BOLD response was significantly more elevated at the CABI site compared to the Emory site. Additionally, there was almost a significant within-subjects effect of site at the CABI site, $F(1,29) = 3.95$, $p = .06$. There was no significant within-subjects effect of site at Emory, $F(1,29) = .65$, $p = .43$.

Table 7 Mixed ANOVA results for examining site differences in response to co-player feedback in the aMCC

Test of Between-Subject Effects

Site	Source	Degrees of Freedom	Mean Square	*F*	Sig
CABI	Intercept	1	129.27	71.86	.000**
	Error	16	1.80		
Emory	Intercept	1	10.16	9.42	.009**
	Error	13	1.08		

Test of Within-Subject Effects

Site	Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
CABI	Feedback	1	2.48	3.95	.06
	Error	16	.63		
Emory	Feedback	1	.25	.65	.43
	Error	13	.39		

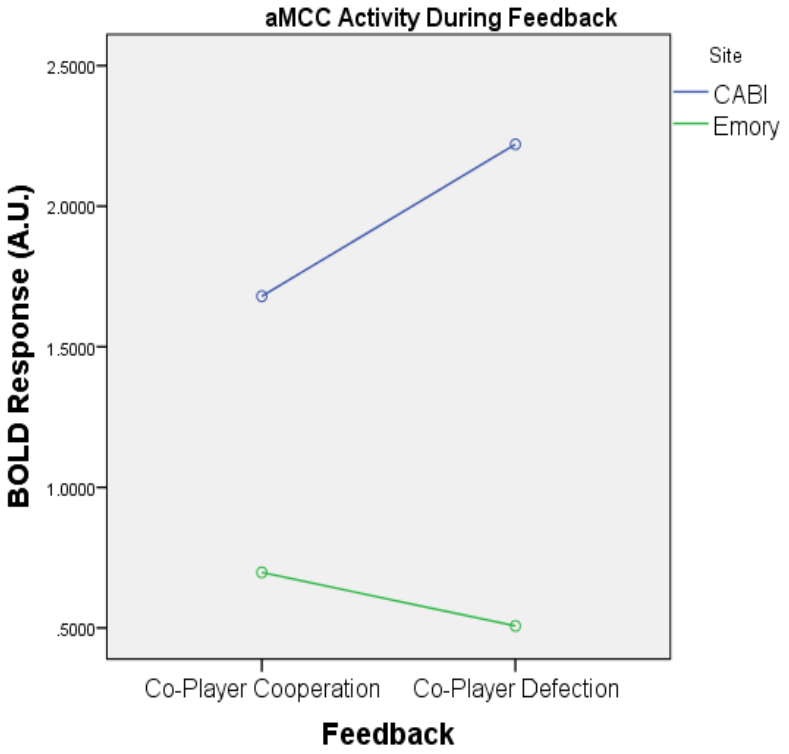

Figure 11 Site-by-site comparison of mean BOLD response in aMCC while processing co-player feedback

3.3.4 Effect of Site on TPJ activity during Co-player Feedback

We also conducted a post-hoc mixed ANOVA including site as the between-subjects factor predicting response to co-player feedback in the TPJ. There was a significant difference in BOLD response between sites at CABI, $F(1,29) = 55.52$, $p < .001$ and at Emory, $F(1,29) = 20.40$, $p < .001$. BOLD response was significantly more elevated at the CABI site compared to the Emory site. Additionally, there was a significant within-subjects effect of site at the CABI site, $F(1,29) = 5.02$, $p < .05$. There was no significant within-subjects effect of site at Emory, $F(1,29) = .93$, $p = .35$. BOLD response was significantly greater while processing co-player defection in comparison to co-player cooperation at the CABI site, but not the Emory site of collection.

Table 8 Mixed ANOVA results for examining site differences in response to co-player feedback in the TPJ

Test of Between-Subjects Effects

Site	Source	Degrees of Freedom	Mean Square	*F*	Sig
CABI	Intercept	1	152.43	55.52	.000**
	Error	16	2.75		
Emory	Intercept	1	23.03	20.40	.001**
	Error	13	1.13		

Test of Within-Subjects Effects

Site	Variables of Interest	Degrees of Freedom	Mean Square	*F*	Sig
CABI	Feedback	1	4.07	5.02	.04*
	Error	16	.81		
Emory	Feedback	1	.53	.93	.35
	Error	13	.57		

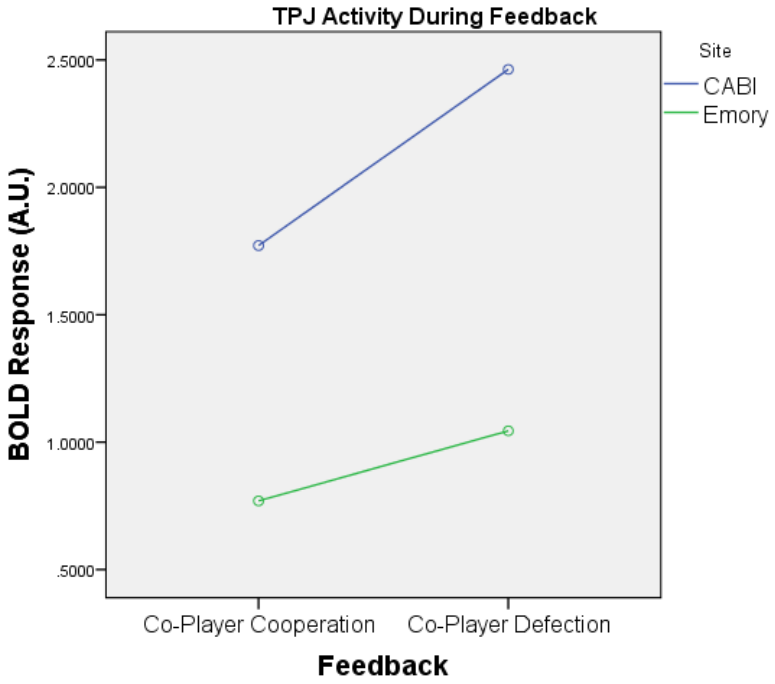

Figure 12 Site-by-site comparison of BOLD response in TPJ while processing co-player feedback

4 CONCLUSIONS

4.1 Discussion

The objective of this thesis was to identify neural regions that mediate the maladaptive cognitive biases that individuals with SA exhibit during interpersonal interactions. Our findings,

in a sample of college students who self-reported high or low levels of SA, contradicted our hypotheses regarding group differences in neural response during processing of feedback about co-player behavior. Results were also inconsistent with our predictions about brain activity during periods of anticipation and uncertainty regarding outcomes of decisions made during task play.

We had predicted that there would be group differences in BOLD activity in the TPJ during anticipation of outcome and feedback appraisal while group differences in the aMCC would only be exhibited during anticipation of outcome. However, BOLD activity in the TPJ and aMCC did not differ between high and low SA individuals during appraisal of co-player cooperation or during appraisal of co-player defection. Furthermore, no significant group differences in BOLD activity in either ROI were apparent during anticipation of outcomes of any type. These findings provide evidence that key neural regions that mediate the processing of social interaction do not exhibit functional differences between subclinical SA and healthy populations.

One potential reason for our failure to detect significant group differences in activation within the ROIs is that we restricted our focus to participants whose SA symptoms were of mild to moderate severity and who had not been formally diagnosed with an anxiety disorder. Interpreted through this lens, the results suggest that abnormal brain activity attributed to clinical samples did not appear in our subclinical sample, which introduces a number of possibilities. One is that with the assessment instruments available to us now, anxious symptoms must pass a specific threshold of severity for brain activity to be noticeably atypical. Evidence from a small body of fMRI research suggests that there may be noticeable differences in brain activity between subclinically and clinically anxious individuals during tasks that involve processing

emotional facial expressions (Carré et al., 2014; Duval et al., 2013) and self-referential/anxiety-relevant information (Abraham et al., 2013). It may thus be that participants in our study did not exceed a critical threshold of anxiety, at which distinctive patterns of brain activity would be evident.

Alternatively, the various types of social feedback generated in the iPD paradigm may be ineffective at evoking the noticeable and robust emotional and neural responses required to differentiate between healthy and subclinical levels of neuropsychiatric symptoms. However, many findings in the PD fMRI literature to date suggest that this possibility is unlikely. iPD fMRI studies that have used subclinical samples recruited from university campuses have repeatedly yielded evidence of significant neural differences between young adults with subclinical symptoms of various types and symptom-free peers (Chen et al., 2016; Gervais, Kline, Ludmer, George, & Manson, 2013; Gradin et al., 2016; Rilling et al., 2007; Schneider-Hassloff et al., 2016). Nevertheless, it is important to note that only one of these studies recruited a subclinical anxious sample (Chen et al., 2016). Additionally, previous fMRI subclinical SA research only implicated regions involved in affective processing and emotional regulation (K. S. Blair et al., 2011; Carré et al., 2014; Duval et al., 2013). Future research must be conducted to further elucidate how subclinical SA groups differ from healthy populations using economic-exchange tasks.

Additionally, there is some evidence that performance-based social fears reflect milder manifestations of SA than do interaction-based fears (Crome & Baillie, 2014). It is possible that individuals who exhibit mild, subclinical symptoms are less likely than more anxious peers to be distressed by one-on-one social interactions like those in the iPD task. However, participants in our study who endorsed high levels of SA reported, on average, both significant interaction fears

and performance fears. These observations generate questions about the degree to which these self-reported fears correlate with neural dysfunction within the subclinical population. Understanding the nature of the underlying fears associated with different degrees of severity in SA would facilitate understanding of the neural structure of the various dimensions of the disorder.

Another important factor to consider is that the type of social feedback being processed can be critical to determining the resulting neural response. The subclinical group exhibited a significant elevation in BOLD signal in comparison to controls when contrasting unreciprocated and reciprocated feedback, results which contradicted the null findings produced when analyzing feedback to partner choice. A strong consensus does not exist within the PD fMRI literature about whether researchers should organize contrasts to focus on comparing social feedback trials based on reciprocated/unreciprocated response (Gradin et al., 2016; Rilling et al., 2002) or partner choice (McClure-Tone et al., 2011; Rilling et al., 2007; Suzuki, Niki, Fujisaki, & Akiyama, 2011). Furthermore, researchers typically do not provide justification for how they group their feedback contrasts for statistical analysis. We contend that responses to co-player cooperation and defection are a function of monetary feedback (cooperation→max reward, defection→diminished), while responses to reciprocated and unreciprocated feedback are a function of social feedback (reciprocated→congruent, unreciprocated→incongruent). Congruent in this case signifies outcomes that are fair and meet social expectations. Incongruent signifies outcomes that are unfair, fail to meet social expectations, and introduce conflict into the interaction. Future work should address whether there are distinct differences in the processing of situational contexts in various forms of anticipation and feedback in SA (e.g. monetary vs. social) and determine whether this affects how they approach developing strategies of iPD task

play. Neuroimaging paradigms utilizing this "monetary vs. social context" framework have already been applied to both neurotypical (Rademacher et al., 2010; Spreckelmeyer et al., 2009) and neuropsychiatric (Delmonte et al., 2012; Gonzalez-Gadea et al., 2016) populations, providing a solid foundation for these questions to be addressed.

An aspect of our study to consider is that the failure to detect significant group differences in BOLD activity during feedback following defection versus cooperation in either the TPJ or the aMCC is partially inconsistent with findings from an earlier study with a similar methodological framework that was used to model our own experiment (McClure-Tone et al., 2011). This earlier study compared neural activity during iPD game play between adolescents diagnosed with a range of anxiety and mood disorders (e.g. GAD, SAD, and MDD) and diagnosis-free controls. In their study, which focused exclusively on brain activity during the processing of feedback during co-player defection versus cooperation, McClure-Tone and colleagues found evidence of elevated BOLD activity in the TPJ, precuneus, and insula (relative to baseline) in patients, relative to controls.

These inconsistent findings could at least partially stem from a number of methodological differences between the two studies. First, McClure-Tone et al. (2011) presented data from a smaller sample (N = 29; n = 12 anxious and n = 17 controls) than that recruited for the present study. Moreover, McClure-Tone et al.'s sample included adolescents with a variety of anxiety and mood disorders (only 3 met criteria for SAD). Finally, the earlier study presented results at a liberal uncorrected statistical threshold of $p < .05$, which increases the possibility that chance findings were inaccurately identified as significant.

Finally, the issue of multicenter collection also warrants attention when interpreting the results of our study. The data collected at Emory were acquired using a ZSAGA MR sequence

that was designed to account for the negative influence magnetic susceptibility artifacts have on the ability to detect signal in certain regions of the brain (Heberlein & Hu, 2004). However, a post hoc analysis revealed that when site was included as a between-subjects variable, across all events of interest, the eigenvalues were persistently diminished in the Emory data in comparison to the eigenvalues extracted from CABI subjects. Despite these lingering concerns about the influence of site on the quality of data collected, it is important to note that site was included as a covariate in our mixed ANCOVA statistical designs with the results revealing that site did not significantly account for variance within the current analyses, although one interaction was close to approaching significance (see Table 3).

4.2 Limitations

There are a few limitations of this study. 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 time of collection. Diverging scanner protocols were utilized to collect the data; we thus needed to correct some of the data for these differences during preprocessing to ensure that parameters were consistent. In an effort to minimize the effects of any remaining differences, we also included site as a regressor in all analyses and, in preliminary analyses, we compared the two datasets directly and found evidence of similar patterns of activation between them. However, as stated earlier in the discussion, it is apparent that data collected at Emory still affected our overall analysis.

Other limitations have to do with participant biases affecting gameplay strategy. For example, a number of participants used strategies that favored defection over cooperation, which limited the number of CD trials that could be sampled from those subjects. These contrast images

were still included in the subsequent group analysis and possibly reduced the overall power of the analysis by introducing noise associated with the lack of variability in those trials. Another limitation is that the complexities of real-life social interactions cannot fully be captured currently with the paradigms currently available to social neuroscientists. Differences in how participants anticipate and appraise social feedback could reflect processes that are insensitive to the parameters established by the task.

4.3 Future Directions

Despite these limitations, the present study makes a contribution to the literature by generating new knowledge about the neural underpinnings of subclinical SA. Advances in social neuroscience are anticipated with the hope that further progress will be made in the isolation of the neural correlates of abnormal social and behavioral experience in psychiatric disorders.

The importance of categorization of social feedback is the most critical takeaway from the results of the current 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 context without justification. This analysis should be supplemented with a debriefing questionnaire that rates whether the participants were more concerned with monetary reward or the maintenance of the relationship while playing the task. This step would be critical in reinforcing the iPD paradigm as a model of social dilemma and supplement current literature that employs “monetary vs. social context” paradigms (Delmonte et al., 2012; Gonzalez-Gadea et al., 2016; Rademacher et al., 2010; Spreckelmeyer et al., 2009).

Resources should also be directed towards testing direct differences between subclinical and clinical populations utilizing diverse economic-exchange tasks. This would help researchers understand which paradigms are the most effective in eliciting the emotional and neural

responses required to model subtle differences in decision-making, anticipatory processing and feedback appraisal in diverse populations. Finally, an avenue to take with future iPD research is to provide more direct feedback to the participants as they make repeated exchanges. One could either display images of various facial expressions matching the outcome of the trial or provide a real-time video feed of their co-player. To the best of our knowledge, there is currently no precedent for this suggestion and its application would increase the ecological validity of the economic-exchange tasks as models of social interaction that are compatible with fMRI and possibly more effective at teasing out abnormalities within subclinical populations. Overall, clinicians and social neuroscientists will greatly benefit from the information revealed in this current study surrounding a barely touched topic.

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