REWARD PROCESSING IN AUTISM SPECTRUM DISORDER: BEHAVIORAL INDICATORS, NEURAL CORRELATES, AND MECHANISMS OF TREATMENT RESPONSE

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ABSTRACT

Rachel K. Greene: Reward Processing in Autism Spectrum Disorder: Behavioral Indicators, Neural Correlates, and Mechanisms of Treatment Response
(Under the direction of Gabriel S. Dichter)

This integrative dissertation broadly explores reward processing differences in autism spectrum disorder (ASD) using neuroimaging and eye tracking technologies. Study 1 investigated prediction error responses, one aspect of reward processing, in individuals with ASD using an outcome expectancy eye tracking task. The findings corroborate previous reports of aberrant responses to prediction errors in ASD, but did not find that this effect was impacted by reward type (e.g., social vs. nonsocial). Study 2 is the first published neuroimaging study to examine neural responses of individuals with ASD as they win money for others (i.e., vicarious reward). As hypothesized, participants with ASD showed decreased neural activation in key vicarious reward regions when earning rewards for others, potentially shedding light on mechanisms behind social difficulties in ASD. Finally, Study 3 evaluated neural reward responses following intranasal oxytocin administration, and the results showed heightened neural reward circuitry activation in response to non-social rewards following oxytocin administration. Taken together, these studies provide a greater depth of understanding regarding various aspects of reward processing differences in ASD.

To my parents, Mark and Medrith, who made of all this, and so much more, possible. Your support through it all means the world to me.

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LIST OF ABBREVIATIONS

ACC	anterior cingulate cortex
ADOS-2	Autism Diagnostic Observation Schedule, Second Edition
ASD	Autism spectrum disorder
BA	Brodmann Area
DMPFC	dorsomedial prefrontal cortex
fMRI	functional magnetic resonance imaging
FP	frontal pole
FSL	FMIRB's Software Library
GLM	general linear model
gPPI	generalized psychophysiological interaction
IFG	inferior frontal gyrus
IQ	intelligence quotient
MID	monetary incentive delay
MTG	medial temporal gyrus
NAcc	nucleus accumbens
NART-R	National Adult Reading Test – Revised
OFC	orbital frontal cortex
OT	oxytocin
PLC	placebo
ROI	region of interest
SFG	superior frontal gyrus
SRS	Social Responsiveness Scale

STG	superior temporal gyrus
TDC	typically developing control
vmPFC	ventromedial prefrontal cortex
WASI	Wechsler Abbreviated Scale of Intelligence

INTRODUCTION

Social communication and interaction deficits are cardinal features of autism spectrum disorder (ASD; APA, 2013) and were among the most prominent of the behavioral symptoms described in the first accounts of the disorder (Kanner, 1943). Thus, the nature and causes of these social atypicalities have received considerable attention from ASD researchers over the past several decades. One relatively recent mechanistic theory is the social motivation hypothesis of autism (Chevallier et al., 2015), which asserts that individuals with ASD may be less inclined to attend to social stimuli (e.g., faces, voices, eye gaze direction) beginning in the earliest years of life (Chawarska, Macari, & Shic, 2013; Dawson et al., 2004; Klin, 1991). This framework suggests some individuals with ASD experience not only a lack of motivation to initiate engagement with the social world but also diminished pleasure in those interactions (Bottini, 2018; Chevallier, Grezes, Molesworth, Berthoz, & Happé, 2012; Dawson, Bernier, & Ring, 2012; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Dawson, Webb, & McPartland, 2005; Schultz, 2005). This lack of orientation toward the social environment during infancy and childhood may result in fewer opportunities to understand and engage in social contexts, leading to negative downstream effects on the development of social cognitive and interaction skills across the lifespan.

These altered motivational states in ASD are believed to result from reward processing impairments. The term "reward processing" describes a complex set of processes and may bebroken down into distinct components, including: reward anticipation ("wanting"), reward

receipt or outcome ("liking"), and reward learning. Each of these components plays a unique role in experiencing rewarding stimuli and guiding behavior in the presence of particular reward cues in the future (Berridge & Robinson, 2003).

Behaviorally, individuals with ASD display aberrant performance in each of these reward domains. Regarding reward anticipation or social "wanting," individuals with ASD often seek out social interactions and relationships less frequently but demonstrate heightened willingness to expend effort engage with circumscribed interests and other nonsocial activities (Damiano, Aloi, Treadway, Bodfish, & Dichter, 2012; Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2011). In adulthood, diminished social approach is exhibited by individuals with ASD who, on average, report less desire for social relationships (Baron-Cohen & Wheelwright, 2003). Decreased attention to social cues, such as infrequent eye contact or orienting to one's own name, is thought to represent reduced pleasure in the receipt or "liking" of social reward responses (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson et al., 2004). Indeed, children with ASD report experiencing relatively less enjoyment in social interactions compared to their typically-developing peers (Chevallier, Grezes, et al., 2012). Moreover, individuals with ASD tend to show preference for non-social rather than social visual stimuli, potentially reflecting the lessened reward value of social images (Dubey, Ropar, & Hamilton, 2017; Sasson, Turner-Brown, Holtzclaw, Lam, & Bodfish, 2008).

Deficits have also been observed in the reward learning abilities of individuals with ASD. For example, Lin, Adolphs, and Rangel (2012) employed an instrumental reward learning task with both social (i.e., faces) and nonsocial (i.e., money) rewards that revealed significantly delayed learning rates in individuals with ASD in the social condition only. These results suggest

that responses to social stimuli, specifically, may impede reward learning capabilities for those with ASD.

Predictive abilities, an important construct within reward learning processes, have are also been compromised in individuals with ASD. These predictive deficits are evidenced by atypical processing of prediction errors in ASD (Lawson, Rees, & Friston, 2014; Van de Cruys et al., 2014), as well as difficulties interacting with dynamic or inconsistent stimuli, such as those encountered during a change in routine (Sinha et al., 2014). ASD has even been conceptualized as a disorder of impaired predictive ability (Sinha et al., 2014). Specifically, this hypothesis asserts that individuals with ASD struggle to make inferences about future events, particularly those involving uncertain or less structured stimuli (e.g., social situations). It is believed that the discomfort and anxiety associated with constant unpredictability (Gotham et al., 2013) leads individuals with ASD to exhibit greater behavioral rigidity, characterized by instance on sameness, in an attempt to create a more predictable environment. To further investigate the nature of predictive impairments in ASD, Study 1 explored prediction error responses of individuals with ASD using an outcome expectancy eye tracking task. These findings may also shed light on reward learning impairments in ASD that have downstream effects on social learning, and consequently social interaction abilities, throughout development.

The social motivation hypothesis of autism further suggests that characteristic behavioral presentations of ASD are directly linked to disruptions in neural reward circuitry associated with social motivation. Specifically, canonical regions within the reward-associated mesolimbic dopamine pathway have been implicated in the motivational differences observed in individuals with ASD compared to their neurotypical peers (for review see Clements et al., 2018). To date, these studies have examined responses to rewards earned for oneself, yet understanding neural

responses to rewards earned for others (i.e., vicarious reward) may provide insight into ASD-associated social cognitive deficits, including cognitive empathy and theory of mind difficulties. Mosner et al. (2017) found that, behaviorally, individuals with ASD show reduced sensitivity to reward magnitude parameters when earning money for others but not themselves. However, the neural mechanisms behind impairments in vicarious reward responses in ASD has not been explored. Study 2 is the first neuroimaging study to examine ASD responses to vicarious rewards relative to TDCs. Functional activation and connectivity observed during vicarious reward responses will inform our understanding of ASD sensitivity to rewards for others, a construct often associated with perspective taking and social learning abilities.

Finally, with a growing understanding of reward processing impairments in ASD, we can use reward responses as mechanistic targets of behavioral and pharmacological interventions. To date there are no medications that treat the core symptoms of ASD (Dove et al., 2012), and although behavioral interventions show promise, the field lacks mechanistic outcome measures to evaluate the efficacy of these treatments. ASD clinical trials almost exclusively rely on caregiver-reported symptom severity to determine the efficacy of pharmacological and behavioral therapeutics (Busner, Targum, & Miller, 2009; Payakachat, Tilford, Kovacs, & Kuhlthau, 2012); however, caregiver-report measures are limited in their capacity to evaluate symptoms that are not outwardly visible, including abilities in social perception or theory of mind. Alternatively, self-report measures are infrequently used due to impairments with insight into socioemotional states, which is common in individuals with ASD (Payakachat et al., 2012). In addition, many currently used outcome measures were originally designed as diagnostic tools (e.g., Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)) and were not intended to be sensitive to subtle change over time (Kanne et al., 2014). Because the social

motivation hypothesis of ASD asserts that the defining features of the disorder may, in fact, reflect, at least in part, aberrant reward processing abilities, adopting reward processing paradigms as clinical outcome measures to assess the impact of interventions has been suggested. Study 3 exemplifies this approach by evaluating neural responses to rewards of children with ASD following a single administration of intranasal oxytocin (OT). Given its established effects on prosocial behaviors (Insel & Shapiro, 1992; Kirsch et al., 2005; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Quattrocki & Friston, 2014), OT has received considerable attention as a potential treatment for social communication deficits in ASD; however, the mechanisms behind these pharmacological effects are not well understood. Preclinical research suggests neural reward circuitry may be preferentially activated by OT and, therefore, responsible for the associated behavioral effects (Hung et al., 2017; Love, 2014). Therefore, Study 3 examined neural responses during a monetary incentive delay task following intranasal oxytocin (OT) administration to understand the route by which oxytocin asserts its prosocial effect in individuals with ASD.

Together, this program of research aims to further explore the observed reward processing abilities of individuals with ASD and how they relate to core features of the disorder, such as impairments in social communication and interaction. Furthermore, this work leverages our current knowledge of social motivational and reward processing deficits in ASD with the goal of evaluating the efficacy and mechanistic action of potential therapeutics (i.e., intranasal oxytocin). These goals are accomplished in the three aforementioned studies by examining behavioral outcomes and neural substrates of reward processing in ASD, as well as evaluating reward processing responses as mechanistic targets of treatment response. Using the social motivation hypothesis of ASD as a guiding framework for these empirical investigations, I hope

to evaluate previously unstudied aspects of reward processing in ASD to better understand how reward responses may relate to defining features of the disorder, as well as shed light ways to evaluate interventions addressing social communication and interaction deficits in ASD.

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SOCIAL AND NONSOCIAL VISUAL PREDICTION ERRORS IN AUTISM SPECTRUM DISORDER

A recent conceptualization of autism spectrum disorder (ASD) asserts that deficits in predictive ability contribute to core ASD traits (Sinha et al., 2014; Van de Cruys et al., 2014). For example, the "insistence on sameness" commonly observed in individuals with ASD may reflect self-imposed order that helps individuals process what they perceive to be an unpredictable world. Impairments in the capacity to anticipate future outcomes may also impact social functioning. For instance, deficits in theory of mind, a core social cognitive impairment in ASD (Baron-Cohen, Leslie, & Frith, 1985; Perner, Frith, Leslie, & Leekam, 1989), may represent difficulties predicting implicit social meaning as well as the mental states of others.

Deficits in predictive abilities likely impact learning in individuals with ASD. A key component of learning is the expectancy violation that occurs when an outcome differs from an expectation. This expectancy violation promotes changes in behavior during future encounters with a given stimulus (Niv & Schoenbaum, 2008; Schultz, Dayan, & Montague, 1997). If the process of learning from expectancy violations is disrupted, errors with similar events will likely persist. Such learning deficits have been observed in individuals with ASD broadly (Mussey, Travers, Klinger, & Klinger, 2015), as well in the context of reward learning tasks (Lin, Adolphs, & Rangel, 2012). The severity of these learning impairments appears to be moderated by stimulus type, such that individuals with ASD may demonstrate greater impairments in social relative to nonsocial learning paradigms (Lin et al., 2012). Eye tracking methods have been commonly used in studies of ASD as a measure of social visual attention

(Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et al., 2002), and numerous studies have reported significant visual preference for nonsocial over social stimuli in ASD across development (Bird, Press, & Richardson, 2011; Chawarska, Macari, & Shic, 2013; Riby & Hancock, 2008, 2009; Shic, Bradshaw, Klin, Scassellati, & Chawarska, 2011). Additionally, individuals with ASD typically make relatively fewer (Goldberg et al., 2002) and slower predictive saccades (D'Cruz et al., 2009) to visual cues (e.g., dots) compared to their typically-developing peers. However, to date, no study has used eye tracking to examine prediction error processing of individuals with ASD during visual violations of an association. This is a notable omission given that understanding how individuals with ASD respond to violations in learned associations may provide insight into the learning differences observed in this population (Wills, Lavric, Croft, & Hodgson, 2007).

The current study used eye tracking to examine gaze patterns in individuals with ASD in response to violations of learned associations using both social and nonsocial stimuli. It was hypothesized that individuals with ASD would show more impaired predictive coding, as measured by the time spent looking at and the number of gaze visits to the cue-predicted location during expectancy violations, and that the magnitude of this impairment would be associated with ASD symptom severity. Because predictive deficits in ASD may be exacerbated when processing social stimuli (Sinha et al., 2014), it was further hypothesized that greater impairment would be observed in the context of social stimuli.

Methods

Participants

Twenty-five adolescents with ASD (age $M = 14.78$, $SD = 1.62$) and 18 typically-developing control (TDC) adolescents (age $M = 14.81$, $SD = 2.08$) participated in the study (see

Table 1.1). ASD diagnoses were confirmed by the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012) and participants with ASD met a cutoff of at least 15 on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003) at the time of initial screening. Caregivers also completed the Social Communication Questionnaire (SCQ) as an initial screening measure. The SCQ is a parental report instrument designed to identify children with signs of autism that includes 40 yes/no questions and provides a cutoff score higher than 15 that indicates autism risk. The SCQ has strong psychometric properties as a screening tool, with sensitivity of .88 and specificity of .76 when discriminating between autism and non-autism cases (Chandler et al., 2007).

Participants in the TDC group met the following inclusion criteria: 1) no known genetic, psychiatric, or medical conditions, including developmental or cognitive delay; 2) no current psychotropic medications; and 3) score less than 15 on the SCQ. All participants were ambulatory, had no significant physical or sensory impairments (e.g., deafness or blindness), and had a Full-Scale IQ >80, measured by the Kaufman Brief Intelligence Test (KBIT; Kaufman, 1990).

ASD participants were recruited from the Carolina Institute for Developmental Disabilities (CIDD) Autism Subject Registry. TDC participants were recruited using a university-wide mass email system as well as referrals from local public schools. Following consent, diagnostic testing (ASD group only), and cognitive testing, participants completed an eye tracking task, clinical report measures, and stimulus ratings. All participants were compensated $15 per hour.

Materials and Measures

Eye tracking task. The eye tracking paradigm was displayed on a Tobii X120 eye tracker integrated with a 23" display monitor. Before beginning the task, participants' were positioned so that their eyes were approximately 60 cm from the monitor, and their eye gaze was calibrated. Once all nine locations were precisely calibrated, participants were asked to remain still during the task. Participant data with less than 50% gaze acquisition accuracy were excluded from the subsequent analyses, including two TDC participants and three ASD participants.

Participants completed an outcome expectation eye tracking task. Prior to administration of the eye tracking task, participants completed a training session to learn two visual cue associations: they were instructed that whenever they saw the red circle, the image that followed this cue would usually appear on the left, and when they saw the blue square, the image would usually appear on the right (Figure 1.1). They were then shown a booklet with several examples and asked to identify, using the previously learned cues, on which side the subsequent image would appear. When it was clear that the participant understood these instructions, they were told that during the task they should look at the images as soon as they appeared. It was also explained that, although these cues would correctly predict the subsequent image a majority of the time, sometimes the image may not appear on the expected side. Each task trial consisted of the presentation of one of the two learned cues followed by the presentation of a social or nonsocial stimulus. On 80% of the trials, cues accurately predicted the learned image location (left or right; non-violation condition). On 20% of the trials, cues incorrectly predicted the learned image location (left or right; violation condition). The task was presented across two runs: one run containing social stimuli (i.e., faces) and one run containing nonsocial stimuli (i.e., trains, electronics, street signs). The order of these runs was counterbalanced across participants.

Eye Tracking Metrics. Two eye tracking outcome measures were extracted: total fixation duration and visit count. Both metrics were collected starting from the time the image (e.g., face or object) appeared on the screen, just following the presentation of the fixation cross (see Figure 1.1). Rectangular areas of interests for both cue-predicted and cue-unpredicted locations were traced for all trials. The AOIs were the same size and centered around the same locations and captured the entire stimulus.

Social and Nonsocial Stimuli. Social stimuli consisted of Happy-Direct Gaze Closed Mouth Female NimStim images (Tottenham et al., 2009). Nonsocial stimuli did not contain any face or body images and were drawn from a set of nonsocial images used in previous ASD studies (see Sasson, Dichter, & Bodfish, 2012). Following the eye tracking task, participants completed a rating task in which they were shown a subset of the pictures of smiling faces and pictures of nonsocial objects they viewed in the eye tracking paradigm and were asked to rate each image on: 1) how pleasant-to-unpleasant they found the image (i.e., valence), and 2) how boring-to-exciting they found the images (i.e., arousal), using 9-point Likert scales.

Cognitive Assessments. To assess general cognitive functioning, determine study eligibility, and match diagnostic groups, participants were administered the KBIT, a brief measure of verbal and nonverbal intelligence. All participants were required to meet verbal and performance IQ cut offs of 80 or higher. This assessment was administered at the beginning of the testing session and lasted approximately 45 minutes.

Autism Diagnostic Assessment. ASD participants were administered either module 3 or module 4 of the ADOS-2 to confirm diagnoses of ASD. Module administration was determined by developmental age and verbal ability. This measure was administered by a research-reliable clinician. This portion of testing lasted approximately 45 minutes, throughout which participants

were asked to complete activities such as telling a story and giving an account of a routine daily activity. Additionally, they were asked questions regarding their perceived role in social situations and understanding of personal responsibilities. It was determined whether participants met ASD criteria based on the ADOS-2 algorithm cut off scores.

Autism Symptoms. Participants and caregivers in both diagnostic groups completed the Social Responsiveness Scale (SRS; Constantino & Gruber, 2002) as an index of change in ASD symptoms before and after treatment. This 65-item measure served to assess the severity of social deficits associated with ASD as they occur in natural settings. Participants answered each question using a given 4-point Likert scale, which ranged in severity. Questions included content regarding intense interests or preoccupations and perceptions of social ability. The SRS can reliably distinguish individuals with ASD from individuals with other psychiatric diagnoses (Constantino et al., 2003).

Results

All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Ratings of Faces and Objects

Results of 2 (Group: ASD, TDC) × 2 (Stimulus: Social, Nonsocial) ANOVAs revealed main effects of stimulus type on valence and arousal ratings, such that the nonsocial stimuli were rated as more pleasing than social stimuli across participants in both groups, $F(1,43) = 5.99$, $p = .019$, $\eta_{p2}=0.12$, and more arousing, $F(1,43) = 8.13$, $p = .007$, $\eta_{p2}=0.16$. There were no significant interactions with group for either valence or arousal ratings, all *p's* > .05. Finally, *post hoc* analyses revealed ASD participants rated the nonsocial stimuli as significantly more pleasing than did TDCs, $t(43) = 2.07$, $p = .045$, $d = 0.64$. There were no differences between groups in valence or arousal ratings of face stimuli, all *p's* > .05.

Eye Tracking Analyses

Visit Count. Poisson regression analyses of gaze visit count included the following factors: Group (ASD, TDC), Expectancy (Violation, No Violation) and Stimulus Type (Nonsocial, Social). The saturated model examined the number of gaze visit counts participants made to both the cue-predicted location and the cue-unpredicted location during nonsocial and social violation trials. Contrasts between effects revealed group was a significant predictor of gaze preferences for cue-predicted visual targets during violation trials, Wald χ_2 (2, N=43) = 10.06, p = .0065, r = 0.48 (see Figure 1.2), reflecting that individuals with ASD made fewer gaze visits to the cue-predicted location during nonsocial and social violation trials relative to TDC participants. This effect was not moderated by stimulus type, p > .05.

Total Fixation Duration. Visit count results were corroborated by analyses of total fixation durations. A Group (ASD, TDC) × Expectancy (Violation, No Violation) × Stimulus Type (Nonsocial, Social) repeated measures ANOVA revealed no significant interaction between these three factors, p > .05. However, the Group (ASD, TDC) × Expectancy (Violation, No Violation) interaction was significant, F (1, 42) =10.65, p = 0.002, η_{p2}=0.20. Tukey-Kramer adjusted *post hoc* analyses revealed that groups differed in the amount of time spent looking toward or away from the cue-predicted location depending on expectancy (i.e., violation or no violation). Specifically, on violation trials, individuals with ASD spent relatively more time looking at the cue-unpredicted (i.e., the presented social or nonsocial stimuli) relative to the cue-predicted location that was empty, p = 0.02. These results are consistent with analyses of visit count data reported above.

Correlations Between Eye Tracking and ASD Symptoms

Correlational analyses examined the associations between visit counts to the cue-predicted location during violation trials and total scores on the SCQ and SRS. These analyses revealed that the number of visits to the cue-predicted location during violations was significantly negatively correlated with SCQ total scores, $r(42) = -0.34$, $p = .026$; and SRS raw total scores, $r(42) = -0.40$, $p = .009$ across both groups (see Figure 1.3). These results suggest that as ASD symptom severity increases, gaze towards the cue-predicted location during violation trials decreases. The SCQ correlational findings should be considered exploratory, as those results do not survive Bonferroni correction, where $\alpha = 0.017$. The SRS findings do, however, survive Bonferroni correction. Additionally, when examined within diagnostic groups separately, the relationship between SRS and gaze visits to cue-predicted locations during violations was marginally significant for the ASD group, $r(24) = -0.37$, $p = .069$, and nonsignificant for the TDC group, $r(17) = -0.05$, $p = 0.84$. Correlations between eye tracking metrics and SCQ scores were not significant when analyzed within diagnostic groups separately.

Correlations Between Eye Tracking and Verbal IQ

Because of the variability in the verbal IQ (VIQ) of the participants with ASD, correlational analyses were conducted to examine the relationship between VIQ and eye tracking metrics within the ASD group alone. These analyses revealed no significant relationship between the number of gaze visits to cue-predicted locations during violation trials and the VIQs of participants with ASD, $r(24) = 0.18$, $p = 0.39$. Additionally, there were no associations between these eye tracking metrics and nonverbal IQ (NVIQ), $r(24) = 0.28$, $p = 0.18$, or full-scale IQ (FSIQ), $r(24) = 0.25$, $p = 0.22$, in the ASD group.

Discussion

The current study examined social and nonsocial visual prediction errors in ASD. Results revealed that individuals with ASD demonstrated relatively impaired predictive abilities, as evidenced by fewer gaze visits and less time spent looking at the cue-predicted location during violation trials. Because these eye tracking metrics were not significantly associated with the cognitive profiles of participants with ASD, these results are attributable to predictive abilities. These findings support a framework that characterizes ASD as a disorder of prediction (Sinha et al., 2014). These results are also consistent with Pellicano and Burr's (2012) Bayesian perceptual theory of ASD that hypothesizes that individuals with ASD may weigh *in vivo* sensory stimuli more heavily than prior experiences, leading to deficits in inferential abilities and learning. Therefore, it is possible that the simple presence of a visual stimulus, as opposed to a blank location that represented the cue-predicted location, overrode the rule of the learned routine. Lawson, Rees, and Friston (2014) argued that the Bayesian perceptual theory of ASD may, in fact, be attributed to deficits in predictive coding, and the current findings are consistent with that hypothesis.

Visual prediction errors were not impacted by whether the experimental stimuli were social or nonsocial. This finding may reflect broadly impaired predictive ability in ASD, irrespective of stimulus type. It is also possible that the lack of significant stimulus type effects indicates that static images, like those used in the current study, are not as effective as dynamic stimuli within the context of eye tracking studies, as has been demonstrated previously (Chevallier et al., 2015). Social predictive impairments in ASD, in particular, have been attributed to difficulties interacting with dynamic objects (Sinha et al., 2014), and this perceived unpredictability of social situations may not be captured by still images of faces. Because dynamic stimuli could evoke a more polarizing visual response to social relative to nonsocial

stimuli than we have observed in the current study, future studies should employ paradigms utilizing videos or other dynamic presentations to examine responses to visual prediction errors in ASD.

Results may also be understood within the context of increased ASD rule-following behaviors, because participants were not explicitly directed to look in the predicted location during violations. Instead, they were instructed to look at the presented stimuli as quickly as possible. For example, when the task violated instructed rules, individuals with ASD may have been more likely to abide with the task instructions rather than update their cue-outcome associations (Pellicano & Burr, 2012). This tendency may result in challenges when learning novel tasks or generalizing learned rules in distinct settings (e.g., learning in therapy how to use appropriate social greetings during social interactions with a peer). One limitation of the current study is that eye gaze latencies to areas of interest could not be extracted. Latency outcomes were calculated for areas of interest during the image presentation (e.g., faces or objects) portion of the paradigm (i.e., immediately following the fixation cross) and revealed that many participants made saccades in the direction of the stimulus prior to presentation. Future eye tracking studies examining predictive ability in ASD should prioritize examining latency of predictive saccades as an outcome measure of interest.

Learning is largely dependent on prediction error experiences (Kamin, 1967); therefore, responses to violations in routines may provide important insight into learning impairments in ASD (Wills et al., 2007). This study is the first to our knowledge to examine gaze responses to visual routine violations in individuals with ASD, and results revealed significant impairments in social and nonsocial visual predictive ability during rule violations, measured by eye tracking gaze metrics. Furthermore, the severity of predictive impairments was associated with ASD

symptom severity. Overall, these results corroborate theories that characterize ASD as a disorder of prediction and may have relevance for mitigating ASD symptoms related to prediction errors in individuals with ASD (Sinha et al., 2014).

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Table 1.1

Means (Standard Deviations) demographics for the ASD and TDC groups

	ASD (n=25) Mean (SD)	TDC (n=18) Mean (SD)	*p* value
Age	14.78 (1.62)	14.81 (2.08)	0.97
Verbal IQ (VIQ)	105.24 (16.98)	110.78 (11.97)	0.24
Performance IQ (PIQ)	101.80 (18.02)	104.83 (14.98)	0.56
Full scale IQ (FSIQ)	104.40 (18.22)	109.28 (14.88)	0.36
Male: female ratio	22:3	17:11	$<0.0007_{\dagger,**}$
SRS Total Raw Score	92.16 (21.51)	21.61 (14.92)	$<0.0001_{**}$
SCQ Total Score	21.04 (5.21)	1.33 (1.57)	$<0.0001_{**}$
Visit Count to Cue-Predicted Location During Violation	1.72 (0.70)	4.44 (2.06)	0.038_{*}
Visit Count to Cue-Predicted Location During Non-Violation	46.76 (10.90)	47.94 (10.03)	0.72

Note. $_{\dagger}$ = Pearson's χ^2 p value; $_{*}$= p<.05; $_{**}$ = p<.01

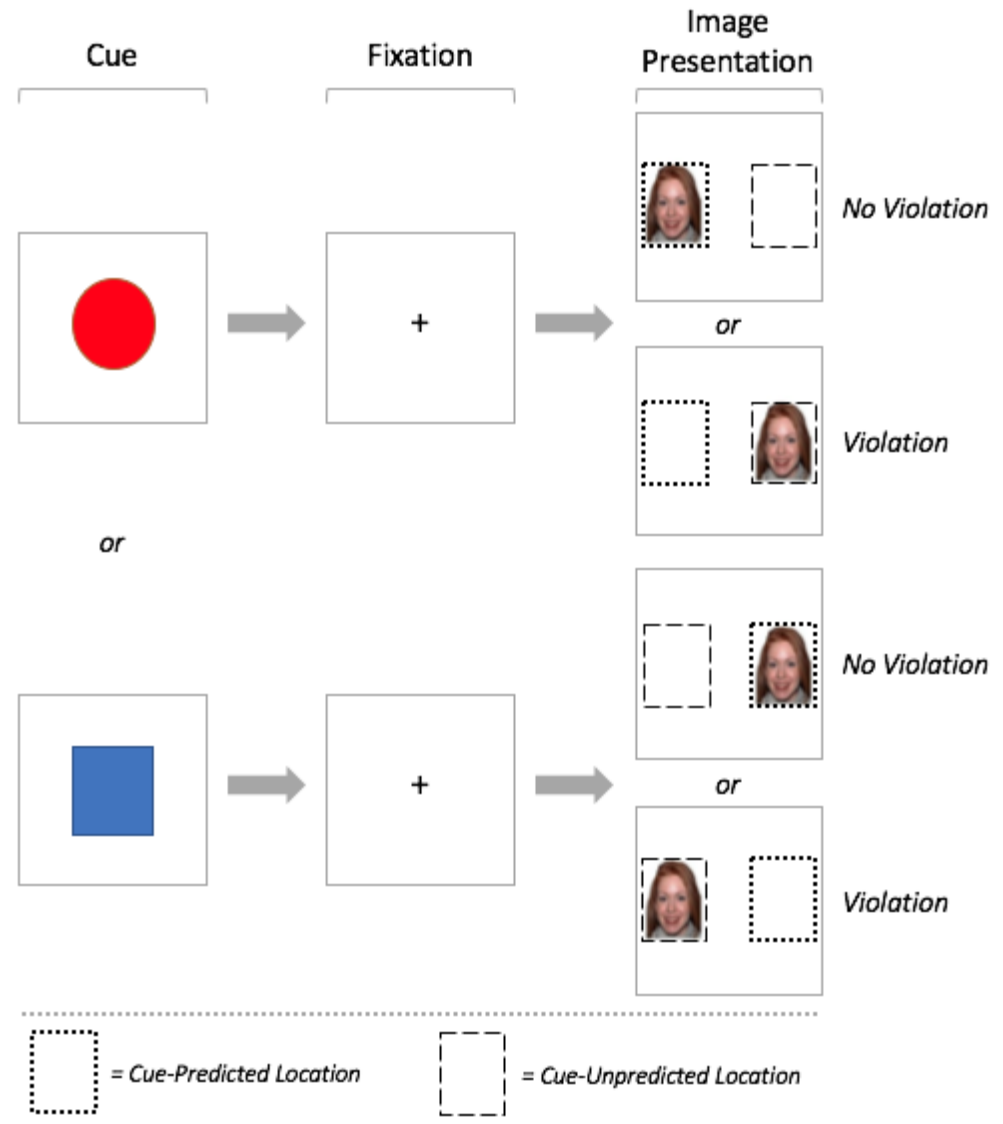

Figure 1.1. The eye tracking task included a cue that predicted on which side (left or right) the forthcoming image would be presented. Prior to the task, participants learned that a circle and a square predicted that the image would appear on the left and right sides of the display, respectively. On 80% of trials, the cues accurately predicted the location (left or right) of the image, and on 20% of trials, the cue incorrectly predicted the location (left or right) of the image. One task block presented social images (as shown here) and one task block presented nonsocial images.

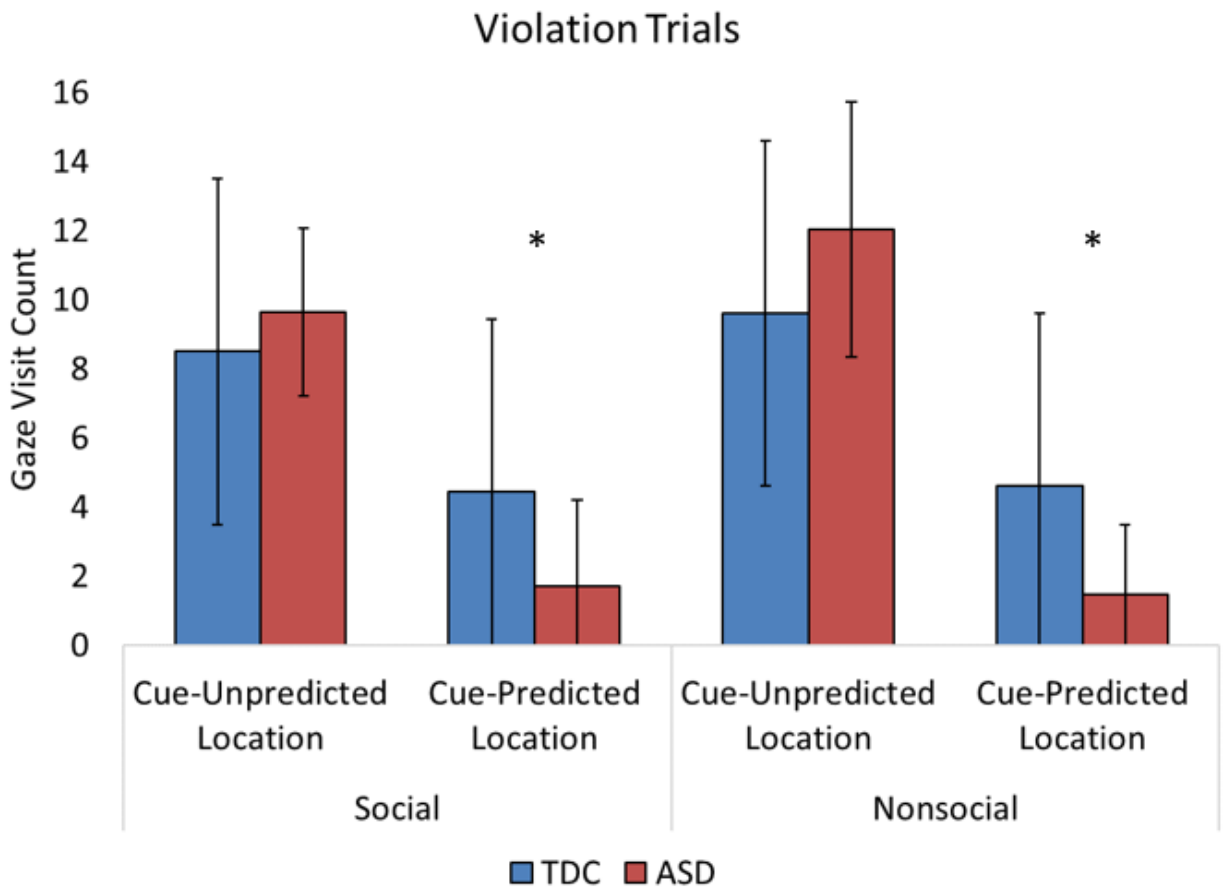

Figure 1.2. * = $p < .05$. Number of gaze visits to cue-predicted and cue-unpredicted locations during social and nonsocial violation trials.

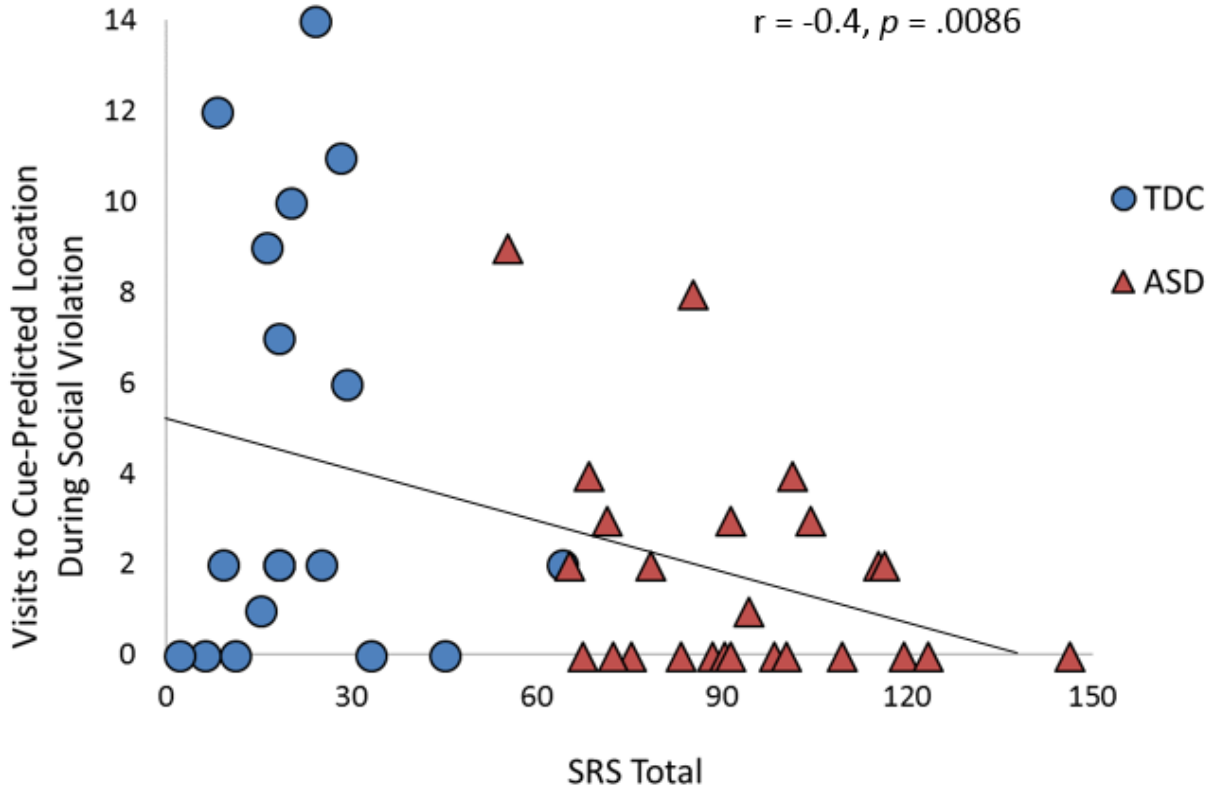

Figure 1.3. Scatterplot of the relations between the number of gaze visits to the cue-predicted location during social violation trials and social impairment, measured by the SRS.

NEURAL MECHANISMS OF VICARIOUS REWARD PROCESSING IN ADULTS WITH AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communicative impairments as well as rigid, repetitive behaviors and restricted interests (APA, 2013). Evidence for impaired social motivation in ASD (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson et al., 2004; Grelotti, Gauthier, & Schultz, 2002), along with enhanced motivation to engage in activities related to repetitive behaviors and restricted interests (Kohls, Antezana, Mosner, Schultz, & Yerys, 2018; Watson et al., 2015) suggests that the processing of rewards may be broadly dysregulated in ASD. Indeed, recent behavioral and fMRI studies in ASD support this pattern of dysregulated reward processing (Cox et al., 2015; Damiano, Aloi, Treadway, Bodfish, & Dichter, 2012; Delmonte et al., 2012; Dichter, Felder, et al., 2012; Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Kohls et al., 2012; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010).

Although previous ASD studies provide evidence for impaired responses to rewards earned for oneself, few have examined responses to rewards earned for others (i.e., vicarious reward). Here, vicarious reward is defined as an individual's experience of another person's anticipated or consumed reward (Lockwood, 2016), and the examination of this construct has facilitated a better understanding of the mechanisms behind certain prosocial behaviors (e.g., empathy and altruism; Mobbs et al., 2009; Morelli, Sacchet, & Zaki, 2015), as well as social decision-making and learning (Ruff & Fehr, 2014). There is support for differences in vicarious

reward responses in individuals with ASD using behavioral tasks. For example, whereas individuals with ASD do not give less money than controls in simulated charitable giving tasks (Izuma, Matsumoto, Camerer, & Adolphs, 2011; Lin, Tsai, Rangel, & Adolphs, 2012), they do give significantly less money to charities benefitting people and are less impacted by information on people-related charities (Lin et al., 2012). Relatedly, individuals with ASD are not as influenced by social context in their willingness to give to others. Whereas control populations have a tendency to be more generous and engage in more prosocial behaviors when observed by others (Bateson, Nettle, & Roberts, 2006; Haley & Fessler, 2005; Kurzban, DeScioli, & O'Brien, 2007; Nowak & Sigmund, 1998; Paulhus, 1984), individuals with ASD appear to be somewhat immune to this effect and are equally generous whether they are observed or not (Izuma et al., 2011). Furthermore, Mosner et al. (2017) reported ASD is characterized by unimpaired expended effort for monetary rewards for oneself, but found that individuals with ASD demonstrated reduced sensitivity to reward magnitude parameters when earning rewards for others. Taken together, these behavioral findings support a hypothesis of altered vicarious reward processing in ASD.

However, to date there have been no studies examining the neural correlates of vicarious reward responses in ASD. Previous research in non-clinical populations suggests that giving monetary rewards to others may be experienced as rewarding itself (Andreoni, 1990) and that similar neurocircuitry recruited for the receipt of rewards for oneself may be involved in vicarious reward processing, including the ventral striatum (Carter, MacInnes, Huettel, & Adcock, 2009; Fareri, Niznikiewicz, Lee, & Delgado, 2012; Harbaugh, Mayr, & Burghart, 2007; Izuma, Saito, & Sadato, 2008; Kuss et al., 2011; Mobbs et al., 2009; Moll et al., 2006; Tricomi, Rangel, Camerer, & O'Doherty, 2010), dorsal striatum (Harbaugh et al., 2007; Morelli et al.,

2015), ventral tegmental area (Moll et al., 2006), insula (Harbaugh et al., 2007; Morelli et al., 2015), anterior cingulate gyrus (Apps & Ramnani, 2014; Lockwood, Apps, Roiser, & Viding, 2015; Morelli et al., 2015), and prefrontal regions, such as orbital frontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC; Fareri et al., 2012; Hare, Camerer, Knoepfle, O'Doherty, & Rangel, 2010; Moll et al., 2006; Morelli et al., 2015; Tricomi et al., 2010). Additionally, a meta-analysis by Morelli et al. (2015) examining vicarious neural reward responses (not restricted to monetary rewards) in typically developing controls (TDCs) found distinct neural activation clusters depending on reward recipient (i.e. self or other). The posterior superior temporal gyrus (STG), the dorsomedial prefrontal cortex (DMPFC), the middle temporal gyrus (MTG), and the superior and middle occipital cortices were more active in response to rewards for others relative to rewards for oneself. Other studies have found preferential activation of the anterior cingulate gyrus in response to vicarious rewards relative to rewards for oneself (Apps, Lesage, & Ramnani, 2015) and revealed significant associations between greater empathic traits and vicarious reward activations in this region (Lockwood et al., 2015). Alternatively, the nucleus accumbens (NAcc), caudate, and thalamus appear to demonstrate greater activation to rewards for oneself relative to vicarious rewards (Morelli et al., 2015).

It is important to examine both the anticipation and outcome phases of reward processing, as these temporal phases are associated with separable functional neural substrates (Berridge & Robinson, 2003). The anticipation phase of reward processing typically corresponds to processes related to reward motivation or to the drive to engage in approach behaviors to obtain rewards (Berridge, 2004; Salamone, Correa, Farrar, Nunes, & Pardo, 2009). Activation during reward anticipation is strongly linked with activation of the ventral striatum, dorsal striatum (e.g.,

caudate, putamen), insula, amygdala, and thalamus (Knutson, Adams, Fong, & Hommer, 2001; Knutson & Greer, 2008). The outcome phase of reward processing, on the other hand, corresponds to hedonic response or experiences of pleasure after obtaining a reward. Although the outcome phase has been linked to mesolimbic regions, it is also strongly linked to activation of prefrontal regions, such as the ventromedial prefrontal cortex (vmPFC) (Knutson, Fong, Adams, Varner, & Hommer, 2001; McClure, York, & Montague, 2004).

The present study, therefore, examined neural activation and connectivity in adults with ASD in response rewards earned for themselves (standard reward condition) and others (vicarious reward condition) using adapted versions of the monetary incentive delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000). Given previous findings that individuals with ASD demonstrate reduced sensitivity to behavioral reward magnitude parameters when earning vicarious rewards, but not rewards for oneself, (Mosner et al., 2017) the current study hypothesized that group differences in neural activation and connectivity in canonical reward processing regions would be relatively more pronounced in response to vicarious reward anticipation and receipt.

Methods

Participants

This study included 16 right-handed adults with a diagnosis of ASD and 15 right-handed age-matched TDCs. Diagnoses of ASD were confirmed with administration of the Autism Diagnostic Observation Schedule – Generic (ADOS-G; Lord et al., 2000) conducted by a research-reliable assessor with standard clinical algorithm cutoffs. Control participants were recruited from databases of TDC participants maintained at the Duke-UNC Brain Imaging and Analysis Center and ASD participants were recruited from the Autism Subject Registry

maintained by the UNC Carolina Institute for Developmental Disabilities.

All participants were male to limit group heterogeneity, since gender is related to differences in reward circuit activation (Spreckelmeyer et al., 2009). Five individuals in the ASD group were taking psychotropic medications, including Risperdal, Citalopram, and Bupropion. Exclusionary criteria for the ASD group included a history of medical conditions associated with ASD, such as Fragile X syndrome, tuberous sclerosis, neurofibromatosis, phenylketouria, epilepsy and gross brain injury, and severe sensory or motor impairments. Participants had no MRI contraindications and were required to meet a full-scale intelligence (IQ) or IQ estimate cutoff of 80. Individuals in the ASD group were administered the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), whereas TDC individuals completed the National Adult Reading Test- Revised to estimate IQ. (NART-R; Blair & Spreen, 1989). Self-reported social communication and interaction impairment was assessed using the Social Responsiveness Scale (SRS; Constantino & Gruber, 2002).

One participant was excluded because of technical issues related to their high-resolution MRI anatomical image. Therefore, the final ASD group (n=15) included 12 Caucasian participants and three Black participants. The TDC group (n=15) included 13 participants of Caucasian descent, one Black participant, and one Asian participant. Analyses of the standard reward condition (i.e., main effect of standard reward and reward condition interaction analyses) included only 14 individuals with ASD because one participant's behavioral data for the standard reward condition was corrupted.

fMRI Task

The MID task variants used in the current study were adapted from a task originally designed by Knutson and colleagues (2000). Participants completed four runs of this task with

four different stimulus types, only two of which are presented here (i.e., reward for self and reward for others). Runs were presented in a randomized order that was counterbalanced across participants. One run involved the opportunity for participants to gain monetary reward ($1 per trial) for themselves if they pressed a button quickly enough following the presentation of a bullseye image (*"self"* condition). In the other run, participants were informed that they had the opportunity to win money for another participant in the study if they pressed the button quickly enough in response to the bullseye (*"other"* condition). Participants were informed that the person for whom they were earning money would later participate in the study and that a previous participant had already won money for them. They were not provided with any additional information about the participant for whom they were winning money or how much the previous participant had won for them. The vicarious condition stimuli were identical to the standard condition except for the instructions provided at the start of the run. All instructions were thoroughly explained to participants before the scan session using both verbal and visual instructions.

Each trial of the MID task consisted of: (1) a 2000 ms cue indicating whether monetary reward could be won (a triangle) or not (a circle) on a given trial; (2) a 2000–2500 ms crosshair fixation; (3) a target bulls-eye presented for up to 500 ms that required a speeded button press; (4) 3000 ms of feedback to indicate whether participants were successful in providing a sufficiently fast response; and (5) a variable length inter-trial interval (ITI) crosshair resulting in a total trial duration of 12 sec. For trials in which a monetary reward was possible (reward trials), a sufficiently fast response resulted in the presentation of an image representing a gain of $1 per successful trial, while a slower response resulted in presentation of an "X" indicating that no money had been won. For trials in which monetary reward was not possible (non-reward trials),

participants were instructed to still respond as quickly as possible to the bulls-eye image. In these non-reward trials, a sufficiently fast response resulted in presentation of checkmark symbol indicating a successful response and no monetary gain, while a slower response resulted in the presentation of an "X" indicating an unsuccessful response and no monetary gain. Potential reward and non-reward trials were aperiodic and pseudorandomly ordered. Each run included 40 trials (50% reward trials, 50% non-reward trials). Participants were instructed to win as much money as possible for themselves or for others and that rewards were contingent on response times. The response time threshold for successful trials was adapted to individual differences in response times, such that all participants were successful on approximately two-thirds of trials (i.e., ~66.67% accuracy). All stimuli were presented using E-Prime presentation software v. 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA) and were viewed through magnet-compatible goggles (Resonance Technology Inc., Northridge CA, USA).

fMRI Acquisition and Preprocessing

Scanning was performed on a General Electric Health Technologies, 3 Tesla Signa Excite HD scanner system with 40-mT/m gradients at 150 T/m/s slew rate (General Electric, Waukesha, WI, USA). Head movement was restricted using foam cushions. An eight-channel head coil was used for parallel imaging. Thirty high-resolution images were acquired using a 3D fast SPGR BRAVO pulse sequence (TR = 7.584 ms; TE = 2.936 ms; FOV = 256^2 mm; voxel size= 1 x 1 x 1 mm; flip angle = 12˚) and used for coregistration with the functional data. These structural images were aligned in the near axial plane defined by the anterior and posterior commissures. Whole brain functional images consisted of 30 slices parallel to the AC-PC plane using a BOLD-sensitive SENSE spiral pulse sequence, at TR of 2000 ms (TE= 30 ms; FOV = 240^2 mm voxel

size: 3.75 x 3.75 x 4 mm; flip angle = 60˚). Runs began with four discarded RF excitations to allow for steady state equilibrium.

Motion Correction

In addition to conducting motion correction using FSL's MCFLIRT (FMRI Expert Analysis Tool; S.M. Smith, 2002; Woolrich et al., 2009), volumes with framewise displacement > 0.9mm (Siegel et al., 2014) were entered into the general linear model (GLM) model as additional confound variables within first-level analyses using FSL's motion outlier detection program (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). All runs included in the analyses were required to retain >40% of their total volumes following the motion outlier correction. Based on this criterion, all runs were included within the analyses. T-tests compared diagnostic groups with respect to motion and found that there was equivalent motion in both groups for both conditions for mean and maximum values along all six axes (i.e., x, y, z, pitch, yaw, and roll), all *p's* > .05.

fMRI Data Analysis

Preprocessing. Functional data were preprocessed using FEAT (S. M. Smith et al., 2004; Woolrich et al., 2009) version 5.0.10 in FSL (FMRIB's Software Library, Oxford University; www.fmrib.ox.ac.uk/fsl). Preprocessing for all functional data involved the following steps: (1) brain extraction to remove all non-brain data (S.M. Smith, 2002); (2) motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002); (3) spatial smoothing using a Gaussian kernel of FWHM 5 mm; (4) FMRIB's Improved Linear Model (FILM) prewhitening; and (5) high-pass filtering (Jenkinson et al., 2002). FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson et al., 2002; Jenkinson & Smith, 2001) was used to register functional images to each subject's T1-weighted structural images with boundary-based registration (BBR; Greve &

Fischl, 2009). These co-registered images were then normalized to a standard stereotaxic Montreal Neurological Institute (MNI) space.

Functional Activation Analyses. For all analyses, anticipation and outcome phases were analyzed separately. Masks were thresholded at 25%, binarized, and then combined into a single mask using fslmaths. Higher-level statistical analyses for within- and between-group analyses were carried out using FLAME 1 (FMRIB's Local Analysis of Mixed Effects; Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Additionally, automatic outlier de-weighting was employed within FLAME 1 to reduce the impact of prefrontal signal drop out within a few participant runs. Key anatomical regions within the reward system (i.e., NAcc , caudate, putamen, thalamus, insula, anterior cingulate gyrus, orbitofrontal cortex, medial prefrontal cortex, superior frontal gyrus; Ernst et al., 2004; Knutson, Fong, et al., 2001; Wacker, Dillon, & Pizzagalli, 2009), as well as regions shown to preferentially respond to vicarious rewards (i.e., STG, MTG; Morelli et al., 2015), were defined *a priori* for small volume correction. For this mask, regions were generated separately for the right and left hemispheres in FSL using the Harvard–Oxford cortical and subcortical structural probabilistic atlases. This mask was then entered within group-level models, in which activation clusters were thresholded at Z=2.58. Supplemental whole-brain analyses were also conducted to examine functional activations during both vicarious and standard reward conditions (see Supplementary Materials). All localizations were based on Harvard-Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView version 5.0.9, and all activations were visualized with MRIcron (https://www.nitrc.org/projects/mricron/).

Symptom analyses. Symptom analyses examined interactions between ASD symptom severity, measured by the SRS, and functional activation during vicarious rewards in the ASD

and TDC groups separately. These analyses were conducted by extracting percent signal change from group-differentiated functional clusters identified within activation analyses. Correlational analyses were then conducted between these parameter estimates and SRS raw total scores.

Functional Connectivity Analyses. Task-based functional connectivity was analyzed using a generalized psychophysiological interaction (gPPI) approach. Voxel-wise models evaluated whole-brain connectivity with functionally- and structurally-defined seeds. For each participant, mean fMRI timecourses (i.e., physiological regressors) were extracted from seed regions for each task run using *fslmeants* in FSL, then multiplied by each psychological regressor of interest (i.e., Trial Type: Reward, Non-reward) to form the PPI interaction terms. The gPPI model included physiological and psychological regressors, as well as their interaction terms to describe the unique effect of these interactions above and beyond the main effect of seed time courses and reward conditions. Significant connections were identified in group-level models using a threshold of Z=2.58.

Results

Behavioral Results

Response times (RTs) for successful reward trials are depicted in Figure 1 and were compared via a 2 (Group: ASD, TDC) × 2 (Reward Recipient: Self, Other) mixed ANOVA. These analyses revealed that there was no significant Group × Reward Recipient interaction, $F(1,27) = 0.79$, $p = .38$ or main effect of Group, $F(1,27) = 0.92$, $p = .35$. The main effect of Reward Recipient neared significance, $F(1,27) = 3.63$, $p = .067$, with participants across both groups responding more quickly to reward for Self ($M = 191.45$, $SD = 56.44$) relative to Other ($M = 205.50$, $SD = 42.43$). Similarly, accuracy (percent of correct trials) was examined within a 2 (Group: ASD, TDC) × 2 (Reward Recipient: Self, Other) mixed ANOVA. These analyses also

revealed no significant Group × Reward Recipient interactions, $F(1,27) = 0.10$, $p = .75$ or main effect of Group, $F(1,27) = 0.00$, $p = .99$. However, again, the main effect of Reward Recipient trended toward significance, $F(1,27) = 3.63$, $p = .068$, such that participants were slightly more accurate when earing reward for Other ($M = 0.69$, $SD = 0.05$) relative to Self ($M = 0.67$, $SD = 0.05$).

Activation Results

Activation analyses presented below represent findings from the Reward > Baseline contrast, as results from the Reward > Non-Reward analyses were non-significant.

Anticipation. Analyses within the TDC group alone revealed significantly greater activation following rewards for Self relative to Other within left orbitofrontal cortex (OFC; see Table 2). However, there were no significant activation clusters with decreased activation in response to rewards for Other compared to Self within the TDC group. Additionally, the ASD group exhibited no differences in neural activation between Self and Other reward conditions. There were also no significant differences in activation between groups for either reward condition main effects or interactions within the anticipation phase.

Outcome. Whereas the TDC group did not show attenuated activation in response to reward outcomes for Other relative to Self, TDCs exhibited augmented activation within right middle temporal gyrus (MTG) and left middle frontal gyrus (MFG) during the receipt of rewards for Other compared to Self (see Table 2). Alternatively, the ASD group demonstrated no significant differences in activation to reward outcomes between recipients. Compared to TDCs, the ASD group showed attenuated responses to rewards for Other within bilateral frontal pole (FP), right MTG, left superior frontal gyrus (SFG), and left caudate nucleus (see Figure 2). In addition, relative to TDC individuals, those with ASD exhibited significantly decreased

activation in right MTG and left FP during reward outcomes for Other relative to Self (see Figure 3).

Main effects analyses for each reward condition by Group are presented within Supplementary Tables 1 and 2. These simple effects analyses revealed that both groups showed activation in mesocorticolimbic reward processing regions in response to both reward conditions. Additionally, results from the whole-brain activation analyses are presented within Supplementary Tables 3 and 4.

Correlations Between Functional Activation and ASD Symptoms

ASD symptom severity was not significantly correlated with functional activation during vicarious reward outcomes within group-differentiated clusters identified within activation analyses described above (i.e., left FP, right MTG, left caudate nucleus), all p's > .05.

Functional Connectivity Results

Functional neural connectivity analyses were conducted using a seed constructed from the group-differentiated functional cluster in the MTG identified within the outcome phase activation Group (ASD, TDC) × Reward Recipient (Self, Other) interaction analyses. Because of our *a priori* interest in the NAcc, connectivity analyses also included structurally-defined left and right NAcc seeds. Because group differences in activation were restricted to the outcome phase of the tasks, all functional connectivity analyses were restricted to the outcome phase only to constrain the number of analyses performed and, thereby, limit the potential for Type I errors.

Functional Middle Temporal Gyrus Seed. During the receipt of rewards for Self, individuals with ASD exhibited decreased functional connectivity relative to TDCs between the right MTG and the left caudate, right thalamus, right FP, right inferior frontal gyrus (IFG), and left superior parietal lobule (see Table 3). Attenuated functional connectivity was also observed

in individuals with ASD relative to TDCs during the receipt of rewards for Others between the right MTG and right FP (see Figure 4). Individuals with ASD showed heightened connectivity, however, between the functional right MTG seed and the left lateral occipital cortex, other regions within the right MTG, and the left lingual gyrus during the receipt of rewards for Others relative to Self.

Structural Right NAcc Seed. During outcomes to rewards in the Self condition, attenuated functional connectivity was observed between right NAcc and the left caudate, right pallidum, bilateral frontal pole, left superior parietal lobule, right thalamus, and left precuneus for individuals with ASD relative to TDCs (see Table 3). Additionally, during reward outcomes for Other, decreased connectivity was exhibited for individuals with ASD relative to TDCs between right NAcc and left caudate, right thalamus, right MTG, left anterior cingulate gyrus (ACG), bilateral frontal pole, and right IFG. No hyperconnectivity with the right NAcc was observed in individuals with ASD relative to TDCs. There were also no significant connections identified in Group (ASD, TDC) × Reward Recipient (Self, Other) interaction analyses with the structural right NAcc seed.

Structural Left NAcc Seed. The left NAcc seed showed similar patterns of hypoconnectivity for individuals with ASD. Specifically, during reward outcomes for Self, individuals with ASD relative to TDCs exhibited attenuated communication between left NAcc and bilateral caudate, left superior parietal lobule, right pallidum, right IFG, left precuneus, and left subcallosal cortex (see Table 3). Connectivity between left NAcc and bilateral caudate, right thalamus, bilateral SFG, bilateral IFG, right FP, left precentral gyrus, left STG, and left MTG was similarly reduced for individuals with ASD relative to TDCs during reward receipt for Other (see Figure 5). Again, there were no brain regions that showed heightened connectivity with left

NAcc in individuals with ASD relative to TDC, and there were no significant connections with left NAcc identified within Group (ASD, TDC) × Reward Recipient (Self, Other) interaction analyses.

Discussion

The goal of the present study was to investigate neural processing of vicarious rewards ("Other" condition) relative to standard rewards ("Self" condition) in adults with ASD. In line with hypotheses, individuals with ASD exhibited attenuated neural activation in key reward regions in response to vicarious reward receipt. Specifically, hypoactivation was observed within bilateral FP, right MTG, left SFG, and left caudate during vicarious reward outcomes in individuals with ASD. Furthermore, right MTG and left FP were preferentially deactivated in individuals with ASD relative to TDCs during vicarious relative to standard reward outcomes. These results corroborate existing ASD reward processing findings, which have largely reported a pattern of hypoactivation in response to reward stimuli (Clements et al., 2018). The MTG plays a key role in vicarious reward processing (Morelli et al., 2015); therefore, it is noteworthy that individuals with ASD recruited this region to a lesser extent than their typically developing peers. The MTG has also previously been implicated in theory of mind abilities (Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Moriguchi et al., 2006), social perception (Allison, Puce, & McCarthy, 2000), and empathic judgements (Farrow et al., 2001), and relatively diminished activation within the MTG in individuals with ASD has previously been reported in response to social mentalizing tasks (Assaf et al., 2013; Assaf et al., 2009). Taken together, ASD hypoactivation in the MTG may underlie observed deficits in behavioral vicarious reward responses (Mosner et al., 2017), as well as broader social cognitive deficits inherent to the disorder.

Whereas the TDC vicarious reward literature does not specifically implicate striatal regions as being preferentially activated for vicarious relative to standard reward processing (Morelli et al., 2015), it is noteworthy that individuals with ASD showed reduced activation during vicarious reward outcomes in the caudate nucleus, given its established role in reward processing. The caudate nucleus is a component of the dorsal striatum which plays a key role in the evaluation of action outcomes (Grahn, Parkinson, & Owen, 2008) and assumes the "critic" role within the actor-critic reinforcement model of reward-based learning (Montague, Dayan, & Sejnowski, 1996), whereas ventral striatal regions play the "actor" role in controlling and enacting reward-related behaviors (O'doherty et al., 2004). The current findings of ASD hypoactivation within the caudate nucleus during the outcome phase of the vicarious reward condition may, thus, suggest the evaluative role of the caudate nucleus in response to vicarious reward receipt is disrupted in ASD.

Contrary to hypotheses, no significant group differences in activation were observed within the anticipation phase. This indicates ASD-associated differences in vicarious reward processing are constrained to reward receipt, whereas responses to reward anticipation are unimpaired. Additionally, there were no group differences in response to reward anticipation or outcomes for oneself. This counters studies that have shown differences in neural activation between individuals with ASD and TDCs in response to monetary rewards for oneself (Dichter, Felder, et al., 2012; Dichter, Richey, et al., 2012; Kohls et al., 2012; Schmitz et al., 2008) but is consistent with others that have found neural responses to standard monetary rewards are unaltered in ASD (Delmonte et al., 2012; Scott-Van Zeeland et al., 2010).

To date no study has compared neural functional connectivity of individuals with ASD to TDCs during a reward-specific task. Altered neural connectivity with key reward regions was

observed in individuals with ASD relative to TDC for both standard and vicarious reward conditions. The functionally-defined right MTG exhibited decreased communication with left caudate, right thalamus, right FP, right IFG, and left superior parietal lobule during standard reward outcomes, as well as reduced connectivity with right FP during vicarious reward outcomes. Alternatively, the Group × Reward Recipient interaction results revealed *hyperconnectivity* between right MTG and left lateral occipital cortex, left lingual gyrus, and other regions within the right MTG. Together, this suggests that, for individuals with ASD, the right MTG may disengage with typical reward-associated regions (i.e., caudate, thalamus, frontal pole) during vicarious reward processing, while recruiting regions less frequently associated with reward processing. When examining connections with both the right and left NAcc, however, there was a consistent pattern of hypoconnectivity with key reward regions when earning both vicarious and standard rewards. There were no significant interactions of Reward Recipient, suggesting this disconnection of the NAcc is equally as impaired in both vicarious and standard reward in individuals with ASD. These findings build on the inconsistent literature addressing functional connectivity in ASD. Although they corroborate findings of reduced intrinsic mesocorticolimbic underconnectivity (Abrams et al., 2013), they are in contrast with resting state reports of frontostriatal hyperconnectivity in ASD (Delmonte, Gallagher, O'Hanlon, Mc Grath, & Balsters, 2013; Di Martino et al., 2011). However, comparisons between task-based and intrinsic connectivity results should be interpreted with caution, given inherent methodological differences between the two (Müller et al., 2011).

Task reaction times showed increased speed of responses to rewards for oneself compared to vicarious rewards, although this effect was only marginally significant. There were no group differences or significant interaction between Group (ASD, TDC) and Reward Recipient (Self,

Other) for reaction times. Similarly, individuals across both groups showed marginally greater accuracy when earning vicarious relative to standard rewards, such that responses to rewards for others were typically more accurate than those for oneself. Again, there were no group differences in accuracy and this difference in accuracy based on reward recipient was not moderated by group. Overall, this suggests a group-independent association between increased reaction times and greater accuracy when earning rewards for others relative to earning for oneself.

Examining reward circuitry responses to vicarious rewards is important in light of the established differences in empathy and perspective-taking or "theory of mind" in ASD (Baron-Cohen, Leslie, & Frith, 1985; Baron-Cohen & Wheelwright, 2004; Dawson & Fernald, 1987; Yirmiya, Sigman, Kasari, & Mundy, 1992). Notably, empathy is defined as a multidimensional construct, consisting of both cognitive and affective components (Decety & Meyer, 2008; Dziobek et al., 2011; Singer, 2006). Individuals with ASD show impairments in the cognitive dimension of empathy, including theory of mind abilities and recognition of emotions in oneself and others, while affective or emotional empathy (i.e., the ability to experience similar emotions as others as a result of the other person's emotional state) appears unimpaired in individuals with ASD (Baron-Cohen, 2011; Mazza et al., 2014). In fact, affective empathy may be heightened for individuals with ASD (A. Smith, 2009), as evidenced by exaggerated facial expressions in children with ASD in response to the distress of a social partner (Capps, Kasari, Yirmiya, & Sigman, 1993). Findings from the current study may represent the neural underpinnings of deficits in cognitive empathy and other social cognitive differences in ASD. Additionally, these results may have implications for social learning and decision-making abilities of individuals with ASD. Specifically, reduced sensitivity to vicarious rewards may weaken the effectiveness of

social learning strategies like vicarious reinforcement, which asserts that individuals emulate their behavior after seeing others rewarded or praised for certain prosocial behaviors (Bandura, Ross, & Ross, 1963). This may also, consequently, contribute to impaired imitation abilities demonstrated by individuals with ASD (Charman et al., 1997; Rogers, Hepburn, Stackhouse, & Wehner, 2003; I. M. Smith & Bryson, 1994).

By comparing standard and vicarious monetary rewards, this study also addresses existing challenges in investigating social rewards in ASD. Specifically, nearly all ASD reward studies have examined this question using monetary rewards as a proxy for non-social rewards and faces as a proxy for social rewards. Using such a restricted range of reward stimuli may limit the generalizability and ecological validity of these studies and raises the possibility that the confounding factors related to monetary and face rewards contributed to their findings. Moreover, face rewards may not be the ideal social reward by which to compare monetary gain. Face and monetary rewards differ in many important aspects, including their associations with future reward, the uniformity across different stimuli, and basic visual properties. While some studies have suggested that reward circuit dysfunction may be somewhat more marked for social rewards in ASD (Delmonte et al., 2012; Richey et al., 2014; Scott-Van Zeeland et al., 2010), it remains unclear whether these results reflect face processing atypicalities associated with ASD and/or other confounding factors that differentiate monetary versus face reward conditions. Additionally, other studies have reported no significant differences between reward responses to money versus faces in individuals with ASD (Dichter, Richey, et al., 2012). The current paradigm utilizing standard and vicarious rewards provides an avenue to investigate social reward responses in ASD, while controlling for potential confounds related to using a personal

monetary reward as a comparison (e.g., the representative nature and visual properties of the stimuli).

Although the current study found no significant association between neural reward activation to reward stimuli and ASD symptom severity, future studies should continue examine this relationship. ASD symptom severity was self-reported by individuals in both groups. The absence of association between ASD symptoms and neural responses may possibly reflect difficulty reporting on socioemotional states for individuals with ASD (Payakachat, Tilford, Kovacs, & Kuhlthau, 2012). Additionally, further studies with larger sample sizes will be needed to replicate these findings. Finally, the implications of this study may be restricted to males with ASD with higher cognitive abilities. Given the significant behavioral (Frazier, Georgiades, Bishop, & Hardan, 2014) and neural (Kirkovski, Enticott, Hughes, Rossell, & Fitzgerald, 2016) sex-based differences in ASD, future reward processing studies should investigate females with ASD, as well.

In summary, individuals with ASD showed typical neural responses during both the anticipation and receipt of rewards earned for themselves, as well as the anticipation of vicarious rewards. However, individuals with ASD demonstrated relatively diminished activation within reward-related regions during the receipt of vicarious, but not standard, rewards. Altered connectivity with the MTG was observed in individuals with ASD during the receipt of rewards for themselves and others. Additionally, decreased connectivity between the NAcc and other canonical neural reward regions was observed in individuals with ASD during vicarious and standard reward outcomes. These findings of reduced neural sensitivity to vicarious reward receipt may represent a mechanism by which theory of mind abilities and social reward learning are disrupted in ASD.

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Table 2.1

Participant Characteristics

	ASD (N=15) Mean (SD)	**Control (N=15) Mean (SD)**	***t***	***p***
Age	27.97 (10.88)	27.47 (8.60)	-0.14	0.89
Full Scale IQ[a]	118.3 (10.51)	117.31 (5.06)	-0.31	0.76
Verbal IQ[a]	115.0 (15.89)	114.62 (5.42)	-0.08	0.94
Performance IQ[a]	117.6 (7.15)	116.13 (5.08)	-0.59	0.56

Note. *= $p < 0.05$; [a] ASD Intelligence Quotient (IQ) scores were calculated based on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and TDC IQ estimates were measured using the National Adult Reading Test – Revised (NART-R; Blair & Spreen, 1989). IQ scores/estimates were missing for three TDC participants and one ASD participant.

Table 2.2

Small Volume-Corrected Significant Functional Activation Clusters During Rewards for Self and Others

Phase	Reward Recipient	Region	Hem	k	BA	x	y	z	Z max
Anticipation	**TDC**								
	Others > Self	Orbitofrontal Cortex	L	167	--	-36	40	-18	3.45
Outcome	**TDC**								
	Others > Self	Middle Temporal Gyrus	R	219	--	50	-46	0	3.78
		Medial Frontal Gyrus	L	191	--	-30	20	50	3.67
	ASD > TDC								
	Others < Self	Middle Temporal Gyrus	R	445	--	52	-52	8	4.11
		Frontal Pole	L	165	--	-46	54	-6	3.74
	ASD < TDC								
	Others	Frontal Pole	L	271	--	-46	46	-2	4.31
			R	139	46	50	38	6	3.90
		Middle Temporal Gyrus	R	155	--	44	-40	2	4.63
		Superior Frontal Gyrus	L	140	6	-22	18	64	3.51
		Caudate Nucleus	L	125	--	-10	-4	18	4.19
	Others > Self	Middle Temporal Gyrus	R	445	--	52	-52	8	4.11
		Frontal Pole	L	165	--	-46	54	-6	3.74

Note. Analyses were conducted examining the main effect of Group (ASD, TDC) and Reward Recipient (Self, Other) and interactions between the two factors. However, only significant activations are presented within this table. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Table 2.3

Significant Functional Connections During Reward Outcomes for Self and Others

Seed	Reward Recipient	Region	Hem	k	BA	x	y	z	Z max
Right MTG	**ASD > TDC**								
	Other > Self	Lateral Occipital Cortex	L	693	--	-20	-72	50	3.39
		Middle Temporal Gyrus	R	670	--	54	-36	-2	3.67
		Lingual Gyrus	L	623	--	-12	-66	0	3.39
	ASD < TDC								
	Self	Caudate†	L	154 12	--	-12	0	12	5.53
		Thalamus	R	--	--	8	-22	14	4.75
		Frontal Pole	R	--	10	-28	48	20	4.72
		Inferior Frontal Gyrus	R	--	--	48	30	8	4.66
		Superior Parietal Lobule	L	152 8	--	-22	-50	58	4.85
		Frontal Pole	R	415	--	-8	-54	8	4.11
	Other	Frontal Pole	R	250	--	14	36	42	3.86
Right NAcc	**ASD < TDC**								
	Self	Caudate†	L	177 11	--	-8	0	12	5.15
		Pallidum	R	--	--	28	-12	-2	4.94
		Frontal Pole	R	--	--	52	34	-4	4.76
		Superior Parietal Lobule	L	--	--	-24	-48	58	4.74
		Frontal Pole	L	--	--	-28	50	20	4.66
		Thalamus	R	--	--	8	-24	14	4.65
		Precuneus	L	516	--	-8	-54	8	4.19
	Other	Caudate†	L	194 8	--	-10	-2	12	5.24
		Thalamus	R	--	--	8	-24	12	4.37
		Middle Temporal Gyrus	R	--	--	54	-26	-12	4.31
		Anterior Cingulate Gyrus	L	109 8	24	-10	18	32	4.52
		Frontal Pole	R	707	--	2	62	34	3.94

			L	345	--	-40	36	0	4.03
			L	230	10	-28	52	18	4.25
		Inferior Frontal Gyrus	R	402	--	32	-4	52	3.92
	ASD < TDC								
	Self	Caudate†	L	20401	--	-8	0	12	5.4
		Superior Parietal Lobule	L	--	--	-22	-50	58	5.03
		Pallidum	R	--	--	28	-18	-2	4.79
		Inferior Frontal Gyrus	R	--	--	54	12	8	4.72
		Caudate	R	--	--	12	14	12	4.66
		Precuneus	L	663	--	-8	-54	8	4.33
		Subcallosal Cortex	L	261	--	-8	8	-20	4.28
Left NAcc	Other	Caudate†	L	1231	--	-10	0	12	5.38
		Thalamus	R	--	--	10	-24	12	4.27
		Caudate	R	--	--	12	12	18	3.68
		Superior Frontal Gyrus	L	789	8	-22	32	50	4.29
			R	452	--	18	32	50	3.75
		Inferior Frontal Gyrus	L	430	--	-40	34	0	4.3
			R	408	--	52	30	-4	4.05
		Frontal Pole	R	341	--	34	58	16	3.54
		Precentral Gyrus	L	307	--	-26	-22	46	3.74
		Superior Temporal Gyrus	L	292	--	-48	-40	10	3.72
		Middle Temporal Gyrus	L	230	--	54	-26	-10	4.11

Note. Analyses were conducted examining the main effect of Group (ASD, TDC) and Reward Recipient (Self, Other) and interactions between the two factors. However, only significant activations are presented within this table. † = Peaks are listed first for each cluster with subpeaks listed in subsequent indented rows. NAcc=Nucleus Accumbens; MTG=Middle Temporal Gyrus; Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

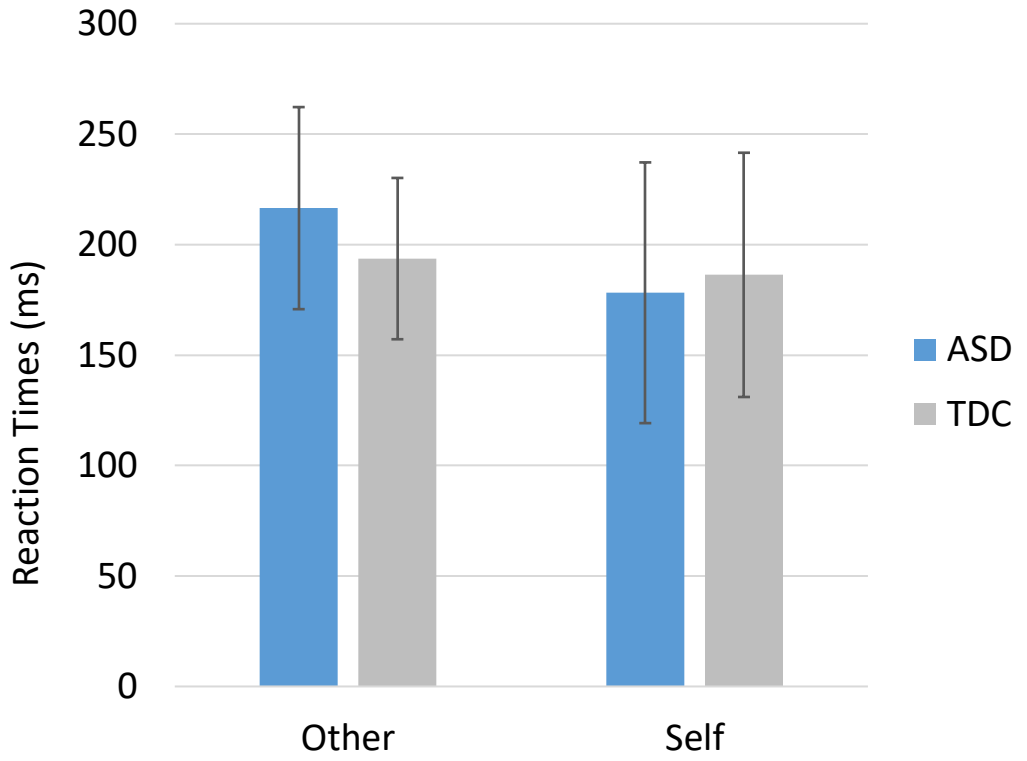

Figure 2.1. ASD and TDC group-averaged reaction times in response to rewards earned for self and other. The difference between reaction times to personal versus vicarious rewards was only marginally significant (p=.067) across groups.

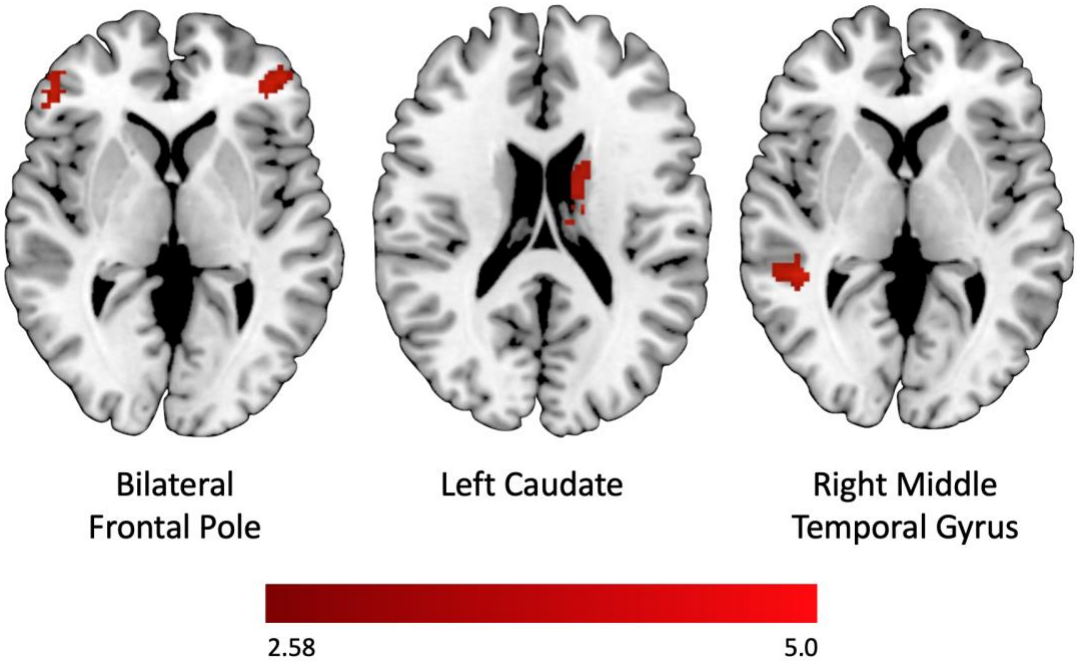

Figure 2.2. Functional activation clusters showing hypoactivation in individuals with ASD relative to TDC during vicarious reward outcome.

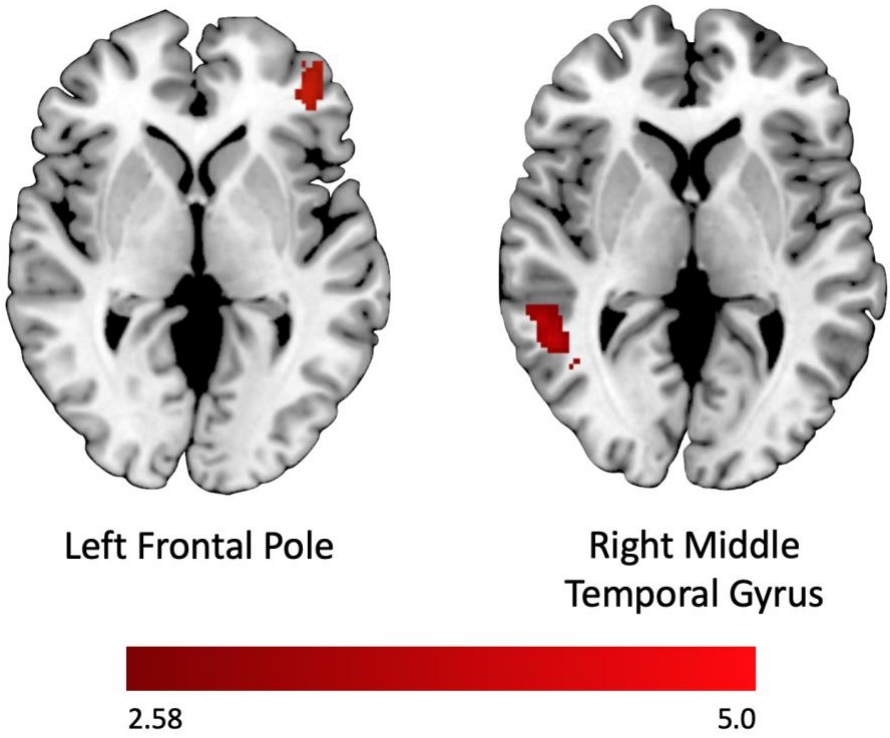

Figure 2.3. Functional activation clusters showing hypoactivation in individuals with ASD relative to TDCs during vicarious relative to standard reward outcome.

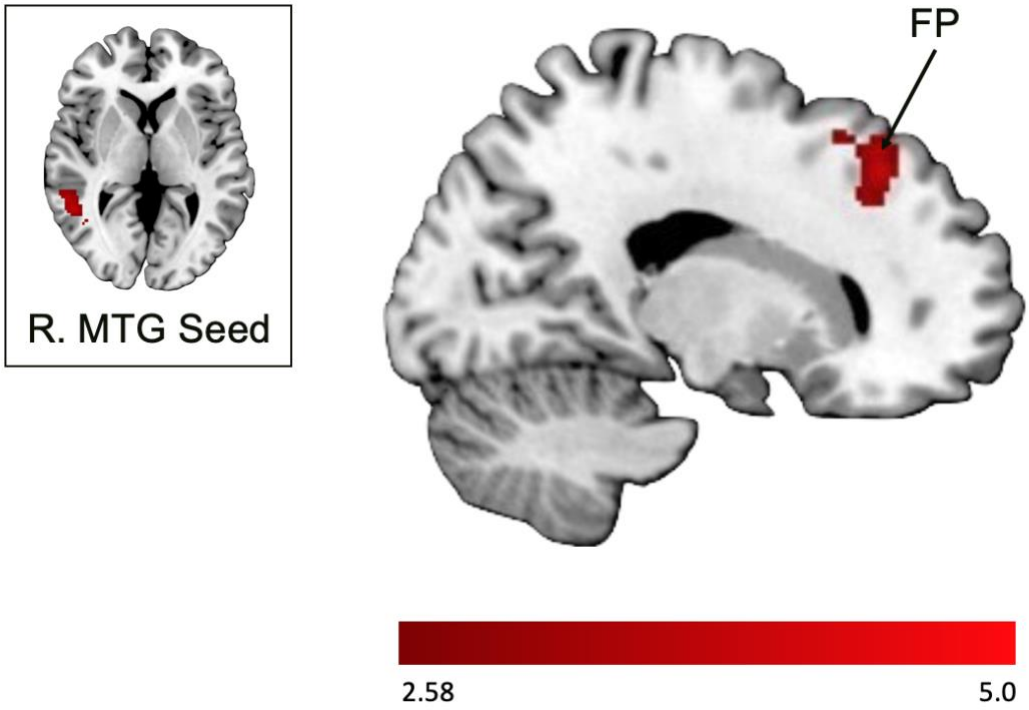

Figure 2.4. Functional connectivity clusters showing decreased connectivity with right middle temporal gyrus (MTG) in individuals with ASD relative to TDCs during vicarious reward outcomes. FP=frontal pole.

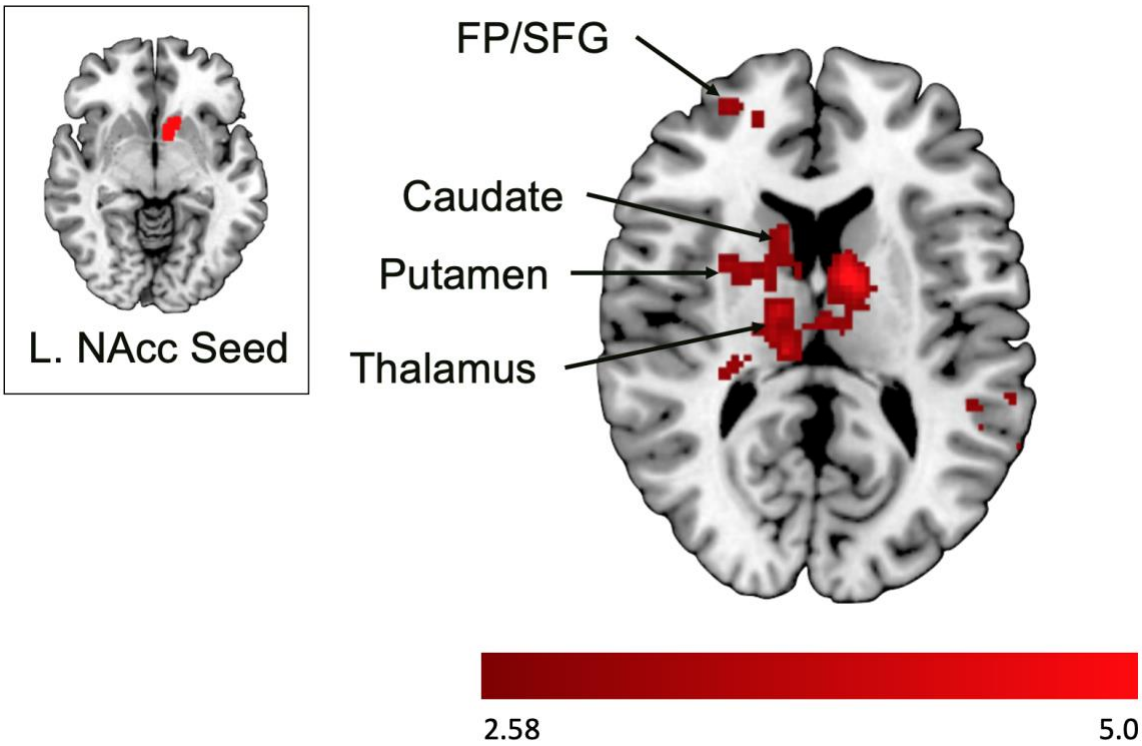

Figure 2.5. Functional connectivity clusters showing decreased connectivity with left Nucleus Accumbens (NAcc) in individuals with ASD relative to TDCs during vicarious reward outcomes. FP=frontal pole; SFG=superior frontal gyrus; MTG=middle temporal gyrus.

Supplementary Materials

Main effect results of reward recipient on small volume corrected neural activation in ASD and TDC groups separately

Activation analyses described below were conducted using the same small volume correction mask as described within the manuscript.

Anticipation. Analyses of functional activation of individuals with ASD during the anticipation of rewards for Self revealed significant activations within right putamen, bilateral MTG, bilateral MFG, left paracingulate gyrus, right precentral gyrus and right SFG (see Supplementary Table 2.1). In response to rewards for Other, individuals with ASD showed heightened activation in right pallidum, left ACG, left caudate, bilateral thalamus, right MFG, left SFG, right central operculum cortex, and right MTG. Individuals within the TDC group exhibited significant activation during reward anticipation for Self within right putamen, right ACG, right thalamus, bilateral SFG, right MTG, and left frontal operculum cortex. Regarding TDC responses to rewards for Other, analyses revealed augmented activation within right pallidum, left ACG, left caudate, right thalamus, bilateral MTG, bilateral SFG, left frontal operculum cortex, bilateral frontal pole, and right posterior STG.

Outcome. Analyses of functional activation of individuals with ASD during the outcome of rewards for Self revealed significant activations within right thalamus, right ACG, right FP, right insular cortex, left MFG, right precentral gyrus, and right MTG (see Supplementary Table 2.2). In response to rewards for Other, individuals with ASD showed heightened activation in right thalamus, right ACG, right insular cortex, right MFG, left central operculum cortex, and right SFG. Individuals within the TDC group exhibited significant activation during reward receipt for Self right thalamus, right ACG, right precentral gyrus, left FP, bilateral SFG, and

bilateral MTG. Regarding TDC responses to rewards for Other, analyses revealed increased activation within left thalamus, bilateral FP, left ACG, bilateral MTG, and bilateral SFG.

Whole-brain analysis results of neural activation during vicarious and standard rewards in ASD and TDC

Activation analyses described below were conducted using a whole-brain approach, and, thus, were not confined to specific pre-defined anatomical regions.

Anticipation. Whole brain functional activation during anticipation of rewards for Self revealed increased neural activations within right lateral occipital cortex for individuals with ASD relative to TDCs (see Supplementary Table 2.3). Individuals with ASD relative to TDCs showed decreased activation in right lateral occipital cortex and left postcentral gyrus during rewards for Other relative to Self. Individuals with ASD showed no significant hyperactivation relative to TDCs in response to rewards for Other. Furthermore, there were no significant activation clusters during the anticipation of rewards for Self or Other for either group within the main effect analyses.

Outcome. Whole brain functional activation analyses of Self and Other reward outcomes showed no significant activation clusters for individuals with ASD. TDCs, however, exhibited greater activation during reward receipt for Other relative to Self within right precuneus, right lateral occipital cortex, right MTG, left supramarginal gyrus, and left MFG (see Supplementary Table 2.4). During reward outcomes for Other, individuals with ASD demonstrated relatively decreased activation in right ACG, right MTG, bilateral FP, left SFG, and left parahippocampal gyrus. Interaction analyses revealed that, when compared to TDCs, individuals with ASD showed attenuated activation during reward outcomes for Other relative to Self within right MTG, left IFG, right lateral occipital cortex, right supramarginal gyrus, and left angular gyrus.

Supplementary Table 2.1

Small Volume-Corrected Main Effect of Group on Functional Activation During Reward Anticipation for Self and Other

Reward Recipient	Region	Hem	k	BA	x	y	z	Z max
ASD								
Self	Putamen†	R	2986	--	22	8	2	5.27
	Putamen	L	--	--	-18	6	0	5.01
	Thalamus	R	--	--	8	-28	0	4.98
	Caudate	R	--	--	14	14	2	4.89
	Middle Temporal Gyrus	R	382	--	50	-64	-2	3.87
	Middle Frontal Gyrus	R	371	--	42	22	24	4.08
		L	224	--	-48	30	28	3.40
	Paracingulate Gyrus	L	292	--	-8	16	38	4.43
	Precentral Gyrus	R	174	6	44	2	48	4.58
	Middle Temporal Gyrus	L	168	--	-46	-54	2	3.67
	Superior Frontal Gyrus	R	159	--	12	4	64	4.54
Other	Pallidum	R	470	--	20	4	2	4.35
	Anterior Cingulate Gyrus	L	465	--	-8	12	36	4.35
	Caudate	L	447	--	-12	10	0	4.57
	Thalamus	L	384	--	-4	-24	-2	4.00
		R	194	--	8	-24	-2	3.80
	Middle Frontal Gyrus	R	296	--	32	36	34	4.05
	Superior Frontal Gyrus	L	213	--	-8	-10	74	4.13
	Central Opercular Cortex	R	163	--	40	10	6	4.08
	Middle Temporal Gyrus	R	147	--	52	-42	10	4.05
TDC								
Self	Putamen†	R	1748	--	20	18	0	5.86

	Frontal Operculum Cortex	R	--	--	34	20	10	4.49
	Caudate	L	--	--	-18	10	12	4.36
	Anterior Cingulate Gyrus	R	770	24	8	6	40	5.4
	Thalamus	R	651	--	2	-28	0	5.23
	Superior Frontal Gyrus	L	445	--	-10	-2	72	4.13
		R	367	--	14	6	64	4.59
	Middle Temporal Gyrus	R	305	--	42	-52	8	4.71
	Frontal Operculum Cortex	L	213	--	-30	20	14	4.72
Other	Pallidum†	R	1271	--	20	2	4	5.16
	Orbitofrontal Cortex	R	--	--	30	28	4	4.91
	Frontal Operculum Cortex	R	--	--	34	22	10	4.82
	Insular Cortex	R	--	--	32	16	8	4.73
	Putamen	R	--	--	22	14	4	4.46
	Anterior Cingulate Gyrus†	L	1125	--	-6	16	34	6.26
	Paracingulate Gyrus	R	--	32	6	18	38	5.22
	Caudate†	L	1070	--	-16	16	8	4.84
	Putamen	L	--	--	-20	4	10	4.83
	Subcallosal Cortex	L	--	--	-4	16	-16	4.04
	Thalamus	R	1011	--	12	-20	-4	5.43
	Middle Temporal Gyrus	R	815	--	42	-60	6	4.86
		L	385	--	-48	-66	-6	4.39
	Superior Frontal Gyrus	L	594	--	-16	4	66	5.28
		R	516	6	10	-4	70	4.62
	Frontal Operculum Cortex	L	273	--	-28	22	12	5.37
	Frontal Pole	R	223	--	38	44	28	3.44

		L	208	--	-24	46	-12	3.99
		L	199	--	-38	38	22	3.26
	Posterior Superior Temporal Gyrus	R	154	22	48	-24	-4	4.27

Note. Analyses were conducted examining the main effect of Group (ASD, TDC) and Reward Recipient (Self, Other). Only significant activations are presented within this table. † = Peaks are listed first for each cluster with subpeaks listed in subsequent indented rows. BA=Brodmann Area; Z max=maximum z-value.

Supplementary Table 2.2

Small Volume-Corrected Main Effect of Group on Functional Activation Reward Outcomes for Self and Other

Reward Recipient	Region	Hem	k	BA	x	y	z	Z max
ASD								
Self	Thalamus†	R	3799	--	6	-4	12	6.88
	Caudate	R	--	--	12	4	14	5.51
		L	--	--	-10	0	12	5.06
	Insular Cortex	L	--	--	-36	8	6	5.37
	Anterior Cingulate Gyrus†	R	1144	--	2	-2	44	5.64
	Juxtapositional Lobule Cortex	R	--	--	2	0	48	4.90
	Anterior Cingulate Gyrus	L	--	--	-8	-2	42	4.58
	Paracingulate Gyrus	R	--	32	4	10	44	4.46
		L	--	--	0	12	42	4.32
	Frontal Pole	R	720	--	38	40	22	4.06
	Insular Cortex	R	680	--	38	6	-2	4.76
	Middle Frontal Gyrus	L	440	9	-34	36	30	4.48
	Precentral Gyrus	R	436	6	48	6	38	5.06
	Middle Temporal Gyrus	R	273	--	44	-62	12	3.81
Other	Thalamus†	R	2594	--	22	-28	0	5.18
	Thalamus	L	--	--	-22	-30	-2	5.14
	Anterior Cingulate Gyrus†	R	1219	32	4	14	38	5.46
	Anterior Cingulate Gyrus	R	--	24	4	0	46	5.37
		L	--	24	-2	12	32	5.34
	Insular Cortex	R	522	--	32	18	4	4.35
	Middle Frontal Gyrus	R	360	8	38	36	44	4.03
		R	269	--	54	16	34	4.02
	Central Opercular Cortex	L	268	13	-42	0	10	3.06

	Superior Frontal Gyrus	R	165	--	8	-2	70	4.88
TDC								
Self	Thalamus†	R	6950	--	6	-4	12	7.31
	Insular Cortex	L	--	--	-36	8	6	6.15
		R	--	--	32	16	8	5.98
	Caudate	R	--	--	12	6	14	6.08
	Thalamus	L	--	--	-16	-32	-4	5.99
	Anterior Cingulate Gyrus†	R	1882	--	2	0	44	6.19
	Juxtapositional Lobule Cortex	R	--	24	4	6	46	5.49
	Precentral Gyrus†	R	1111	6	46	6	38	6.65
	Frontal Pole	R	--	--	38	40	18	4.87
		R	--	46	50	36	6	3.79
	Middle Frontal Gyrus	R	--	--	42	12	30	4.46
	Frontal Pole	L	774	--	-30	46	30	4.59
	Superior Frontal Gyrus	R	608	--	12	10	64	5.18
		L	299	--	-16	-10	72	5.01
	Middle Temporal Gyrus	L	282	--	-56	-64	8	4.59
		R	169	--	52	-56	0	4.11
Other	Thalamus†	L	7887	--	-22	-30	-2	6.77
	Thalamus	R	--	--	6	-8	14	6.58
	Caudate	L	--	--	-12	-4	18	6.40
	Frontal Pole†	R	2778	--	32	54	24	6.00
	Middle Frontal Gyrus	R	--	6	46	6	40	5.39
	Frontal Pole	R	--	46	50	44	4	5.00
	Anterior Cingulate Gyrus†	L	2340	--	0	8	34	7.49
	Anterior Cingulate Gyrus	R	--	--	4	14	36	6.29
		L	--	24	-4	-2	46	5.70
		R	--	24	4	6	44	5.44

	Paracingulate Gyrus	R	--	32	6	28	36	5.47
	Frontal Pole†	L	1308	--	-30	52	24	4.94
	Middle Frontal Gyrus	L	--	--	-38	34	20	4.56
	Middle Temporal Gyrus†	R	1057	--	44	-40	2	5.64
	Superior Temporal Gyrus	R	--	--	46	-30	0	5.61
		R	--	21	54	-30	-2	5.14
	Angular Gyrus	R	--	39	60	-52	14	4.37
	Middle Temporal Gyrus	L	492	--	-52	-66	-8	5.01
	Superior Frontal Gyrus	R	947	--	12	10	70	4.92
		L	611	--	-14	-8	70	4.87

Note. Analyses were conducted examining the main effect of Group (ASD, TDC) and Reward Recipient (Self, Other). Only significant activations are presented within this table. † = Peaks are listed first for each cluster with subpeaks listed in subsequent indented rows. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Supplementary Table 2.3

Whole-Brain Functional Activation During Reward Anticipation for Self and Other

Reward Recipient	**Region**	**Hem**	**k**	**BA**	**x**	**y**	**z**	**Z max**
ASD > TDC								
Self	Lateral Occipital Cortex	R	535	--	40	-78	44	3.68
Other < Self	Lateral Occipital Cortex	R	344	--	54	-72	46	3.73
	Post Central Gyrus	L	293	--	-54	-14	26	3.58
ASD < TDC								
Other > Self	Lateral Occipital Cortex	R	344	--	54	-72	46	3.73
	Post Central Gyrus	L	293	--	-54	-14	26	3.58

Note. Analyses were conducted examining the main effect of Group (ASD, TDC) and Reward Recipient (Self, Other) and interactions between the two factors. However, only significant activations are presented within this table. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Supplementary Table 2.4

Whole-Brain Functional Activation During Reward Outcomes for Self and Other

Reward Recipient	Region	Hem	k	BA	x	y	z	Z max
TDC								
Other > Self	Precuneus	R	429	--	2	-64	34	3.74
	Lateral Occipital Cortex	R	372	--	54	-60	32	3.63
	Middle Temporal Gyrus	R	293	--	48	-46	0	3.82
	Supramarginal Gyrus	L	258	40	-46	-48	56	3.71
	Middle Frontal Gyrus	L	206	--	-30	20	50	3.67
ASD > TDC								
Other < Self	Middle Temporal Gyrus	R	533	--	52	-52	8	4.11
	Inferior Frontal Gyrus	L	434	--	-36	30	16	3.97
	Lateral Occipital Cortex	R	380	--	42	-68	14	3.91
	Supramarginal Gyrus	R	362	40	42	-44	48	3.59
	Angular Gyrus	L	239	--	-34	-60	18	3.43
ASD < TDC								
Other	Anterior Cingulate Gyrus	R	1254	--	12	10	24	4.34
	Middle Temporal Gyrus	R	723	--	44	-40	2	4.63
	Frontal Pole	L	434	--	-46	46	-2	4.31
		R	239	46	50	38	6	3.9
	Superior Frontal Gyrus	L	203	--	-26	18	66	3.89
	Parahippocampal Gyrus	L	178	--	-30	-24	-22	3.76
Other > Self	Middle Temporal Gyrus	R	533	--	52	-52	8	4.11
	Inferior Frontal Gyrus	L	434	--	-36	30	16	3.97
	Lateral Occipital Cortex	R	380	--	42	-68	14	3.91
	Supramarginal Gyrus	R	362	40	42	-44	48	3.59

	Angular Gyrus	L	239	--	-34	-60	18	3.43

Note. Analyses were conducted examining the main effect of Group (ASD, TDC) and Reward Recipient (Self, Other) and interactions between the two factors. However, only significant activations are presented within this table. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

THE EFFECTS OF INTRANASAL OXYTOCIN ON REWARD CIRCUITRY RESPONSES IN CHILDREN WITH AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and interaction, as well as restricted and repetitive behaviors (APA, 2013). Although various pharmacological treatments are commonly prescribed to treat associated symptoms of ASD (e.g., irritability, inattention, and aggression), there are currently no pharmacological treatments approved to treat the core features of the disorder (Dove et al., 2012; Farmer, Thurm, & Grant, 2013; Jesner, Aref-Adib, & Coren, 2007).

The neuropeptide oxytocin (OT) has been shown to increase pro-social behaviors in human studies and in preclinical model organisms. Studies in typically developing individuals have shown that intranasal OT administration increases in-group trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) and interoceptive awareness (Quattrocki & Friston, 2014) while also reducing fear (Kirsch et al., 2005). Preclinical studies, on the other hand, have established the vital role of OT in sociality. For example, in mammalian nonhuman models, OT moderates or initiates paternal and reproductive behaviors, as well as other pro-social behaviors such as grooming and social recognition (Carter, Grippo, Pournajafinazarloo, Ruscio, & Porges, 2008; Insel & Fernald, 2004).

Because of the need for effective treatments for core ASD symptoms, there has been increasing interest in the potential for OT to ameliorate social communication impairments in ASD. Some, but not all, studies of the effects of OT in ASD have reported benefits in social functioning, including enhanced emotion recognition (Guastella et al., 2010), increased eye gaze

(Guastella, Mitchell, & Dadds, 2008), and enhanced feelings of trust in others (Andari et al., 2010). Other studies, however, have failed to find clinical benefits of OT on primary social outcome measures (Anagnostou et al., 2012; Dadds et al., 2014), and a recent trial found that the beneficial effects of OT on social functioning in ASD were moderated by pre-treatment endogenous OT levels, suggesting that OT may be beneficial for some, but not all, individuals with ASD (Parker et al., 2017).

Although there is emerging evidence that OT may be clinically beneficial for at least a significant subset of individuals with ASD, the mechanisms of action of OT are not well understood. One potential mechanism of action may be the capacity of OT to modulate sensitivity to, and the perceived salience of, external rewards that influence behavior and facilitate reward-based learning. Preclinical studies implicate the mesocorticolimbic dopamine (DA) system as a mechanism by which OT exerts its pro-social effects (Hung et al., 2017; Love, 2014). This neural network is comprised of midbrain structures (the ventral tegmental area (VTA) and substantia nigra), the striatum, and cortical regions including the orbital frontal, anterior cingulate and prefrontal cortices (Haber & Knutson, 2010). OT and mesocorticolimbic dopamine interact in such a manner that the activation of OT-responsive neurons in the VTA increases dopaminergic activity in the broader mesocorticolimbic system (Melis et al., 2007; Melis, Succu, Sanna, Boi, & Argiolas, 2009; Xiao, Priest, Nasenbeny, Lu, & Kozorovitskiy, 2017). Furthermore, when administered an OT receptor agonist, mice demonstrate a subsequent decrease in dopaminergic release within the nucleus accumbens, reflecting the influence of OT on mesocorticolimbic DA transmission (Melis et al., 2007).

To date, no functional neuroimaging study has examined the effects of OT on the mesocorticolimbic system in response to rewards in ASD. However, two functional

neuroimaging studies indicate the relevance of mesocorticolimbic brain regions to the potential mechanisms of action of OT in ASD. Gordon et al. found increased activation in the ventral striatum, left posterior superior temporal sulcus, and left premotor cortex in ASD in response to acute intranasal OT administration during a socio-emotional recognition task and that these same brain regions showed decreased activation to nonsocial (i.e., object) judgements. Other research from this group found that intranasal OT administration increased functional connectivity between the ventral striatum and ventromedial prefrontal cortex in ASD in response to a biological motion task, underscoring the potential centrality of mesocorticolimbic brain regions to the mechanism of action of OT (Gordon et al., 2016).

Although both of these studies highlight the potential relevance of reward-responsive mesocorticolimbic brain regions to the mechanism of action of OT in ASD, neither used a reward task to directly test this hypothesis. Thus, the goal of the present study was to extend these findings by assessing the impact of acute intranasal OT administration on response to rewards in ASD using social and nonsocial incentive delay tasks. Social and nonsocial incentive delay tasks have been used in multiple studies to investigate reward processing in ASD (for review see G. Kohls et al., 2012). These studies have consistently revealed reduced ventral striatal activation during social and nonsocial reward anticipation in ASD (G. S. Dichter et al., 2012; Gabriel S Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Richey et al., 2013; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010). Although the pattern of mesocorticolimbic responses to rewards in ASD is complex (i.e., different studies with different sample characteristics have reported decreased ventral striatal responses to social, but not nonsocial, reward anticipation in ASD (Scott-Van Zeeland et al., 2010; Stavropoulos & Carver, 2014) whereas others have reported decreased ventral striatal responses to nonsocial, but

not social, reward anticipation in ASD (Gabriel S Dichter, J Anthony Richey, et al., 2012; Gregor Kohls et al., 2012)), it is clear that mesocorticolimbic responses to rewards in ASD are impaired and that incentive tasks are suitable to study the functional integrity of this system.

Participants in the current study completed functional neuroimaging scans after double-blind administration of OT or PLC, and responses to nonsocial and social rewards were examined. We hypothesized that intranasal OT administration, relative to PLC, would result in greater activation and connectivity within mesocorticolimbic brain regions (frontal lobes, amygdala, nucleus accumbens (NAcc), insula, thalamus, caudate nucleus, anterior cingulate cortex (ACC), and putamen) that have previously been found to be functionally impaired during reward processing in ASD (Gabriel S Dichter, Jennifer N Felder, et al., 2012; Schmitz et al., 2008). We also hypothesized that the effects of OT would be more pronounced in the social, relative to nonsocial, reward context because of the putative pro-social effects of OT described earlier (Gordon et al., 2016). Finally, we explored relations between neural response to OT, symptom severity, and salivary OT concentrations.

Methods

Participants

This protocol was approved by the Institutional Review Boards at the University of North Carolina at Chapel Hill and Duke University Medical Center, and informed consent was obtained from the parent or guardian of each participant before testing. Participants older than 11 also provided verbal and written assent. Participants were recruited through the Autism Research Registry maintained through the Carolina Institute for Developmental Disabilities. Exclusion criteria included a history of medical conditions associated with ASD, including Fragile X

syndrome, tuberous sclerosis, neuro-fibromatosis, phenylketonuria, epilepsy and traumatic brain injury, full-scale intelligence <70, and MRI contraindications.

The study enrolled 33 children and adolescents with ASD ages 10 to 17 years-old. Diagnoses were based on a history of clinical diagnosis confirmed by proband assessment by a research reliable assessor via Module 3 or 4 of the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012) using standard clinical algorithm cutoffs. Of the 33 individuals enrolled, data from 28 were analyzable (see Table 3.1): one participant elected to discontinue testing during the first visit, another was unable to complete the scan due to claustrophobia, and three participants were excluded due to excessive motion (see Data Analysis for details).

After providing informed consent, participants completed two fMRI sessions (one after OT administration and one after PLC administration, with the order of scans counter-balanced across participants). The two scan sessions were scheduled at least 72 hours apart to minimize the possibility of carry-over effects of OT administration (mean time between scans 15 days (range: 3 – 46)). Participants were offered the opportunity to participate in an optional mock scan prior to the neuroimaging sessions. Families were compensated $50 for each visit attended.

Drug Protocol

Oxytocin (Syntocinon®, Novartis, Switzerland) and a matched solution containing no medication (PLC) were repackaged into identically appearing bottles. The administration sequence was counter-balanced by UNC Investigational Drug Service and Triangle Compounding Pharmacy, and OT and PLC were administered to participants by a blinded research assistant. A 24 international unit (IU)/mL dose of each solution was administered in alternating-nostril insufflations (six total puffs) over the course of several minutes. This dose was

the same as those used in multiple previous studies examining the effect of OT in adults, adolescents and children with ASD (Dadds et al., 2014; Gordon et al., 2016; Gordon et al., 2013; Guastella et al., 2010; Guastella et al., 2008). Recent clinical and preclinical findings have demonstrated intranasal OT's ability to increase peripheral (i.e., cerebrospinal fluid, plasma) OT concentrations (Striepens et al., 2013), while preclinical research has reported augmented brain OT levels following intranasal OT administration (Dal Monte, Noble, Turchi, Cummins, & Averbeck, 2014; Neumann, Maloumby, Beiderbeck, Lukas, & Landgraf, 2013; Tanaka et al., 2018).

fMRI Task

As described in Richey et al. , participants completed two versions of an incentive delay tasks (Brian Knutson, Fong, Adams, Varner, & Hommer, 2001) such that nonsocial rewards (money) and social rewards (pictures of smiling faces) were presented as rewards on alternating runs . Participants were presented with two runs of the nonsocial reward condition and two runs of the social reward condition. On all runs, rewards could be won or not won (i.e., there was no "loss" condition). Face stimuli were smiling images from the NimStim set of facial expressions (Tottenham et al., 2009). Each run began with a 10 second instructional screen indicating the forthcoming reward type (i.e., nonsocial or social), and the two task types were segregated by run to minimize the number of cues to be memorized.

Each trial consisted of: (1) a 2,000 ms cue indicating whether adequately quick responses to the bulls-eye would result in a "win" (a triangle) or not (a circle); (2) a 2,000 – 2,500 ms crosshair fixation; (3) a target bulls-eye presented for up to 500 ms that requires a speeded button press; (4) 3,000 ms of feedback that indicated whether that trial was a "win" or not, with wins accompanied by either an image of money or a face; and (5) a variable length ITI crosshair

resulting in a total trial duration of 12 seconds. Potential win and non-win trials were aperiodic and psuedorandomly ordered. Each 8-min run contained 40 trails, half of which were potential win trials. The task was adaptive such that participants were successful on two-thirds of trials, regardless of individual differences in RTs (confirmed via inspection of behavioral data collected during scanning). Mean reaction times were calculated during practice trials prior to the scan and then entered into the fMRI paradigm to ensure that participants succeeded on 66% of their responses (as described in Brian Knutson et al., 2001).

During nonsocial runs, participants won $1 per trial if bulls-eye responses were adequately quick. During social runs, participants viewed a face image if bulls-eye responses were adequately quick. Coincident with feedback, cumulative win totals were presented. Participants were instructed to respond to all target bulls-eyes as quickly as possible to win on as many trials as possible and win or non-win outcomes were contingent on reaction times (RTs). Standard administration of incentive delay tasks involves showing participants rewards that may be won prior to scanning (Brian Knutson et al., 2001). Consistent with this procedure, participants were shown the money they could win based on scanner task performance and were informed that they would receive the total amount of money won during the scan. Prior to scanning, participants rated face stimuli on the dimensions of valence and arousal. Stimuli were presented using E-Prime presentation software version 2.0 (Psychology Software Tools Inc., Pittsburgh, PA, USA).

Prior to and immediately following each scan, participants were asked to rate face stimuli on the dimensions of valence, arousal, and trust using Qualtrics software (Qualtrics, Provo, UT) on a computer outside of the scanner (pre-scan ratings were completed prior to the nasal spray administration).

Imaging Methods and Preprocessing

Functional imaging data were acquired at the Duke-UNC Brain Imaging and Analysis Center (BIAC) on a 3.0 T General Electric (Waukesha, WI, USA) MR750 scanner system equipped with 50 mT/m gradients and an eight-channel head coil. High-resolution T1-weighted anatomical images were acquired with 256 axial slices using an FSPGR pulse sequence (TR = 8.16 ms, TE = 3.18ms; flip angle = 12°; FOV = 256; image matrix = 256mm2; voxel size = 1 x 1 x 1 mm) for normalization and co-registration. Whole brain functional images were acquired with 64 axial slices oriented parallel to the AC-PC plane using a spiral-in SENSE sequence (TR = 1500 ms, TE = 30ms; flip angle = 60°; FOV = 240; image matrix = 64mm2; voxel size = 3.75 x 3.75 x 4 mm). The first four volumes of each functional task were discarded to allow for steady state equilibrium.

Functional data were preprocessed using FSL version 5.0.1 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, U.K.). Preprocessing was applied as follows: (1) brain extraction for non-brain removal (Smith et al., 2004), (2) motion correction using MCFLIRT (Smith, 2002), (3) spatial smoothing using a Gaussian kernel of FWHM 5 mm, (4) mean-based intensity normalization of all volumes by the same factor, and (5) high-pass filtering (Jenkinson, Bannister, Brady, & Smith, 2002). Functional images were co-registered to structural images in native space, and structural images were normalized into a standard stereotaxic space (Montreal Neurological Institute). Registrations used an intermodal registration tool (Jenkinson et al., 2002; Smith et al., 2004). Voxel-wise temporal autocorrelation was estimated and corrected using FMRIB's Improved Linear Model (Jenkinson & Smith, 2001).

Motion Correction. Consistent with motion thresholds used in Gordon et al., 2013, runs with maximum motion >3mm along any of six axes (i.e., x, y, z, pitch, yaw, and roll) were excluded from analyses. Due to excessive motion (>3mm), some participants only had one social and/or nonsocial reward condition run per scan. Participants were only included in the final analyses if they had at least one nonsocial and one social run that met motion criteria for both their OT and PLC scans. Either due to motion or the participant's ability to stay in the scanner for the entire length of the scan, 17 of the 56 scans had less than four total runs. 66% of runs included in analyses had <1.0 mm of motion in any axis (pitch, roll, yaw, x, y, z), 26% had 1.0 – 1.99 mm of motion, and 8% had motion between 2.0 – 2.9 mm. In addition to conducting motion correction using MCFLIRT (Smith, 2002), timepoints with large motion, as defined by FSL, were entered into the general linear model (GLM) model as additional confound variables within first-level analyses using FSL's motion outlier detection program (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers). Following motion correction, paired t-tests were used to compare differences in motion between OT and PLC groups: there was equivalent motion for mean and maximum values along all six axes (i.e., x, y, z, pitch, yaw, and roll), all *p's* > .05.

fMRI Analysis. Planned analyses included: (1) treatment group (OT vs. PLC) differences in frontostriatal functional activation and connectivity in response to social reward anticipation and outcomes, (2) treatment group differences in frontostriatal functional activation and connectivity in response to nonsocial reward anticipation and outcomes, (3) treatment group differences in frontostriatal functional activation in response to nonsocial relative to social reward anticipation and outcomes, conducted also with a small volume correction for the striatum alone given the centrality of this region for reward processing, and (4) correlations

between frontostriatal functional activation and connectivity with ASD symptoms and salivary OT analyses.

Supplemental analyses included: (1) main effects of OT and PLC separately on whole brain functional activation in response to nonsocial and social reward anticipation and outcomes, (2) treatment group (OT vs. PLC) differences in frontostriatal structural activation in response to social and nonsocial reward anticipation and outcomes, (3) correlations between structural activation with ASD symptoms, and (4) treatment group differences in frontostriatal functional connectivity of structurally-defined clusters in response to social and nonsocial reward anticipation and outcomes.

Small Volume Corrections. For all analyses, anticipation and outcome phases were analyzed separately. Key anatomical regions within the reward system (superior frontal gyrus, medial frontal gyrus, orbitofrontal gyrus, paracingulate gyrus, amygdala, nucleus accumbens (NAcc), insula, thalamus, caudate nucleus, anterior cingulate cortex (ACC), and putamen) were defined *a priori* for small volume correction. These regions were generated separately for the right and left hemispheres in FSL using the Harvard–Oxford cortical and subcortical structural probabilistic atlases. Masks were thresholded at 25%, binarized, and then combined into a single mask using fslmaths. For planned main effect analyses (i.e., nonsocial and social reward conditions analyzed independently) and planned interaction analyses (i.e., nonsocial > social, social > nonsocial), voxels were considered significant is they passed a threshold of $p<.005$ and were part of a 39-voxel cluster of contiguous significant voxels, resulting in a cluster-corrected $p<.05$. This cluster size was determined by performing 1000 Monte Carlo simulations using 3dClustSim (Ward, 2000). Interaction analyses (e.g., nonsocial>social) also included an analysis using a small volume correction that included only the striatum given our *a priori* interest in the

striatum. Due to this small volume correction, interaction clusters within the striatum were considered significant if they passed a statistical threshold of $p<.005$ and were part of a 17-voxel cluster of contiguous significant voxels, resulting in a cluster-corrected threshold of $p<.05$ (again determined by performing 1000 Monte Carlo simulations using 3dClustSim; Ward, 2000). Localizations were based on Harvard-Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView version 3.1.8, and all activations were visualized with MRIcron (https://www.nitrc.org/projects/mricron/).

Activation Analyses. Whole brain general linear model (GLM) activation analyses were conducted using the FSL expert analysis tool (FEAT). For ROI analyses, each participant's condition-specific mean percent signal change was calculated for both the social and nonsocial conditions. Within-participant activation differences were analyzed for treatment effects using paired t-tests and using a 2 (Treatment Group: OT, PLC) x 2 (Reward Condition: Nonsocial, Social) ANOVA (see Supplementary Materials). Structural ROI activation results are also provided in Supplementary Materials.

Connectivity Analyses. Task-based functional connectivity was analyzed using a generalized psychophysiological interaction (gPPI) approach due to its improved power, sensitivity, and specificity in detecting context-dependent functional connectivity (Cisler, Bush, & Steele, 2014; McLaren, Ries, Xu, & Johnson, 2012). Functional seeds were derived from activation clusters showing significant OT>PLC effects. These seeds were supplemented with structural left and right NAcc seeds because of the centrality of the NAcc to the mesocorticolimbic reward processing system (Brian Knutson et al., 2001), once again defined using the Harvard-Oxford subcortical structural probabilistic atlas. Voxel-wise models evaluated whole-brain connectivity with these seeds. For each participant, mean fMRI timecourses (i.e.,

physiological regressors) were extracted from seed regions for each task run using *fslmeants* in FSL, then multiplied by each psychological regressor of interest (i.e., Trial Type: Reward, Non-reward) to form the PPI interaction terms. The gPPI model included physiological and psychological regressors, as well as their interaction terms to describe the unique effect of these interactions above and beyond the main effect of seed time courses and reward conditions. Our contrasts of interest evaluated the reward condition alone. No additional preprocessing procedures were completed beyond what has been described above. Supplemental analyses examined functional connectivity with anatomically-defined right and left NAcc using the same procedures described for the functional connectivity analyses (see Supplementary Materials).

Symptom Analyses

Symptom analyses examined interactions between ASD symptom severity, measured by the Social Responsiveness Scale (SRS; Constantino & Todd, 2000), and functional activation and connectivity in the OT relative to PLC condition, conducted by including demeaned SRS values as a covariate within frontostriatal general linear models within the ASD group. Supplementary analyses examined interactions between ASD symptoms and structural activation, as well as functional activation of structurally-defined clusters (see Supplementary Materials).

Salivary Analyses

Saliva samples were collected using pediatric oral swabs (Salimetrics) prior to each nasal drug administration (i.e. OT and PLC) and immediately following the fMRI scan (time between samples in minutes $M = 85$; $SD = 9$). During each sample, participants were asked to place the swab under their tongue for approximately one minute or until it was saturated with saliva. Samples were stored on ice for up to two hours prior to liquid extraction and were permanently

stored at -70° C. See Supplementary Materials for a more detailed description of the salivary analyses.

Results

Face Image Ratings

Participants rated the faces seen in the social reward condition on the dimensions of valence, arousal, and trust prior to and immediately following each scan. Results from a 2 (Treatment Group: OT, PLC) × 2 (Timepoint: Pre- or Post-scan) ANOVA revealed a main effect of Timepoint for the dimension of trust, such that participants were more likely to rate the faces as more trustworthy at the post-scan rating (M = 5.07; SD = 1.59) compared to the pre-scan rating (M = 4.86; SD = 1.63), regardless of treatment condition, $F(1,54) = 8.37$, p=.006 (see Figure 3.1). Additionally, a main effect of Timepoint for the dimension of arousal was observed, reflecting that participants perceived the faces at the post-scan rating (M = 5.04; SD = 1.75) to be more arousing than those at the pre-scan rating (M = 4.91; SD = 1.80) across treatment groups, $F(1,54) = 4.42$, p=.040. No other main effects or interactions between Treatment Group and Time Point for the perceived valence, arousal, or trust of the faces were significant, all p's > .05.

Task Reaction Times

Reaction times (RTs) to task bulls-eyes are depicted in Figure 3.2 and were evaluated via a 2 (Treatment Group: OT, PLC) × 2 (Reward Condition: Nonsocial, Social) × 2 (Trial Type: Reward, Non-reward) mixed ANOVA. There was a main effect for Trial Type, $F(1,54) = 18.67$, p<.0001, such that individuals responded more quickly to trials during which they could receive a reward (M = 226.49; SD = 59.73) compared to trials in which they could not receive a reward (M = 242.03; SD = 60.91). No other main effects or interactions between Treatment Group, Reward Condition or Trial Type were significant, all p's > .05.

Functional Activation Results

Nonsocial Reward. During nonsocial reward anticipation, there were no regions with relatively decreased activation in the OT relative to the PLC condition. However, there were several clusters with greater activation during nonsocial reward anticipation in the OT condition relative to PLC, including the right NAcc, right frontal pole (FP), left ACC, left superior frontal cortex, and bilateral orbital frontal cortex (OFC) (see Figure 3.3 and Table 3.2)[1]. Significant increases in activation were observed during nonsocial reward outcomes after OT relative to PLC administration in the right OFC and left FP (see Figure 3.4).

Supplementary analyses for OT and PLC conditions separately are presented in Supplementary Figures 3.1 and 3.2. These simple effects analyses revealed that both groups showed activation in mesocorticolimbic reward processing regions in response to the social and nonsocial incentive delay tasks.

Social Reward. During social reward outcomes, there was significantly decreased activation in the right frontal pole in the OT condition relative to the PLC condition. There were no other clusters with significant changes in activation during social anticipation or social outcomes in the OT condition relative to the PLC condition. See Supplementary Materials for structural activation results for social and nonsocial reward anticipatory and outcomes.

Treatment Group × Reward Condition Interaction. We next evaluated the impact of OT, relative to PLC, on nonsocial versus social reward processing by evaluating a Treatment Group × Reward Condition interaction general linear model. OT increased activation in the right

[1] Similar analyses during the anticipation of nonsocial rewards were conducted after removing both female participants, as well as a participant with outlying salivary OT concentrations (see Figure 3.7A). Results from these analyses remained statistically significant within all regions reported in Table 3.2. Therefore, all activation results include both females and the participant with outlying salivary OT levels.

caudate nucleus, left ACC, bilateral FP, right insular cortex, and right OFC in response to nonsocial compared to social reward outcomes (see Table 3.2). Planned analyses within the striatal small volume revealed greater activation during nonsocial relative to social reward anticipation after intranasal OT relative to PLC in the right NAcc. There were no regions with greater activation during social relative to nonsocial reward anticipation or outcomes after intranasal OT relative to PLC.

Correlations Between Functional Activation and ASD symptoms. Increased ASD symptom severity, as measured by SRS total scores, was associated with greater activation in the right FP and the right ACC during nonsocial reward anticipation and greater activation in the right precentral gyrus and left caudate nucleus during nonsocial reward outcome following the administration of OT relative to PLC (see Figure 3.6 and Table 3.3). This finding within the left caudate nucleus was corroborated by structural activation analyses (see Supplementary Materials). There were no relations between symptom severity and brain activation in the anticipation or outcome phases of the social reward condition.

Functional Connectivity Results

Given the prominent roles of the NAcc and ACC in reward processing (Bush et al., 2002; B. Knutson, Adams, Fong, & Hommer, 2001b), functional connectivity analyses were seeded by the right NAcc and left ACC functional clusters that showed increased activation to OT relative to PLC during nonsocial reward anticipation in the functional activation analyses. Because there were no clusters that differentiated conditions in the social reward condition, functional connectivity results are only reported for connectivity in the nonsocial reward condition (functional connectivity of structurally-defined clusters are presented in Supplementary Materials).

Right Nucleus Accumbens Seed. During nonsocial reward anticipation, OT relative to PLC administration resulted in increased functional connectivity between the right NAcc seed and the right frontal pole (see Figure 3.6), whereas OT-induced decreases in functional connectivity were observed between the right NAcc seed and the left precentral gyrus and the right superior frontal gyrus (see Table 3.4). These findings were further corroborated by functional connectivity analyses of structurally-defined clusters using a structural right NAcc seed (see Supplementary Materials). During nonsocial reward outcomes, increased functional connectivity was observed between the right NAcc and the right OFC and left FP in response to OT relative to PLC. Finally, decreased functional connectivity was exhibited between the right NAcc and right postcentral gyrus during nonsocial reward outcomes following OT administration relative to PLC.

Anterior Cingulate Cortex Seed. During the anticipation of nonsocial rewards, there was decreased functional connectivity between the left ACC and the left precentral gyrus, the right frontal pole and the right superior frontal gyrus after OT relative to PLC (see Table 3.5). Attenuated functional connectivity with the left ACC was also observed with bilateral postcentral gyrus, left inferior frontal gyrus, left precentral gyrus, and left medial frontal gyrus during nonsocial reward outcomes following OT relative to PLC. No increases in connectivity were exhibited with the left ACC for nonsocial reward anticipation or outcomes, all *p's* > .05.

Correlations Between Functional Connectivity and ASD symptoms. For the right NAcc and left ACC seeds, greater ASD symptom severity, measured by SRS total scores, was associated with increased connectivity with the right postcentral gyrus during nonsocial reward outcomes following OT relative to PLC (see Table 3.6). During nonsocial reward anticipation, there were no significant correlations between SRS scores and connectivity with the right NAcc or left ACC following OT relative to PLC.

Salivary Oxytocin

To examine changes in OT concentration levels, salivary samples were collected prior to OT administration and immediately following the fMRI scan. There were considerable individual differences in the magnitude of salivary OT change from baseline to post-scan following OT administration, and, thus, one outlier was removed from salivary analyses due to significantly elevated OT concentration levels (754.17 pg/ml) in the PLC condition. After the removal of this outlier, as expected, there was a significant increase in mean peripheral OT levels following OT administration relative to PLC, $t = 3.57$; $p = 0.0016$ (see Figure 3.7).

Because of the primary role of the NAcc in reward processing (B. Knutson et al., 2001b), correlation analyses examined relations between changes in peripheral OT and neural activation within the right NAcc functional activation cluster identified in the nonsocial anticipation activation analysis. This revealed a significant positive correlation indicating that individuals with greater changes in peripheral OT concentrations following OT administration showed greater increased activation within the right NAcc functional activation cluster during nonsocial reward anticipation, $r = 0.56$; $p = 0.005$ (see Figure 3.8). However, when a significant outlier (2 SD's > the salivary group mean; 3 SD's > the activation group mean) was removed, the relation was no longer significant, $r = 0.26$; $p = 0.232$.

Discussion

The purpose of this investigation was to examine the effects of acute intranasal OT administration on functional activation and connectivity within mesocorticolimbic brain regions during the anticipation and receipt of social and nonsocial rewards in ASD. OT administration,

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2 We thank an anonymous reviewer for highlighting this. This outlier was not the same outlier as the one mentioned in the previous salivary analyses examining treatment group (OT vs. PLC) differences in OT concentrations.

relative to PLC administration, was associated with increased activity in the right NAcc, the right FP, the left ACC, the left superior frontal cortex, and bilateral OFC during anticipation of nonsocial rewards. These findings combined with prior ASD research demonstrating increased activation in the NAcc following OT administration during a social judgement task (Gordon et al., 2013) suggest that whether OT impacts social or nonsocial processing is contingent on task context. In addition, the correlation between salivary OT concentrations and changes in right NAcc activation indicates that this region may be particularly sensitive to the acute effects of OT (though this correlation was not significant following removal of an outlier). This is consistent with preclinical findings, which indicate that the NAcc is among several neural regions with the highest OT receptor density (Insel & Shapiro, 1992).

Although we found increased left ACC activation after OT administration during nonsocial reward anticipation, Watanabe and colleagues reported increased ACC activation after OT administration during a social judgement task, reflecting the task-dependent nature of the effects of OT on neural responses to social or nonsocial processing. Our finding of increased activation of OFC, a region with an established role in reward processes documented in preclinical and clinical studies (Rolls, 2000; Tremblay & Schultz, 1999), during the anticipation and receipt of nonsocial rewards after OT administration is consistent with prior findings that ASD is characterized by attenuated OFC activation during nonsocial reward anticipation (Gabriel S Dichter, J Anthony Richey, et al., 2012) and suggests a remediation of this pattern in ASD after OT.

In contrast to previous studies examining the neural impact of OT in response to social stimuli in individuals with ASD (Gordon et al., 2016; Gordon et al., 2013), we did not find evidence of increased activity in mesocorticolimbic regions during social reward processing

following OT administration. Further, interaction analyses showed increased activity in the right nucleus accumbens and right caudate nucleus during nonsocial reward anticipation relative to social reward anticipation. The lack of effects of OT in the social reward conditions are surprising and stand in contrast to preclinical findings that OT enhances neural responses to a range of social stimuli, including conditioned social preference (Choe et al., 2015; Kent, Arientyl, Khachatryan, & Wood, 2013; Kosaki & Watanabe, 2016) and reproductive behaviors (Borrow & Cameron, 2012; Nakajima, Görlich, & Heintz, 2014) as well of the prosocial effects of OT in ASD (Yamasue & Domes, 2017). These unexpected findings highlight that OT may serve to increase neural activations in response to nonsocial rewards. These effects are consistent with preclinical findings that the impact of OT is apparent in the context of a certain nonsocial rewards, including food cues (Herisson et al., 2016; Klockars, Brunton, Li, Levine, & Olszewski, 2017) and place preferences (Moaddab, Hyland, & Brown, 2015; Subiah, Mabandla, Phulukdaree, Chuturgoon, & Daniels, 2012), and it may be the case that the clinical benefits of OT on social functioning in ASD (e.g., enhanced emotion recognition and increased eye gaze) reflect the influence of OT on mesocorticolimbic reward processing systems that mediate nonsocial incentive salience processing, reward valuation, and reward-based learning (Daniel & Pollmann, 2014) rather than responses specifically to social rewards. Alternatively, it may be the case that the static social rewards used in this study impeded our capacity to detect OT-related neural changes given that dynamic stimuli have been shown to be more potent elicitors of social impairments in ASD than static stimuli (Chevallier et al., 2015). Future studies that evaluate the impact of OT on neural responses to dynamic social rewards will be needed to evaluate this possibility.

We observed significant correlations between ASD symptom severity and increased activity within the right frontal pole and the left ACC during nonsocial reward anticipation in response to OT relative to PLC. Additionally, during nonsocial reward outcomes, increases in left caudate nucleus and right precentral gyrus activity after OT relative to PLC were significantly correlated with symptom severity. The postcentral gyrus also showed greater connectivity with both the right NAcc and left ACC functional seeds as ASD symptom severity increased. These regions may be most responsive to neural effects of OT administration in individuals with more severe ASD presentations. Alternatively, these associations suggest that the impact of OT on responses to nonsocial rewards may be conditional on ASD symptom severity. These associations may also reflect mechanisms described by Parker and colleagues (Parker et al., 2017) which revealed that individuals with ASD with lower endogenous levels of OT benefited the most from OT. Thus, it may be the case that individuals with greater ASD symptoms demonstrated greater regional activation changes during reward anticipation in response to OT. It is noteworthy that symptom correlations with neural responses to nonsocial reward anticipation were apparent in brain regions (FP and ACC) implicated in higher-order executive processing (Mansouri, Buckley, Mahboubi, & Tanaka, 2015) and known to show functional impairments in ASD in the context of cognitive control tasks (Agam, Joseph, Barton, & Manoach, 2010; G. S. Dichter, 2012). Conversely, regions showing symptom correlations with neural responses to social reward anticipation involved regions implicated in other functioning, including imitation (precentral gyrus (Wu et al., 2017)) and learning (the caudate nucleus (Chiu, Jiang, & Egner, 2017)), though the replicability of these patterns is not yet known.

OT administration was associated broadly with decreased connectivity with functional seeds. Decreased connectivity was observed between the right NAcc and the left precentral gyrus and right superior frontal gyrus during the anticipation of nonsocial rewards as well as with the postcentral gyrus during nonsocial reward outcomes following OT administration relative to PLC. Further, OT-induced attenuation in functional connectivity was observed between the left ACC functional seed and the left precentral gyrus, the right frontal pole, and the right superior frontal gyrus during nonsocial reward anticipation. During nonsocial reward outcomes, decreased functional connectivity was observed between the left ACC and bilateral postcentral gyrus, left inferior frontal gyrus, left precentral gyrus, and left medial frontal gyrus following OT relative to PLC. Resting state functional connectivity findings suggest that ASD is largely characterized by increased frontostriatal connectivity relative to typically developing controls (Dajani & Uddin, 2016; Delmonte, Gallagher, O'Hanlon, Mc Grath, & Balsters, 2013; Adriana Di Martino et al., 2011; Turner, Frost, Linsenbardt, McIlroy, & Müller, 2006), and the results of the present study suggest that OT may normalize these increased frontostriatal functional connections.

There were additionally findings of increased functional connectivity after OT administration, including increased connectivity between the right NAcc and the right FP during nonsocial reward anticipation. OT-induced increased connectivity between the right NAcc and right FP was also reported by Gordon et al. using a biological motion task. This finding across two different task contexts highlights a neural pathway by which OT may exert a therapeutic effect by potentiating neural connectivity. The FP plays a critical role in the cognitive processing of future events (Okuda et al., 2003), a process that may be particularly relevant to reward contexts. Additionally, the right NAcc demonstrated relatively greater connectivity with the right

FP and right OFC during nonsocial reward outcomes following OT administration relative to PLC, though the directionality of this effect was unexpected given that increased functional connectivity between the striatum and the OFC has been reported in ASD during resting-state functional connectivity (Delmonte et al., 2013). It is also noteworthy that the effects of OT on the NAcc and ACC exhibited right-lateralized effects given evidence of right lateralization of functional neural responses to social and nonsocial stimuli in ASD (A. Di Martino et al., 2009; Pantelis, Byrge, Tyszka, Adolphs, & Kennedy, 2015), though it should be noted that incentive delay tasks do not reliably evoke greater activation in one hemisphere or the other but rather tend to evoke bilateral reward-related frontostriatal activations (B. Knutson, Adams, Fong, & Hommer, 2001a; Liu, Hairston, Schrier, & Fan, 2011).

Ratings of faces in the social task revealed a significant increase in ratings of trustworthiness and arousal for faces following the scan. These main effects were not moderated by Treatment Group (i.e., OT, PLC), indicating that individuals rated faces they had seen previously as more trustworthy across both treatment groups. Previous studies have reported that individuals with ASD reliably understand the concept of trustworthiness and distinguish trustworthy versus non-trustworthy faces (Caulfield, Ewing, Burton, Avard, & Rhodes, 2014; Ewing, Caulfield, Read, & Rhodes, 2015). Our results suggest that familiarity with faces may increase ratings of trustworthiness and arousal for individuals with ASD. No effects were observed for ratings of valence.

Task reaction times showed increased speed of responses to reward relative to non-reward trials, with no significant interactions of Treatment Group (OT, PLC) or Reward Type (nonsocial, social). These findings are consistent with reports of decreased reaction times for reward compared to non-reward trial in ASD (Delmonte et al., 2012). Delmonte and colleagues

reported no relation between reward condition (e.g., nonsocial vs. social) and reaction times. However, this stands in contrast with other ASD reward studies that have reported faster reaction times in response to nonsocial rewards compared to social rewards (Gabriel S Dichter, J Anthony Richey, et al., 2012; Rademacher et al., 2010). This discrepancy may reflect different ages of participants across studies: the current study and others showing no differences in reaction times based on reward condition were conducted in child and adolescent populations, whereas those showing faster responses for nonsocial versus social rewards were completed using adult participants. This may suggest that during development, nonsocial rewards may begin to have increased salience relative to social rewards in individuals with ASD. This might be related to increased awareness of the relationship between money and acquiring objects of interest and/or to increased demands in financial responsibility for adults living independently. This developmental interaction should be noted in future studies examining differential responses to nonsocial versus social rewards in ASD. It may also be useful to explore the salience of other nonsocial rewards in ASD.

In addition to the substantive findings reported here, these results have implications for future experimental therapeutic trials that seek to evaluate novel ASD therapeutics. The National Institute of Health has emphasized the use of translational research to speed the discovery of treatments through pipelines that evaluate the potential for novel compounds to engage brain targets relevant to disease etiology (Insel & Gogtay, 2014). In addition to providing substantive results about the neural impact of acute intranasal OT administration on reward processing brain systems, the present study also suggests that optimal approaches to evaluate novel ASD treatments with putative effects on brain systems that support social reward processing may not be constrained to evaluating responses to only social stimuli. Rather, novel pro-social ASD

therapeutics may exert their influence on relevant brain targets in a range of social and/or nonsocial contexts. In this regard, these results provide preliminary data to guide the development of optimal targets for use in future experimental therapeutics trials that evaluate novel ASD social communication treatments.

The present study had some limitations. Developmental stage plays a particularly important moderating role in the strength of functional connectivity patterns in individuals with ASD, with younger individuals showing increased connectivity compared to adolescents and adults with ASD (Uddin, Supekar, & Menon, 2013). Future studies with large sample sizes will be needed to examine the moderating effect of developmental stage on the effects of OT on brain activation and connectivity in ASD. Additionally, the effects of prolonged OT administration are likely to be distinct from the effects of a single dose, and future research should examine the effect of chronic OT administration on neural functioning in ASD. Additionally, the order of social and nonsocial runs was not randomized across participants in this study. Because the current study found no behavioral changes due a single OT administration, interpretations regarding associations between behavioral and neural effects of OT must be cautious. Finally, because all participants in the present study met a minimum IQ cutoff of 70, findings from this study may be restricted to individuals with ASD with higher cognitive ability.

Conclusions

Despite these limitations, these findings indicate a mechanistic role for the mesocorticolimbic system in the potentially therapeutic effect of oxytocin in individuals with ASD. These findings align with prior studies that highlight the important role of enhanced functioning of striatal regions as a potential mechanism of action of OT (Gordon et al., 2016; Gordon et al., 2013) and extend this area of research into the domain of striatal functioning in

response to reward-based tasks. When the present findings are considered along with these prior fMRI studies, it appears that the role of the mesocorticolimbic system in the effects of OT on neural functioning is not confined to social rewards but may extend to nonsocial responses more broadly, depending on task contexts.

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Table 3.1. Participant Characteristics

Characteristic	**Mean**	**Standard Deviation**	**Range**
Age	13.43	2.36	10 – 17
Full-Scale IQ	103.55	15.19	75 – 128
ADOS-2 Calibrated Severity Score	8.46	1.29	7 – 10
SRS Total T-Score	76.19	10.66	49 – 90
Sex	26 males, 2 females		

Note. ADOS-2 Calibrated Severity Scores were calculated for Modules 3 and 4 using guidelines established by Gotham, Pickles and Lord (Gotham, Pickles, & Lord, 2009) and Hus and Lord (Hus & Lord, 2014). ADOS-2: Autism Diagnostic Observation Schedule, Second Edition.

Table 3.2. Effects of oxytocin on functional activation

Phase	Reward Condition	Region	Hem	k	BA	x	y	z	Z max
OT > PLC									
Anticipation	Nonsocial	Frontal Pole	R	316	10	41	95	38	3.99
		Anterior Cingulate Cortex	L	182	32	46	83	46	3.97
		Superior Frontal Cortex	L	83	--	49	74	65	3.31
		Orbital Frontal Cortex	R	76	--	23	79	30	3.26
			L	52	--	58	72	27	3.16
		Nucleus Accumbens	R	56	--	43	72	30	3.42
	Nonsocial>Social	Anterior Cingulate Cortex	L	441	--	46	84	46	3.91
		Frontal Pole	L	69	--	54	91	29	3.12
			R	40	--	38	87	56	3.17
		Insular Cortex	R	65	47	25	72	31	3.24
		Caudate Nucleus	R	64	--	42	67	36	3.11
		Orbital Frontal Cortex	R	47	--	29	76	29	3.34
		Nucleus Accumbens	R	21	--	42	71	30	3.09
Outcome	Nonsocial	Frontal Pole	L	42		55	91	52	3.28
		Orbital Frontal Cortex	R	39	--	21	75	30	3.35
OT < PLC									
Outcome	Social	Frontal Pole	R	50	--	24	91	37	3.29

Note. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Table 3.3. Correlations between ASD Symptoms and Functional Activation to Oxytocin relative to Placebo

Phase	Reward Condition	Region	Hem	k	BA	x	y	z	Z max
Anticipation	Nonsocial	Frontal Pole	R	95	10	41	95	38	3.53
		Anterior Cingulate Cortex	L	82	32	46	83	46	3.41
Outcome	Nonsocial	Precentral Gyrus	R	48	--	18	59	51	3.29
		Caudate Nucleus	L	51	--	58	63	47	3.27

Note. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Table 3.4. Functional connectivity with the Right NAcc Seed

Phase	Reward Condition	Region	Hem	k	BA	x	y	z	Z max
OT > PLC									
Anticipation	Nonsocial	Frontal Pole	R	45	--	39	95	39	3.39
Outcome		Orbital Frontal Cortex	R	82	--	22	75	31	3.96
		Frontal Pole	L	41	9	54	92	52	3.19
OT < PLC									
Anticipation	Nonsocial	Precentral Gyrus	L	266	--	54	62	63	3.64
		Superior Frontal Gyrus	R	53	--	37	63	69	3.6
Outcome		Postcentral Gyrus	R	42	--	19	58	51	3.4

Note. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Table 3.5. Functional Connectivity with the Left ACC Seed

Phase	Reward Condition	Region	Hem	k	BA	x	y	z	Z max
OT < PLC									
Anticipation	Nonsocial	Precentral Gyrus	L	206	--	58	58	63	3.86
		Frontal Pole	R	197	--	30	83	48	3.34
		Superior Frontal Gyrus	R	39	--	37	63	69	3.66
Outcome		Postcentral Gyrus	R	179	--	21	57	51	3.72
			L	90	3	75	57	50	3.13
		Inferior Frontal Gyrus	L	55	--	70	78	42	3.64
		Precentral Gyrus	L	49	--	73	64	54	3.13
		Medial Frontal Gyrus	L	42	6	57	66	59	3.09

Note. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

Table 3.6. Correlations between ASD Symptoms and Functional Connectivity for Oxytocin relative to Placebo

Phase	**Reward Condition**	**Region**	**Hem**	**k**	**BA**	**x**	**y**	**z**	**Z max**
Right NAcc Seed									
Outcome	Nonsocial	Postcentral Gyrus	R	74	--	18	58	51	3.37
Left ACC Seed									
Outcome	Nonsocial	Postcentral Gyrus	R	131	--	18	58	51	3.5

Note. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.

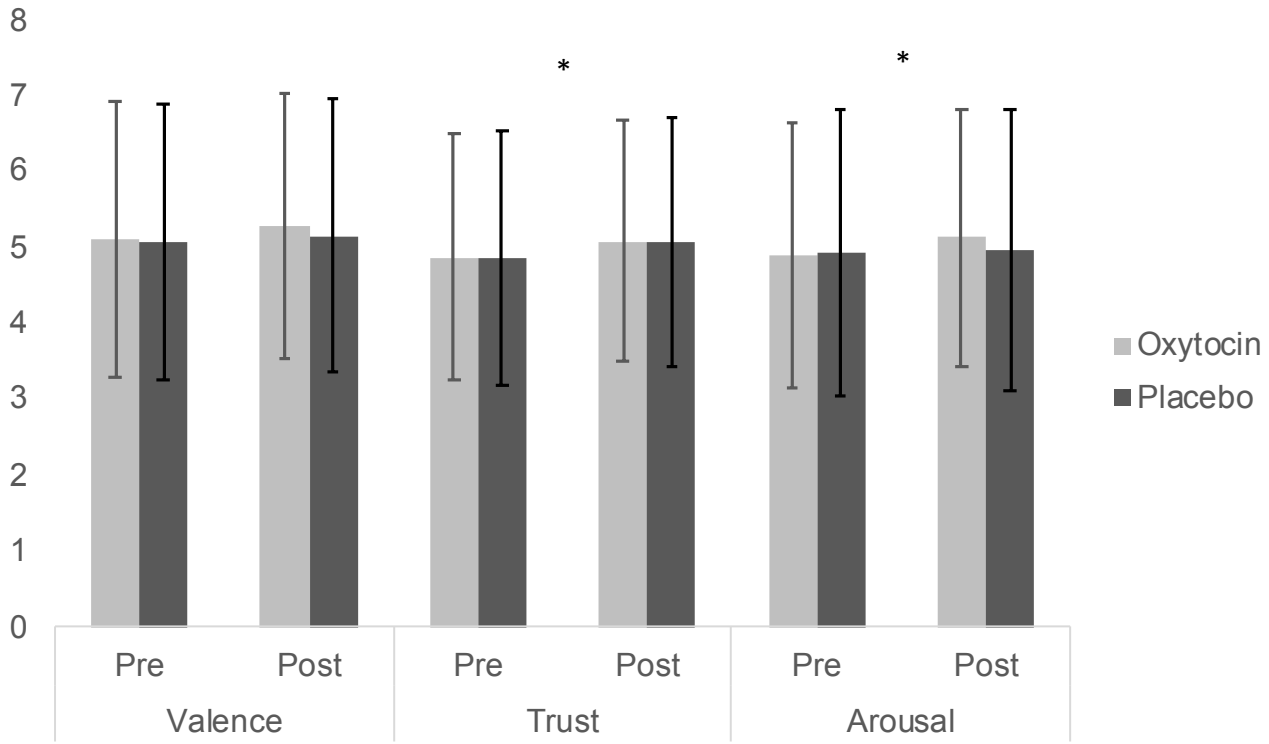


Figure 3.1. *Subjective Ratings of Faces.* Average ratings of valence, arousal and trust of faces. Valence = 0 (extremely unpleasant) to 8 (extremely pleasant); Arousal = 0 (not at all aroused) to 8 (extremely aroused); Trust = 0 (not at all trustworthy) to 8 (extremely trustworthy). * = $p<.05$.

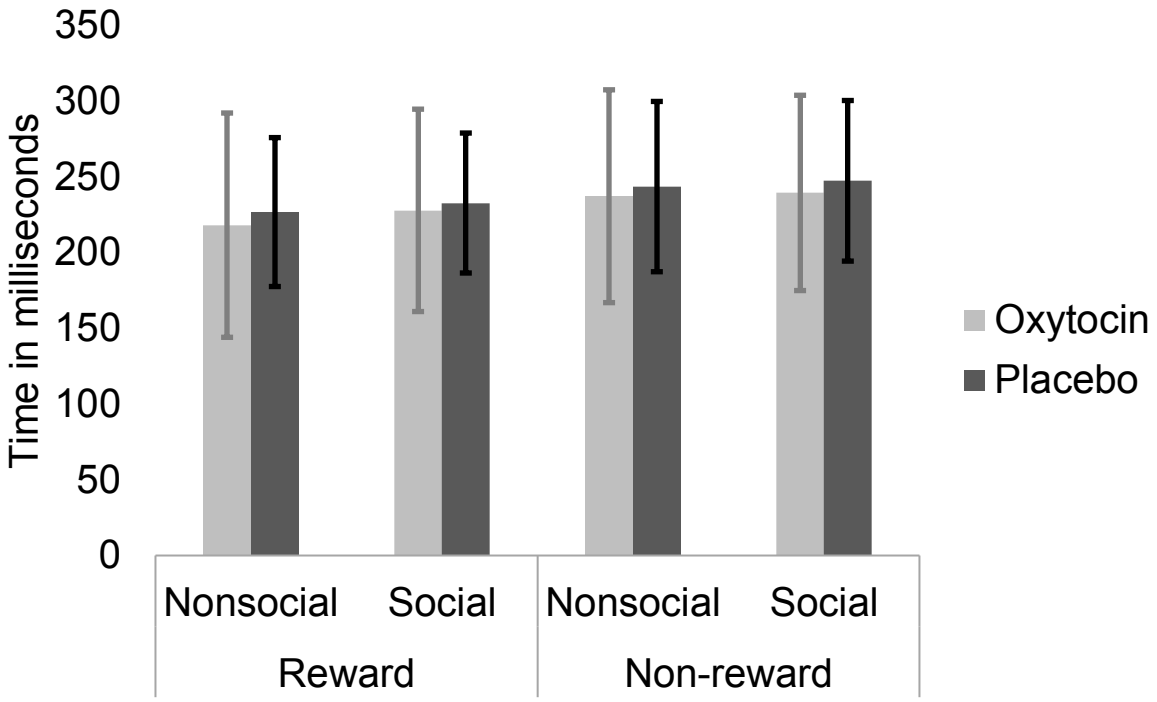


Figure 3.2. *fMRI Task Reaction Times*. Mean reaction times of reward and non-reward trials during the social and nonsocial reward tasks. * = $p<.05$.

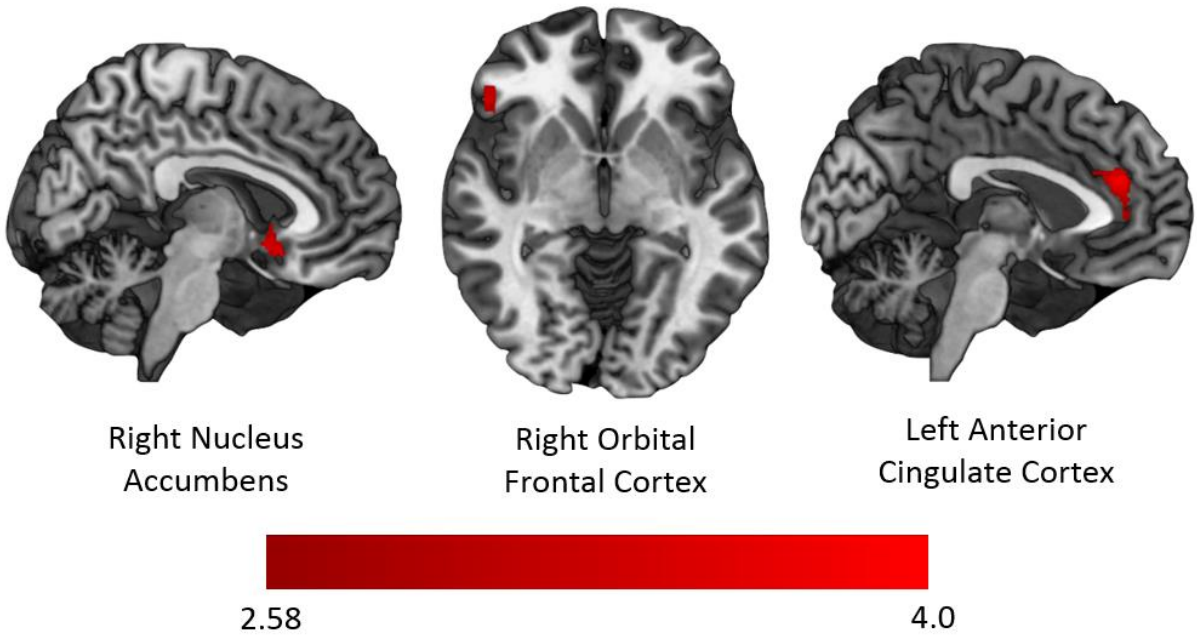


Figure 3.3. *Differential functional activation after OT relative to PLC administration during nonsocial reward anticipation.* Brain areas with greater activation during nonsocial reward anticipation after intranasal OT administration relative to PLC administration include the right nucleus accumbens (left), the right orbital frontal cortex (center), and the left anterior cingulate cortex (right).

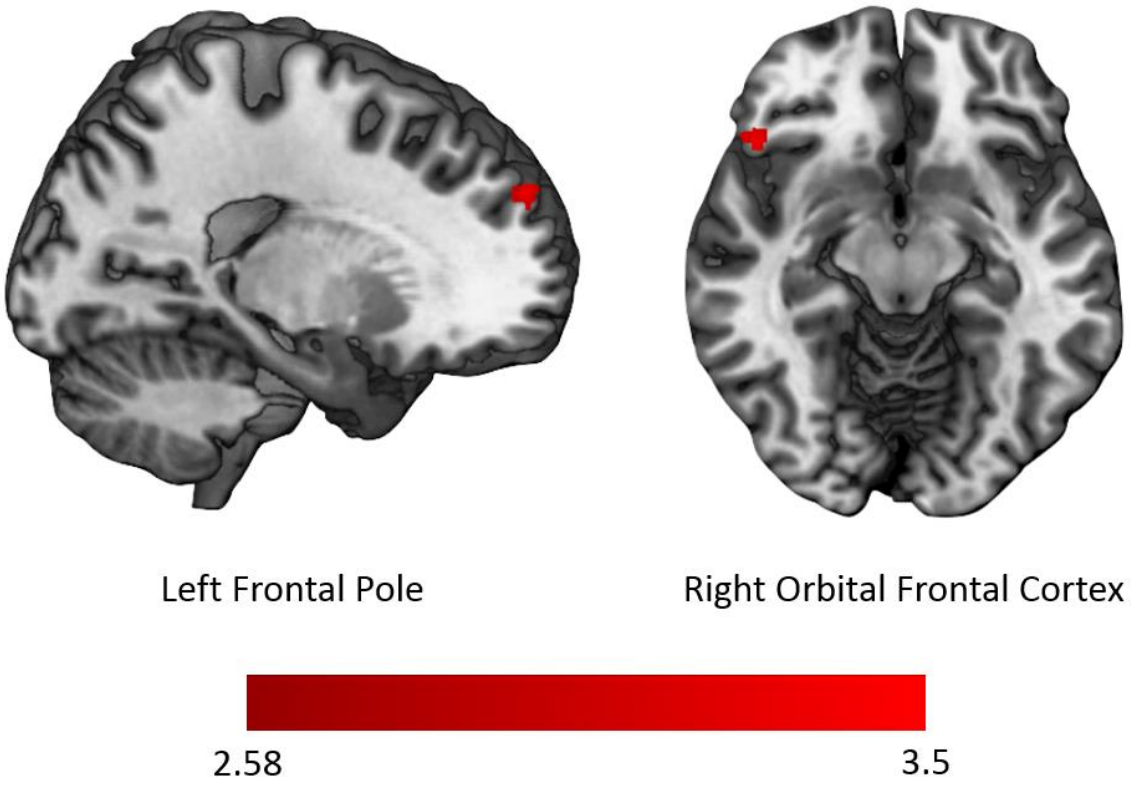


Figure 3.4. *Differences in functional activation after OT relative to PLC administration during nonsocial reward outcomes.* Brain areas with greater activation during nonsocial reward outcome after intranasal OT administration relative to PLC administration include the left frontal pole (left) and the right orbital frontal cortex (right).

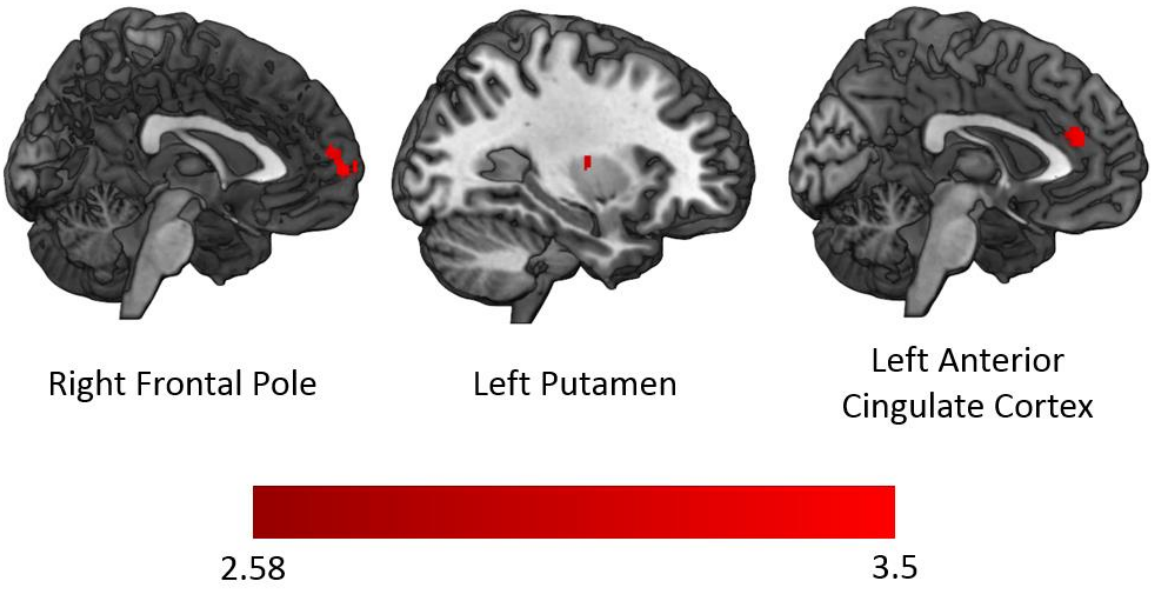


Figure 3.5. *Correlations between SRS and differences in functional activation after OT vs. PLC during nonsocial reward anticipation.* The right frontal pole, left putamen, and left anterior cingulate cortex showed increased activation in individuals with greater ASD symptoms during nonsocial reward anticipation following OT relative to PLC administration.

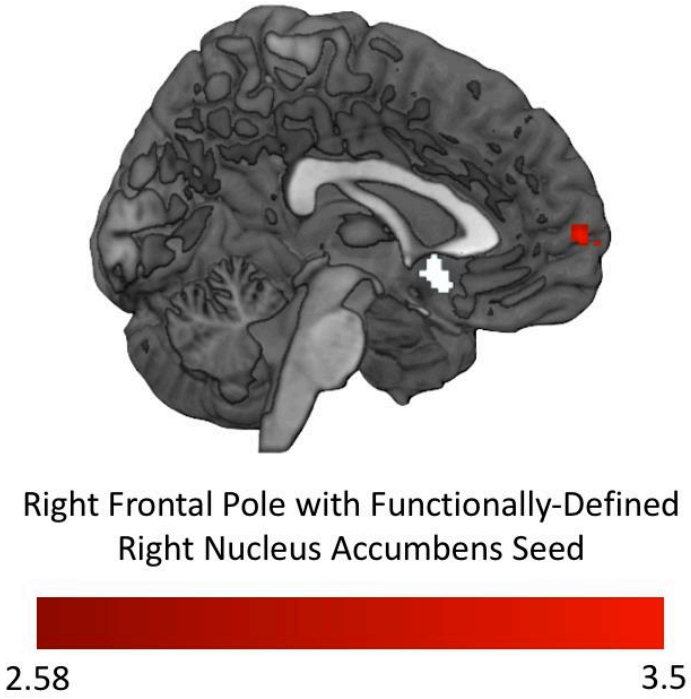


Figure 3.6. *Functional connectivity during nonsocial reward anticipation with the functionally-defined right nucleus accumbens seed.* The right frontal pole (red) shows greater functional connectivity with the right NAcc (white) during nonsocial reward anticipation after intranasal OT administration relative to PLC administration.

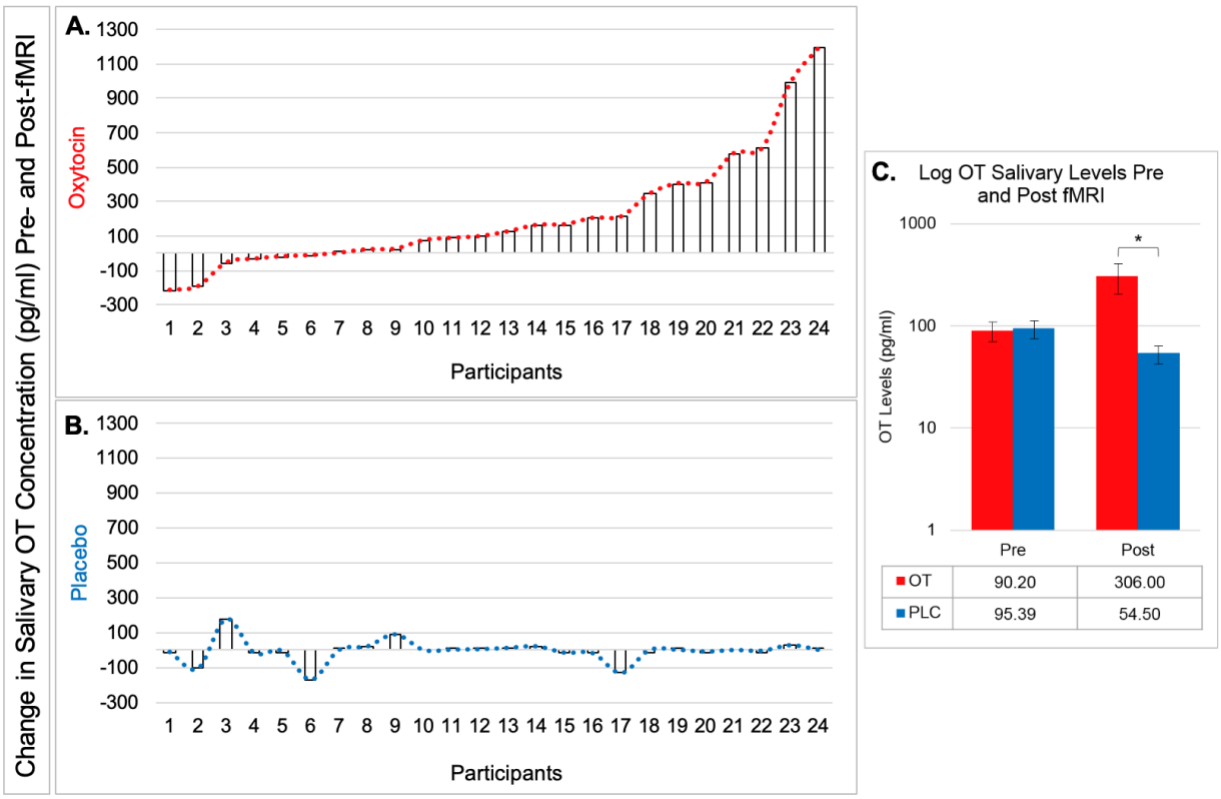


Figure 3.7. *Salivary OT Concentrations.* Change in log-transformed salivary OT levels (pg/ml) for 24 participants (minutes between samples M =85; SD = 9). Four participants were unable to provide adequate saliva samples and were not included in the salivary analyses. A) Change in salivary OT following nasal-OT administration. B) Change in salivary OT following nasal-PLC administration. Because participant 10 was a significant outlier (change in OT concentration after PLC = -723.59), their data is not included in the graph above. C) * = p<.05. Salivary samples collected after OT administration showed significantly greater OT concentrations compared to those following the PLC nasal spray, t = 3. 57; p = 0.0016.

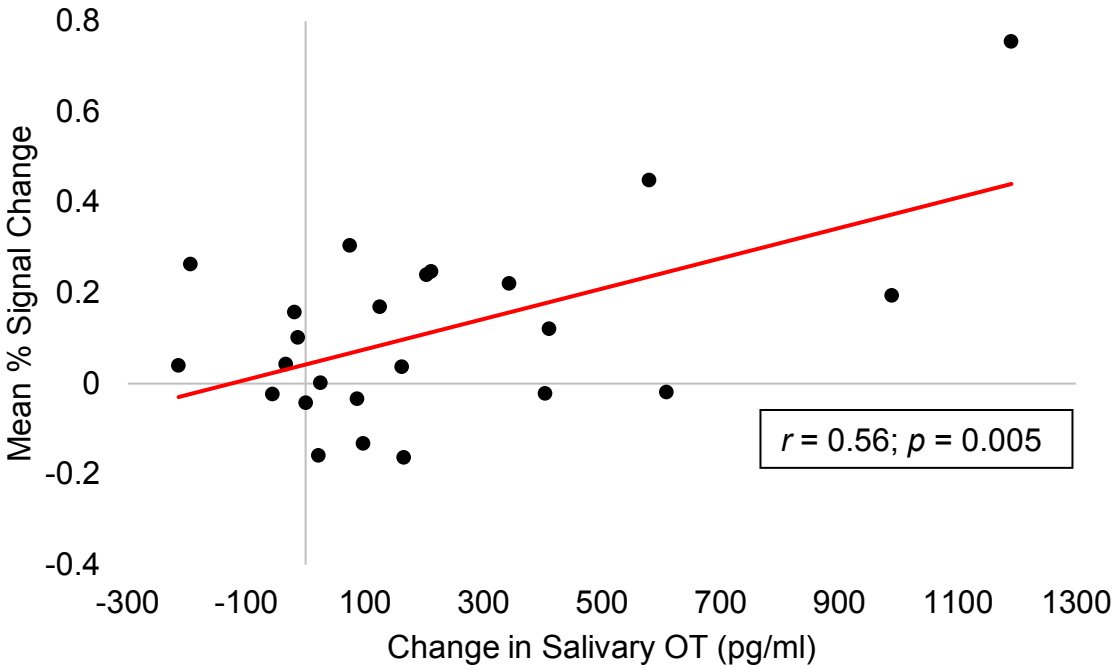


Figure 3.8. *Correlations between OT related neural activation and OT salivary concentration changes following OT administration.* Correlation between mean percent signal change in the right NAcc functional activation cluster during the anticipatory phase of the nonsocial reward condition and change in peripheral OT levels following OT administration.

Supplementary Materials

Main Effect of OT and PLC on nonsocial and social tasks

Anticipation. Whole brain functional activation during anticipation revealed increased neural activations within midbrain and striatal regions, as well as bilateral ACC, bilateral paracingulate gyrus, bilateral precentral gyrus, bilateral occipital pole, bilateral lingual gyrus, and cerebellum. This pattern was broadly observed during the anticipation of both social and nonsocial rewards following OT and PLC administrations to varying degrees of intensity (see Supplementary Figure 3.1).

Outcome. Whole brain functional activation during anticipation revealed increased neural responses in bilateral occipital pole, bilateral ACC, bilateral orbital frontal cortex, bilateral insular cortex, bilateral frontal pole, and striatal regions during nonsocial and social reward outcomes following OT or PLC administration (see Supplementary Figure 3.2). These findings indicate that neural activations largely demonstrated phase-specific (i.e., Anticipation, Outcome) patterns across Treatment Group (i.e., OT, PLC) and Reward Condition (i.e., Nonsocial, Social).

Structural Activation Analyses & Results

For each ROI and participant, treatment-group- and run-specific mean parameter estimates reflecting activation were calculated and extracted using the Featquery tool within FSL separately for anticipation and outcome phases of the social and nonsocial tasks. A 2 (Treatment Group: OT, PLC) × 2 (Reward Condition: Nonsocial, Social) ANOVA was conducted for each of the six striatal regions of interest (right/left NAcc, right/left caudate nucleus, and right/left putamen). No significant Treatment Group × Reward Condition interactions were found. Because of the significant functional activation differences seen between treatment groups,

paired t-tests were employed to examine structural activation differences within the six striatal regions of interest. These analyses were conducted separately for nonsocial and social anticipation and outcomes.

Nonsocial Reward Condition. During nonsocial reward anticipation, results revealed significant treatment group differences in structural activation within the right NAcc, $t(27) = 2.56$, $p = 0.017$, with increased activation associated with OT administration as compared to PLC (see the left side of Supplementary Figure 3.3). No other significant treatment group differences in structural activation were found within either the anticipatory or outcome phase analyses.

Social Reward Condition. No significant treatment group differences in structural activation were found during either social anticipation or outcomes, all p's $> .05$ (see the right side of Supplementary Figure 3.3).

Functional Connectivity of Structurally-Defined Clusters Analyses & Results

Right Nucleus Accumbens.

Nonsocial Task. During nonsocial reward anticipation, the OT group exhibited increased connectivity, relative to PLC, between the right NAcc seed and right frontal pole (see Supplementary Figure 3.4). Additionally, during nonsocial reward anticipation, decreased connectivity was seen between the right NAcc seed and the left superior frontal gyrus for OT compared to PLC. Treatment group differences in task-dependent structural connectivity are illustrated in Supplementary Table 3.1.

Social Task. During social reward anticipation, the OT group showed significant decreased connectivity between the right NAcc seed and the left caudate nucleus. There were no significant increased effects of OT with connectivity during either social or nonsocial outcomes.

Left Nucleus Accumbens.

Nonsocial Reward Condition. The OT group exhibited increased connectivity, relative to PLC, between the left NAcc seed and right FP and left ACC during nonsocial reward anticipation (see Supplementary Table 3.1). Increased connectivity was also observed in the right OFC during nonsocial reward outcomes following OT relative to PLC. Finally, our findings revealed OT-induced decreases in connectivity in the left precentral gyrus during nonsocial reward anticipation and outcomes when compared to PLC.

Social Reward Condition. Decreased connectivity was also observed in the right FP and left caudate nucleus during social reward anticipation following OT compared to PLC. There were no effects of OT relative to PLC on left NAcc connectivity in social reward outcomes in frontostriatal regions.

Correlations Between Structural Activation and ASD symptoms

Increased ASD symptom severity, as measured by SRS total scores, was associated with greater activation in the left caudate nucleus during nonsocial reward outcome following the administration of OT, $r(26) = .43$, $p = .023$. Additionally, findings from correlational analyses between SRS total scores and activation in response to nonsocial reward outcome within the right caudate nucleus, $r(26) = .37$, $p = .052$, and left putamen, $r(26) = .35$, $p = .066$, trended toward significance. There were no significant relations between symptom severity and brain activation during the anticipation of nonsocial rewards or the anticipation or outcome of social rewards.

Correlations Between Functional Connectivity of Structurally-Defined Clusters and ASD symptoms

Additionally, increased ASD symptoms were associated with greater functional connectivity between the structurally-defined right NAcc seed and the right FP during the anticipation of nonsocial rewards. For both the structurally-defined right and left NAcc seeds,

increased connectivity with the right postcentral gyrus was associated with more severe symptomatology during the outcome of nonsocial rewards. Finally, increased connectivity between the right NAcc seed and the right paracingulate gyrus was associated with greater ASD severity in response to social reward outcomes. There were no significant relations between symptom severity and functional connectivity of structurally-defined left NAcc during nonsocial anticipation or social anticipation or outcomes. Similarly, there were no significant associations between functional connectivity of structurally-defined right NAcc and ASD behavioral measures during the anticipation of social rewards.

Salivary Analysis Methods

All samples were extracted prior to oxytocin analysis using strata-X 33µm polymeric reversed phase SPE sorbent in a 96-well plate containing 60 mg sorbent per well, Phenomenex, Torrance CA. Plasma and saliva were acified with 1.5% trifluoroacetic acid (TFA) and centrifuged at 6,000 x g for 20 minutes at 4°C. The supernatant was loaded onto an activated strata-X plate. Wells were washed with 1.5 ml of 0.1% TFA, and then the oxytocin peptide eluted with 1ml of 80% acetonitrile. The eluant was evaporated to dryness under a N2 stream and reconstituted in 250ul of assay buffer. Extraction efficiency was determined by spiking a sample with a known amount of hormone and extracting with the other samples (typically > 90%).

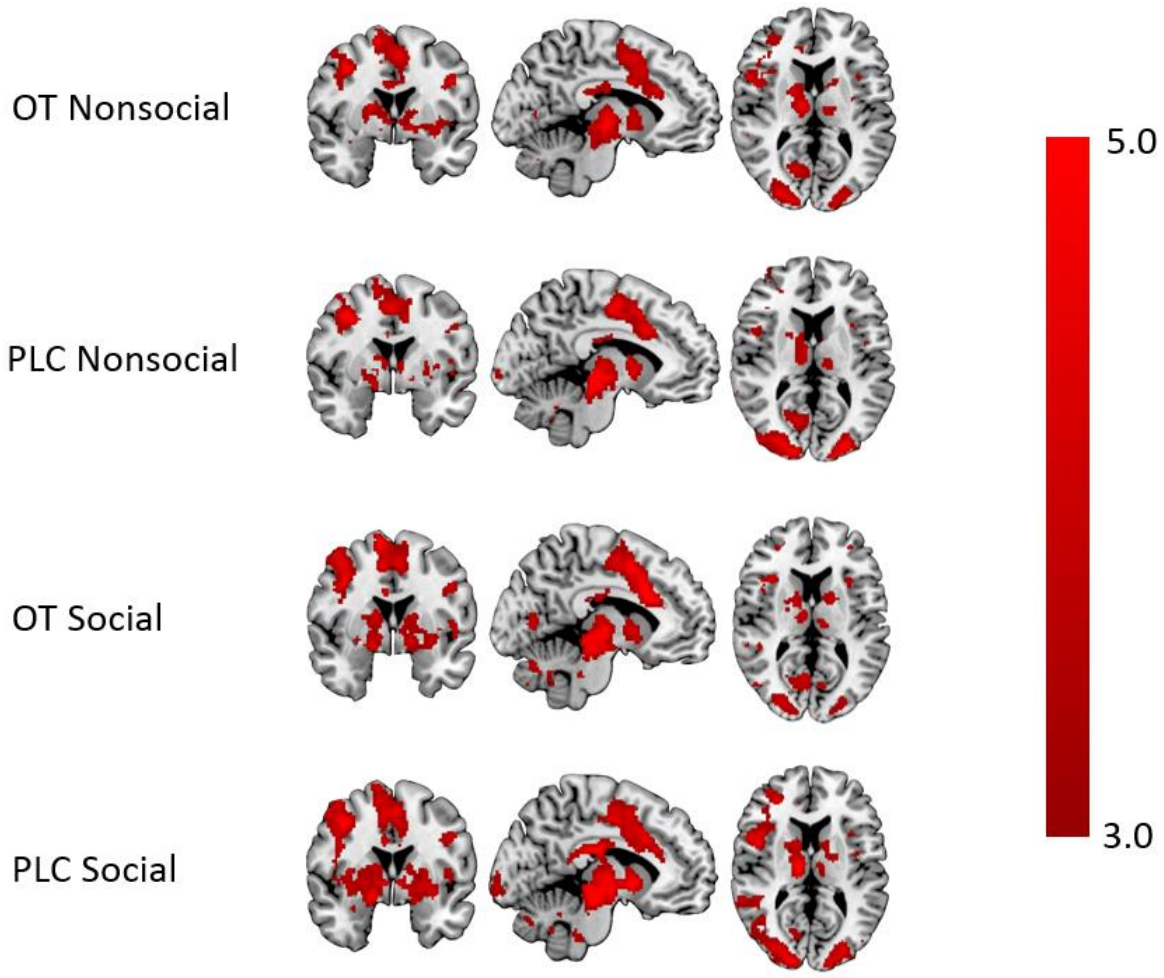
Oxytocin levels in extracted saliva were measured using an assay kit and protocol from Enzo Life Sciences, Ann Arbor, MI. The endogenous OT hormone competes with oxytocin linked to alkaline phosphatase for the oxytocin antibody binding sites. After the overnight incubation at 4°C, the excess reagents are washed away and the bound oxytocin phosphatase was incubated with substrate and after 1 hour this colormetric enzyme reaction was stopped. The

hormone content (pg/ml) is determined by plotting the OD of each sample against a standard curve. The sensitivity of the assay is 2.4 pg/ml with a standard range of 5 to 320 pg/ml. The intra- and inter- assay variations are 4.8% and 8% respectively. Enzo Life Sciences reports cross-reactivity for similar neuropeptides found in mammalian sera at less than 0.001.

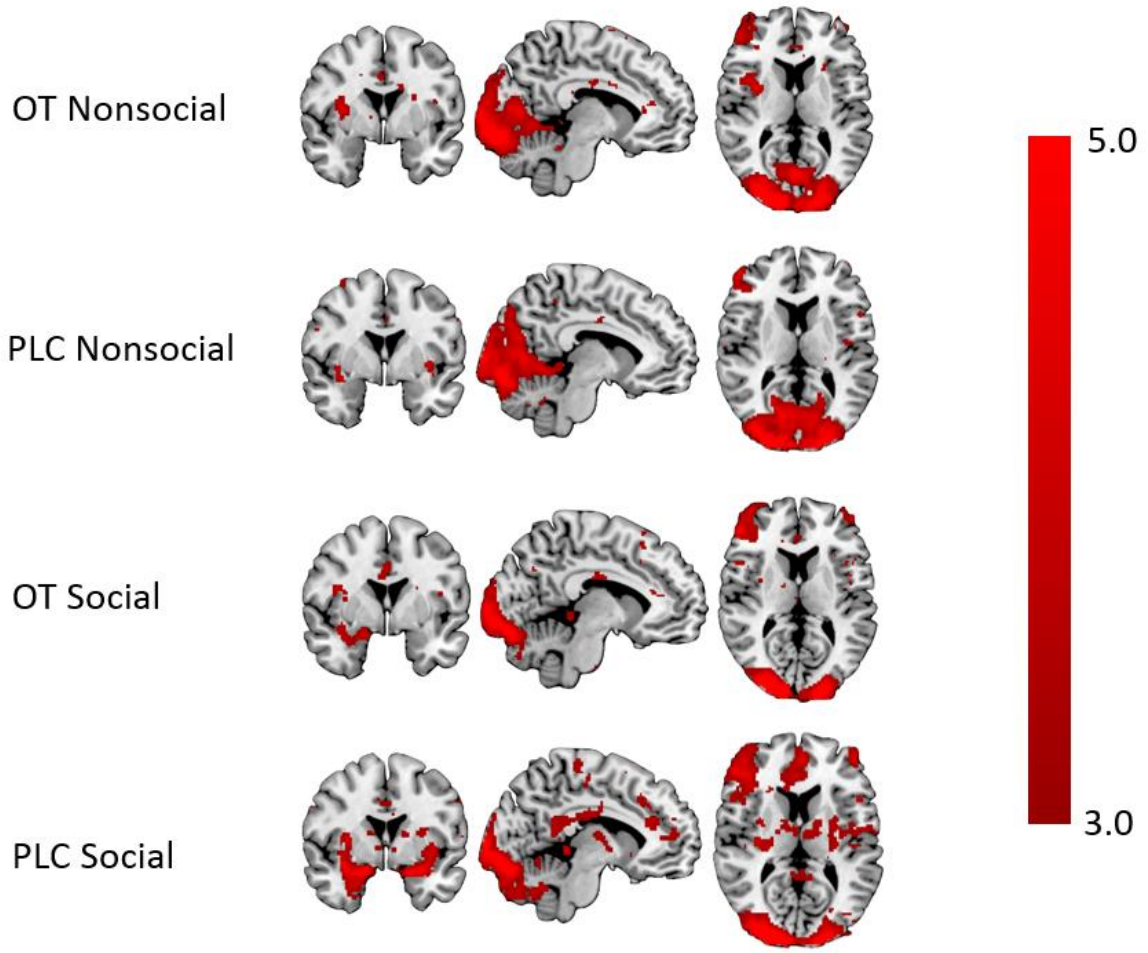
Supplementary Table 3.1. Functional Connectivity of Structurally-Defined Clusters

Phase	Reward Condition	Region	Hem	k	BA	x	y	z	Z max
Right Nucleus Accumbens Seed									
OT > PLC									
Anticipation	Nonsocial	Frontal Pole	R	101	--	40	95	38	3.73
OT < PLC									
Anticipation	Nonsocial	Superior Frontal Gyrus	L	49	--	54	62	63	3.46
	Social	Caudate Nucleus	L	47	--	52	61	48	3.5
Left Nucleus Accumbens Seed									
OT > PLC									
Anticipation	Nonsocial	Frontal Pole	R	76	--	40	95	38	3.61
		Anterior Cingulate Cortex	L	58	32	46	83	46	3.43
Outcome	Nonsocial	Orbital Frontal Cortex	R	120	--	22	75	31	3.42
OT < PLC									
Anticipation	Nonsocial	Precentral Gyrus	L	117	--	57	58	63	3.53
	Social	Frontal Pole	R	54	--	24	88	37	3.23
		Caudate Nucleus	L	44	--	52	61	48	3.47
Outcome	Nonsocial	Precentral Gyrus	L	40	--	71	67	53	3.12

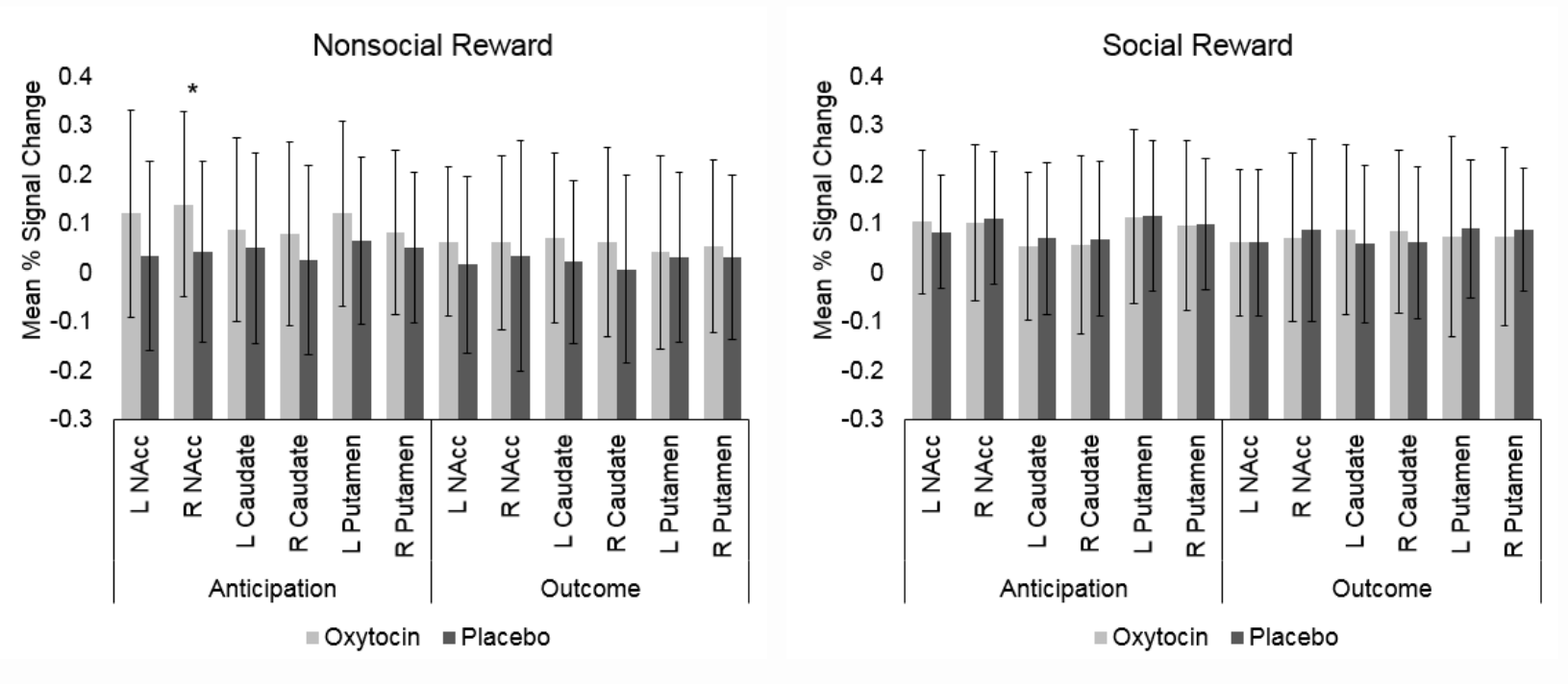
Note. Frontostriatal structural connectivity clusters showing treatment group differences (minimum cluster size = 39 voxels) with the right and left NAcc as structural seeds. Hem=Hemisphere; k=cluster size in voxels; BA=Brodmann Area; Z max=maximum z-value.



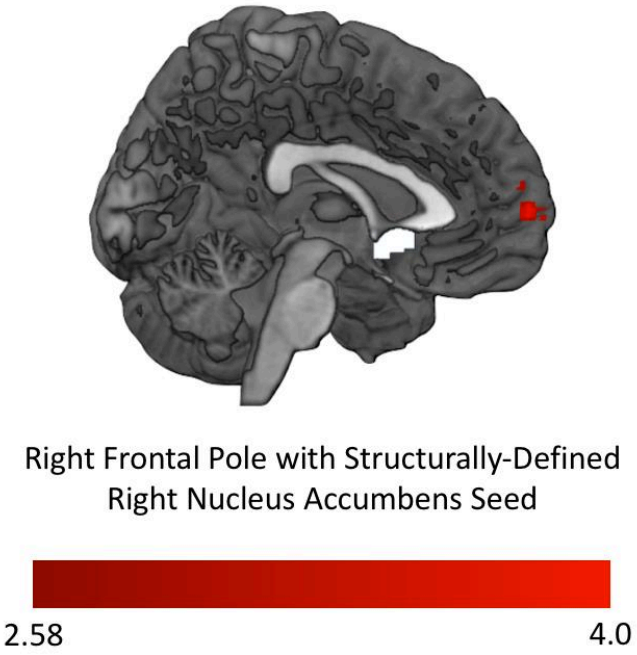
Supplementary Figure 3.1. *Functional activation during the anticipatory phase of the nonsocial and social tasks for OT and PLC.*



Supplementary Figure 3.2. *Functional activation during the outcome phase of the nonsocial and social tasks for OT and PLC.*



Supplementary Figure 3.3. *Structural activation in striatal regions during the anticipation and outcome of nonsocial and social rewards.* Frontostriatal structural activation during nonsocial (left) and social (right) reward anticipation and outcome after intranasal OT relative to PLC administration. In the nonsocial reward condition, the right NAcc showed relatively increased activation during reward anticipation following OT relative to PLC administration. No significant differences in activation were observed during nonsocial outcomes following OT relative to PLC administration. In the social reward conditions, none of the regions queried showed differential activation during either the anticipation or outcome phases after intranasal OT relative to PLC administration. NAcc = nucleus accumbens. *= $p<.05$.



Supplementary Figure 3.4. *Functional connectivity with structurally-defined right NAcc during nonsocial reward anticipation.* The right frontal pole (red) shows greater structural connectivity with the right NAcc (white) during nonsocial reward anticipation after intranasal OT administration relative to PLC administration.

INTEGRATIVE DISCUSSION

Impairments in social motivation, and reward processing more broadly, have recently been implicated within causal theories of core ASD symptom development and maintenance (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Greene, Walsh, Mosner, & Dichter, 2018). The current program of research aimed to explore this theory and its nuances in greater detail by using novel methods and probing previously unexplored aspects of reward processing in individuals with ASD. The overarching goal was to examine how disruptions in reward processing abilities of individuals with ASD may relate to defining features of the disorder and be leveraged as mechanistic targets of treatment response in this population. This was accomplished across three distinct studies with individuals with ASD examining 1) responses to visual prediction errors, a key component of reward learning, 2) neural responses to vicarious rewards, as a means of investigating a component of social cognitive deficits inherent to ASD, 3) and neural responses within mesocorticolimbic regions following intranasal oxytocin administration, to better understand the treatment's mechanistic action.

Study 1 explored prediction error responses of individuals with ASD using an outcome expectancy eye tracking task. The aim of this study was to investigate responses to prediction errors in ASD, given their central role within reward learning, as well as to better understand previous reports of predictive impairments in ASD. The findings from Study 1 corroborate previous reports of predictive impairment in ASD (Sinha et al., 2014; Van de Cruys et al., 2014), but did not find that this effect was impacted by reward type (e.g., social vs. nonsocial), such that

deficits in predictive coding were commensurate in individuals with ASD across both social and nonsocial rewards. Furthermore, predictive impairment was marginally associated with greater ASD symptom severity within the ASD group. Results from Study 1 provide additional evidence of disrupted predictive ability in ASD (Sinha et al., 2014) and for the first time explicitly expand these findings to the domains of social and nonsocial prediction errors. These findings have broad implications for reward learning impairments in individuals with ASD.

Study 2 is the first neuroimaging study to examine responses to vicarious rewards in ASD. By examining responses to rewards for others, we may better understand various social cognitive (e.g., theory of mind) social-learning impairments associated with ASD. These vicarious responses were compared to a standard reward condition, in which participants earned money for themselves. Because previous findings reported no impairments in ASD in expended effort for monetary rewards for oneself, but, instead, found that individuals with ASD demonstrated reduced sensitivity to reward magnitude parameters when earning rewards for others (Mosner et al., 2017), we hypothesized that neural responses to vicarious reward in ASD would be relatively attenuated compared to responses during the standard reward condition. Our hypotheses were supported by our findings in Study 2 that individuals with ASD showed reduced activation in reward-related regions in response to vicarious reward, suggesting that adults with ASD may be less sensitive to rewards that other people receive. Furthermore, our findings revealed aberrant connectivity between key reward regions during vicarious reward outcomes. Taken together, this decreased vicarious reward sensitivity may reflect a neural mechanism by which social deficits arise in ASD.

Finally, Study 3 used neural reward responses as an outcome measure for a pharmacological intervention for ASD. Specifically, this study examined neural responses during

nonsocial and social incentive delay tasks following intranasal oxytocin (OT) administration in individuals with ASD. Preclinical research has suggested that OT may impact behavior by preferentially acting on reward neural circuitry within the mesolimbic dopamine system (Hung et al., 2017; Love, 2014), yet this had not been explored in individuals with ASD using a reward task. Results showed that OT preferentially increased neural activation within key reward regions (i.e., nucleus accumbens, orbitofrontal cortex, and anterior cingulate cortex) in response to nonsocial, but not social, reward cues. These findings validated the hypothesis that OT impacts mesocorticolimbic areas specifically, yet they also countered original hypotheses that individuals with ASD to show greater activation in response to social rewards following OT administration. This discrepancy across reward types (i.e., social and nonsocial) may also be attributed to the perceived value of both rewards. Specifically, it is possible that the social stimuli did not evoke as strong of a reward response relative to the nonsocial condition. Overall, these findings suggest OT may exert it's beneficial effects by acting on neural reward circuitry more broadly, as opposed to targeting social rewards exclusively.

Each of these studies provides a unique perspective into the nature of ASD reward processing deficits. Although the social motivation theory of autism implicates aberrant responses to social rewards, specifically, in the development and maintenance of core ASD symptoms (Chevallier et al., 2012), recent findings have revealed evidence of more pervasive reward processing impairments (i.e. not limited to social rewards) in ASD (Cascio et al., 2014; Cascio et al., 2012; Dichter, 2018; Kohls, Antezana, Mosner, Schultz, & Yerys, 2018). Study 1 aligned with this theory of broader reward dysfunction in ASD, in that it showed evidence of impaired responses to both social and nonsocial rewards. Similarly, Study 3 revealed that OT preferentially increased neural reward responses to nonsocial stimuli in individuals with ASD,

but the same effect was not observed in response to social stimuli. Study 3 did not include a TDC sample, therefore, it cannot speak to whether this same response to OT would be observed in typically developing individuals. Although, together both Studies 1 and 3 suggest broader reward dysfunction may be present in ASD and may contribute to the characteristic behavioral presentation of the disorder. These findings of pervasive reward deficits in ASD are in concordance with a recent etiological theory that suggests neuroimmune dysregulation preferentially impacts mesocorticolimbic dopamine functioning in ASD. Evidence of this theory suggests dopaminergic disruptions would impact motivational and reward processing nonspecifically, and, thus, would affect responses to a variety of reward types.

Study 2, however, revealed decreased sensitivity to monetary rewards for others in individuals with ASD, whereas there was no ASD impairment in responses to money earned for themselves. These results deviate somewhat from Studies 1 and 3, which found no group differences between the nonsocial and social condition and more prominent effects for the nonsocial condition, respectively. It is possible that the discrepant findings across studies may result, in part, from the unique stimuli employed in each. Specifically, Studies 1 and 3 used static images of faces as a proxy for social reward, whereas Study 2 used money earned for others as a social comparison to the standard monetary reward condition, in which money is earned for oneself. This nuanced social comparison used in Study 2 may represent a more etiologically valid approach to studying social reward processing in ASD. When examined together, these findings are not necessarily conflicting, as they each measure unique constructs and have distinct comparison groups. Importantly, Study 3, unlike Studies 1 and 2, assessed the effect of oxytocin on reward responses and did not measure differences in reward responses between ASD and TDC groups; therefore, the results of this specific study reflect pharmacological effects in an

ASD sample rather than the underlying reward processing deficit itself. However, the results highlight the complexity of reward processing disruptions in individuals with ASD and the need for additional, larger-scale studies examining responses to a variety of reward types in ASD. Although these works are unique in many aspects, they each complement one another in that they corroborate and contribute to the theory of impaired reward processing in ASD and largely support a profile of ASD reward hyposensitivity (for a review see Clements et al., 2018).

Although our understanding of the etiological factors contributing to ASD symptoms are still not fully understood, it is our hope that by studying novel aspects of behavioral and neural reward processing in ASD, we may shed light on the underlying mechanisms of the disorder's core deficits. In addition, responses to reward stimuli may continue to serve as measures of treatment outcomes by which to evaluate the efficacy and mechanistic actions of various interventions aimed at ameliorating ASD symptoms.

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