Malleability of Neural Activity in Response to Treatment: fMRI Biomarkers Across Intervention for Autistic Adolescents

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MALLEABILITY OF NEURAL ACTIVITY IN RESPONSE TO TREATMENT: FMRI BIOMARKERS ACROSS INTERVENTION FOR AUTISTIC ADOLESCENTS

by

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ABSTRACT
MALLEABILITY OF NEURAL ACTIVITY IN RESPONSE
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Autistic adolescents frequently experience clinical levels of anxiety which exacerbate social difficulties. Those that receive a well-validated social skills intervention, the Program for the Education and Enrichment of Relational Skills (PEERS®), have shown improvements in both social behavior and anxiety. Prior literature has demonstrated neural changes in response to this intervention using EEG, and recent literature highlights the importance of using neural markers to assess for intervention response in autism. No study to date, however, has examined changes in neural activity *via* fMRI and links with social behavior and anxiety across the PEERS® intervention for autistic adolescents. Thus, the present study employed a randomized clinical trial to examine these effects.

As expected, results from the primary ANOVA analyses showed no effects of intervention on amygdala activity when anxiety was not considered. Unexpectedly, no effect was observed when anxiety was held constant. When anxiety was examined as a predictor of change in amygdala activity, however, results showed that parent reported fear of negative evaluation predicted change in amygdala activity across the intervention.

These findings point to the importance of considering anxiety in the examination of amygdala activity in autism, including as a biomarker of intervention response.

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Introduction

Social behavioral interventions for autistic[1] adolescents have been shown to improve social competence (Gates et al., 2017), and preliminary evidence points to secondary declines in anxiety symptoms (Corbett et al., 2017; Lei et al., 2017; McVey, Dolan, et al., 2016; Schohl et al., 2014) following this type of intervention. Employing neural biomarkers of intervention response in autism has recently been identified as a top priority (Stavropoulos, 2017). A large body of literature has examined neural activity in brain regions linked with the processing of affective social information—the amygdalae—in autism, with mixed findings. Two competing hypotheses have been put forth, each with conflicting and mixed empirical evidence. An underlying mechanism that may better explain the confluence is the presence or absence of anxiety in autism.

Here, the influence of anxiety, with a particular focus on social anxiety, on relationships among people autism will be discussed, followed by an examination of the literature pertaining to interventions shown to ameliorate both social behavioral difficulties and anxiety in autism. Next, the importance of neurobiological markers of intervention response in autism are highlighted, and identified markers are reviewed, with a specific focus on the amygdalae. These constructs will be considered in light of the present study which examined 1) changes in amygdalae activity across the Program for the Education and Enrichment of Relational Skills (PEERS®) intervention for youth with

[1] In this manuscript, identity-first (i.e., "autistic person") and person-first language (i.e., "person with autism") are both used. This is done intentionally to reflect individual preferences within the autistic community. Refer to https://www.thinkinclusive.us/why-person-first-language-doesnt-always-put-the-person-first/, https://autisticadvocacy.org/about-asan/identity-first-language/, and/or (Kenny et al., 2015) for more information.

autism and 2) whether anxiety before intervention was a meaningful predictor of change in amygdalae activity across intervention.

Effects of Anxiety on Social Competence in Autism

Interpersonal relationships are integral to adjustment and success in adolescence and adulthood, however, anxiety—in particular social anxiety—is linked with unsuccessful social behavior and barriers to the development of meaningful relationships for youth with autism (White et al., 2014). Roughly 40% of autistic youth meet diagnostic criteria for an anxiety disorder (van Steensel et al., 2011; van Steensel & Heeman, 2017), and prevalence rates of anxiety among autistic people have been positively linked with age (Magiati et al., 2016; van Steensel & Heeman, 2017) and IQ (Sukhodolsky et al., 2008; van Steensel & Heeman, 2017). Better understanding the intertwining processes of anxiety and social behavior in autism are of utmost importance. Although evidence points to the influence of any anxiety disorder on additive difficulties among autistic youth (Kerns et al., 2015), perhaps unsurprisingly, social anxiety especially has been shown to impede effective social engagement for this population. Specifically, social anxiety has been linked with greater social difficulties and lower social motivation in autism (Spain et al., 2018).

Two prominent models have been put forth to describe the interplay between social anxiety and social difficulties in autism. First, a developmental pathways model was proposed by Bellini (2006), wherein a physiological predisposition of hyperarousal was posited to contribute to social withdrawal, followed by difficulties with social skills, leading to unsuccessful social interactions. These factors in combination, then, were theorized to contribute to the development of social anxiety. In a second model, Wood

and Gadow proposed that the presence of stressors inherent to autism including "social confusion" and "peer rejection" were thought to lead to social anxiety (Wood & Gadow, 2010, p. 287). Social anxiety then promoted behavioral challenges (more autism symptoms) and social avoidance. Taken together, these models suggest, perhaps not a linear process, but rather, a looped cycle wherein social difficulties contribute to social anxiety, which leads to unsuccessful social interactions, followed by avoidance, which loops back to promote greater social difficulties, as social skills go unlearned and the social environment avoided. A handful of studies have begun to test these processes, and the literature shows support for links between social anxiety and social communication difficulties (Duvekot et al., 2017), social reciprocity limitations (Sukhodolsky et al., 2008), social skills challenges (Bellini, 2004, 2006), lesser social assertion and responsibility (Chang et al., 2012), and greater stereotypies (Magiati et al., 2016; Rodgers et al., 2012; Sukhodolsky et al., 2008) in autism. Furthermore, an evaluation of the factor structure of two commonly-used screening tools for autism and social anxiety showed that the disorders may be "similar but distinct" (White et al., 2012, p. 881), highlighting the potential for unique challenges when there is a confluence of both disorders. Therefore, the presence of social anxiety seems to result in multiplicative effects that compound against the successful development of social relationships for autistic youth.

Social Behavioral Interventions for Autism and Effects on Anxiety

A variety of social behavioral interventions have been developed to address social difficulties among autistic youth. The vast majority of these are delivered in group-based settings (Gates et al., 2017). Considering this type of intervention broadly, group-based social behavioral interventions have been found to be efficacious when conducted in

highly controlled environments, such as laboratory settings (Corbett et al., 2016; Laugeson et al., 2012; Maddox et al., 2017; Schohl et al., 2014; White et al., 2013; Yoo et al., 2014), and pilot studies demonstrate preliminary effectiveness in community settings (Choque Olsson et al., 2017; Hill et al., 2017).

As social challenges are ameliorated, there is growing evidence to suggest that effects on social competence may coincide with improvements in other domains—namely, symptoms of anxiety—albeit incidentally. In fact, a growing number of studies demonstrates that receiving a social behavioral intervention may have a positive secondary impact on anxiety symptoms. Young autistic children ages four to eight who received Pivotal Response Treatment (PRT; Koegel & Koegel, 2012), an intervention based on Applied Behavioral Analysis (ABA) principles with the goal of improving social interactions, demonstrated secondary declines in parent-reported internalizing symptoms, including anxiety, following intervention (Lei et al., 2017). Autistic youth ages 8 to 14 who underwent a peer-mediated, theater-based intervention designed to improve social competence, Social Emotional NeuroScience Endocrinology (SENSE) Theater (Corbett et al., 2016), showed reduced self-reported trait anxiety following intervention, while a waitlist control group demonstrated no change (Corbett et al., 2017). Similar outcomes across several studies have been uncovered among autistic adolescents and young adults receiving a manualized social skills intervention, PEERS® (Laugeson, 2017; Laugeson & Frankel, 2010). Researchers have found declines in general anxiety symptoms (Hill et al., 2017; Lordo et al., 2017) and social anxiety symptoms (McVey, Dolan, et al., 2016; Schohl et al., 2014) for autistic youth receiving PEERS®. Lastly, an enhanced cognitive behavioral therapy intervention for social skills and anxiety, the

Multimodal Anxiety and Social Skills Intervention (MASSI; White et al., 2013) has been found to affect both social behavior (Maddox et al., 2017; White et al., 2013) and anxiety (White, Schry, et al., 2015).

It is crucial to consider why social behavioral interventions, specifically those without explicit anxiety-reduction and/or coping techniques, may result in these observed secondary declines in anxiety symptoms. Given the models of social anxiety in autism described above, receiving a social behavioral treatment may indirectly improve anxiety symptoms because, as social skills are gained and applied, social situations elicit less anxiety (Corbett et al., 2017). This may be related to a level of predictability provided by the interventions that helps to reduce anxiety symptoms (Lei et al., 2017). Another interpretation is that these interventions function secondarily on anxiety symptoms through exposure-like processes (McVey, Dolan, et al., 2016). This may be especially true for social anxiety, wherein, as social skills are learned and applied, exposure to a previously avoided social environment and new learning occurs.

Existing evaluations of the effect of social behavioral intervention has relied heavily on self- and parent-report measures (Gates et al., 2017), which limit the field's understanding of underlying processes of change. This has led to the identification of the need for other methods to provide richer information.

Neural Biomarkers of Intervention Response in Autism

Recently, using neural biomarkers as measures of response to intervention in autism has been highlighted as an imperative (Stavropoulos, 2017). Broadly speaking, biomarkers are thought to allow for more precise measurement of particular constructs in autism, such as social motivation (Lerner et al., 2012), which may be difficult to

otherwise assess. They may also help to "parse the heterogeneity," that is, to tease apart subgroups or syndromes currently clustered together under the umbrella of 'autism spectrum disorder' (McPartland & Pelphrey, 2012, p. 1258). Furthermore, biomarkers of intervention response may be used to inform the selection (McPartland & Pelphrey, 2012) and/or tailoring (Stavropoulos, 2017) of interventions, allowing for greater specificity and accuracy in addressing particular domains of need on an individual level (i.e., treatment customization; Lerner et al., 2012). Although physiological biomarkers are also being evaluated, the use of neural biomarkers is highly recommended due to the neurological basis of autism (Beauchaine & Hinshaw, 2017; Stavropoulos, 2017).

Two apparatuses have been widely used to identify neural biomarkers in much of autism research, and all known social behavioral intervention research, to date: electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI). The use of EEG is often indicated when gathering rich temporal data, specifically understanding when in time the brain responds to a stimulus, while fMRI allows for more detailed spatial information, that is, a depiction of the areas of the brain responding to a given stimulus.

A recent systematic review of neural biomarkers of intervention response among autistic children and adolescents identified just four studies, two of which utilized EEG and two used MRI (Stavropoulos, 2017). Of the EEG studies, the first utilized a passive viewing task (faces and objects) among young children with autism participating in an RCT of Early Start Denver Model (ESDM), a behavioral intervention (Dawson et al., 2010). Findings demonstrated more cortical activation among the children who received ESDM when viewing faces vs. objects. The second EEG study examined resting state

neural activity among adolescents participating in an RCT of PEERS® (Van Hecke et al., 2013). Here, results demonstrated that the adolescents with autism who received PEERS® had increased left-hemispheric asymmetry after intervention while the waitlist control group showed no change over time. The first MRI study was a report of two five-year old autistic children receiving PRT (Voos et al., 2013). Results, using a biological motion paradigm, demonstrated greater activation of brain regions associated with social cues after intervention (e.g., fusiform gyrus, superior temporal sulcus) in both children. The second MRI study, by the same group, examined 10 autistic children and 5 neurotypical children (Ventola et al., 2015). The children with autism were split into two groups, hyperactive and hypoactive, based on neural activity in the superior temporal sulcus and comparison to the neurotypical group prior to PRT (also using a biological motion paradigm). The hyperactive group was found to have more anxiety symptoms *via* behavioral questionnaire measures. Following PRT, the hypoactive group showed increased activity in parts of the reward network of the brain, while the hyperactive group showed lesser activity in several brain regions, including the amygdalae.

While these studies provide only preliminary results, they point to changes in neural activity in response to a social behavioral intervention. Although many brain regions were examined in these studies, several were specific to social processing, which has important implications for the present study. The proposed study employs fMRI in an attempt to test spatially-defined neural biomarkers, thus, existing work of this kind is the focus of the discussion to follow.

The Social Brain in Autism

Areas of the brain involved in the processing of social information (i.e., the "social brain" Brothers, 1990) include the superior temporal sulcus, orbital frontal cortex, fusiform gyrus, and amygdala. These areas are thought to work in consort for global social information processing, as well as independently to hone in on specific aspects of the social world (McPartland & Pelphrey, 2012). Activity in the superior temporal sulcus is associated with processing biological motion (Puce & Perrett, 2003), while the orbital frontal cortex is involved in reward processing (Rolls, 2000). The fusiform gyrus is linked with facial recognition processing (e.g., McCarthy, Puce, Gore, & Allison, 1997), and the amygdala has been found to be associated with the processing of affective faces (e.g., Morris et al., 1996).

Adolescence represents an important and often difficult developmental period for those with autism, both in terms of the increase in complexity of the social world (Carter et al., 2014; Nelson et al., 2016), as well as the neural vulnerability conferred during this time (Picci & Scherf, 2015). Social and biological maturation parallel one another throughout adolescence (Lamblin et al., 2017). Based on neurotypical literature, changes in neural structure and function align with the increased focus on and importance of social relationships (Foulkes & Blakemore, 2018). The amygdala becomes fully developed during preadolescence (around 9 to 11 years of age; Payne et al., 2010; Uematsu et al., 2012), while the prefrontal cortex—associated with executive functions such as planning, organizing, and decision making—demonstrates growth in childhood, a decrease in adolescence, and full maturation into adulthood (Teffer & Semendeferi, 2012). Because these two structures work together, adolescents, without fully-developed

prefrontal cortices, may be more likely to act on their emotion (Albert & Steinberg, 2011). This tendency, combined with the increased importance of peers during this time, may be especially prominent in social situations (Albert & Steinberg, 2011). Furthermore, social exclusion in youth seems to evoke a greater response from affective brain regions, rather than from areas of executive function as adult brains do (Lamblin et al., 2017). Social exclusion is closely tied with anxiety, depression, suicidal ideation, and cognitive decline (Bearman & Moody, 2004; Cacioppo et al., 2014; Rosenquist et al., 2011). The development of brain regions such as the amygdala may differ in autistic (e.g., Schumann et al., 2004) compared to neurotypical development. Nonetheless, given the high rates of social exclusion and victimization among youth with autism (van Roekel et al., 2010), examining these neural processes in this population and their relation to comorbidities is of great importance.

Social behavioral interventions for youth with autism teach social skills with the goal of improving social competence leading to greater social connection and, ultimately, the development of rich and fulfilling social relationships. Social behavioral interventions for adolescents naturally differ from those designed for young children. Namely, they generally rely less on the use of in-session behavioral principles and more on didactic delivery of content, paired with opportunities to practice the skills in and out of session (Lerner et al., 2012). As youth proceed through these interventions, secondary effects on anxiety symptoms may be related to improvements in social skills and exposure to previously avoided social stimuli (Corbett et al., 2017; McVey, Dolan, et al., 2016). Considering these processes together, that is, the design of social behavioral interventions for youth and secondary effects on anxiety, these factors are most closely aligned with

the processing of social and affective cues (e.g., knowing when a social approach may be wanted or unwanted). In light of this, the region of the social brain most in line with these processes is the amygdala. Unsurprisingly, the amygdala has long been studied in autism research and anxiety research, with some literature examining the confluence of the two.

Amygdala Activity in Autism

The amygdala has been stated to have a "checkered history" in autism research (Adolphs, 2013, p. 1)—evidence does not demonstrate a clear relation between amygdala activity and autism. Originally, the *Amygdala Theory of Autism* put forth by Baron-Cohen and colleagues (2000) posited that the amygdala was hypoactive in autism, that is, it performed weaker among autistic people than neurotypical people when evaluating social affective information. A body of work was later found to complexify this theory, demonstrating that it was not entirely accurate (Zalla & Sperduti, 2013). Two camps later developed: the *hypoactive* and the *hyperactive*. The first posited that the amygdala in autism may not tag social information as important or rewarding, thus, the brain region is underactive to facial stimuli (Schultz, 2005). This has been further linked with the *Social Motivation Theory* of autism, wherein a decreased drive to attend to social information (i.e., hypoactivation of the amygdala) results in a cascading effect on social and neural development (Chevallier et al., 2012; Dawson et al., 2005). The second theory put forth that people with autism are, conversely, highly sensitive to social content, which is thought to elicit hyperactivation of the amygdala, which then results in the avoidance of social (i.e., facial) stimuli (Dalton et al., 2005), specifically decreased looking at the eyes (Hutt & Ounsted, 1966). This has since been further developed into the *Intense World Theory* in which studies have utilized rat models to argue the neurobiological basis of

hypersensitivity to social cues in autism (Markram, Rinaldi, & Markram, 2007; Markram & Markram, 2010).

Empirically, there are now many studies examining amygdala activity among people with autism, demonstrating mixed results—studies show support for each of these two theories (Aoki et al., 2015). To better understand the broader scope of these findings, a recent meta-analysis of 13 whole-brain fMRI studies identified hypoactivation in the amygdala for people with autism compared with neurotypicals in paradigms of affective face *versus* non-face stimuli (Aoki et al., 2015). This finding, however, was only apparent in sub-analyses, indicating that the result was not sufficiently robust to evidence significance in the primary analysis. Thus, it seems that empirical findings do not provide clear, unwavering support for either the *Social Motivation* or *Intense World* theory alone.

Another recently developed theory posits that the presence of co-occurring anxiety may account for the differences previously identified in studies of the amygdala in autism, rather than assuming people with autism broadly fall into one of the two camps described above (Herrington et al., 2016). Certainly, literature on amygdala activity in anxiety is pertinent in this context.

Amygdala Activity in Anxiety

Early work on amygdala activity in anxiety described the role of conditioned fear (summarized by Davis, 1992), which is not unlike current Research Domain Criteria (RDoC; NIMH, 2016), which includes areas of the amygdala in the Negative Valence System of Acute Threat ("Fear;" https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/acute-threat-fear.shtml). More recent literature has robustly linked amygdala activity with social anxiety and, to a lesser degree, generalized anxiety. A

recent meta-analysis, reviewing 36 fMRI studies of social anxiety disorder, consistently identified hyperactivation of the amygdala in people with social anxiety disorder compared to those without the disorder (Brühl et al., 2014). Furthermore, a review of stress and anxiety disorders found that the vast majority of studies of social anxiety disorder showed increased amygdala activation when compared to a non-anxious group (Duval et al., 2015); here two studies on generalized anxiety disorder were uncovered with one study showing hyperactivation and the other no difference. Another systematic review focusing on generalized anxiety disorder also found mixed results, such that studies utilized various methods and models, making comparison of finding difficult (Mochcovitch et al., 2014). Nonetheless, the authors identified emotion dysregulation and corresponding cognitive functioning (i.e., hypoactivity in the prefrontal cortex and anterior cingulate cortex and poor cortex-amygdala functional connectivity) was identified as one possible cognitive model (Mochcovitch et al., 2014). The differences observed in social *versus* generalized anxiety disorders have been speculated to be attributed to the social nature of the former and the more diffuse, ruminative nature of the latter (Duval et al., 2015). Considering the role of the amygdala as part of the social brain, it is logical that this brain region would be more explicitly linked to social rather than generalized anxiety and empirical evidence seems to support this notion.

The amygdala as a neural biomarker of intervention response in anxiety has also been studied. A recent meta-analysis identified that connectivity between the amygdala and the anterior cingulate cortex may be a promising marker of treatment response in anxiety (Lueken et al., 2016). Additionally, Cognitive Behavioral Therapy (CBT) may increase the ability of the prefrontal cortex to exert “control” over areas of the brain

associated with anxiety, including the amygdala (Brooks & Stein, 2015), which is commensurate with the identified decrease in amygdala activity following CBT for social anxiety disorder (Porto et al., 2009). Admittedly, lesser attention has been paid to biomarkers of intervention response in the treatment of anxiety among youth. One known study, however, suggested a similar response in children and adolescents, with youth demonstrating overactivation of the amygdala before intervention and heightened activity predicting greater improvements using psychopharmacological treatment or CBT (McClure et al., 2007).

Amygdala activity, considering the overlap of anxiety and autism, has been explored in a few instances. Each of these disorders may result in unique cognitive processes, the confluence of which seem to have important considerations for intervention.

Amygdala Activity in Autism with Anxiety

The link between amygdala activity and anxiety in autism was first posed by Amaral and Corbett (2003), wherein they stated:

> ...an important role for the amygdala is in the detection of threats and mobilizing an appropriate behavioral response, part of which is fear. If the amygdala is pathological in subjects with autism, it may contribute to their abnormal fears and increased anxiety rather than their abnormal social behavior. (p. 2)

Since that time, some empirical support has been found for this hypothesis. Amygdala hyperactivity has been linked with anxiety symptoms in preschool-aged children with autism (Ventola et al., 2015), separation anxiety in youth with autism (Herrington et al., 2016), social anxiety in adults with autism (Corden et al., 2008; Kleinhans et al., 2010), and any anxiety disorder diagnosis in youth with autism (Herrington et al., 2017).

Since neither the *Social Motivation Theory* (hypoactive) nor the *Intense World Hypothesis* (hyperactive) has been found to hold up in isolation, perhaps a combination of the two is merited (e.g., Ventola et al., 2015). It might be that some people with autism experience decreased social motivation and hypoactivation of the amygdala, while others are hypersensitive to the social world and experience hyperactivation of the amygdala. Given the links between amygdala hyperactivation and anxiety, autistic people who fall into this group may be at particular risk for clinically-significant levels of anxiety. If this is the case, providing youth with social skills during the highly sensitive and important developmental period of adolescence may result in unique neural changes depending upon underlying etiology (i.e., amygdala hyper- or hypoactivation) that may parallel a more optimal level of social functioning. On one hand, if youth with limited social drive receive skills to navigate the social world, they may demonstrate an improvement in effective social behaviors and, in congruence, experience heightened amygdala activity. On the other hand, if youth who are highly sensitive to social cues and who experience anxiety in these situations are given tools and opportunities for skillful exposure, they might respond with improved social behavior and a decline in anxious arousal and amygdala activation. This notion, what the authors are coining the *Goldilocks Theory of Amygdala Activity in Autism*, posits that there is a range of ideal amygdala activity levels that may pertain to skillful navigation of the social world. This proposition has far-reaching impacts, including the promotion of more successful adaptive functioning in adolescence and adulthood, which may meaningfully contribute to improvements in the quality of life for young people with autism.

Summary and Aims of the Current Study

Social behavior and anxiety appear to demonstrate important links among autistic youth, and both have been shown to respond to social behavioral intervention. One key area of the brain, the amygdala, has been implicated in both social behavior (i.e., decreased social drive) and anxiety (i.e., hypersensitivity) in autism. No empirical study to date, however, has evaluated changes in activation in this region across a well-validated social behavioral intervention for youth with autism. The goal of the study was to begin to address this important gap in the research. Stavropoulos (2017), in light of her review, set forth four recommended strategies for research studies that employ a neural marker of intervention response in autism: 1) select brain regions based on empirical knowledge of the condition being studied, 2) design a paradigm to elicit activity in these brain regions, 3) carefully choose measures of the intervention targets—both broad and specific, and 4) link the neural activity and behavioral measures in a meaningful way to assess changes in accordance with the intervention. The author also identified that the lack of data at pre- and posttest from neurotypical control groups in existing studies limits the possibility of relating results to neurotypical neural functioning (Stavropoulos, 2017). The present study attempted to adhere closely to these guidelines in the following ways.

First, an area of the brain robustly linked with affective social processing, the amygdala, was chosen as the focus of this study for reasons described above. Second, an affective face-processing task was designed to evoke activity in this brain region, based on existing literature (e.g., Herrington et al., 2016). Third, measures of intervention targets included both questionnaires of social behavior previously employed in the evaluation of the intervention, as well as several measures of both anxiety (broadly) and

social anxiety (specifically). Fourth, analyses functioned to first identify relations between amygdala activity and 1) social behavior, 2) anxiety broadly, and 3) social anxiety specifically before assessing changes across the intervention.

The present study was designed to address two primary aims. The first aim was to examine changes in amygdala activity across the intervention. We conducted an ANOVA to examine possible change in amygdala activity between the experimental, waitlist, and neurotypical groups across time, as well as an ANCOVA controlling for anxiety, to see whether differences in the groups could be observed when anxiety was held constant. It was hypothesized that no change in amygdala activity would be observed in these groups across time, without accounting for anxiety. When anxiety was held constant, we hypothesized that the experimental group would show an increase in amygdala activity across the intervention, indicative of an increase in attention to social stimuli. Although it would be ideal to utilize measures of social motivation here to best understand possible links with lower amygdala activity, those measures were not available for this sample.

The second aim was to test anxiety before the intervention as a predictor of amygdala activity after intervention. We expected that greater levels of anxiety, especially social anxiety, before the intervention would predict greater declines in amygdala activity after the intervention, indicating improvements in (i.e., lesser) neural arousal in response to social stimuli, aligning with more effective social behavior and reduced social anxiety.

Method

Participants

Adolescent males between the ages of 11 and 16 with an IQ of ≥ 70 comprised the sample for this study. These demographics were chosen given the challenges of social development in adolescence for this population (Carter et al., 2014; Nelson et al., 2016), links between anxiety, age, and IQ in autism (Magiati et al., 2016; Sukhodolsky et al., 2008; van Steensel & Heeman, 2017) as well as prior efficacy studies of PEERS® (Laugeson et al., 2009, 2012; Schohl et al., 2014). Only males were invited to participate due to concerns of adequate power to statistically assess for possible neural differences between males and females (Björnsdotter et al., 2016; Lai et al., 2013, 2015). Power analyses for the Aim 1 ANOVA were conducted using G*Power 3.1.9.2 (Faul et al., 2009). To detect a within-between interaction among the three groups at the $1\text{-}\beta = 0.90$ level with a large effect ($\eta^2_p = 0.14$), results indicated that 24 adolescents would be needed; for a medium effect ($\eta^2_p = 0.06$), 54 adolescents would be needed. Therefore, the intended sample size of 60 was adequate for statistical power. In order to obtain the desired sample size of 60, more than 80 male adolescents were recruited, as previous literature suggests that samples of 20–30% more for autism and 10–20% more for typically development must be recruited to account for unusable MRI data among youth (Yerys et al., 2009).

Procedure

Adolescents with autism were recruited using methods described previously (Schohl et al., 2014), that is, via established relationships with local assessment and

intervention agencies, autism support groups, an in-house waiting list, and word-of-mouth. Neurotypical adolescents were recruited from Marquette University and the broader Milwaukee community using flyers, emails, and word-of-mouth strategies. Institutional Review Board (IRB) approval was attained prior to recruitment. Informed caregiver consent and youth assent was obtained with all individual participants in the study. Caregivers of adolescents who indicated interest received a telephone screening interview conducted by a graduate student research assistant to discuss the details of the research (and intervention for the autism sample) and to review inclusion criteria. Core inclusion criteria for all adolescents were: 1) aged 11 to 16 years at the time of the first research appointment, 2) English fluency, 3) parent, guardian, or other adult family member[2] was English speaking and willing to participate, 4) absence of major mental illness such as bipolar disorder, schizophrenia, or psychosis, 5) absence of hearing, visual, or physical impairments that would impede participation, 6) full-scale and/or verbal IQ $\geq$ 70. Additional inclusion criteria for participation in the MRI required: 1) absence of metal in the body, 2) absence of tics or other involuntary movements, 3) absence of claustrophobia, and 4) successful completion of a mock MRI scan. Neurotypical adolescents must also have had an absence of any psychiatric disorder (including autism). Additional criteria for the adolescents with autism were: 1) a previous and current diagnosis of autism and 2) a stated interest and motivation for participation in the intervention. Roughly half of the autistic adolescents were recruited based on the presence of anxiety symptoms (screened using the Anxiety Problems subscale of the Child Behavior Checklist, described in more detail below).

[2] Family members who participated in the intervention with the adolescents were parents, legal guardians, or grandparents. For simplicity, however, the term “caregiver” is used hereafter.

After the telephone screening interview, and upon meeting initial criteria, adolescents with autism were randomly assigned to either the experimental (EXP) or waitlist control (WL) group. All adolescents then attended a two-part pretest research appointment where final decisions regarding inclusion in the study were determined, and data were collected. Adolescents with autism who did not meet criteria for the MRI or who did not complete the MRI, and met all other inclusion criteria, were invited to receive the intervention (data for these youth were not included here).

Intervention

PEERS® (Laugeson & Frankel, 2010) is a manualized intervention designed to teach social skills needed to identify potential friends, engage in conversations and get-togethers with peers, and navigate challenges pertaining to social relationships (i.e., humor, relational aggression, and conflict). Session content is presented in Table 1. Evaluation of the intervention's efficacy, using randomized clinical trials (RCTs), has been conducted by the creators (Laugeson et al., 2009, 2012) and replicated independently in the U.S. (Schohl et al., 2014) and with cultural adaptation in several countries outside of the U.S. (Rabin et al., 2018; Shum et al., 2018; Yamada et al., 2019; Yoo et al., 2014). Modified versions of the intervention, including one targeting repetitive and restricted behaviors (Radley et al., 2018), a second accelerated program (Matthews et al., 2019), and a third peer-mediated format (Matthews et al., 2018) were recently found to be efficacious. A pilot effectiveness trial was also recently conducted, suggesting the intervention's effect is upheld in community settings (Hill et al., 2017).

Table 1

PEERS® for Adolescents Sessions and Corresponding Topics

Session	Didactic
1	Introduction and Conversational Skills I: Trading Information
2	Conversational Skills II: Two-Way Conversations
3	Conversational Skills III: Electronic Communication
4	Choosing Appropriate Friends
5	Appropriate Use of Humor
6	Peer Entry I: Entering a Conversation
7	Peer Entry II: Exiting a Conversation
8	Get-Togethers
9	Good Sportsmanship
10	Rejection I: Teasing and Embarrassing Feedback
11	Rejection II: Bullying and Bad Reputations
12	Handling Disagreements
13	Rumors and Gossip
14	Graduation and Termination

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In the present study, PEERS® was delivered as specified in the manual (Laugeson & Frankel, 2010), that is, with 14, weekly, 90-minute, simultaneously-occurring adolescent and caregiver group sessions, with groups of no more than 10 adolescents and their caregivers. Adolescent group sessions were comprised of homework review (except the initial session), skills didactic, role plays, assignment of homework, and behavioral rehearsal. Caregiver group sessions were similar and included homework review for the adolescent and troubleshooting of barriers, skills didactic complementary to that delivered to the adolescents, and a discussion of methods to support adolescents in their successful completion of homework for the upcoming week. Handouts detailing the session content and homework assignment were provided to caregivers. Adolescents and caregivers coalesced into a single room for reunification wherein adolescents

demonstrated knowledge of the new skills, were praised for their efforts, and homework assignments for the coming week were reviewed. By the fourth week of the intervention, adolescents were expected to have joined, enrolled in, and begun attending a social group based on one of their stated interests.

Training on the delivery of the intervention consisted of the following. The primary investigator was certified in the delivery of PEERS® via the creators at UCLA and subsequently trained graduate student clinicians in a clinical psychology doctoral program to lead the groups. That is, the certified leader facilitated the first adolescent group with a graduate student trainee. Following, trainees began by co-leading a caregiver group with a trained leader or the certified leader, then co-led an adolescent group with a trained leader or the certified leader. Lastly, trainees led an adolescent group independently. Two PEERS® cohorts included here received the intervention through a newly developed interdisciplinary clinic that was comprised of graduate student clinicians in both clinical psychology and speech and language pathology programs. Adolescent and caregiver group leaders were graduate students in a doctoral-level clinical psychology program, and groups were co-facilitated by masters-level speech and language clinicians, who assisted with *in vivo* behavioral interventions one-on-one with adolescents, as needed, and delivered portions of the intervention content to the adolescent and caregiver groups. One interdisciplinary graduate student received the certified training at UCLA in November 2017, during the course of the intervention delivery. Graduate student clinicians received regular supervision directly from the certified leader and a licensed clinical psychologist (as well as a licensed speech and language pathologist for the two interdisciplinary cohorts) to ensure quality and fidelity

of the intervention as well as for training purposes. When possible, sessions were videotaped and reviewed during supervision.

In addition to group leaders, undergraduate research assistants in the lab assisted with the delivery of the intervention as coaches. Coaches were responsible for 1) intervention fidelity and adherence, 2) tracking adolescents' participation, 3) behavioral role plays, and 4) individual behavioral interventions. To achieve adherence to the manual, coaches tracked session content in the manual in real-time to ensure all portions were delivered as specified. When necessary, coaches intervened by identifying missed items to the leader (e.g., "Before we talk about being a conversation hog, don't you think it would be important to discuss not getting too personal?"), at which point the leader provided the missing content.

Dismissal from the intervention occurred based on the following circumstances: 1) adolescents and caregivers withdrew from the intervention, 2) adolescents had three missed homework assignments, 3) adolescents missed more than two sessions, 4) adolescents had not joined or attended a social group by week four. Behavioral contracts indicating the above were reviewed and signed by the caregivers during the first session and reviewed by the adolescents during the fourth session (when adolescents must have joined a social group).

Because the intervention was delivered by graduate and undergraduate students at a university, sessions were offered coinciding with academic semesters (fall: August/September through December and spring: January through May). Data for the current study were comprised of seven PEERS® cohorts conducted between March 2015 and December 2017.

Measures

Sample Characteristics and Eligibility

During the pretest research appointment, adolescents' caregivers completed a demographic form and a questionnaire regarding their child's medication history and current medication status. The *Kaufman Brief Intelligence Test, 2nd Edition* (KBIT-2; Kaufman & Kaufman, 2004) and the *Autism Diagnostic Observation Schedule, Generic* (ADOS-G; Lord, Rutter, DiLavore, & Risi, 2002) were administered. Handedness was assessed during the mock scan using a modified version of the *Edinburgh Handedness Inventory* (Cohen, 2008; Oldfield, 1971) which was delivered as an interview by a trained research assistant using gestural prompts, as needed.

Kaufman Brief Intelligence Test, 2nd Edition. Estimates of cognitive functioning were assessed using the *Kaufman Brief Intelligence Test, 2nd Edition* (KBIT-2; Kaufman & Kaufman, 2004). The KBIT-2 provides a Verbal score, a Nonverbal score, and an IQ Composite using standard scores ($M = 100$; $sd = 15$). To meet inclusion criteria for the intervention, adolescents had to demonstrate Verbal and/or IQ Composite scores of 70 or greater; this threshold was also used for the neurotypical adolescents, for sample matching.

Autism Diagnostic Observation Schedule, Generic. The presence of autism was confirmed *via* the *Autism Diagnostic Observation Schedule, Generic* (ADOS-G; Lord et al., 2002) administered by a research assistant trained to reliability in the lab. The ADOS-G is a semi-structured assessment tool used to provide an estimated risk of the presence of autism. Modules 3 and 4 were used for the present study, based on the language

abilities of the adolescent and clinical judgement of the administrator (Lord et al., 2002). To meet inclusion criteria, autistic adolescents were required to meet threshold-level total scores (combined Communication and Social Interaction) indicative of autism or autism spectrum. Neurotypical adolescents did not receive the ADOS-G.

Questionnaires

Adolescents (with and without autism) and caregivers each completed a battery of questionnaires during the pretest and posttest research appointments.

Social Behavior. Because the purpose of the present study was to evaluate links between social behavior, anxiety, and amygdala activity, not to evaluate the intervention's efficacy, questionnaires deemed by the developer of PEERS® to assess response to treatment (L. Laugeson, personal communication 2016) were used as a manipulation check to ensure that the intervention was functioning as it should. These included: the *Social Skills Improvement System-Rating Scales, Social Skills* subscale (SSIS-RS; Gresham & Elliott, 2008), the *Social Responsiveness Scale* (SRS; Constantino & Gruber, 2002), and the *Test of Adolescent Social Skills Knowledge* (TASSK; Laugeson & Frankel, 2010). The Total scores from each of these measures at pretest and posttest were used. The SSIS-RS and SRS were completed by caregivers, while the TASSK was completed by adolescents. Internal consistency for these measures at pretest was Excellent for the SSIS-RS ($\alpha = 0.92$) and SRS ($\alpha = 0.97$), and Questionable for the TASSK ($\alpha = 0.64$) in the present sample. These values generally align with previous psychometric evaluation of these measures (Bruni, 2014; Constantino & Gruber, 2012; Crosby, 2011; Gresham & Elliott, 2008; Laugeson et al., 2009; Schohl et al., 2014).

Anxiety. Symptoms of anxiety, broadly, and social anxiety, specifically, were assessed *via* questionnaire measures at pretest and posttest. Recent literature demonstrates that the assessment of anxiety in autism is complex; traditional anxiety scales may or may not align with the presentation of anxiety in autism (Kerns, Rump, et al., 2016; Mazefsky et al., 2012; South & Rodgers, 2017; White et al., 2014). Therefore, in order to best capture anxiety in the present sample and relate these symptoms to neural activity, several measures were employed, as recommended (Spain et al., 2018).

The Achenbach System of Empirically Based Assessment, Parent and Adolescent. The Achenbach System of Empirically Based Assessment (ASEBA; Achenbach, McConaughy, & Howell, 1987) is set of a broadband assessment measures of psychological functioning. There are several forms that make up the ASEBA; only the School-Age Child Behavior Checklist (CBCL) and Youth Self-Report (YSR), indicated for youth aged 6–18 (Achenbach & Rescorla, 2001), were used here. The CBCL and YSR are each comprised of 113 items that load into three domain scores: Internalizing Problems, Externalizing Problems, and Total Problems. Subscale scores are available for: Anxious/Depressed, Withdrawn/Depressed, Somatic Complains, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, Aggressive Behavior, Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems. Only the Anxiety Problems subscale will be used here. The measures use a 3-point Likert scale, “Not true (as far as you know),” “Somewhat or sometimes true,” and “Very true or often true” and asks about the past six months. An example item from the Anxiety Problems subscale is, “I worry a lot/Your child worries.” Although the School-Age

CBCL has been found to demonstrate excellent psychometric properties in general (Achenbach et al., 2002), research suggests good sensitivity but low specificity for identifying comorbidities in autism (Pandolfi et al., 2012). Unpublished data, however, suggest that the CBCL Anxiety Problems subscale has good predictive validity of the presence of any anxiety disorder among autistic youth (Bennett et al., 2016). As described above, the CBCL was used to ensure that a sufficient number of adolescents with autism with and without clinically-elevated anxiety was recruited. Therefore, the CBCL Anxiety Problems subscale was used in Aim 2. Internal consistency for the Anxiety Problems subscale at pretest was Acceptable for both the CBCL ($\alpha = 0.77$) and the YSR ($\alpha = 0.74$) in this sample.

Spence Children's Anxiety Scale, Parent and Adolescent. The Spence Children's Anxiety Scale (SCAS; Nauta et al., 2004; Spence, 1999) was used as a measure of broad anxiety symptoms and was completed by both caregivers and adolescents. The SCAS is a 44-item questionnaire with a 4-point Likert scale, "Never," "Sometimes," "Often," and "Always" validated using a sample of 8-12 year-old children (Spence, 1998). Six items are considered "positive filler items" used to ameliorate negative response bias (Spence, 1998, p. 549). The SCAS produces a Total score (a sum of the core 38 items) and six subscale scores, which include: Separation, Social, Generalized, Panic/Agoraphobia, Physical Injury/Specific Phobias, and Obsessive-Compulsive Disorder. An example item is, "I worry about things." Assessment of the measure in typical development has demonstrated good psychometric properties, including high internal consistency, acceptable test-retest reliability, good validity (Spence, 1998), and good parent-child agreement (Nauta et al., 2004). Psychometric properties in autism suggest that the SCAS-

P shows excellent internal consistency and convergent, divergent, and discriminant validity, however, it is recommended that only the Total score be used with autistic samples, due to a poor factor structure fit (Magiati et al., 2017). Therefore, only the Total scores were used in Aim 2 as broad measures of anxiety symptoms. For this sample, internal consistency for the Total score at pretest was Excellent for both the parent version ($\alpha = 0.90$) and the adolescent version ($\alpha = 0.91$).

Social Anxiety Scale for Adolescents, Parent and Adolescent. Symptoms of social anxiety were measured *via* the Social Anxiety Scale for Adolescents (SAS-A; La Greca & Lopez, 1998); caregivers and adolescents each completed the respective versions of this questionnaire. The SAS-A was adapted from the Social Anxiety Scale for Children-Revised (SASC-R La Greca & Stone, 1993) for use with adolescents 15-18 years of age. It is a 22-item questionnaire that utilizes a 5-point Likert scale, "Not at all," "Hardly ever," "Sometimes," "Most of the time," and "All of the time." An example item will not be reported, due to copyright restrictions. The measure boasts high internal consistency (0.87–0.91 for the Total score), good test-retest reliability (0.47–0.78 across various durations), and good validity (Inderbitzen-Nolan & Walters, 2000). In several examinations, a three-factor structure has been found, indicating that the measure includes three subscales: Fear of Negative Evaluation, General Social Avoidance and Distress, and Avoidance and Distress in New Situations (Inderbitzen-Nolan & Walters, 2000; La Greca & Lopez, 1998; Storch et al., 2004). Recent work using an autism sample, however (Schiltz et al., 2019), indicates that a two-factor structure (Fear of Negative Evaluation and Social Avoidance and Distress) is more appropriate in this population and, thus, was used in Aim 2 analyses of social anxiety. For this sample,

internal consistency for the Fear of Negative Evaluation subscale at pretest was Excellent for both the parent ($\alpha = 0.93$) and the adolescent ($\alpha = 0.93$) version. Internal consistency for the Social Avoidance and Distress subscale was Good for both the parent ($\alpha = 0.89$) and the adolescent ($\alpha = 0.89$) version.

NIMH Diagnostic Interview Schedule for Children, Social Phobia, Parent. The Social Phobia module of the National Institute of Mental Health Diagnostic Interview Schedule for Children for DSM-IV (NIMH DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was conducted with caregivers by research assistants trained by the lead graduate student researcher (also the lead author). The DISC-IV is a structured, branching clinical interview and does not include item-level or total scores. Therefore, the DISC-IV was planned to be used to dichotomously classify adolescents as meeting or not meeting clinical criteria for social anxiety disorder based on the DSM-5 (American Psychiatric Association, 2013) resulting in Aut+SAD and Aut–SAD groups. Internal consistency was not calculated. Because data loss prevented the subgrouping of the autism sample, this measure was not utilized.

Social Interaction Anxiety Scale, Adolescent. In addition to the SAS-A, adolescents completed the Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998), due to its focus on direct social interactions, which are the primary target of the intervention. The measure has also been recommended to evaluate response to intervention for social anxiety (Brown et al., 1997; Mattick & Clarke, 1998). The SIAS is a 20-item measure that uses a 5-point Likert scale of “Not at all,” “Slightly,” “Moderately,” “Very,” and “Extremely” and produces a total score. An example item is, “I have difficulty talking with other people.” The SIAS has been validated using adult

samples, though studies of autism samples have included adolescents (Schohl et al., 2014). The measure has shown excellent internal consistency (0.94), test-retest reliability (0.92), and validity (Brown et al., 1997; Mattick & Clarke, 1998) in neurotypical samples. Psychometric evaluation of the measure in an autism sample has not yet been conducted. The Total score was used in Aim 2 as a measure of social anxiety. Internal consistency at pretest for the Total score was Good ($\alpha = 0.88$) in this sample.

MRI Session

The MRI session consisted of three separate components: 1) mock scan, 2) MRI at pretest, 3) MRI at posttest.

Mock Scan. Adolescents prepared for the MRI session by engaging in a mock or pretend MRI scan. The mock scan session lasted approximately 30 minutes and involved 1) engaging in an interactive "Going to MRI for a Research Study©" application delivered *via* iPad technology (Johnson et al., 2017), 2) discussing with a trained research assistant MR technology and the purpose of the study, 3) practicing for the MRI while wearing ear plugs, lying still in the mock scanner, and listening to audio recordings from the MRI, 4) engaging in a practice version of the task, and 5) completing the *Edinburgh Handedness Inventory*. The purpose of the mock scan was to acclimate the youth to the scanning environment; the use of mock scans have been found to significantly improve the quality of data collected from youth (Bie et al., 2010). Adolescents could engage in a second mock scan at posttest, if desired by the youth or if indicated by the research assistant.

fMRI Acquisition at Pretest and Posttest. Adolescents were scanned using a GE Healthcare MR750 3T Human MRI scanner, equipped with a 32-channel adult or

child head coil in the Froedtert Pavilion of the Medical College of Wisconsin. Anatomical images were acquired using a 3D-SPGR pulse sequence with 176 T1-weighted AC–PC aligned sagittal slices (TR/TE/TI = 8.2, 3.2, 450ms; voxel size = 1mm^3, FOV = 256 x 256, iPAT = 2). Functional EPI images were acquired in 41 AC-PC aligned slices, covering most of the brain and all of the frontal, parietal, occipital, and temporal lobes (TR/TE/TI = 2000, 24ms; voxel size = 3mm^3, FOV = 64 x 64, iPAT = 2); in some instances, areas of the cerebellum were excluded. Whole brain analysis was conducted. Resting state and diffusion tensor imaging data were acquired during the scan, therefore, the data from the entire brain was needed. These data are beyond the scope of the current study, however, and are not examined here. Adolescents were compensated $15, delivered in the form of Target gift cards, per hour of MRI participation.

fMRI Paradigm. An affective face processing task was chosen for the fMRI paradigm, based on the large body of literature linking this type of stimuli with amygdala activity in autism (Zalla & Sperduti, 2013), anxiety (Duval et al., 2015), and anxiety in autism (Herrington et al., 2016, 2017). Functional images were acquired across two runs of a 1-back task which included gray-scale visual stimuli of angry faces, happy faces, neutral faces, houses, and scrambled images (see Figure 1). Because the sample was comprised of male youth, faces of age-matched, gender-matched adolescents were used, rather than adult faces; research suggests that youth demonstrate differences in neural activity in response to child *versus* adult faces (Coffman et al., 2015; Hoehl et al., 2010; Marusak et al., 2013). Facial images in the current study were selected from the National Institute of Mental Health Child Emotional Faces Picture Set (NIMH-ChEFS; Egger et al., 2011). Much of the work examining amygdala activation has utilized fearful faces,

however, results of a meta-analysis suggest that *any* affective expression elicits amygdala activity, regardless of valence (Sergerie et al., 2008), including pleasant affect (Sergerie et al., 2008; Vuilleumier, 2005). Intensity, rather than valence, may be more important in activating the amygdala (Zalla & Sperduti, 2013). Therefore, angry and happy facial images were chosen along with neutral facial images as the control condition (i.e., the absence of emotional valence). Images of houses and scrambled images were drawn from the Park Aging Mind Laboratory (2015).

Figure 1
fMRI Paradigm Stimuli

Angry Happy Neutral

Face images from The NIMH Child Emotional Faces Picture Set (NIMH-ChEFS; Egger, et al., 2015)

House Scrambled House Image

House and scrambled images from Park Aging Mind Laboratory (http://agingmind.utdallas.edu/other-stimulus/)

Stimuli were presented electronically using E-Prime 2.0 software (Schneider et al., 2002). Each run lasted 7 minutes and 53 seconds. The first run began with two introductory text slides, each requiring a button press from the research assistant. This was followed by a "get ready" prompt which was initiated by the MRI signal. The second run began with one introductory text slide, requiring a button press, followed by the "get ready" prompt. An 8-second fixation was then presented. Blocks of stimuli were then presented in a sequential order each followed by fixation (16 seconds). Within a block, 30 stimuli were each presented for 8 seconds with a 2-second ITI. The order of the images was sequential within each block. Adolescents were asked to indicate, *via* button press (using their dominant hand), when they detected two identical images in a row. There was a 5-second task completion slide at the end of each run. Within each run, there were two blocks of each stimulus category (neutral faces, angry faces, happy faces, houses, scrambled images), therefore, when combined, each youth observed four blocks of each stimulus category at each timepoint. The version of the task presented during the mock scan differed from that during the MRI—specifically, images of youth aged 11 and 12 were presented, and these were not included in the primary MRI task. The practice task also provided the youth with feedback, and it was shorter—only neutral faces, houses, and scrambled images were presented.

Data Analytic Plan

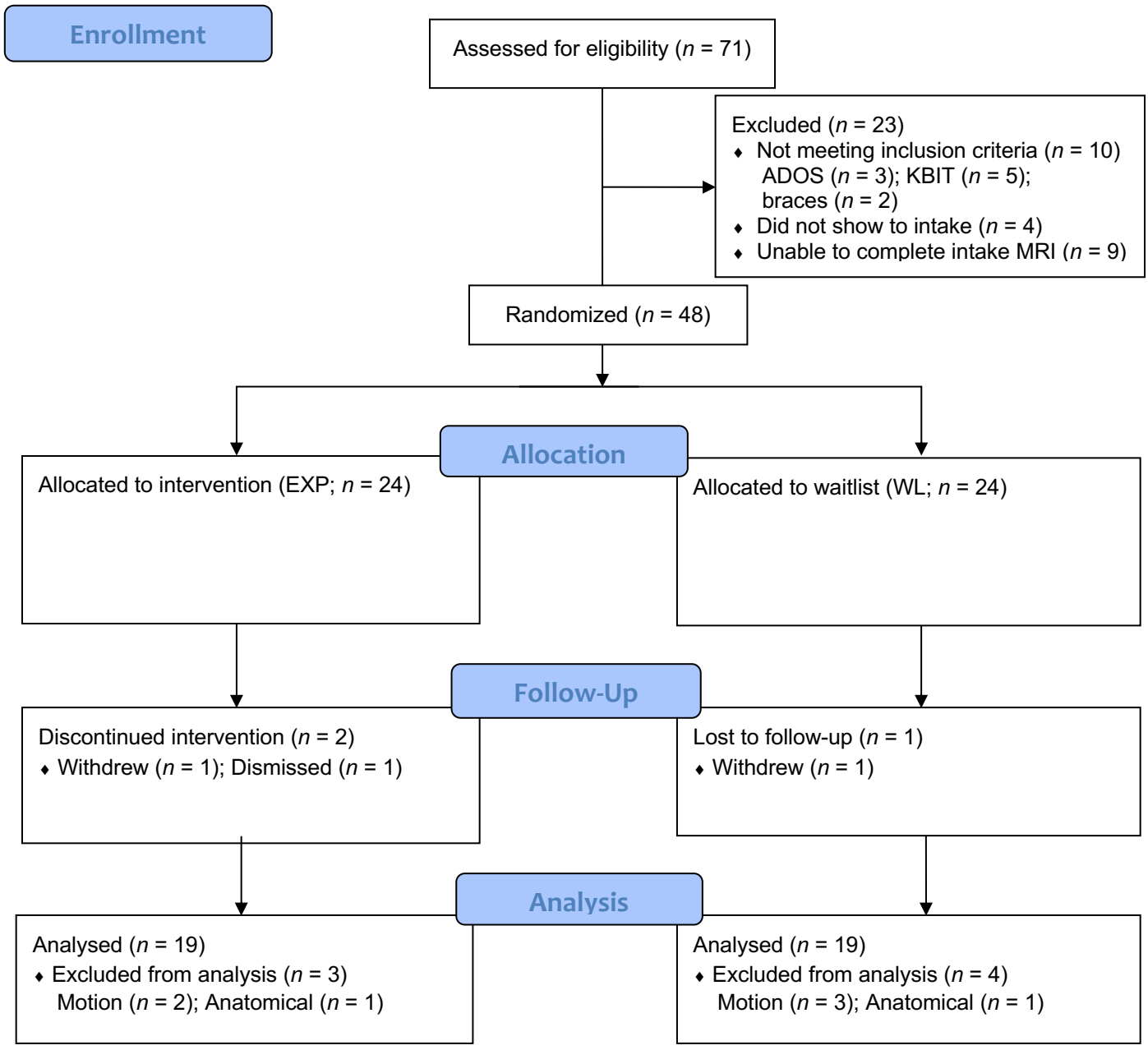
Statistical analyses were conducted using SPSS 26.0 (IBM Corp., 2019) and FSL (Smith et al., 2004). An alpha level of 0.05 was used as the significance criterion for

hypothesis tests. Behavioral data were screened for normality, univariate outliers, and impossible values. Missing data were evaluated with Little's MCAR Test and multiple imputation was conducted (Tabachnick & Fidell, 2013). fMRI data were preprocessed as described below. Examination of change in amygdala activity across the intervention (Aim 1) was achieved using a face-processing task and linking amygdala activity with measures of social behavior and anxiety. Amygdala activity for a group of adolescents with autism who received the intervention were compared to an autism waitlist control group and a neurotypical group. Because one identified limitation of existing studies of this kind is the lack of a second timepoint in assessing a neurotypical group (Stavropoulos, 2017), data were collected at two timepoints for all three groups, including the neurotypical sample. To assess for the effect of anxiety, we originally planned to use clinical threshold markers (on the CBCL for anxiety and DISC for social anxiety) to group the autism sample into subgroups with and without anxiety (Aut+Anx) and/or social anxiety (Aut+SAD). It had been hypothesized that autistic adolescents high in anxiety (Aut+Anx) and/or social anxiety (Aut+SAD) prior to intervention, would show declines in amygdala activity across the intervention, that is, lesser responsiveness to social stimuli, corresponding with improvements in social behavior and reductions in anxiety. Adolescents with autism low in anxiety (Aut–Anx) and/or social anxiety (Aut–SAD) prior to the intervention, were expected to demonstrate increased amygdala activity across the intervention, indicating greater attention to social stimuli, indicative of improvements in social behavior and no change in anxiety. Due to data loss, the groups could not be subdivided by anxiety (see Participants section). Primary hypotheses were examined using mixed model ANOVAs and ANCOVAs, and multiple linear regression.

Results

See Figure 2 for a CONSORT recruitment diagram for the RCT depicting the flow of autistic adolescents through each stage of the study. As seen, 71 youth with autism were assessed for eligibility. Twenty-three of those did not meet inclusion criteria (n = 10), no-showed to the intake appointment (n = 4), or did not complete the intake MRI (n = 9). This left 48 youth with autism for randomization; 24 were allocated to the experimental group and 24 to the waitlist group. For the experimental group, two youth were lost to follow-up (n = 1 withdrew, n = 1 was dismissed due to homework non-compliance). For the waitlist control group, one youth withdrew (n = 1). At the fMRI preprocessing stage, data were excluded due to motion (n = 2 in the experimental group; n = 3 in the waitlist group) and anatomical abnormality (n = 1 in the experimental group and n = 1 in the waitlist group). The final sample was comprised of n = 19 experimental and n = 19 waitlist youths' data for analysis.

Figure 2
CONSORT recruitment diagram for the randomized clinical trial (autism group only)



For the neurotypical (NT) adolescents, 15 youth and their parents were invited to participate. Of those, two were lost at pretest due to no-show (n = 1) and being unable to complete the MRI because of previously unreported claustrophobia (n = 1). This left data from 13 NT adolescents at pretest. Finally, data at posttest were excluded due to no-show (n = 1) and motion (n = 1). Therefore, complete MRI data were available for 11 NT adolescents at both timepoints. Following preprocessing, all data were determined to be usable.

Sample Characteristics and Data Screening

Data were screened for normality, univariate outliers, and impossible values and found to be within normal limits. That is, there were no significant outliers and normality, skew (cutoff = 1), and kurtosis (cutoff = 3) were within normal limits. Due to an administrative error, data from n = 13 (21.3%) of the SCAS Parent at pretest were missing. The available SCAS Parent data were significantly correlated with the CBCL Anxiety Problems (r = 0.55, p < 0.001), SAS Parent FNE (r = 0.45, p = 0.001), SAS Parent SAD (r = 0.38, p = 0.009), and SCAS Adolescent (r = 0.43, p = 0.003) at pretest, therefore, the SCAS Parent was dropped from the dataset at both time points (Tabachnick & Fidell, 2013). Following this, missing data for the remaining dataset (62 data points; 4.62%) were evaluated using Little's MCAR test (Tabachnick & Fidell, 2013) and found to be missing completely at random (χ^2 = 85.21, p = 0.730). Multiple imputation (five iterations) was conducted for the missing items (Tabachnick & Fidell, 2013). Differences in sample characteristics for the EXP, WL, NT groups were examined using one-way ANOVAs, t-tests, and/or χ^2 tests for independence. Results indicated no significant differences by group in terms of age (ranges: NT 11–15, EXP 12–16, WL 11–16),

Composite IQ (ranges: NT 79–122, EXP 69–126, WL 71–133), ADOS (ranges: EXP 7–19, WL 7–21) gender, race, household income, or parental education. There was a significant difference in the groups based on Ethnicity ($\chi^2 = 8.66$, $p = 0.013$). Upon further examination, this difference was only apparent between the autism and NT groups (autism vs. NT; $\chi^2 = 7.68$, $p = 0.006$), not within the two autism groups (EXP vs. WL; $\chi^2 = 2.11$, $p = 0.146$). Therefore, analyses for these groups were run separately (autism and NT). See Table 2 for demographic characteristics of the sample.

Table 2

Sample Characteristics and Group Comparisons

	Group (n = 49)				
	NT (n = 11)	EXP (n = 19)	WL (n = 19)		
	M(sd)	*M(sd)*	*M(sd)*	$F/t/\chi^2$	p
Age	13.91(1.45)	13.68(1.34)	13.58(1.80)	0.16	.855
KBIT-2 IQ Composite	104.45(14.00)	98.89(19.02)	108.79(17.50)	1.54	.226
ADOS-G Total	--	12.84(3.91)	12.68(4.11)	0.12	.904
Gender					--
% Male	100.00	100.00	100.00		
% Female	0.00	0.00	0.00		
Race				5.29	.508
% White	72.70	73.70	84.20		
% Asian	9.10	5.30	0.00		
% Black	0.00	15.80	5.30		
% Biracial/Multiracial	18.20	5.30	10.50		
% Not reported	0.00	0.00	0.00		
Ethnicity				8.66	.013*
% Non-Hispanic/Latinx	63.60	89.50	100.00		
% Hispanic/Latinx	36.40	10.05	0.00		
% Not reported	0.00	0.00	0.00		
Household income				12.74	.238
% Under 25K	0.00	5.30	10.50		
% 25–50K	18.20	0.00	0.00		
% 50–75K	27.30	15.80	15.80		
% 75–100K	9.10	21.10	36.80		
% > 100K	45.50	52.60	31.60		

% Not reported	0.00	5.30	5.30		
Primary parent education				9.34	.501
% Some high school	0.00	0.00	0.00		
% High school completion	0.00	0.00	5.30		
% Voc/tech training	18.20	0.00	5.30		
% Some college	18.20	15.80	5.30		
% Associate's degree	0.00	15.80	21.10		
% Bachelor's degree	27.30	21.10	26.30		
% Master's degree	36.40	47.40	36.80		
% Doctoral degree	0.00	0.00	0.00		

NT Neurotypical *EXP* Experimental Group *WL* Waitlist Control Group *KBIT-2* Kaufman Brief Intelligence Test, Second Edition; *ADOS-G* Autism Diagnostic Observation Schedule-Generic; *K* thousand; *Voc/tech* Vocational/technical; *$p < .05$

MRI Preprocessing

Preprocessing for the fMRI data included the following. First, the data were low-pass filtered (to remove linear trends) and spatially smoothed (using 5-mm Gaussian kernel) using FEAT (Woolrich et al., 2001). Head motion estimation and correction were accomplished using MCFLIRT (Jenkinson et al., 2002). Data were placed into 2-mm isotropic Montreal Neurological Institute (MNI) space by merging affine transformation matrices (calculated *via* FLIRT; Jenkinson et al., 2002) between the following volumes: fMRI to fast low angle shot, fast low angle shot to magnetization prepared rapid acquisition gradient-echo, and magnetization prepared rapid acquisition gradient-echo to MNI. Removal of volume-to-volume displacement ("spikes") was conducted with AFNI 3dDespike (Cox, 1996). Following despiking, data with > 1 voxel (2 mm) spikes were evaluated on a case-by-case basis. When a spike occurred early or late in the scan (within the first or last 60 volumes), those sections were trimmed, and the remaining data were preserved ($n = 9$). As stated above, data ($n = 6$) were excluded from analyses due to large (i.e., > 2 mm) spikes that occurred throughout the scan and/or within volumes 60–180.

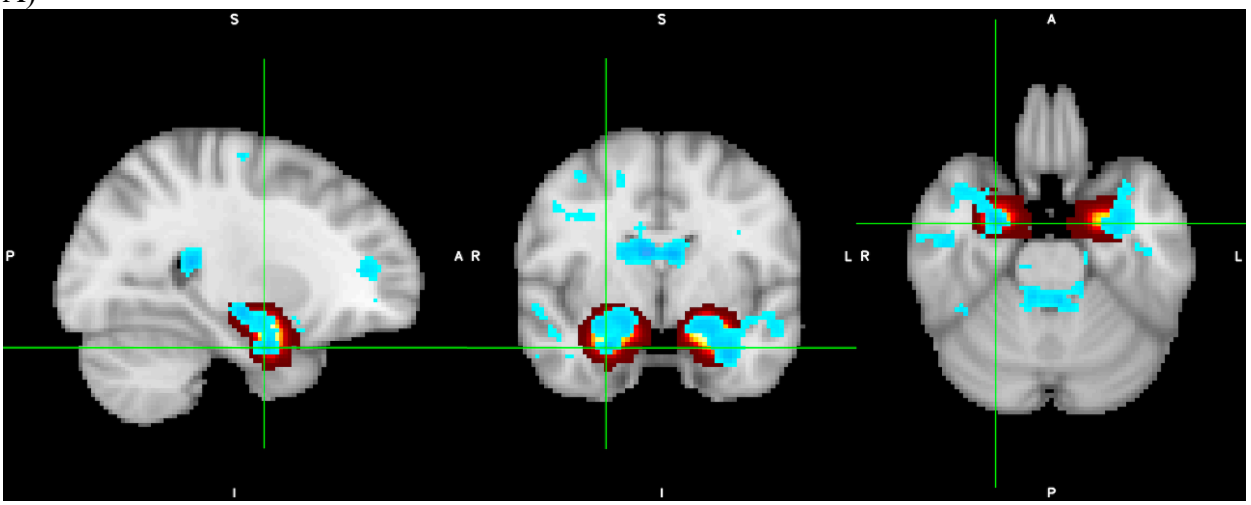
Amygdala Data Acquisition

Activation of the amygdala was explored using a face (happy, angry, and neutral) *versus* house contrast based on the literature demonstrating that this contrast would reliably elicit amygdala activation (e.g., Aoki et al., 2015). Amygdala activation was confirmed by inspecting the cluster list from the single-group average analysis separately for the autism and NT groups. Each cluster peak was examined using FSLeyes (McCarthy, 2018) and the MNI atlas. Average and peak amygdala values were extracted. Average values were extracted using z-stat maps, with thresholds set at 2.57 (e.g., Pisauro et al., 2017). Regions of interest (ROIs) were defined using the Harvard-Oxford Subcortical Atlas (https://identifiers.org/neurovault.collection:262) and a binarized mask was created. Peaks were created by identifying the value as described above and drawing a 3mm spherical mask around the peaks. Peaks were visually inspected in FSLeyes (McCarthy, 2018). Of note, for the autism group, amygdala average activity was related to peak activity for the left ($r = 0.35$, $p = 0.030$), but not right amygdala ($r = 0.24$, $p = 0.145$). Upon visual inspection, the peak activity for the left amygdala fell toward the outside of the atlas-defined amygdala region, while the activity in the right amygdala fell entirely within the atlas-defined region. For the NT group, only the right amygdala peak reached significance. Threshold free cluster enhancement (TFCE; Smith & Nichols, 2009) was used to correct for multiple comparisons. Results demonstrated that amygdala activity remained significant. See Figures 3–12 for visual depictions of the amygdala activity generated by FSLeyes.

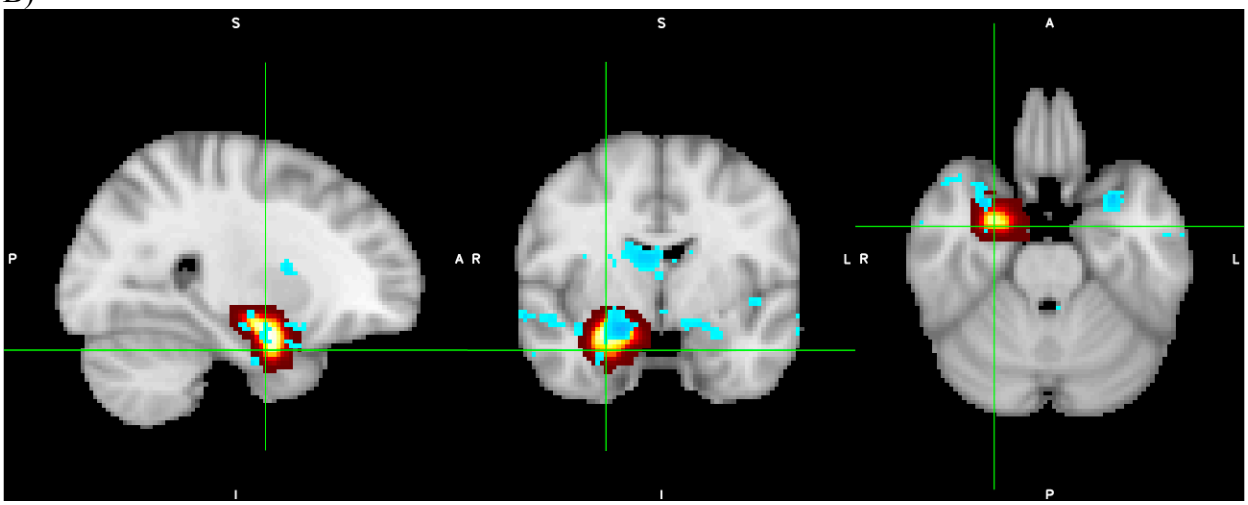
Figure 3

Right Amygdala Activity for the Autism Group at Pretest and Posttest

A)

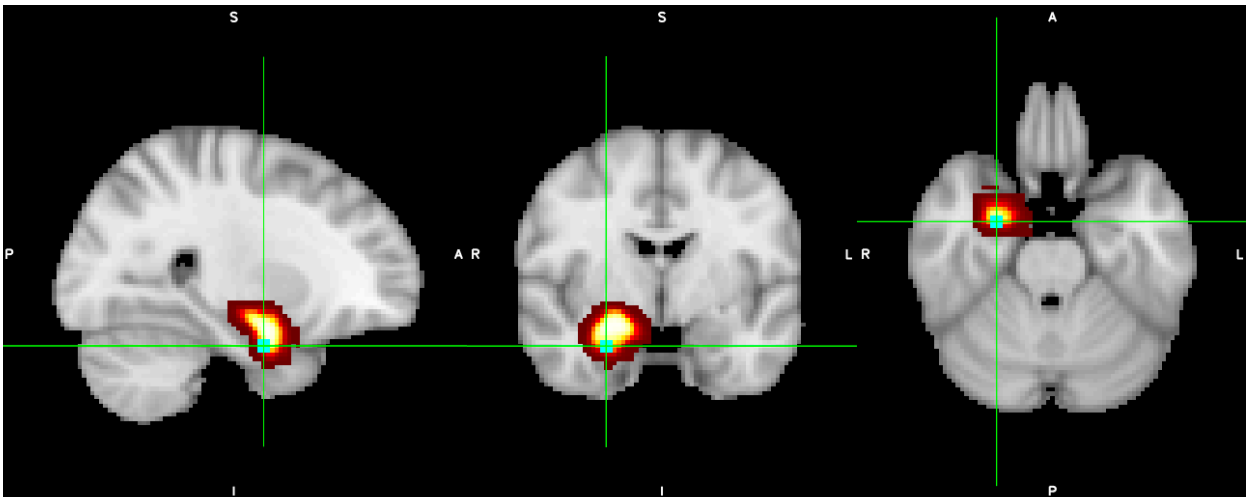


B)



Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity at pretest.

Figure 4
Right Amygdala 3mm Peak for the Autism Group at Pretest

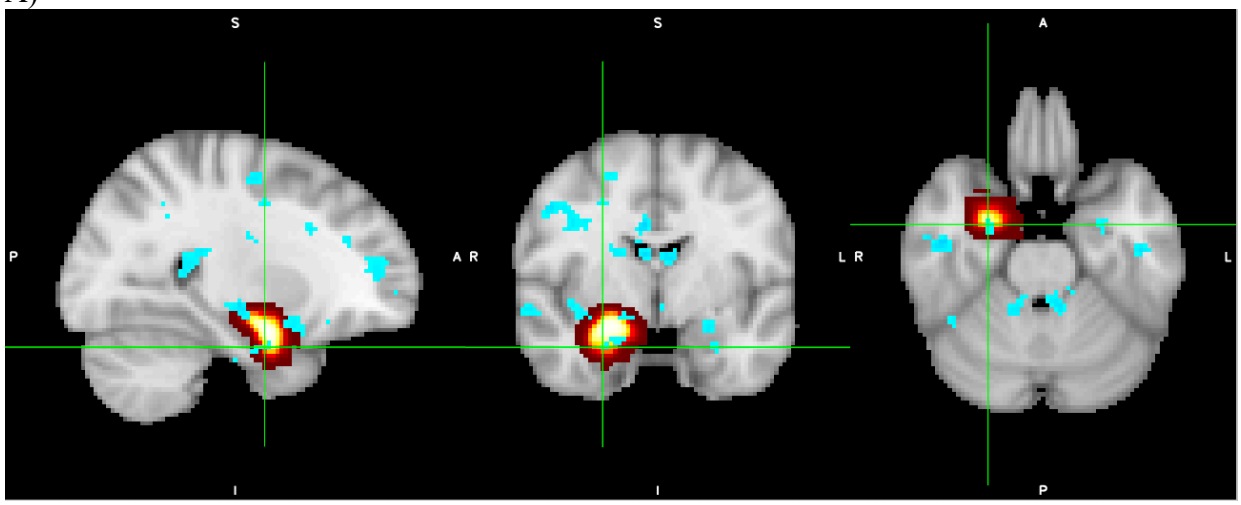


Note: Peak is designated in turquoise. Red represents standard amygdala area. Crosshairs show the point of peak activity.

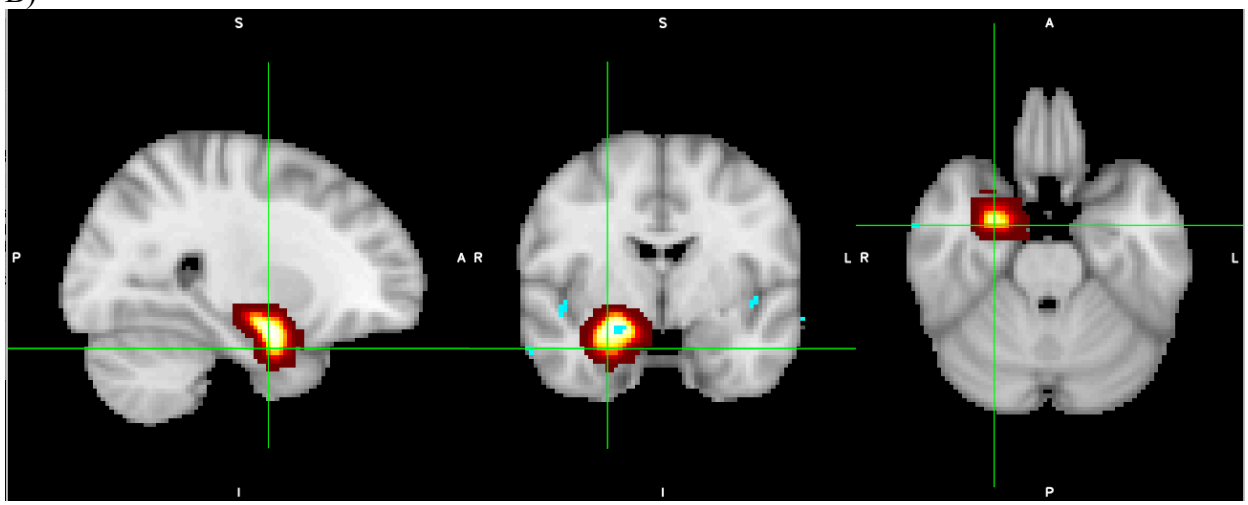
Figure 5

Right Amygdala Activity for the Experimental Group at Pretest and Posttest

A)



B)

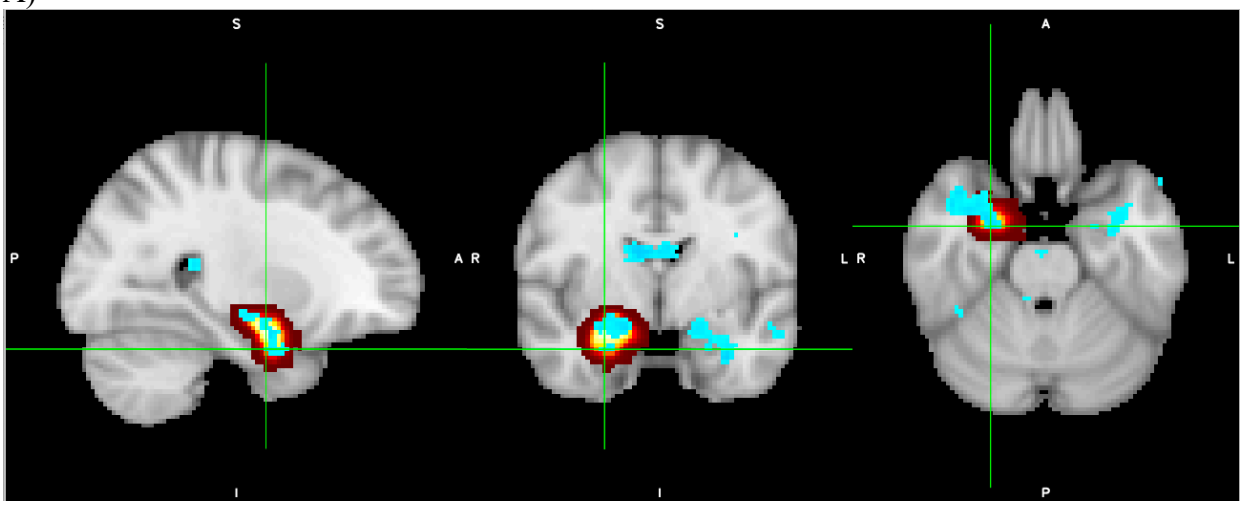


Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity for the entire autism group at pretest.

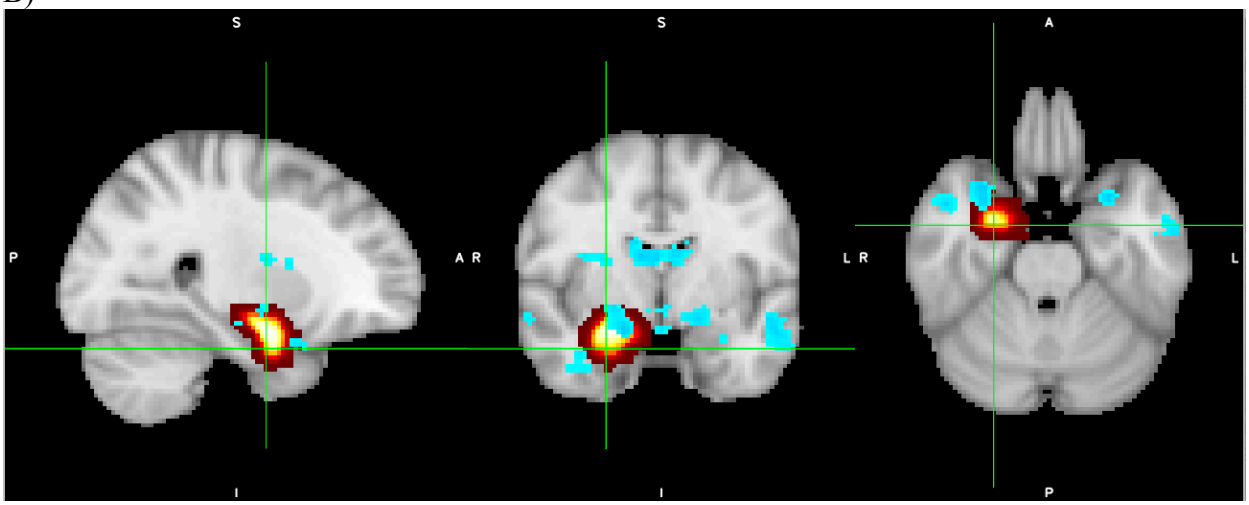
Figure 6

Right Amygdala Activity for the Waitlist Group at Pretest and Posttest

A)



B)

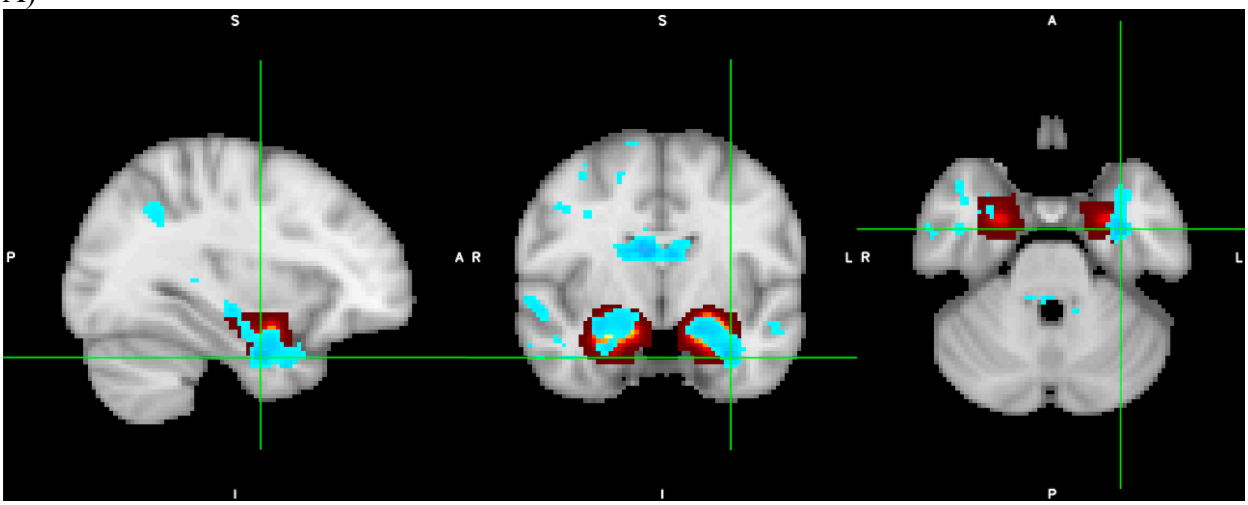


Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity for the entire autism group at pretest.

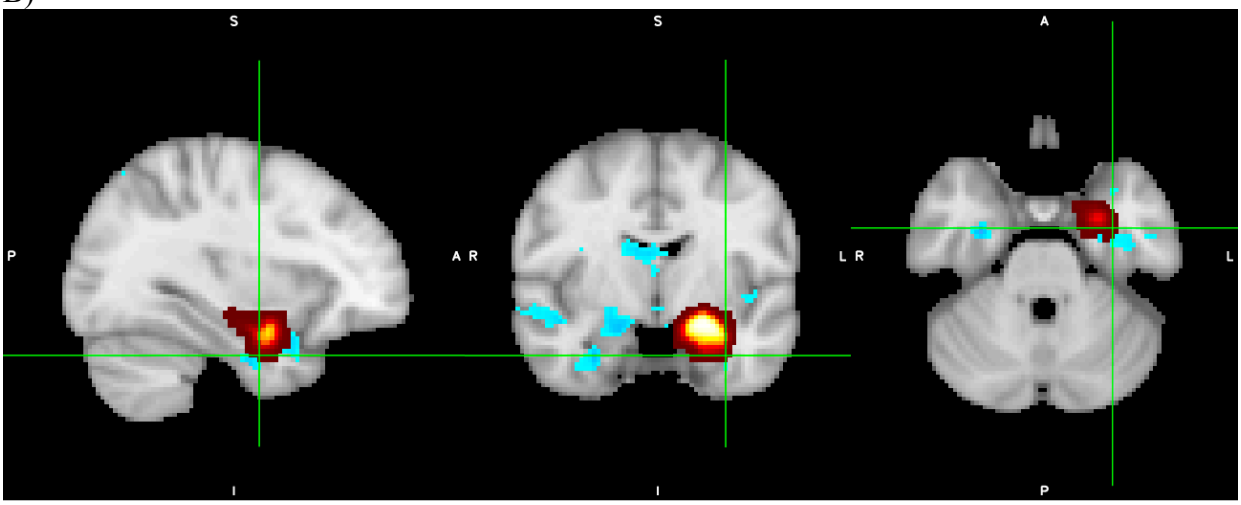
Figure 7

Left Amygdala Activity for the Autism Group at Pretest and Posttest

A)

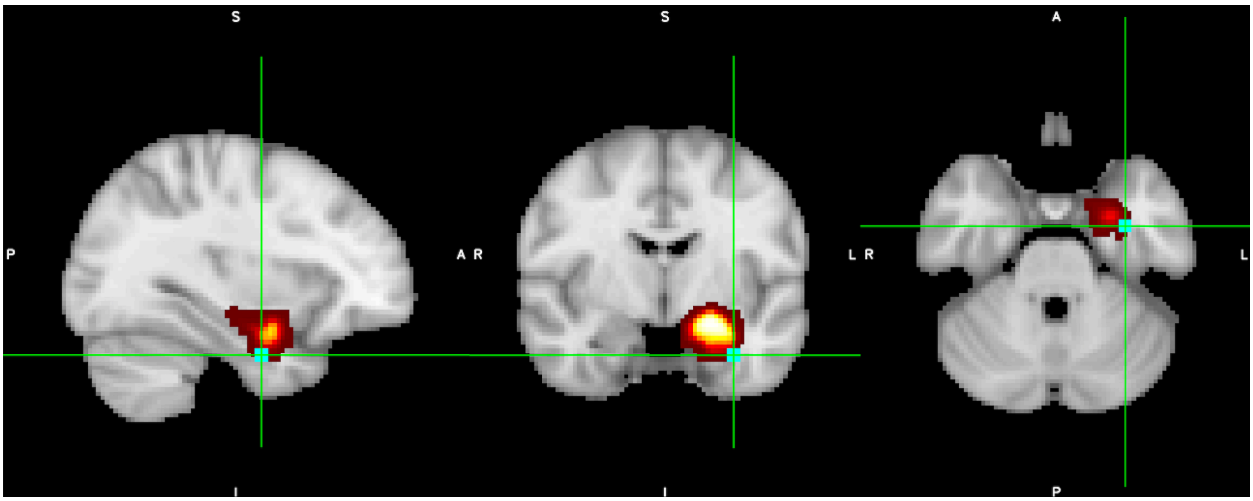


B)



Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity at pretest.

Figure 8
Left Amygdala 3mm Peak for the Autism Group at Pretest

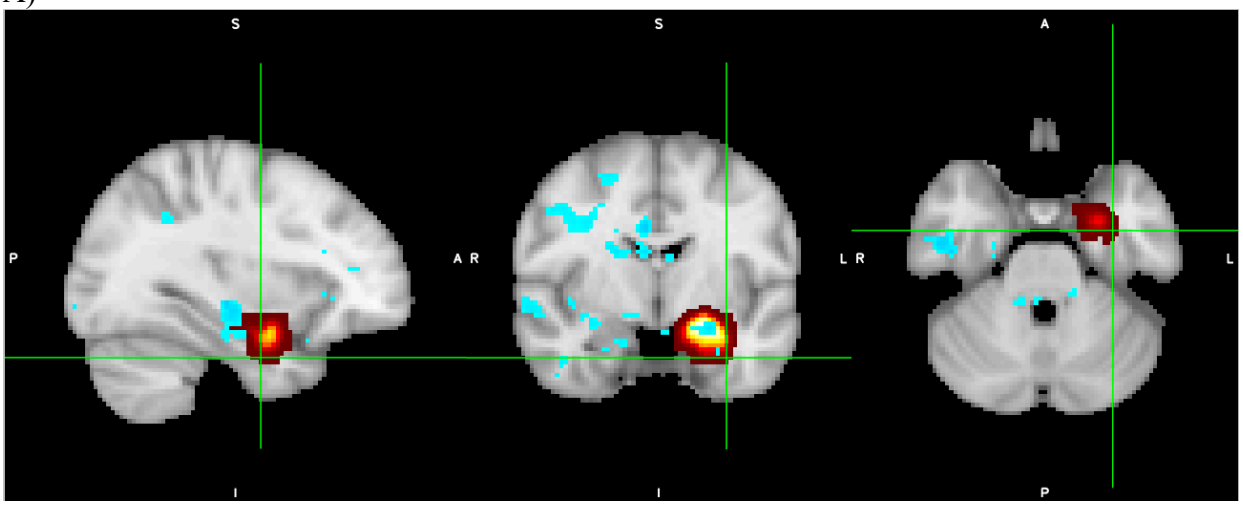


Note: Peak is designated in turquoise. Red represents standard amygdala area. Crosshairs show the point of peak activity.

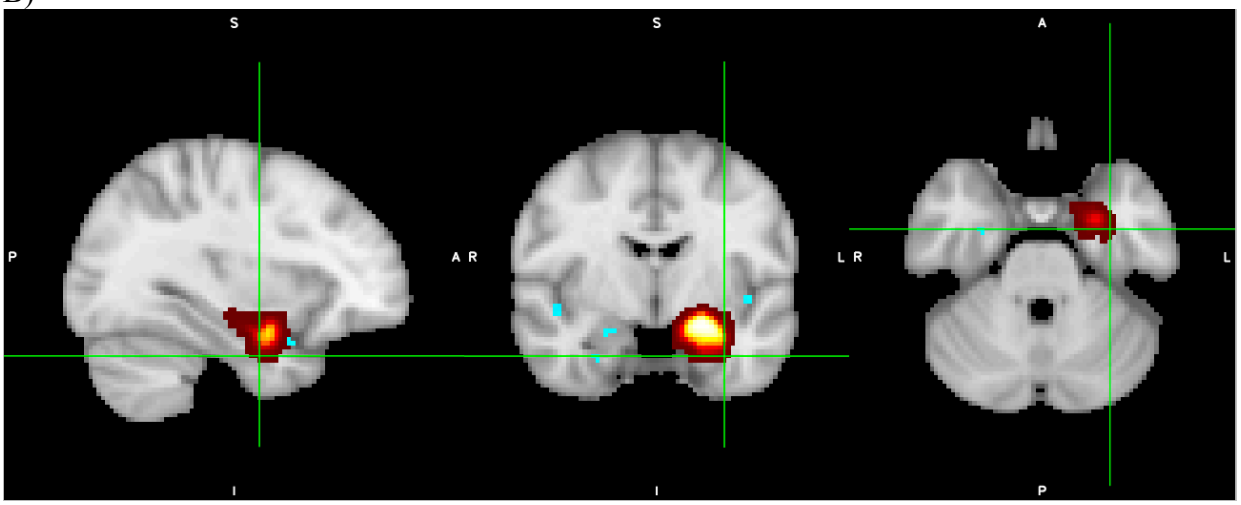
Figure 9

Left Amygdala Activity for the Experimental Group at Pretest and Posttest

A)



B)

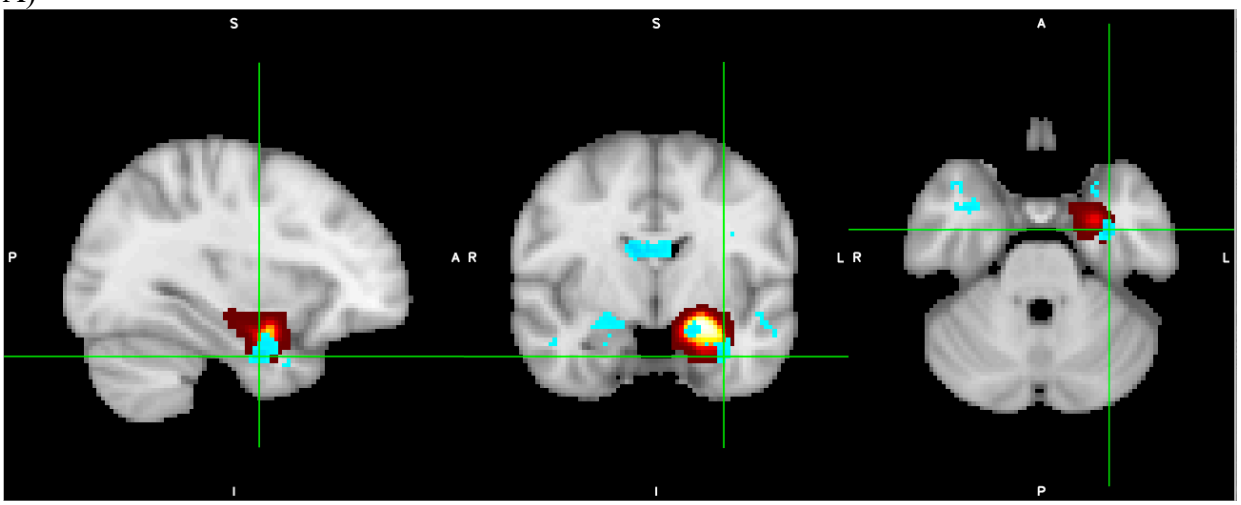


Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity for the entire autism group at pretest.

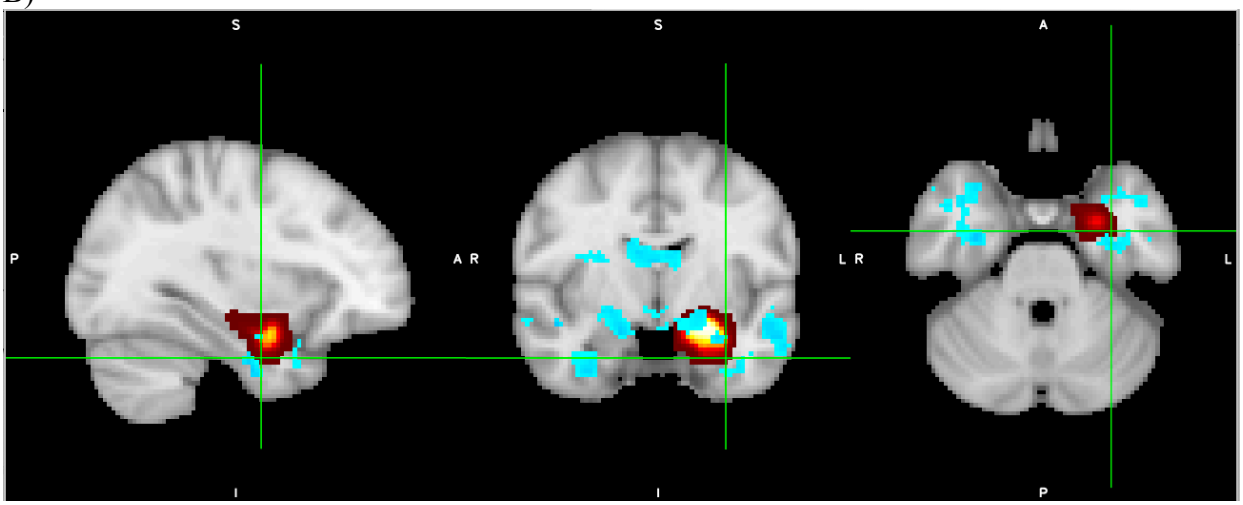
Figure 10

Left Amygdala Activity for the Waitlist Group at Pretest and Posttest

A)



B)

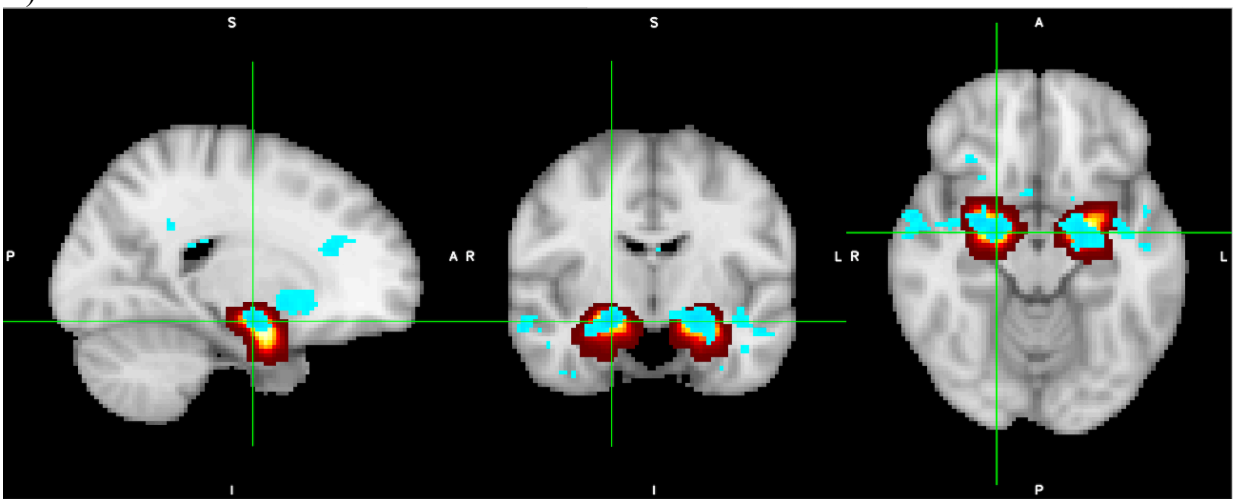


Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity for the entire autism group at pretest.

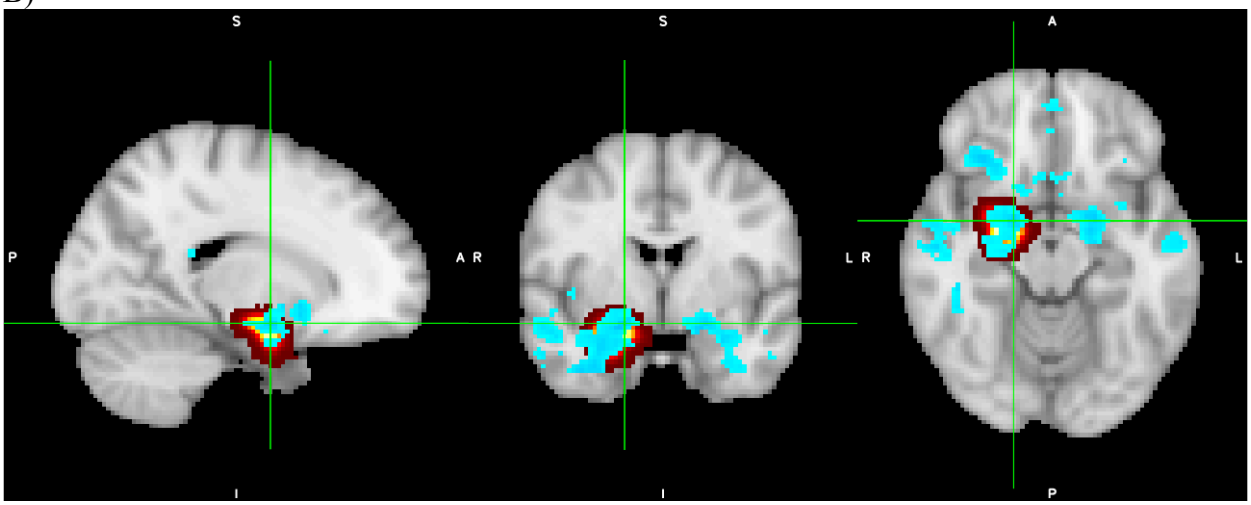
Figure 11

Right Amygdala Activity for the Neurotypical Group at Pretest and Posttest

A)

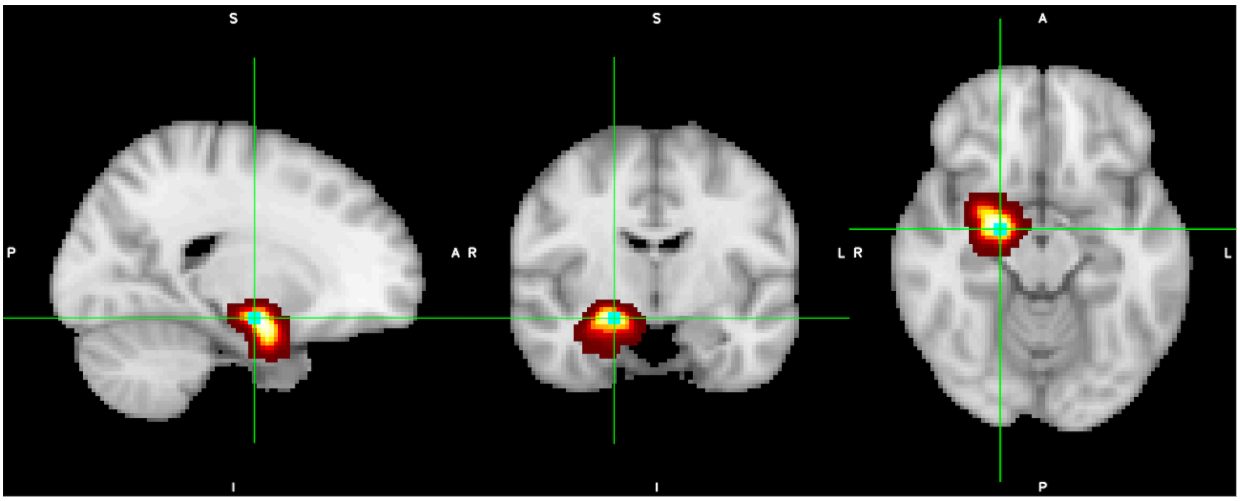


B)



Note: A) Pretest, B) Posttest. Activity is designated in turquoise; threshold = 2.57. Red represents standard amygdala area. Crosshairs show the point of peak activity at each respective timepoint.

Figure 12
Right Amygdala 3mm Peak for the Neurotypical Group at Pretest



Note: Peak is designated in turquoise. Red represents standard amygdala area. Crosshairs show the point of peak activity.

During data collection for the first cohort of autistic adolescents (n = 6), the E-Prime task required unpredicted troubleshooting. Specifically, the computer being used lagged upon presenting the stimuli, resulting in unusual presentation times. In order to control for this, analyses that follow were run twice—first with these data, and a second time without them included.

Pearson's Correlations

Prior to the primary analyses, Pearson's correlations were conducted to examine relations between amygdala activity and 1) social behavior, 2) anxiety (broadly), and 3) social anxiety specifically at pretest using the multiply imputed data. Correlations were conducted with 1) average amygdala values and 2) peak amygdala values. Additionally, as stated above, correlations were run with 1) the entire autism sample including the first cohort, 2) the autism sample without the first cohort, and 3) the NT sample. Data are presented in this order below. We expected that social behavior would be negatively

related, and anxiety would be positively related, to amygdala activity in the autism but not the NT group.

Average Amygdala Values. Correlations among the entire autism sample showed one significant positive association between the right amygdala and the TASSK at pretest ($r = 0.33$, $p = 0.043$), indicating that more social knowledge was associated with greater amygdala activity. No other associations between the right or left amygdala and social behavioral (SSIS-RS, SRS) or anxiety (general or social; CBCL, YSR, SCAS, SAS Adolescent, SAS Parent, or SIAS) measures at pretest reached significance. One association, between the SAS Parent FNE and the right amygdala, however, was trending ($r = 0.27$, $p = 0.099$), indicating that greater fear of negative evaluation was linked with greater right amygdala activity. See Table 3. These correlations were also conducted for the autism group without the first cohort, and results showed a significant positive relation between the left amygdala and the SSIS-RS ($r = 0.36$, $p = 0.042$), a positive link between the right amygdala and the SAS Parent FNE ($r = 0.38$, $p = 0.032$), and, unexpectedly, a negative correlation between the left amygdala and the CBCL ($r = -0.36$, $p = 0.043$). See Table 4. That is, better social skills, greater fear of negative evaluation, and lower general anxiety symptoms via parent report were associated with greater amygdala activity. No significant or trending correlations emerged for the right amygdala in the NT group (Table 5).

Table 3
Correlations between Amygdala Activity, Social Behavior, and Anxiety at Pretest for the Autism Groups (EXP and WL Combined, Including First Cohort) Pooled

	SSIS-RS	SRS	TASSK	CBCL-AP	YSR-AP	SCAS-A	SAS-A FNE	SAS-A SAD	SAS-P FNE	SAS-P SAD	SIAS
Right Amygdala Average	.056	-.030	.330*	-.220	-.146	-.015	.129	-.075	.272†	.046	.010
Left Amygdala Average	.230	.014	.193	-.271	.005	.025	.112	-.110	.135	-.140	-.066
Right Amygdala Peak	.262	-.126	.263	.147	-.003	-.029	-.135	-.128	-.079	-.048	-.123
Left Amygdala Peak	.292†	.173	.030	.004	.034	-.051	.013	.082	-.022	.068	.084

SSIS-RS Social Skills Improvement System, Rating Scales; *SRS* Social Responsiveness Scale; *TASSK* Test of Adolescent Social Skills Knowledge; *CBCL-AP* Child Behavior Checklist, Anxiety Problems subscale; *YSR-SP* Youth Self Report, Anxiety Problems subscale; *SCAS-A* Spence Children's' Anxiety Scale, Adolescent self-report; *SAS-A* Social Anxiety Scale, Adolescent self-report; *SAS-P* Parent report; *FNE* Fear of Negative Evaluation; *SAD* Social Anxiety Disorder; *SIAS* Social Interaction Anxiety Scale; † $p < .10$; *$p < .05$

Table 4
Correlations between Amygdala Activity, Social Behavior, and Anxiety at Pretest for the Autism Groups (EXP and WL Combined, ***Excluding*** *First Cohort) Pooled*

	SSIS-RS	SRS	TASSK	CBCL-AP	YSR-AP	SCAS-A	SAS-A FNE	SAS-A SAD	SAS-P FNE	SAS-P SAD	SIAS
Right Amygdala Average	.167	-.097	.269	-.313†	-.090	-.016	.233	-.051	.379*	.074	.080
Left Amygdala Average	.360*	-.056	.115	-.359*	.070	.029	.165	-.145	.184	-.140	-.074
Right Amygdala Peak	.213	-.144	.189	.080	.148	.087	-.192	-.180	-.237	-.187	-.170
Left Amygdala Peak	.307†	.170	.022	.010	.120	.001	-.001	.012	-.022	.028	.033

SSIS-RS Social Skills Improvement System, Rating Scales; *SRS* Social Responsiveness Scale; *TASSK* Test of Adolescent Social Skills Knowledge; *CBCL-AP* Child Behavior Checklist, Anxiety Problems subscale; *YSR-SP* Youth Self Report, Anxiety Problems subscale; *SCAS-A* Spence Children's' Anxiety Scale, Adolescent self-report; *SAS-A* Social Anxiety Scale, Adolescent self-report; *SAS-P* Parent report; *FNE* Fear of Negative Evaluation; *SAD* Social Anxiety Disorder; *SIAS* Social Interaction Anxiety Scale; † $p < .10$; *$p < .05$

Table 5
Correlations between Amygdala Activity, Social Behavior, and Anxiety at Pretest for the Neurotypical Group, Pooled

	SSIS-RS	SRS	TASSK	CBCL-AP	YSR-AP	SCAS-A	SAS-A FNE	SAS-A SAD	SAS-P FNE	SAS-P SAD	SIAS
Right Amygdala Average	-.097	.176	-.185	-.305	-.456	-.180	.275	.235	-.010	.164	.173
Left Amygdala Average	--	--	--	--	--	--	--	--	--	--	--
Right Amygdala Peak	.340	-.309	-.557†	-.519	-.628*	-.465	-.080	-.212	-.431	-.246	-.216
Left Amygdala Peak	--	--	--	--	--	--	--	--	--	--	--

SSIS-RS Social Skills Improvement System, Rating Scales; *SRS* Social Responsiveness Scale; *TASSK* Test of Adolescent Social Skills Knowledge; *CBCL-AP* Child Behavior Checklist, Anxiety Problems subscale; *YSR-SP* Youth Self Report, Anxiety Problems subscale; *SCAS-A* Spence Children's' Anxiety Scale, Adolescent self-report; *SAS-A* Social Anxiety Scale, Adolescent self-report; *SAS-P* Parent report; *FNE* Fear of Negative Evaluation; *SAD* Social Anxiety Disorder; *SIAS* Social Interaction Anxiety Scale; † $p < .10$; *$p < .05$ Note: Left amygdala peak did not reach significance so correlations were not conducted.

Peak Amygdala Values. Correlations among the entire autism sample showed one trending relation between the left amygdala and SSIS-RS ($r = 0.29$, $p = 0.075$), indicating better social skills were linked with greater peak amygdala activity. See Table 3. This relation was observed to be trending when this analysis was run without the first cohort ($r = 0.31$, $p = 0.088$; Table 4). Correlations for the NT group showed one significant negative link between the right amygdala and the YSR Anxiety Problems subscale ($r = -0.63$, $p = 0.037$), that is, less anxiety was associated with more peak amygdala activity. A second negative relation between the right amygdala and the TASSK was trending ($r = -0.56$, $p = 0.075$), demonstrating that poorer social knowledge was linked with greater peak amygdala activity. As stated above, activation in the left amygdala did not reach significance for the NT group, so correlations were not conducted for this region. See Table 5.

Partial Correlations

Secondly, partial correlations were used to examine relations between amygdala activity and social behavior at pretest controlling for anxiety. As above, analyses were planned to be conducted with 1) average amygdala values and 2) peak amygdala values, as well as with 1) the entire autism sample including the first cohort, 2) the autism sample without the first cohort, and 3) the NT sample. For the autism group, we expected that social behavior would be negatively related to amygdala activity when anxiety was held constant. No relation between social behavior and amygdala activity in the NT group was anticipated.

Average Amygdala Values. In the correlation analysis above, the relation between the right amygdala and the SAS Parent FNE was found to be approaching significance for the entire autism sample. Therefore, partial correlations were used to examine relations between right amygdala activity and social behavior controlling for the SAS Parent FNE. Results were not significant for any social behavioral measure (SSIS-RS, SRS, TASSK). For the autism group without the first cohort, the relation between the right amygdala and the SAS-P FNE was significant, the correlation between the left amygdala and the CBCL Anxiety Problems subscale was significant, and the link between the right amygdala and the CBCL Anxiety Problems subscale was trending. Therefore, partial correlations with social behavioral measures were examined for the right and left amygdala controlling for the CBCL Anxiety Problems subscale and for the right amygdala and the SAS-P FNE. Results showed a significant positive relation between the left amygdala and the SSIS-RS ($r = 0.36$, $p = 0.044$); no other partial

correlations were significant. This analysis was omitted for the NT group, since no associations between amygdala activity and anxiety were identified above.

Peak Amygdala Values. Partial correlations were not conducted using the peak amygdala values for the entire autism group or the autism group without the first cohort, given no significant correlations with any anxiety measures emerged (above). For the NT group, partial correlations were conducted controlling for YSR Anxiety Problems, and results showed a significant negative relation between the right amygdala and the TASSK (r = -0.62, p = 0.041). This indicates that poorer social knowledge was linked with greater right amygdala activity for the NT group, controlling for self-reported anxiety symptoms.

Paired Samples* t-*tests

Lastly, paired samples *t*-tests were conducted with the SSIS-RS, SRS, and TASSK for the each of the autism groups (EXP and WL) for the intervention manipulation check. It was expected that the EXP group would show improvements on these measures, while the WL group would show no change. Here, using the pooled data, results demonstrated no significant difference in social skills improvement (SSIS-RS) for either group (EXP: $t(785) = -1.41$, $p = 0.157$; WL: $t(785) = -1.78$, $p = 0.076$), a significant decline in autism symptoms (SRS) for the EXP, but not the WL group (EXP: $t(217) = 3.25$, $p = 0.001$; WL: $t(217) = 1.46$, $p = 0.145$), and a significant improvement in PEERS® knowledge (TASSK) for the EXP, but not the WL group (EXP: $t(712) = -10.10$, $p < 0.001$; WL: $t(712) = -1.93$, $p = 0.054$). Despite the lack of changes in the SSIS-RS, these findings generally align with previous examinations of PEERS® (Laugeson et al., 2009; Schohl et al., 2014).

Aim 1: Change in Amygdala Activity Across Intervention

To assess Aim 1, a 2-way Mixed Effect ANOVA, Group (EXP *versus* WL) x Time (pretest *versus* posttest), was conducted to examine changes in amygdala activity using FSL's FEAT (Woolrich et al., 2004). For the omnibus Group x Time analysis, we expected to see no differences in amygdala activity, since anxiety was not considered. Findings aligned with this; no significant within groups or interaction effects were observed in the omnibus Mixed Effect (Group x Time) ANOVA. This indicates no difference in activity averaged amongst all groups between the two time points (the within groups Time effect, comparing pre and post activation), and no effect of the groups on amygdala activation differences, depending on time (the mixed Between-Within Interaction effect). Because FSL's Mixed Effect ANOVA conducts only the interaction and within groups effects (it cannot conduct the between groups effect), a Two-group Mean comparison, averaging over Time, was also conducted. Results from this analysis also showed no differences in amygdala activation. Planned univariate analyses included Single-group Paired Difference (Paired *t*-tests) run separately for the EXP and WL groups and Two-group Difference (Two-sample Unpaired *t*-tests) at pretest and posttest. Results from the Paired *t*-tests for the EXP and WL groups showed no amygdala activity differences. The Unpaired *t*-tests for pretest and posttest also revealed no amygdala activity differences. These results aligned with our hypotheses. When the ANOVA was conducted without the first cohort, the results were the same—no differences in amygdala activity were observed for the omnibus ANOVA. As expected, the Single-group Paired Difference analysis (Paired *t*-test) for the NT group showed no significant amygdala activation differences.

To control for the possible effect of anxiety, a Two-Group Difference Adjusted for Covariate analysis (i.e., ANCOVA) was conducted in FSL at pretest and posttest for the autism groups (EXP versus WL) using continuous data from the CBCL at pretest. Results demonstrated no amygdala activity differences between the groups, controlling for anxiety. To follow up on this analysis, Single-Group Averages with an Additional Covariate were conducted separately for the EXP and WL groups at pretest and posttest. Results for each the EXP and WL groups at each pretest and posttest showed no significant amygdala activity. Single-Group Averages with an Additional Covariate were also conducted for the NT group at pretest and posttest. Results for the NT group at each pretest and posttest demonstrated no significant amygdala activity at pretest or posttest.

Aim 2: Anxiety as a Predictor of Change in Amygdala Activity

Aim 2 was assessed using multiple linear regression analyses. Symptoms of anxiety and social anxiety at pretest for the EXP group were used to predict change in amygdala activation at posttest. Measures of anxiety employed in the linear regressions were chosen based on correlations with amygdala activity at pretest (SAS Parent FNE). It was hypothesized that higher anxiety scores would predict greater declines in amygdala activity at posttest. Results demonstrated that higher scores on the SAS Parent FNE predicted greater change in amygdala activation ($F(1, 17) = 5.00$, $p = 0.040$, $\beta = 0.49$, $R^2 = 0.238$), and aligned with our predictions; higher anxiety (SAS Parent FNE) at pretest was associated with a larger decline in amygdala activity across the intervention, while lower anxiety at pretest was associated with a smaller decline in amygdala activity across the intervention. When regression analyses were conducted without the first cohort, the SAS Parent FNE still predicted change in right amygdala for the EXP group ($F(1, 11) =$

8.56, $p = 0.014$, $\beta = 0.66$, $R^2 = 0.437$). Because the CBCL was associated with the left amygdala in the correlations without the first cohort, as described above, partial correlations were conducted for this association as well. Results showed that the model was not significant ($F(1, 11) = 0.39$, $p = 0.545$, $\beta = -0.19$, $R^2 = 0.34$), therefore, the CBCL at pretest did not predict change in left amygdala for the EXP group.

Discussion

The present study is among the first of its kind to test a neural biomarker of social skills intervention response for autistic adolescents. Employing a RCT, using fMRI, and examining links with social behavior and anxiety, this study found neural changes across the PEERS® intervention that coincide with improvements at the group level.

Pearson's Correlations

Results from correlations between amygdala activity and social behavior at pretest were partially in line with our hypotheses. With the entire autism sample, results showed one significant positive relation, between the average right amygdala data and social knowledge (TASSK), with a second positive link between the peak left amygdala data and social skills (SSIS-RS) trending. When the first cohort was excluded, the link between the right amygdala and TASSK was no longer significant, but a positive relation between the average left amygdala data and social skills (SSIS-RS) emerged. The peak left amygdala data and the SSIS-RS correlation remained trending. Given that the amygdala is part of the social brain, it is fitting that measures of social knowledge and social skills (TASSK and SSIS-RS) would be linked with activity in this region. It is possible, though unknown, that considering the social situations described in the TASSK and SSIS-RS (e.g., "If you try to join a conversation and people ignore you..." and "Starts conversations with peers," respectively) evoked amygdala activity in a similar manner as viewing emotional faces in the MRI scanner. What is perhaps more complex to understand is the absence of consistent significant links between amygdala activity and measures of social behavior (SRS and SSIS-RS). Perhaps because the SRS is a measure

of autism symptoms, rather than a measure of social behavior, per se, this link was not observed. In a previous study, amygdala habituation to sad and neutral faces among youth with autism was negatively correlated with the SRS; that is, decreased habituation was linked with more autism symptoms (Swartz et al., 2013). Because amygdala habituation was not measured in the current study, nor were sad faces utilized, a direct comparison of results is not possible. In another study, thinner cortex in the right and left insula (a brain region connected with the amygdala and thought to be important for social cognition (Mesulam & Mufson, 1982)), was associated with higher scores on the SRS (Tu et al., 2016). It may be that structural differences in social brain regions are linked with autism symptoms, as measured by the SRS, though this question is beyond the scope of the current study.

Results from correlations between amygdala activity and anxiety among the entire autism sample revealed a trending positive link between the right amygdala and social anxiety (SAS Parent FNE). When the first cohort was excluded, the positive correlation between the right amygdala average and the SAS-P FNE reached significance. Additionally, one significant negative correlation between the left amygdala and the CBCL and one trending negative correlation between the right amygdala and the CBCL emerged. Regarding the link between social anxiety (SAS Parent FNE) and the right amygdala, it is possible that social scenarios parents observe or about which adolescents speak with their parents (e.g., “My child is afraid that others will not like him/her”) align with youths’ neural response to affective faces in the MRI scanner. This is in line with previously identified links between social anxiety and amygdala activity among autistic (Kleinhans et al., 2010) and neurotypical youth (Killgore & Yurgelun-Todd, 2005). This

finding speaks to the importance of social evaluation in autism. It is important to note that the youth included in the present study demonstrated a stated interest in improving their social competence, and half of the autism sample was recruited to have elevated anxiety symptoms, therefore, these results may not be representative of the larger autism population. The negative links between the right and left amygdala and the CBCL are more perplexing. Perhaps because the CBCL captures anxiety symptoms broadly, and the task used here examined response to affective stimuli, rather than general anxiety-provoking stimuli, overall anxiety symptoms were related to lesser amygdala activity. In a previous study, the Anxious/Depressed subscale on the CBCL (which includes many of the same items as the Anxiety Problems subscale) was positively correlated with total and right amygdala volumes among autistic youth (Juranek et al., 2006). One study of amygdala activity using the CBCL Anxiety Problems subscale also examined sensory over-responsivity and, although the authors found a positive link between the CBCL and amygdala activity, sensory over-responsivity predicted amygdala activity when anxiety was held constant (Green et al., 2013). These studies, although not directly comparable to the current one, present contradicting evidence to that uncovered here. Further work is needed to better understand these negative links between amygdala activity and the CBCL Anxiety Problems subscale among youth with autism.

No significant correlations were found between measures of social behavior and amygdala activity in the NT group. One negative relation between the YSR Anxiety Problems subscale and the right amygdala peak was identified. Because this comparison group was recruited to be free from psychiatric symptoms, this finding is surprising. Amygdala activity has been positively linked with anxiety symptoms among

neurotypicals (Brühl et al., 2014; Duval et al., 2015; Mochcovitch et al., 2014). In the present sample, anxiety symptoms at the group level did not exceed clinical thresholds (CBCL at pretest; $M = 54.69$, $sd = 5.81$), and the group did not demonstrate a full range of possible scores on this subscale. Since no other anxiety measure was associated with amygdala activity, it is possible that some of the youth in this group experienced emotional arousal at the neural level, but they did not report anxious symptoms on the YSR. Replication is needed to better understand this finding.

Partial Correlations

Contrary to our hypotheses, partial correlations examining links between amygdala activity and social behavior controlling for anxiety were not significant. We had expected that measures of social behavior (SRS, SSIS-RS, TASSK) would be negatively related to amygdala activity when anxiety was held constant, and we had planned to employ the anxiety measures previously found to be linked with amygdala activity. This meant only the SAS Parent FNE was utilized in this analysis. Because the link between this measure and amygdala activity was trending (it did not reach significance), it may be that the effect was not robust enough to control for the influence of anxiety on amygdala activity. Alternatively, it may be that difficulties in social behavior, when anxiety was controlled for, were not distinct enough to have strong effects on amygdala activity. That is, we did not observe the expected negative correlation between social behavior and amygdala activity when anxiety was held constant because the effect was not present. This finding is in contrast to the notion of a negative relation between autism symptoms and amygdala activity, or the *Social*

Motivation Theory (Baron-Cohen et al., 2000; Chevallier et al., 2012; Dawson et al., 2005; Schultz, 2005).

Paired Samples *t*-tests

As expected, evidence for the effect of the intervention was demonstrated in significant group-level change in two of the three measures used—the SRS and TASSK but not SSIS-RS. This generally aligns with prior studies of PEERS® efficacy in the U.S., which have found significant improvements in the TASSK (Laugeson et al., 2009, 2012; Schohl et al., 2014), Social Skills Rating Scale (precursor to the SSIS-RS) (Laugeson et al., 2009, 2012), and SRS (Schohl et al., 2014). Therefore, it seems the intervention functioned as expected.

Change in Amygdala Activity Across Intervention

As predicted, results from the Mixed Effects ANOVA examining amygdala activity indicated no significant main effects of group or time nor an interaction effect of group by time when anxiety was not considered. Because prior research demonstrates that amygdala activity in autism may be more tied to anxiety than autism itself, and half of the autism sample was recruited to demonstrate clinically-significant anxiety symptoms, we anticipated that our omnibus ANOVA examining change in amygdala activity over time would show no effect if we did not control for anxiety symptoms. This hypothesis was driven by studies that identified positive relations between anxiety and amygdala activity (Corden et al., 2008; Herrington et al., 2016, 2017; Kleinhans et al., 2010; Ventola et al., 2015), leading us to believe that more amygdala activity would be present in the anxiety subgroup than the subgroup without anxiety, therefore washing out

any differences. Surprisingly, however, when anxiety was controlled for in the ANCOVA analysis, our expectation that an increase in amygdala activity may have occurred for the autism subsample without anxiety was not borne out in the analyses. It is difficult to compare this finding to existing literature, as no known study to date has examined amygdala activity across a social skills intervention for autistic adolescents. Because this study is the first of its kind to examine neural changes across a social skills intervention for youth with autism, using an affective face processing task, it is difficult to draw comparisons with existing literature. It may be that the intervention did not elicit an effect on the amygdala for those youth with low anxiety, and that is why we did not see significant changes in the ANCOVA analysis. We also did not utilize a measure of social motivation, and therefore, could not examine links between amygdala activity and social drive, per the *Social Motivation Theory* (Baron-Cohen et al., 2000; Chevallier et al., 2012; Dawson et al., 2005; Schultz, 2005). It is important to note that one inclusion criterion for participation in the intervention was the stated desire to improve social competence, therefore, youth with lower social motivation were excluded. This may help to explain our lack of findings regarding increases in amygdala activity across intervention, controlling for anxiety.

Anxiety as a Predictor of Change in Amygdala Activity

Partially in line with our expectations, results demonstrated that anxiety, as indicated by parent-reported fear of negative evaluation (SAS Parent FNE), predicted change in amygdala activity across the intervention. These results suggest that adolescents with higher levels of social anxiety (in particular, greater fear of negative evaluation) prior to the intervention demonstrated more change (i.e., a greater decline) in

amygdala activity in response to PEERS®. This finding is in consort with previous literature that has shown improvements in social anxiety for adolescents completing the PEERS® intervention (Schohl et al., 2014). It may also suggest that those youth who demonstrate high social anxiety may also be those most likely to engage in social approach, and therefore benefit most from the intervention (McVey, Willar, et al., 2016). Furthermore, fear of negative evaluation in particular may be an especially important construct in autism. For instance, one study found that fear of negative evaluation was predictive of greater gaze duration to emotional faces (i.e., disgust and anger) among autistic but not neurotypical adolescents (White, Maddox, et al., 2015). This effect may have played a role in the present study, though since eye tracking data were not collected here, cannot be tested for this sample. Theoretically, however, if autistic adolescents with greater fear of negative evaluation demonstrated increased gaze duration to the anger faces used here (disgust was not utilized), it is possible that this aligned with greater amygdala activity at pretest and predicted lesser amygdala activity across the intervention. Therefore, fear of negative evaluation is likely a crucial component pertaining to the changes in amygdala activity found across the intervention in this study.

Limitations and Future Directions

Although innovative in its use of fMRI to examine neural changes across a social skills intervention for autistic youth, this study was not without its limitations. Perhaps the most notable limitation was the small sample size. Despite an attempt to overrecruit based on recommendations in the autism field (Yerys et al., 2009), difficulties collecting usable fMRI data resulted in significant data loss. This is not an uncommon issue, and efforts are being made to ameliorate this challenge (e.g., head molds; Power et al., 2019).

A second major limitation was the relative demographic homogeneity of the sample, which was predominantly White, non-Hispanic/Latinx, and of moderate-to-high SES. A related concern was an inability to assess possible gender differences due to recruitment limitations.

Further research is needed to elucidate links between measures commonly used to assess intervention response in autism (e.g., TASSK, SRS, and SSIS) and neural activity.

Recent recommendations for testing biomarkers provide excellent resources for future studies that may build upon this work. While this study closely adhered to recommendations put forth by Stavropoulos (2017) including: 1) being selective in the choice of brain region to examine (i.e., amygdala), 2) design of a paradigm with this region in mind, 3) careful selection of behavioral measures, and 4) conceptual link between the brain region and behavioral targets, some improvements may be made in future studies. This may include examination of more than a single brain region (e.g., including the prefrontal cortex, insula, etc.), use of an anxiety-provoking task, and more thorough phenotyping of the sample.

A recent review of the literature on the neurobiology of anxiety in autism (McVey, 2019) points to several considerations that may strengthen future studies of this kind. First, the present study did not include a neurotypical subsample with anxiety, which would be helpful for specificity.

Second, while one gold-standard tool was implemented to assess autism (i.e., ADOS), the parent interview recommended to be conducted in conjunction, the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), was not administered. Furthermore, although questionnaire measures of anxiety with some psychometric

evaluation in autism were collected, gold-standard assessment of anxiety (*via* the Anxiety Disorders Interview Schedule (ADIS; Di Nardo & Barlow, 1988) with the Autism Addendum (Kerns, Renno, et al., 2016) was not conducted, nor were questionnaires developed specifically for autism samples used here.

Third, and perhaps the largest limitation in this study's design, the paradigm employed, though based on literature demonstrating its effect at activating amygdala, this type of paradigm has not been identified by the RDoC initiative as one to evoke Perceived Threat "Anxiety" and, thus, may not have elicited an anxious state among the adolescents in the study. With this in mind, future studies may wish to utilize tasks that robustly evoke an anxious or ruminative state. One such paradigm may be a recent adaptation of a task developed by Vuilleumier (Vuilleumier, 2002; Vuilleumier et al., 2001, 2004) that utilizes peripheral presentation of anxiety-provoking stimuli to evoke an anxious state, recently used in a study of anxiety in autism (Herrington et al., 2017). Another possible option, the sole task recommended by the RDoC initiative for Perceived Threat—the Neutral, Predictable, Unpredictable (NPU) Threat Task—has begun to be tested in autistic samples (e.g., Chamberlain et al., 2013). A third option, especially for the activation of social anxiety, may be a paradigm such as Cyberball (Williams et al., 2000), that has been shown to elicit ruminative states regarding social exclusion among neurotypicals, and has shown to function similarly with an autism sample (Sebastian et al., 2009). Tasks such as these may more reliably activate anxious arousal than the one-back face/house processing task used here.

Conclusion

The present study was the first to test neural changes via fMRI in response to the PEERS® intervention for autistic youth. As expected, without accounting for anxiety, results demonstrated no significant amygdala activation or change in activation across the intervention period for the autism groups. The presence of anxiety, namely parent-reported fear of negative evaluation, predicted change in amygdala activity across the intervention for adolescents who underwent PEERS®, though, unexpectedly, other measures of anxiety did not show this effect. It may be that those youth with autism and symptoms of social anxiety are the best candidates for the PEERS® intervention and may show the greatest improvements (McVey, Willar, et al., 2016). Clinical implications of this study highlight the importance of identifying social anxiety among youth with autism participating in social skills interventions for youth with autism, as these youth may be most ripe for the greatest benefits from such an intervention.

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