UNIVERSITY OF CALIFORNIA, SAN DIEGO

Towards a better understanding of the reward system in autism spectrum disorders: empirical tests of the social motivation hypothesis

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Psychology

by

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DEDICATION

This dissertation is dedicated to my parents, for their support and for instilling in me a passion for academic endeavors, and to my husband Trevor Stavropoulos, for his steadfast confidence in me.

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Chapter 1, in full, is a reprint of the material as it appears in Reward sensitivity to faces versus objects in children: an ERP study in *Social Cognitive and Affective Neuroscience*. Stavropoulos, Katherine K.M; Carver, Leslie J. (2013). The dissertation author was the primary investigator and author of this paper.

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ABSTRACT OF THE DISSERTATION

Towards a better understanding of the reward system in autism spectrum disorders: empirical tests of the social motivation hypothesis

by

Katherine Kuhl Meltzoff Stavropoulos

Doctor of Philosophy in Psychology

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Professor Leslie Carver, Chair

This dissertation examined the reward system in children with autism spectrum disorders (ASD). I empirically tested the social motivation hypothesis as a potential explanation for social impairments in ASD.

Chapter 1 investigated typically developing (TD) children's electrophysiological responses to rewards accompanied by incidental social versus nonsocial stimuli. This chapter introduced a paradigm that allows reward anticipation

to be measured while controlling for both reward and stimulus properties. TD children had increased activation while anticipating rewards accompanied by social versus nonsocial stimuli, suggesting that TD children find social stimuli more rewarding than nonsocial stimuli.

Chapter 2 investigated how children with ASD compare to TD children on reward anticipation and processing using the paradigm described in Chapter 1. TD children had larger reward anticipation for social versus nonsocial stimuli, while children with ASD did not. Children with ASD also processed social versus nonsocial stimuli differently than their TD peers. These results suggest that children with ASD have selective deficits in anticipation and processing of social rewards.

Chapter 3 examined whether familiarity might normalize social reward anticipation for children with ASD. Neither children with nor without ASD had different magnitudes of reward anticipation for familiar versus unfamiliar faces, or scrambled versions of those pictures. However, when collapsing across familiarity, results from Chapter 2 were replicated—TD children had larger reward anticipation for social versus nonsocial stimuli, while children with ASD did not. Chapter 3 also found evidence for an Nc-like component that occurred prior to social stimuli. This component was larger for TD children versus those with ASD.

To explore possible mechanisms for these differences in social reward processing, Chapter 4 proposes oxytocin as a potential neuropeptide involved in social motivation. Chapter 4 reviews research on oxytocin's effect on social behavior in individuals with and without ASD, as well as implications for treatment of joint

attention deficits in ASD. This chapter makes suggestions for future research that combine pharmacological and behavioral interventions in order to optimize outcomes.

Collectively, this dissertation provides evidence in favor of the social motivation hypothesis, and important information about the nature of the reward system in children with ASD.|

INTRODUCTION

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by atypicalities in social behavior and social cognition. Although it is clear that individuals with ASD are impaired in multiple facets of social behavior, the basis for these difficulties has been the subject of debate. Understanding the basis for social deficits in ASD is crucial in order to improve the efficacy of intervention strategies, as well as to assist in the creation of novel interventions. Multiple theories have been proposed to explain the social deficits in ASD. This dissertation was designed to empirically test one such theory—the social motivation hypothesis—and to gain a better understanding of the reward system in both TD children and those with ASD.

The *Social Motivation Hypothesis* [1–6] has been proposed as the basis for social deficits in ASD. According to this hypothesis, children with ASD lack motivation to engage in social activities, and thus engage in these behaviors less frequently (e.g., eye contact, joint attention) because they find these activities less rewarding than typically developing (TD) children. According to the social motivation hypothesis, decreased social engagement early in life leads to later autism symptomology such as abnormal brain responses to faces [7], language and communication deficits [8], and impaired joint attention [8–10], due to the importance of experience in social learning and cortical specialization. The social motivation hypothesis implicates the reward systems of the brain, and is the first theory to suggest that a lack of social motivation itself leads to symptoms of ASD, rather than the alternative proposal that specific brain structures (e.g., amygdala, fusiform face area) are abnormal and cause the symptoms of autism.

Only a small number of neuroscience studies have directly investigated social motivation via the brain's neural reward system in adolescents and adults with ASD [11–16].

Before endeavoring to test social motivation in individuals with ASD, it is important to understand how social motivation develops in typically developing (TD) individuals. Previous research has established that neural reward circuits in TD individuals are activated by social rewards such as faces [17–19]. Thus, it appears that TD individuals are motivated and rewarded by social stimuli. However, this research has been limited to testing adolescents and adults, rather than children, and it has not directly contrasted the reward value of social versus nonsocial stimuli. Testing how TD children respond to social versus nonsocial rewards is a crucial first step in understanding how the brain's reward system develops typically—and what may be going awry in this system for children with ASD.

A few recent studies have directly contrasted responses to social and nonsocial rewards in typically developing individuals [20–22], and in individuals with ASD [11–16]. In the studies of typically developing individuals only, the results highlight the complexity of the neural reward system, and suggest that some areas of the reward circuit might be especially sensitive to social rewards, whereas others may not. Of the studies that compared TD individuals to those with ASD, some found evidence for specific social reward deficits [11,16], while others found reward deficits in ASD for monetary rewards, or more global reward deficits for both social and nonsocial rewards [12–14].

Importantly, a defining feature of nearly all the aforementioned studies is that nonsocial rewards were primarily tangible (e.g., money), and social rewards were not tangible. More specifically, in the nonsocial reward conditions, participants could earn money, while during social reward trials, participants saw pictures of faces or compliments displayed on-screen. Thus, in one condition, participants received a tangible item for reward (e.g., money), whereas in the other condition, they viewed a social stimulus, but received nothing tangible. It is not difficult to imagine why, for both individuals with and without ASD, earning money might be more rewarding compared to simply looking at pictures of faces. It is unclear, then, whether social versus nonsocial rewards are processed differently in TD individuals or those with ASD when controlling for reward properties between conditions.

The research in this dissertation was designed to empirically test the social motivation hypothesis while keeping tangible rewards controlled between social and nonsocial conditions.

Chapter 1 introduces a novel event-related-potential (ERP) task that controls for reward properties between social and nonsocial conditions, as well as physical stimulus properties. This chapter reports an experiment with 6- to 8-year-old TD children that was designed to investigate how reward anticipation for social versus nonsocial stimuli occurs in a neurotypical population. Reward anticipation for social versus nonsocial stimuli was measured via the stimulus preceding negativity (SPN) ERP component. The SPN reflects brain activity that occurs before expected feedback

about one's performance [23]. The SPN component is thought to reflect the expectation of reward, and related activity of the dopaminergic reward system [24,25].

Chapter 2 examines the differences between 6- to 10-year-old children with and without ASD on both reward anticipation and reward processing of social versus nonsocial stimuli. Similarly to Chapter 1, reward *anticipation* was measured via the SPN component. Reward *processing* was measured via the Feedback Related Negativity (FRN) component. The FRN is an ERP component occurring 200-300ms after feedback, and is characterized by a negativity in response to "loss" versus "gain" trials [26]. Source localization studies suggest that the FRN reflects activity in the dopamine reward system [27], and is generated by the striatum, medial-frontal cortex and anterior cingulate cortex—areas related to reward processing [28,29]. By collecting data on both reward anticipation and processing in children with and without ASD, we gain a more complete understanding of the reward system in children with ASD, and how different temporal phases of reward affect these two populations.

Chapter 3 was designed to better understand the boundaries of the social motivation hypothesis. That is, do children with ASD have social reward deficits for all social stimuli, or do particular social stimuli, such as one's own mother's face, cause the reward system to "normalize"? There is a relatively small literature on the effect of familiarity in ASD, and the studies done to date focus on the effect of familiarity on face processing [3,30–38]. The studies have varied results, likely due to differences in subject's age, methodologies, and stimuli between studies. This chapter

compared reward anticipation in children with and without ASD for familiar faces (caregivers) versus unfamiliar faces.

Chapter 4 reviews existing literature on the social motivation hypothesis, and proposes that the neuropeptide oxytocin may be a candidate for the underlying mechanisms behind the social motivation deficits seen in individuals with ASD. This chapter uses a core social deficit in ASD, joint attention, as a test case. Suggestions are proposed for future directions in intervention and clinical trials research in order to improve social motivation in children with ASD.

Overall, this dissertation research provides a more complete understanding of the reward system in both TD children and those with ASD. The set of experiments described here is the first to empirically investigate the social motivation hypothesis while controlling for reward and stimulus properties. Taken together, these studies expand upon previous investigations and can inform future research into more effective interventions for children with ASD.

REFERENCES

1. Dawson G (2008) Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. Dev Psychopathol 20: 775–803.

2. Dawson G, Bernier R (2007) Development of social brain circuitry in Autism. Human behavior learning and the developing brain Atypical development. New York: Guilford Press. pp. 28–56.

3. Dawson G, Carver L, Meltzoff AN, Panagiotides H, McPartland J, Webb SJ (2002) Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. Child Dev 73: 700–717.

4. Dawson G, Webb SJ, Mcpartland J (2005) Understanding the Nature of Face Processing Impairment in Autism : Insights From Behavioral and Electrophysiological Studies. Dev Neuropsychol 27: 403-424.

5. Grelotti D, Gauthier I, Schultz R (2002) Social Interest and the Development of Cortical Face Specialization : What Autism Teaches Us About Face Processing. Dev Psychobiol 40: 213–225.

6. Schultz RT (2005) Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int J Dev Neurosci 23: 125–141.

7. McPartland J, Dawson G, Webb SJ, Panagiotides H, Carver LJ (2004) Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. J Child Psychol Psychiatry 45: 1235–1245.

8. Charman T (2003) Why is joint attention a pivotal skill in autism? Philos Trans R Soc Lond B Biol Sci 358: 315–324.

9. Mundy P, Crowson M (1997) Joint attention and early social communication: implications for research on intervention with autism. J Autism Dev Disord 27: 653–676.

10. Mundy P, Sigman M, Ungerer J, Sherman T (1986) Defining the social deficits of autism: the contribution of non-verbal communication measures. J Child Psychol Psychiatry 27: 657–669.

11. Delmonte S, Balsters JH, McGrath J, Fitzgerald J, Brennan S, Fagan AJ, Gallagher L (2012) Social and monetary reward processing in autism spectrum disorders. Mol Autism 3: 1–13.

12. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW (2012) Reward circuitry function in autism during face anticipation and outcomes. J Autism Dev Disord 42: 147–160.

13. Kohls G, Peltzer J, Schulte-Rüther M, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Konrad K (2011) Atypical brain responses to reward cues in autism as revealed by event-related potentials. J Autism Dev Disord 41: 1523–1533.

14. Kohls G, Schulte-Rüther M, Nehrkorn B, Müller K, Fink GR, Kamp-Becker I, Herpertz-Dahlmann B, Schultz RT, Konrad K (2013) Reward system dysfunction in autism spectrum disorders. Soc Cogn Affect Neurosci 8: 565–572.

15. Richey JA, Rittenberg A, Hughes L, Damiano CR, Sabatino A, Miller S, Hanna E, Bodfish JW, Dichter GS (2013) Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. Soc Cogn Affect Neurosci: 1–11.

16. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY (2010) Reward processing in autism. Autism Res 3: 53–67.

17. Chatterjee A, Thomas A, Smith SE, Aguirre GK (2009) The neural response to facial attractiveness. Neuropsychology 23: 135–143.

18. Kampe K, Frith C, Dolan R, Frith U (2001) Reward value of attractiveness and gaze - Making eye contact enhances the appeal of a pleasing face, irrespective of gender. Nature 413: 589.

19. Vrticka P, Andersson F, Grandjean D, Sander D, Vuilleumier P (2008) Individual attachment style modulates human amygdala and striatum activation during social appraisal. PLoS One 3: e2868.

20. Kohls G, Herpertz-Dahlmann B, Konrad K (2009) Hyperresponsiveness to social rewards in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Behav Brain Funct 5: 20.

21. Lin A, Adolphs R, Rangel A (2012) Social and monetary reward learning engage overlapping neural substrates. Soc Cogn Affect Neurosci 7: 274–281.

22. Rademacher L, Krach S, Kohls G, Irmak A, Gründer G, Spreckelmeyer, KN (2010) Dissociation of neural networks for anticipation and consumption of monetary and social rewards. Neuroimage 49: 3276–3285.

23. Damen EJ., Brunia CHM (1987) Changes in heart rate and slow brain potentials related to motor preparation and stimulus anticipation in a time estimation task. Psychophysiology 24: 700–713.

24. Boxtel GJM Van, Böcker KBE (2004) Cortical Measures of Anticipation. J Psychophysiol 18: 61–76.

25. Mattox ST, Valle-Inclán F, Hackley SA (2006) Psychophysiological evidence for impaired reward anticipation in Parkinson's disease. Clin Neurophysiol 117: 2144–2153.

26. Hajcak G, Moser JS, Holroyd CB, Simons RF (2006) The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. Biol Psychol 71: 148–154.

27. Holroyd CB, Coles MGH (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol Rev 109: 679–709.

28. Foti D, Weinberg A, Dien J, Hajcak G (2011) Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: temporospatial principal components analysis and source localization of the feedback negativity. Hum Brain Mapp 32: 2207–2216.

29. Nieuwenhuis S, Slagter HA, von Geusau NJA, Heslenfeld DJ, Holroyd CB (2005) Knowing good from bad: differential activation of human cortical areas by positive and negative outcomes. Eur J Neurosci 21: 3161–3168.

30. Gunji A, Inagaki M, Inoue Y, Takeshima Y, Kaga M (2009) Event-related potentials of self-face recognition in children with pervasive developmental disorders. Brain Dev 31: 139–147.

31. Gunji A, Goto T, Kita Y, Sakuma R, Kokubo N, Koike T, Sakihara K, Kaga M, Inagaki M (2013) Facial identity recognition in children with autism spectrum disorders revealed by P300 analysis: a preliminary study. Brain Dev 35: 293–298.

32. Key APF, Stone WL (2012) Processing of novel and familiar faces in infants at average and high risk for autism. Dev Cogn Neurosci 2: 244–255.

33. Kylliäinen A, Wallace S, Coutanche MN, Leppänen JM, Cusack J, Bailey AJ, Hietanen JK (2012) Affective-motivational brain responses to direct gaze in children with autism spectrum disorder. J Child Psychol Psychiatry 53: 790–797.

34. Luyster RJ, Wagner JB, Vogel-Farley V, Tager-Flusberg H, Nelson CA (2011) Neural correlates of familiar and unfamiliar face processing in infants at risk for autism spectrum disorders. Brain Topogr 24: 220–228.

35. Pierce K, Redcay E (2008) Fusiform function in children with an autism spectrum disorder is a matter of "who". Biol Psychiatry 64: 552–560.

36. Pierce K, Haist F, Sedaghat F, Courchesne E (2004) The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain 127: 2703–2716.

37. Webb SJ, Jones EJH, Merkle K, Murias M, Greenson J, Richards T, Aylward E (2010) Response to familiar faces, newly familiar faces, and novel faces as assessed by ERPs is intact in adults with autism spectrum disorders. Int J Psychophysiol 77: 106–117.

38. Webb SJ, Jones EJH, Merkle K, Venema K, Greenson J, Murias M, Dawson G (2011) Developmental change in the ERP responses to familiar faces in toddlers with autism spectrum disorders versus typical development. Child Dev 82: 1868–1886.

Chapter 1

Reward sensitivity to faces versus objects in children: an ERP study

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Reward sensitivity to faces versus objects in children: an ERP study

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How children respond to social and nonsocial rewards has important implications for understanding social cognitive development. Adults find faces intrinsically rewarding. However, little is known about how children respond to face *vs* nonface rewards. We utilized event-related potentials (the stimulus-preceding negativity, SPN) to measure differences in reward anticipation during a guessing game in 6- to 8-year-olds. Children were presented with reward indicators accompanied by incidental face or nonface stimuli. Nonface stimuli were comprised of scrambled faces in the shape of arrows, controlling for low-level properties of the two conditions. Children showed an increased SPN when the reward stimuli were accompanied by faces, relative to nonface stimuli. This suggests that children find a face stimulus more rewarding than a nonface stimulus. The results have important implications for processing social *vs* nonsocial rewards in typically developing children, and allow testing of populations with deficits in social reward processing, such as autism spectrum disorder.

Keywords: event-related potentials; reward processing; faces; children; social motivation

INTRODUCTION

Most people find social interactions to be intrinsically rewarding. From birth, we have a bias to attend to faces and face-like objects (Johnson *et al.*, 1991). Although this drive toward social stimuli is quite important for normal social functioning, we understand relatively little about the brain systems that underlie it, or how those systems develop. In addition, we know little about how social rewards are different than other kinds of rewards. The main goal of the current research is to understand how social reward systems in the brain are activated in children, and how social rewards differ from nonsocial rewards in this population.

Previous research has established that pictures of attractive faces activate reward centers of the brain (Kampe *et al.*, 2001; Winston *et al.*, 2007; Chatterjee *et al.*, 2009). However, if faces themselves are rewarding, how might they compare with more concrete rewards such as money?

Multiple experiments have compared brain activity or behavioral accuracy and reaction times with faces *vs* money—but most of these studies have focused on between group comparisons between typically developing children and those with social impairments such as autism spectrum disorders (ASD) or attention-deficit hyperactivity disorder (ADHD) (Kohls *et al.*, 2009b; Scott-Van Zeeland *et al.*, 2010; Demurie *et al.*, 2011; Kohls *et al.*, 2011; Dichter *et al.*, 2012;, Kohls *et al.*, 2013). Only a few studies have directly compared responses to social and nonsocial rewards in typically developing individuals (Kohls *et al.*, 2009a; Spreckelmeyer *et al.*, 2009; Rademacher *et al.*, 2010; Lin *et al.*, 2012). In the next sections, we review previous research on behavioral, neuroimaging and electrophysiological studies.

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Studies with typically developing children

Behavioral studies

To our knowledge, only one study has used behavior alone to measure reward sensitivity in typically developing children. Kohls and colleagues (2009a) used behavioral measures of reaction time and accuracy in a go/no-go task. Participants saw a stream of letters presented, and responded with button press to all letters with the exception of X. Successful inhibitions of response to X trials were rewarded with either social (happy faces) or nonsocial (monetary) feedback. Feedback for false alarms (incorrectly responding to the X) consisted of neutral faces in the social condition, or pictures of an empty wallet, signifying no money for that trial in the nonsocial condition. Response inhibition improved for both social and monetary reward conditions in this study. However, typically developing children demonstrated larger task improvement during monetary reward conditions than in the social condition.

Functional neuroimaging studies

Several studies have used functional neuroimaging to measure reward sensitivity in typically developing adults and children. Using fMRI, Spreckelmeyer *et al.* (2009) had participants engage in an incentive delay task with money or faces at varying degrees of reward (small, medium and large). Participants were asked to press a button as quickly as possible after seeing a target stimulus in order to get a reward. The authors found that the nucleus accumbens, putamen and thalamus were activated in a linear pattern as rewards increased for both money and face tasks. Moreover, when the authors compared brain activity patterns of males *vs* females, they found that monetary rewards activated a wide range of brain areas in men, while the opposite was true of women. Using the same task, Rademacher *et al.* (2010) found differential neural activation patterns between the social and monetary reward conditions. During cued anticipation of both reward types, the authors found activation of the nucleus accumbens. However, during the 'consumption phase' of reward processing (e.g. when participants saw the reward as opposed to when they anticipated the reward type), the authors found amygdala activity for social rewards, and thalamic activity during monetary rewards. Taken together, these studies suggest that the reward system is activated in

response to both monetary and social rewards, but that this activation may be different between genders as well as between phases of reward processing.

In a study of typical adults, Lin *et al.* (2012) had participants engage in a probabilistic learning task. Participants were tested in one of two conditions. In the choice condition, participants saw two different slot machines, and were instructed to choose one. In this condition, participants' choice led to positive, negative or neutral outcomes, depending on the slot machine chose. Participants were reinforced by either a social stimulus (a happy face and positive word for the positive slot machine, an angry face and a negative word for the slot machine associated with negative outcomes, or a blank screen for the machine associated with neutral outcomes) or a nonsocial stimulus (a dollar bill for positive outcomes, signifying that the participant would gain one dollar, and a crossed out dollar bill for negative outcomes, signifying that the participant would lose $1 or a blank screen for neutral outcomes). Thus, participants learned via trial and error during the task which slot machines were associated with positive, negative or neutral outcomes. The authors found that both monetary and social conditions caused activation in overlapping brain regions; in both conditions, activity was observed in the ventromedial prefrontal cortex and striatum that was correlated with reward magnitude (Lin *et al.*, 2012). These results provide evidence that several types of rewards elicit brain activity in shared regions in typically developing individuals. However, it is important to note that the study utilized methods slightly different from previously discussed, because it involved probabilistic learning rather than an incentive delay procedure.

Regardless of the method employed it is likely that participants need to feel some control over the task to activate the reward system. In one fMRI study, Tsukamoto *et al.* (2006) found increased reward system activation in response to trials with feedback dependent on the participants' response *vs* feedback given at random. This result suggests that reward systems are sensitive to the participants' perceptions of their actions and are important to the outcome of the task.

Studies comparing typically developing children and clinical populations

Behavioral studies

Demurie *et al.* (2011) used an incentive delay task similar to Spreckelmeyer *et al.* (2009) and Rademacher *et al.* (2010) to measure reward sensitivity in typically developing children and children with ASD and ADHD. They found that children with both ASD and ADHD demonstrated faster reaction times in response to a monetary incentive delay task than a modified social incentive delay task, suggesting that they found the monetary reward more motivating than the social reward. Interestingly, however, typically developing children did not show this pattern—there were no differences in accuracy or reaction time between reward types for typically developing children.

FMRI studies

Dichter *et al.* (2012) reported that typically developing individuals demonstrated greater activation in reward circuits on money runs *vs* face runs during an fMRI incentive delay task. Kohls *et al.* (2009b) measure response inhibition using a go/no-go task in children with ADHD. Performance on the task improved during both monetary and social reward conditions in both the ADHD and control sample. In another study, Kohls and colleagues compared go/no go activation in typical development and ASD. In typically developing participants, Kohls *et al.* (2013) found increased activation in money *vs* face runs in an fMRI go/no-go task in the following reward circuit areas: caudate, putamen, thalamus and insula. However, social brain areas were more strongly activated in the face *vs* money runs (e.g. amygdala, fusiform gyrus, superior temporal sulcus, temporal pole and ventromedial prefrontal cortex). In contrast, participants with ASD showed hypoactivation in reward systems.

Electrophysiological studies

Event-related potentials (ERP) are brain potentials recorded at the scalp that reflect synchronous firing of groups of synapses. ERPs are temporally sensitive, and thus are an ideal metric of the anticipation of forthcoming rewards. In one study that used ERP to measure reward sensitivity, Kohls *et al.* (2011) reported increased neural activation as measured by a cued 'go/no-go' ERP paradigm in response to monetary *vs* social trials. These results highlight the complexity of the neural reward system, and suggest that some areas of the reward circuit might be especially sensitive to social rewards, whereas others may not.

The ERP literature has established that a component known as the stimulus preceding negativity (SPN) reflects brain activity that occurs before expected feedback about one's performance (Damen and Brunia, 1987). In past decades, this component was sometimes known as the contingent negative variation (CNV) (Walter *et al.*, 1964). Currently, the CNV and SPN are differentiated, and the CNV is thought to occur during preparation to *respond* to a stimulus (e.g. in 'go/no-go' tasks), and the SPN is thought to occur *after* a response is made but before feedback about whether or not the response was correct. The SPN is a slow wave that is prominent over the right hemisphere. It is typically measured during the last 200 ms before feedback is provided (e.g. Kotani *et al.*, 2001; Ohgami *et al.*, 2006). Previous studies have not measured the SPN in children, so it is unknown whether the amplitude and distribution of the SPN is similar in children and adults.

Multiple studies have confirmed that the SPN is sensitive to whether or not participants perceive feedback to be informative. Chwilla and Brunia (1991) were the first to investigate this, and found that the SPN was larger before trials with true feedback compared with false or no feedback. In the true feedback condition, participants were informed that the feedback was dependent upon their responses, whereas in the false feedback conditions, positive *vs* negative feedback was presented randomly. In the no feedback condition no feedback was presented. Ohgami *et al.* (2004) found that the SPN was larger before trials with feedback *vs* without feedback. Masaki *et al.* (2010) found similar results when participants either attempted to make a profitable choice (choice condition) *vs* trials where the participant's choice had no bearing the results (no-choice). The SPN was larger for choice *vs* no-choice trials. Interestingly, ERP and fMRI evidence (reviewed above) converge to suggest that larger neural activation is observed when participants feel control over task outcomes and receive informative feedback. This is consistent with fMRI studies that suggest that perception of control is important for activation of the reward system (Tsukamoto *et al.*, 2006). Together, these studies suggest that the SPN is sensitive to manipulations of feedback accuracy and whether or not the subject feels control over the outcome of any given trial.

The SPN component is thought to reflect the expectation of reward, and related activity of the dopaminergic reward system (Van Boxtel and Bocker, 2004; Mattox *et al.*, 2006). fMRI studies provide evidence that SPN tasks elicit activity in the insular cortex (Tsukamoto *et al.*, 2006; Kotani *et al.*, 2009) and caudate nucleus (Delgado *et al.*, 2000, 2003; Tricomi *et al.*, 2004). A spatiotemporal dipole model of the SPN (Bocker *et al.*, 1994) suggested the SPN was likely generated from the insular cortex. Both fMRI and spatiotemporal ERP studies confirm activity in the insular cortex during SPN tasks. The anterior insula is innervated with dopamine neurons (Gaspar *et al.*, 1989), which provides further support for the idea that the SPN is related to activity in the dopamine reward system.

If the SPN component is related to activity in the reward system, it seems likely that individuals with degradation or damage to structures involving reward would show deficits in the SPN. This is demonstrated in studies comparing individuals with Parkinson's disease (and therefore degradation of structures responsible for dopamine production, a major neurotransmitter involved in reward pathways) and control individuals. Mattox *et al.* (2006) demonstrated that the SPN is less pronounced in patients with Parkinson's disease compared with healthy individuals—even when controlling for memory performance on the Weschler Memory Scale-III. This suggests that the SPN reflects activity in response to feedback concerning rewards, and is reduced in persons who have disruptions in the dopamine systems largely responsible for processing reward.

Summary

The results of previous studies of reward motivation highlight the complexity of the neural reward system, and suggest that some areas of the reward circuit might be especially sensitive to social rewards, whereas others may not. Importantly, in all of the aforementioned studies' money runs, participants could earn money, while during face 'runs' participants saw pictures of faces or saw compliments displayed on-screen (e.g. Demurie *et al.*, 2011). Thus, in one condition, participants received a tangible item for reward, whereas in the other condition, they viewed a social stimulus, but received nothing tangible. It is not difficult to imagine why earning money might be more rewarding compared with simply looking at pictures of faces. In the present study, we aimed to hold the reward constant between 'face' and 'nonface' trial blocks. By doing so, we hoped to clarify whether faces elicit greater reward-related brain activity compared with visually matched nonface stimuli, even when the pictures do not have an effect on the outcome of the task. We utilized ERPs in a SPN paradigm to measure reward anticipation-related brain activity in young children. Previous research has examined the SPN before the subject receives feedback about whether he or she is correct and therefore whether or not he or she will receive a reward (e.g. 10 cents for each correct answer) (Ohgami *et al.*, 2004; Mattox *et al.*, 2006; Ohgami *et al.*, 2006; Masaki *et al.*, 2010). We designed the current study to examine the SPN in the same way—using goldfish crackers or an equivalent snack as a reward, with an incidental social or nonsocial stimulus manipulation.

Here, we address two aspects currently missing from the literature: controlling for rewards between 'face' and 'nonface' trial blocks, and utilizing ERP methodology in order to facilitate testing younger participants. This study sheds light on the neural underpinnings of reward anticipation in children, and is informative for how typically developing children anticipate rewards that are accompanied by either social or nonsocial stimuli.

METHODS

Participants

Twenty-six participants (17 males and 9 females) were included. Participants were between 6 and 10 years old ($M = 7.49$, $SD = 0.91$). All subjects were native English speakers with no history of developmental disabilities or psychiatric conditions, and were not taking any medications for psychiatric of neurological conditions, as reported by their caregivers. One additional male participant was tested, but was excluded because we later learned that he had a first degree relative with autism spectrum disorder. This study was reviewed and approved by the University of California, San Diego institutional review board. Participants were recruited through the UCSD subject pool, and their guardians were paid $35 for their time and participation. All participants over 7 years old signed a child assent form.

Recording conditions

Participants wore a standard, fitted cap (Electrocap International, Eaton, OH, USA) with electrodes placed according to the international 10–20 system. Continuous EEG was recorded with a NeuroScan 4.5 System (Compumedics, Charlotte, NC, USA) with a reference electrode at Cz and re-referenced offline to the average activity at left and right mastoids. ERPs were recorded at 33 scalp locations using silver/silver-chloride (Ag/AgCl) electrodes at standard sites (Pz, Fz, O1, O2, P3, P4, T3, T4, T5, T6, C3, C4, Cz, F3, F4, F7, F8, A1, A2) and additional sites (CPz, FCz, CP5, CP6, CP1, CP2, FC1, FC2, FC5, FC6, FP1, FP2, AF7, AF8). Electrode resistance was kept under 10 kΩ. Continuous EEG was amplified with a low pass filter (70 Hz), a directly coupled high-pass filter (DC), and a notch filter (60 Hz). The signal was digitized at a rate of 250 samples per second via an Analog-to-Digital converter. Eye movement artifacts and blinks were monitored via horizontal electrooculogram (EOG) placed at the outer canthi of each eye and vertical EOG placed above and below the left eye. ERP trials were time locked to the onset of the reward stimulus. The baseline period was −2200 to −2000. Data were epoched from −2200 to 100 ms. The ITI was varied (1800–2000 ms between trials). Trials with no behavioral response, or electrophysiological artifacts, were excluded from the averages.

Artifacts were removed via a four step process. Initially, the first author visually inspected all data for drift exceeding +/−200 mV in all electrodes, high frequency noise visible in all electrodes >100 mV and all flatlined data. Following initial inspection, the data were epoched and eyeblink artifacts were identified using individual component analysis (ICA). Individual components were inspected alongside epoched data and blink components were removed. Next, we utilized a moving window peak-to-peak procedure in ERPlab (http://erpinfo.org/erplab. ERPLAB toolbox user's manual, Markley *et al.*, 2012). We utilized a 200 ms moving window, a 100 ms window step, and a 150 mV voltage threshold. An experimenter in an adjacent room observed participants during the task via webcam. Any trials during which participants looked away from the screen during or immediately prior to feedback were marked and excluded prior to final analysis. Participants were highly attentive, and rarely disengaged from the task. Most participants had no trials removed for this reason, and no participants had more than five trials removed due to eye movements or inattention. We excluded subjects who had fewer than 10 trials in their final average ($N = 1$). Thus, all of our statistics include data from the remaining 25 participants.

Stimuli and task

The current study had two blocks of trials, each with different feedback condition: social and nonsocial. In both blocks, at the beginning of each trial, a fixation cross appeared on screen for 500 ms. After the fixation cross, two boxes were displayed for 3000 ms; each box contained a question mark inside it. Participants were asked to guess which question mark was correct using a button pad. After participants chose the left or right box, an arrow appeared in between the question marks for 2000 ms indicating their choice (e.g. the arrow pointed left if the participant chose the left box, and right if the participant chose the right box). After 2000 ms, feedback about whether the participant guessed correctly appeared on screen for 1000 ms.

In the social block, feedback was an image of a smiling face surrounded by goldfish crackers for correct answers, and an image of a frowning face surrounded by crossed out goldfish crackers for incorrect answers. Faces were obtained from the NimStim database (Tottenham *et al.*, 2009). In order to avoid confounds specific to gender or race, 33 faces (18 female, 15 male) from the NimStim database were utilized in the social condition. The faces were presented in

pseudorandom order, with no face appearing more than once in a row. Figure 1a depicts a detailed schematic exemplar of our stimuli and timeline in the social block. In the nonsocial trial block feedback was an image of an upward facing arrow (made of scrambled face images from the social condition) surrounded by a ring of goldfish for correct answers and an image of a downwards facing arrow surrounded by a ring of crossed out goldfish crackers for incorrect answers. Figure 1b depicts a detailed schematic of our stimuli in the nonsocial block. In order to control for visual differences between the social and nonsocial feedback trials, the arrows were composed of scrambled fragments of the faces used in the social trials.

If no choice was made, the trial ended, and the fixation cross appeared again signaling the beginning of the next trial. Participants were told that the reward for correct answers was a goldfish cracker. If participants did not want goldfish, they were told that they could trade in goldfish crackers for fruit snacks. Importantly, in both the social and nonsocial feedback trials, the face/arrow information was incidental. It was not necessary for the participant to determine whether or not their response was correct. The participants were told that correct *vs* incorrect responses were signaled by whether or not the goldfish were intact or crossed out. In order to control for differences in accuracy between participants, correct *vs* incorrect answers were predetermined by the computer program. That is, each trial was marked to be correct *vs* incorrect regardless of the participant's response. There were equal numbers of 'correct' and 'incorrect' answers in pseudorandom order, with no more than three of the same answer in a row.

The two kinds of feedback trials ('face'/'social' trials and arrow/'non-social' trials) were tested in separate blocks, each composed of 80 trials. Within each block of 80 trials, there were 30-s breaks every 15 trials. During these breaks, participants were told to relax, or move if they felt restless. Between blocks, a longer break (5–10 min) was available if the participant wished to take it.

As a manipulation check, immediately after the completion of each block, 19 of the participants rated how much they enjoyed each block of the task as well as whether they felt as though they were able to figure out the correct answers during the task on a scale from 1 to 7. We included this in order to insure that participants were equally motivated and engaged in the task across conditions.

RESULTS

All results were analyzed using JMP (version 10.0). We used repeated measures ANOVA to test for differences between conditions, hemisphere and caudality (anterior–posterior differences).

Behavioral measures

Participant's responses about liking the guessing game, as well as their responses about getting correct answers were analyzed using matched-pairs *t*-tests. There was no difference between conditions for participant's enjoyment of the game, $t(18) = -0.66$, $P = 0.52$, ns, or their perceived ability to obtain correct answers, $t(18) = -0.52$, $P = 0.61$, ns.

EEG results

The SPN was measured as mean amplitude between −210 and −10 ms before feedback onset. The final 200 ms prior to feedback onset has been utilized in previous studies (Kotani *et al.*, 2001; Ohgami *et al.*, 2006). Here, we chose to analyze mean amplitude between −210 and −10 ms in order to avoid artifacts associated with feedback onset (i.e. 0 ms). We analyzed electrode F3/F4, C3/C4, P3/P4 and T3/T4, as these are the typical electrodes with maximal SPN amplitudes (Kotani *et al.*, 2003). Grand average waveforms for the face and arrow conditions are plotted for the eight electrodes associated with the SPN in previous literature (F3, F4, C3, C4, P3, P4, T5, T6) in Figure 2. A 2 (condition) × 2 (hemisphere) × 4 (caudality) within subjects ANOVA was conducted for the eight aforementioned electrodes. Significant block effects were found such that the SPN was larger (more negative) in the face *vs* nonface condition, $F(1, 24.1) = 7.46$, $P = 0.01$. Significant electrode effects were observed, $F(3, 70.95) = 5.27$, $P = 0.002$. Tukey HSDs *post hoc* tests revealed that SPN amplitude in temporal electrodes was

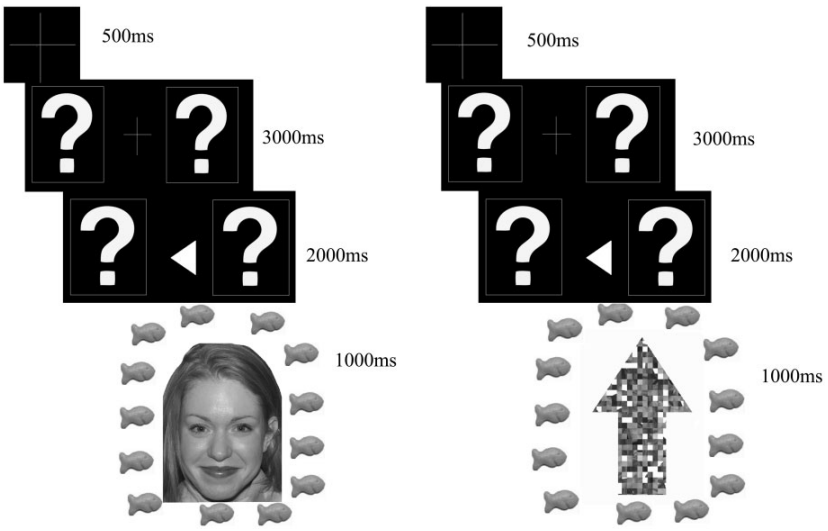

Fig. 1 (**a**) Schematic of the stimuli and timing used in the 'social' or 'face' block for correct answers. Stimuli and timing for incorrect answers was identical except the goldfish were crossed out and the face was frowning. Note the arrow points in the direction of the question mark the participant selected (e.g. it points left if the participant chose the left question mark, and right if the participant chose the right question mark). (**b**) Schematic of the task and timing used in the 'nonface' or 'arrow' block for correct answers. Stimuli and timing was identical for incorrect answers except the goldfish were crossed out and the arrow pointed downwards.

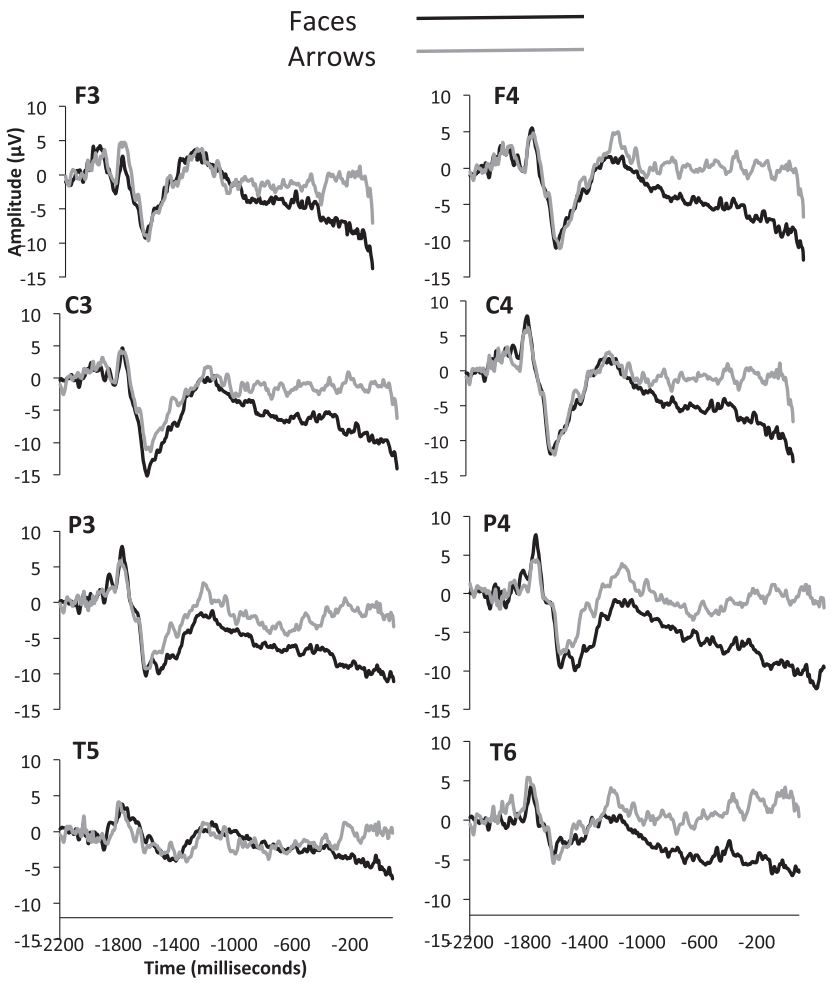

Fig. 2 Grand averaged ERP waveforms from the electrodes analyzed for the SPN. Face trials are depicted with a black line, and arrow trials are depicted with a grey line.

significantly smaller than observed in central and parietal electrodes ($P < 0.05$). No significant amplitude difference was observed between frontal and temporal electrodes ($P > 0.05$). Furthermore, there was no significant amplitude difference between frontal, temporal and parietal electrode sites. No significant effect of hemisphere was observed, $F(1, 24.29) = 0.001$, ns. Because there was no effect of hemisphere, we re-ran the analysis collapsed across hemispheres. All previously reported significant effects remained. In order to assess for effects of gender, we re-ran the analysis with gender as a factor. No significant effect of gender was observed, $F(1, 23.06) = 0002$, ns.

DISCUSSION

Our results showed that children's brain response in anticipation of a social stimulus was larger than in anticipation of a nonsocial stimulus, even when that stimulus was incidental to the expected reward. Previous studies that have used a variety of methods for measuring responses to social and nonsocial feedback (typically in functional imaging paradigms) have contrasted tangible, monetary rewards with a social (but nontangible) reward consisting of the chance to look at a face. The current study is the first to investigate neural response to social *vs* nonsocial rewards while keeping the rewards and visual stimuli constant between conditions. By telling participants they would earn goldfish or an equivalent snack for right answers irrespective of block type, we assured that differences between conditions were not due to varying reward values (e.g. a picture of a face *vs* physical money after the experiment).

Our results differ from those of Demurie *et al.* (2011) and Kohls *et al.* (2009b, 2011, 2013). These studies have generally found that performance and brain activation are enhanced when the expected reward is monetary. However, it is important to note the critical differences between these previous studies and our own. In previous studies, tangible monetary reward was contrasted with intangible, but social rewards (viewing faces). Thus it is possible that the results from the previous studies were driven by the tangibility of the reward, and that this effect masked effects of social motivation. Thus, while we found results different from previous authors, we suspect that those differences are largely accounted for by task differences.

The current study presents a novel use of the SPN component. We utilized the SPN component in order to better understand

reward anticipation of social *vs* nonsocial stimuli. Previous research has provided important information about the location of brain structures that may respond differently to social and nonsocial rewards. However, many of these studies have generally lacked the temporal resolution necessary for clearly delineating the brain functions that anticipate the acquisition of reward. In contrast, previous SPN studies, which are ideal for measuring reward anticipation with exceptional temporal resolution, have not directly compared responses with social and nonsocial rewards.

In contrast with previous SPN literature, the current study did not observe larger SPN amplitudes in the right hemisphere (Kotani *et al.*, 2001; Ohgami *et al.*, 2006; Mattox *et al.*, 2006; Masaki *et al.*, 2010). However, Brunia *et al.* (2011) suggested that SPN paradigms that do not employ punishment conditions often do not find larger SPN amplitudes in the right hemisphere (Chwilla and Brunia, 1991; Kotani *et al.*, 2003; Ohgami *et al.*, 2004). The present study did not utilize punishment for incorrect responses, which we believe accounts for the lack of amplitude difference between hemispheres. Previous literature varies in the observed amplitudes of the SPN. Our observed mean amplitudes for the nonsocial condition are similar to those of Ohgami *et al.* (2006), but smaller than those reported by Kotani *et al.* (2003). Our observed mean amplitudes for the social condition, however, are larger than those reported in previous SPN literature. Amplitude differences between studies are likely due to variation in task requirements and stimuli. Furthermore, the previously reported SPN paradigms have utilized adult participants, while our participants were young children. It is not uncommon for ERP components to be larger in children when compared with adult participants (e.g. Taylor *et al.*, 1999). It cannot be ruled out, therefore, whether observed amplitude differences might be due to participant age.

Finally, our study has provocative implications for the development of the reward system in young children. As the SPN is thought to reflect activity from the dopamine reward system, this study suggests that this system is highly developed in children as young as 6 years of age. Several theories of social cognitive development suggest that motivation to attend to social stimuli, or the reward that accompanies encountering social stimuli, plays a pivotal role in the development of social cognition and understanding. It is somewhat unclear, however, when this type of motivation and anticipation begins in children. Interestingly, in an ERP version of a Posner cued location paradigm, Perchet and Garcia-Larrea (2005) found that while adults demonstrated a slow negative potential akin to the CNV prior to the target, children did not demonstrate this neural pattern. The authors suggest that this CNV activity in adults reflects highly developed executive functioning, and the lack-thereof in children. In contrast, in a four choice ERP gambling task, Carlson *et al.* (2009), found that 8-year-old children demonstrated a clear SPN in the time between decision making and feedback.

However, it is important to note that our paradigm, as well as the gambling task used by Carlson *et al.* (2009) are both very different from the task used by Perchet and Garcia-Larrea (2005). In both our task and the task used by Carlson *et al.* (2009), participants were asked to choose a correct answer by guessing between various options. Furthermore, these paradigms were designed to elicit the SPN response, which require *anticipation* of an outcome. In Perchet and Garcia-Larrea's (2005) task, however, participants were told to respond to a star, which was either correctly or incorrectly cued with a preceding rectangle. In this way, participants could use the rectangle in order to anticipate the location of the star. The task did not involve a response and anticipation of feedback, but rather a cue and then a target. Furthermore, as the task was not designed to elicit the SPN, the time between the cue (rectangle) and target (star) was only 500 ms, as opposed to typical SPN paradigms which have anticipatory periods of 2000–3000 ms. It perhaps is not surprising, then, that Perchet and Garcia-Larrea (2005), did not find evidence of anticipatory brain activity in children. Future studies might benefit from examining how early the SPN component can be measured in children and the role that task differences and complexity plays in these measurements.

Future directions

This paradigm demonstrates a novel method of successfully comparing the reward value of social *vs* nonsocial stimuli in young children. Several developmental disorders, including autism spectrum disorder and ADHD, are thought to involve deficits or differences in social motivation or general reward processing. In the future, studies should attempt to utilize this paradigm to better understand disorders of social or reward processing deficits. Additionally, social motivation may play a role in a number of problems of childhood and adolescence (e.g. social anxiety, substance abuse). These problems and disorders may benefit from the present methodology.

Conflict of Interest

None declared.

REFERENCES

Böcker, K.B.E., Brunia, C.H.M., van den Berg-Lenssen, M.C. (1994). A spatiotemporal dipole model of the stimulus preceding negativity (SPN) prior to feedback stimuli. *Brain Topography*, *7*, 71–88.

Brunia, C.H.M., Hackley, S.A., van Boxtel, G.J.M., Kotani, Y., Ohgami, Y. (2011). Waiting to perceive: reward or punishment? *Clinical Neurophysiology*, *122*, 858–68.

Carlson, S.M., Zayas, V., Guthormsen, A. (2009). Neural correlates of decision making on a gambling task. *Child Development*, *80*, 1076–96.

Chatterjee, A., Thomas, A., Smith, S.E., Aguirre, G.K. (2009). The neural response to facial attractiveness. *Neuropsychology*, *23*, 135–43.

Chwilla, D.J., Brunia, C.H.M. (1991). Event-related potentials to different feedback stimuli. *Psychophysiology*, *28*, 123–32.

Damen, E.J., Brunia, C.H. (1987). Changes in heart rate and slow brain potentials related to motor preparation and stimulus anticipation in a time estimation task. *Psychophysiology*, *24*, 700–13.

Demurie, E., Roeyers, H., Baeyens, D., Sonuga-Barke, E. (2011). Common alterations in sensitivity to type but not amount of reward in ADHD and autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *52*, 1164–73.

Delgado, M.R., Locke, H.M., Stenger, V.A., Fiez, J.A. (2003). Dorsal striatum responses to reward and punishment: effects of valence and magnitude manipulations. *Cognitive, Affective, and Behavioral Neuroscience*, *3*, 27–38.

Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Neurophysiology*, *84*, 3072–7.

Dichter, G.S., Richey, J.A., Rittenberg, A.M., Sabatino, A., Bodfish, J.W. (2012). Reward circuitry function in autism during face anticipation and outcomes. *Journal of Autism and Developmental Disorders*, *42*, 147–60.

Gaspar, P., Berger, B., Febvret, A., Vigny, A., Henry, J.P. (1989). Catecholamine innervation of the human cerebral cortex as revealed by immunohistochemistry of tyrosine hydroxlase and dopamine-beta-hydroxylase. *Comparative Neurology*, *279*, 249–71.

Johnson, M.H., Dziurawiec, S., Ellis, H., Morton, J. (1991). Newborns' preferential tracking of face-like stimuli and its subsequent decline. *Cognition*, *40*, 1–19.

Kampe, K.K.W., Frith, C.D., Dolan, R.J., Frith, U. (2001). Reward value of attractiveness and gaze. *Nature*, *413*, 589.

Kohls, G., Peltzer, J., Herpertz-Dahlmann, B., Konrad, K. (2009a). Differential effects of social and non-social reward on response inhibition in children and adolescents. *Developmental Science*, *12*, 614–25.

Kohls, G., Herpertz-Dahlmann, B., Konrad, K. (2009b). Hyperresponsiveness to social rewards in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Behavioral and Brain Functions*, *5*. doi: 10.1186/1744-9081-5-20.

Kohls, G., Peltzer, J., Schulte-Rüther, M., et al. (2011). Atypical brain responses to reward cues in autism as revealed by event-related potentials. *Journal of Autism and Developmental Disorders*, *41*, 1523–33.

Kohls, G., Schulte-Rüther, M., Nehrkorn, B., et al. (2013). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *8*, 565–72.

Kotani, Y., Hiraku, S., Suda, K., Aihara, Y. (2001). Effect of positive and negative emotion on stimulus-preceding negativity prior to feedback stimuli. *Psychophysiology*, *38*, 873–8.

Kotani, Y., Kishida, S., Hiraku, S., Suda, K., Ishii, M., Aihara, Y. (2003). Effects of information and reward on stimulus-preceding negativity prior to feedback stimuli. *Psychophysiology*, *40*, 818–26.

Kotani, Y., Ohgami, Y., Kuramoto, Y., Tsukamoto, T., Inoue, Y., Aihara, Y. (2009). The role of the right anterior insular cortext in the right hemisphere preponderance of stimulus-preceding negativity (SPN): An fMRI study. *Neuroscience Letters, 450*, 75–9.

Lin, A., Adolphs, R., Rangel, A. (2012). Social and monetary reward learning engage overlapping neural substrates. *Social Cognitive and Affective Neuroscience, 7*, 274–81.

Markley, C., Luck, S., Lopez-Calderon, J. (2012). ERPlab toolbox users manual version 3.0. Retrieved from http://erpinfo.org/erplab/erplab-documentation/manual/index.html. (10 October 2012, date last accessed).

Masaki, H., Yamazaki, K., Hackley, S.H. (2010). Stimulus-preceding negativity is modulated by action-outcome contingency. *Neuroreport, 21*, 277–81.

Mattox, S.T., Valle-Inclán, F., Hackley, S.A. (2006). Psychophysiological evidence for impaired reward anticipation in Parkinson's disease. *Clinical Neurophysiology, 117*, 2144–53.

Ohgami, Y., Kotani, Y., Hiraku, S., Aihara, Y., Ishii, M. (2004). Effects of reward and stimulus modality on stimulus-preceding negativity. *Psychophysiology*, *41*, 729–38.

Ohgami, Y., Kotani, Y., Tsukamoto, T., et al. (2006). Effects of monetary reward and punishment on stimulus-preceding negativity. *Psychophysiology, 43*, 227–36.

Perchet, C., Garcia-Larrea, L. (2005). Learning to react: Anticipatory mechanisms in children and adults during a visuospatial attention task. *Clinical Neurophysiology*, *116*, 1906–17.

Poli, S., Sarlo, M., Bortoletto, M., Buodo, G., Palomba, D. (2007). Stimulus-Preceding negativity and heart rate changes in anticipation of affective pictures. *International Journal of Psychophysiology*, *65*, 32–9.

Rademacher, L., Krach, S., Kohls, G., Irmak, A., Gründer, G., Spreckelmeyer, K.N. (2010). Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *NeuroImage, 49*, 3276–85.

Scott-Van Zeeland, A.A., Dapretto, M., Ghahremani, D.G., Poldrack, R.A., Bookheimer, S.Y. (2010). Reward processing in autism. *Autism Research*, *3*, 53–67.

Spreckelmeyer, K.N., Krach, S., Kohls, G., et al. (2009). Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Social Cognitive and Affective Neuroscience*, *4*, 158–65.

Takeuchi, S., Mochizuki, Y., Masaki, H., Takasawa, N., Yamazaki, K. (2005). Stimulus preceding negativity represents arousal induced by affective picture. *International Congress Series, 1278*, 385–8.

Taylor, M.J., McCarthy, G., Saliba, E., Degiovanni, E. (1999). ERP evidence of developmental changes in processing of faces. *Clinical Neurophysiology, 110*, 910–5.

Tottenham, N., Tanaka, J.W., Leon, A.C., et al. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research, 168*, 242–9.

Tricomi, E.M., Delgado, M.R., Fiez, J.A. (2004). Modulation of caudate activity by action contingency. *Neuron*, *41*, 281–92.

Tsukamoto, T., Kotani, Y., Ohgami, Y., Omura, K., Inoue, Y., Aihara, Y. (2006). *Neuroscience Letters*, *399*, 39–44.

Van Boxtel, G.J., Böcker, K.B. (2004). Cortical measures of anticipation. *Journal of Psychophysiology*, *18*, 61–76.

Walter, W.G., Cooper, R., Aldridge, V.J., McCallum, W.C., Winter, A.L. (1964). Contingent negative variation: an electric sign of sensory-motor association and expectation in the human brain. *Nature*, *203*, 380–4.

Winston, J.S., O'Doherty, J., Kliner, J.M., Perrett, D.I., Dolan, R.J. (2007). *Neuropsychologica*, *45*, 195–206.

Chapter 1, in full, is a reprint of the material as it appears in Reward sensitivity to faces versus objects in children: an ERP study in *Social Cognitive and Affective Neuroscience*. Stavropoulos, Katherine K. M; Carver, Leslie J. (2013). The dissertation author was the primary investigator and author of this paper.

Chapter 2

Reward anticipation and processing of social versus nonsocial stimuli in children with and without autism spectrum disorder

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Reward anticipation and processing of social versus nonsocial stimuli in children with and without autism spectrum disorders

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Background: How children respond to social and nonsocial rewards has important implications for both typical and atypical social-cognitive development. Individuals with autism spectrum disorders (ASD) are thought to process rewards differently than typically developing (TD) individuals. However, there is little direct evidence to support this claim. **Methods:** Two event-related potentials were measured. The stimulus preceding negativity (SPN) was utilized to measure reward anticipation, and the feedback related negativity (FRN) was utilized to measure reward processing. Participants were 6- to 8-year-olds with (N = 20) and without (N = 23) ASD. Children were presented with rewards accompanied by incidental face or nonface stimuli. Nonface stimuli were composed of scrambled face elements in the shape of arrows, controlling for low-level visual properties. **Results:** Children with ASD showed smaller responses while anticipating and processing rewards accompanied by social stimuli than TD children. Anticipation and processing of rewards accompanied by nonsocial stimuli was intact in children with ASD. **Conclusions:** This is the first study to measure both reward anticipation and processing in ASD while controlling for reward properties. The findings provide evidence that children with autism have reward anticipation and processing deficits for social stimuli only. Our results suggest that while typically developing children find social stimuli more salient than nonsocial stimuli, children with ASD may have the opposite preference. **Keywords:** Autism spectrum disorder, social motivation, event-related potentials, social stimuli.

Introduction

Children's learning is strongly motivated by social signals such as eye contact, smiling, speech sounds, and contingent interaction. For example, language learning requires a socially interactive context rather than auditory exposure alone (Kuhl, Tsao, & Liu, 2003). In typically developing individuals, at least one kind of social stimulation, eye contact, activates the brain's reward system (Kampe, Frith, Dolan, & Frith, 2001). Children with autism spectrum disorders (ASD) have profound social deficits that may be linked to a neural reward system that differs from typically developing (TD) individuals. Here, we empirically compare social motivation and reward processing using electrophysiology in TD and ASD children.

Children with ASD appear to lack enjoyment in social activities, and the *social motivation hypothesis* (SMH; Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dawson, 2008; Dawson et al., 2002, 2005; Grelotti, Gauthier, & Schultz, 2002; Schultz, 2005) suggests that this leads to downstream autism symptomology including: abnormal brain responses to faces (e.g., McPartland, Dawson, Webb, Panagiotides, & Carver, 2004), language impairments (e.g., Charman et al., 1998), and joint attention deficits (e.g., Mundy, Sigman, Ungerer, & Sherman, 1986). In ASD interventions, the lack of enjoyment in social interaction is often referred to as lack of *intrinsic* motivation. Behavioral interventionists often utilize extrinsic means to motivate children with ASD to socially engage, for example using candy to reward children for making eye contact (Jones & Carr, 2004). This is problematic because when the extrinsic motivator is no longer presented, social behaviors can regress (Whalen & Schreibman, 2003). Increasing social motivation in ASD is a critical step in improving the efficacy of behavioral interventions (Stavropoulos & Carver, 2013a).

A small number of neuroscience studies have evaluated social motivation in adolescents and adults with ASD (Delmonte et al., 2012; Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Kohls et al., 2011, 2013; Richey et al., 2014; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010). Results suggest that individuals with ASD anticipate and process rewards differently than TD individuals. However, studies differ with regard to whether reward anticipation, reward processing, or both were tested and also varied regarding whether monetary rewards, social rewards, or both were employed.

One potential issue in previous studies is that the rewards for social and nonsocial conditions were not equated. Tangible rewards, such as money, were contrasted with intangible incentives (e.g., pictures of faces). It is not clear, then, whether differences between the responses of individuals with ASD and typical development are due to differences in reward processing, or differences in responses to tangible versus intangible rewards.

Conflict of interest statement: No conflicts declared.

Anticipation phase: stimulus preceding negativity

One effective way to investigate neural anticipation of rewards is by using electrophysiology, specifically event-related-potentials (ERPs). The SPN is a component of the ERP that reflects brain activity occurring before expected feedback about one's performance (Brunia, Hackley, van Boxtel, Kotani, & Ohgami, 2011). SPN reflects the *expectation* of reward, and related activity of the dopaminergic reward system (van Boxtel & Böcker, 2004). fMRI studies provide evidence that tasks typically used to elicit the SPN lead to activity in the insular cortex (Tsukamoto et al., 2006) and caudate nucleus (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000), brain areas involved in reward processing. A spatiotemporal dipole model of the SPN (Böcker, Brunia, & van den Berg-Lenssen, 1994) suggested the SPN is generated in the insular cortex, which is innervated with dopamine neurons (Gaspar, Berger, Febvret, Vigny, & Henry, 1989). Further evidence that the SPN involves the dopamine reward system comes from studies showing a reduced SPN in individuals with Parkinson's disease (who have a degradation of structures responsible for dopamine production) compared to control individuals (Mattox, Valle-Inclán, & Hackley, 2006).

Two studies have compared reward anticipation between TD individuals and those with ASD (Groen et al., 2008; Kohls et al., 2011). One study used a probabilistic learning task with monetary rewards. Children with ASD and ADHD demonstrated larger SPN amplitudes than TD children when anticipating positive outcomes, but equivalent SPN amplitudes anticipating negative outcomes (Groen et al., 2008). A second study measured the P300 in response to cues triggering trials with social versus nonsocial reward anticipation in adolescents with and without ASD. As a control, a condition without rewards was used. TD children exhibited larger P300s during reward versus nonreward conditions, but children with autism did not. In addition, children with autism exhibited smaller P300s after cues initiating social reward anticipation trials (Kohls et al., 2011).

Response phase: feedback related negativity component

It is also informative to investigate the neural underpinnings of reward processing *after* feedback. The feedback related negativity (FRN) is an ERP component occurring 200–300 ms after feedback, and characterized by a negativity in response to 'loss' versus 'gain' trials (Hajcak, Moser, Holroyd, & Simons, 2006). Source localization studies suggest that the FRN reflects activity in the dopamine reward system (Holroyd & Coles, 2002), and is generated by the striatum, medial-frontal cortex and anterior cingulate cortex – areas related to reward processing (Foti, Weinberg, Dien, & Hajcak, 2011; Nieuwenhuis, Slagter, von Geusau, Heslenfeld, & Holroyd, 2005).

Previous studies compared the FRN in adolescents and young adults with and without ASD during a guessing game in which participants won money for correct answers, and lost money for incorrect answers (Larson, South, Krauskopf, Clawson, & Crowley, 2011), or won money for correct answers, and did not lose or win anything for incorrect answers (McPartland et al., 2012). Both studies found similar activation patterns in individuals with and without ASD, suggesting that individuals with ASD do not demonstrate deficits in feedback processing when the rewards involve money. No previous studies have measured the FRN in response to social versus nonsocial rewards in TD, or in ASD compared with TD.

Design of the study

Previous studies provide mixed results about whether reward anticipation and reward processing after feedback are dampened in individuals with ASD for monetary rewards, social rewards, or both. Although the social motivation hypothesis suggests that children lack motivation for social interaction, no evidence exists to clarify whether differences in motivation in children with ASD are due to a *lack* of social motivation or an *increase* in nonsocial motivation. Social deficits could occur because children with ASD are impaired in social motivation, because they are more motivated by nonsocial rewards than typically developing children, or a combination of the two. Previous authors have raised this possibility (Kohls, Chevallier, Troiani, & Schultz, 2012; Richey et al., 2014), but it has not been explored directly.

This study expands upon previous investigations and seeks to add additional information about the reward system in ASD. We have developed an ERP paradigm, in which the reward for correct answers is controlled between social and nonsocial conditions, and the low-level physical properties of social versus nonsocial stimuli are matched (Stavropoulos & Carver, 2013b). Previous studies have not combined the SPN and FRN components in investigations of responses to social stimuli. Here, we contrast performance on this task between individuals with ASD and TD, and measure both the anticipation and outcome phases of reward processing. We hypothesize that children with ASD will demonstrate attenuated ERP responses while anticipating feedback accompanied by social stimuli (reflected in a reduced amplitude of the SPN), and attenuated response to feedback accompanied by social stimuli (via the FRN). Examining both the SPN and FRN in the same children has the potential to reveal the time course of reward anticipation and processing in children with ASD.

Methods

Participants

We tested TD children ($N = 23$) and children with ASD ($N = 20$). Exclusionary criteria for participants with ASD included history of seizures, brain injury, neurological disorders, or any concurrent psychiatric condition (other than ASD), based on parent report. Exclusionary criteria for TD participants included all of the above criteria, plus an immediate family history of ASD. None of the children in the TD group were taking psychoactive medications. Three children in the ASD group were taking medication in order to improve concentration, but one of the three did not take his medication on the day he came in for this study. Participants were recruited from a UC San Diego subject pool and through postings on websites for parents of children on the autism spectrum. All participants had normal hearing and normal or corrected to normal vision. Procedures were approved by the institutional review board, and written consent was obtained from caregivers. All children over 7 years of age signed an assent form. Data from 17 children in the TD group were reported previously (Stavropoulos & Carver, 2013b), and were used to match children tested in the ASD group on gender and full-scale IQ.

Table 1 provides detailed participant information. IQ scores (Wechsler Abbreviated Scale of Intelligence, Wechsler, 1999) were available for all 20 children with ASD, and 22 of 23 TD children (one TD child was unable to complete the WASI due to time constraints). Of the final sample of 43 children, no significant differences were found between groups on full-scale IQ scores $F(1,40) = .36$. There were differences between the TD and ASD groups in chronological age, $F(1,41) = 5.86$, $p = .02$. In order to confirm that age did not affect SPN or FRN amplitude in our sample, we examined correlations between age and ERP amplitude for all conditions for the SPN and FRN. These analyses revealed no correlation between age and ERP amplitude (all rs $< .13$). Children in the ASD group had been previously diagnosed with ASD through various sources (e.g. formal evaluations through an autism center, or school diagnosis). Diagnosis was confirmed for this study with Module 3 of the ADOS-2 (Lord et al., 2012). The ADOS-2 was administered by an individual trained to research reliability on administration, scoring, and interpretation of the measure.

Behavioral measures

Participants' caregivers completed the Social Responsiveness Scales (SRS-2; Constantino & Gruber, 2012), which measure social responsiveness and behavior. We also tested for overt motivation or affective differences between groups for each condition. To accomplish this, children ($N = 21$ TD, 19 ASD) completed a 1–7 Likert rating scale of how much they enjoyed the game (1 = 'I do not like this game', and 7 = 'I love this game') after each block. This was used in order to gather more information about whether one group felt more or less motivated to engage in the task. Previous research suggests that the presence of reward versus no-reward affects SPN amplitude – with greater SPN amplitude in reward versus no-reward conditions (Kotani et al., 2003) – and we wished to assess whether both groups felt equally invested in the game. Participants also completed a 1–7 Likert scale about their perception of getting correct answers (1 = 'I never got correct answers', and 7 = 'I always got correct answers'). In reality, the correct versus incorrect answers was predetermined and controlled by experimental design, and the rating was used to verify that the groups did not differ in their perception that they were obtaining correct answers.

Stimuli and task

The stimuli and task are described in detail in Stavropoulos and Carver (2013b). Briefly, the task was a guessing game that presented blocks of trials that used left and right visual stimuli (question marks). Participants were asked to indicate their guess via button press whether the left or right stimulus was 'correct.' After this choice, the left and right question marks were replaced with an arrow in the middle pointing toward whichever question mark the participant chose. This was done to reinforce the idea that participants had control over the task and their responses were being recorded.

There were two blocked feedback conditions: *social* versus *nonsocial*. Incidental stimuli in the social condition were faces obtained from the NimStim database (Tottenham et al., 2009) that were smiling for 'correct' answers and frowning for 'incorrect' answers. In order to avoid confounds resulting from use of a single face or gender, 33 faces (18 female, 15 male) from the database were utilized. Incidental stimuli in the nonsocial condition were composed of scrambled face elements from the social condition formed into an arrow that pointed upwards for 'correct' answers and downwards for 'incorrect' answers. The use of scrambled faces to construct the arrow controlled for low-level visual features of the stimuli. Both faces and arrows were presented in pseudorandom order, with no image repeating on consecutive trials. Presented stimuli subtended a horizontal visual angle of 14.5°, and a vertical visual angle of 10.67°. Each participant viewed identical stimuli in the same order for each condition (e.g. the social feedback block was the same for each participant), but whether individuals viewed the social versus nonsocial block first was counterbalanced between participants.

Participants were told that the reward for each correct answer was a goldfish cracker, or if they preferred, fruit snacks. Participants were told there was no penalty for incorrect answers. Participants were told that if they guessed correctly, they would see a ring of intact goldfish crackers, and the goldfish would be crossed out for incorrect answers. Importantly, in both the social and nonsocial feedback trials, the face/arrow information was incidental. Figure 1 depicts the stimuli and timeline in the social and nonsocial conditions. A computer program predetermined correct versus incorrect answers in pseudorandom order such that children got 50% 'correct' and 50% 'incorrect', with no more than three of the same answer in a row.

Table 1 Participant characteristics including: IQ (WASI), age, gender, SRS-2 T-score, and ADOS-2 severity scores for the ASD group

Group	Participants	WASI (full-scale)	Age	Gender	SRS-2 SCI T-Score	SRS-2 RBB T-Score	ADOS-2 Severity score
ASD	20	M = 107.35 SE = 3.54	M = 8.28* SE = .23	19 M 1 F	M = 71.26** SE = 2.14	M = 69.63** SE = 2.26	M = 6.88 SE = .48
TD	23	M = 111.60 SE = 3.30	M = 7.47* SE = .21	22 M 1 F	M = 48.52** SE = 1.95	M = 50.69** SE = 2.07	N/A

*$p = .02$.
**$p \leq .0001$.

The two feedback conditions (face/'social' trials and arrow/'nonsocial' trials) were tested in separate blocks, each composed of 80 trials. Within each block of 80 trials, there were 30-s breaks every 15 trials. During breaks, participants were asked to relax, or move if they felt restless. Between blocks, a longer break (5–10 min) was taken. To control attentional effects, children were observed via webcam, and trials in which they were not attending to the stimulus were marked and discarded during analysis. Of the final sample, three children had trials excluded for this reason, and of those three, none had more than 10 trials excluded in this way.

EEG recording

Participants wore a standard, fitted cap (Electrocap International) with 33 silver/silver-chloride (Ag/AgCl) electrodes placed according to the extended international 10–20 system. Continuous EEG was recorded with a NeuroScan 4.5 System with a reference electrode at Cz and re-referenced offline to the average activity at left and right mastoids. Electrode resistance was kept under 10 kOhms. Continuous EEG was amplified with a low pass filter (70 Hz), a directly coupled high pass filter (DC), and a notch filter (60 Hz). The signal was digitized at a rate of 250 samples per second via an Analog-to-Digital converter. Eye movement artifacts and blinks were monitored via horizontal electrooculogram (EOG) placed at the outer canthi of each eye and vertical EOG placed above and below the left eye. ERP trials were time locked to the onset of the feedback stimulus. For the SPN component, the baseline period was −2,200 to −2,000 ms, and the data were epoched from −2200 to 100 ms. For the FRN component, the baseline period was −200 to 0 ms, and the data were epoched from −200 to 800 ms. The interval between trials was varied between 1,800–2,000 ms. Trials with no behavioral response, or containing electrophysiological artifacts, were excluded from the averages.

Artifacts were removed via a four-step process. Data were visually inspected for drift exceeding ±200 mV in all electrodes, high frequency noise visible in all electrodes larger than 100 mV, and flatlined data. Following inspection, data were epoched and eyeblink artifacts were identified using independent component analysis (ICA). Individual components were inspected alongside epoched data, and blink components were removed. To remove additional artifacts, we utilized a moving window peak-to-peak procedure in ERPlab (Lopez-Calderon & Luck, 2014), with a 200 ms moving window, a 100 ms window step, and a 150 mV voltage threshold. We excluded FRN data from one subject because they had fewer than 10 trials in their final average. Our final

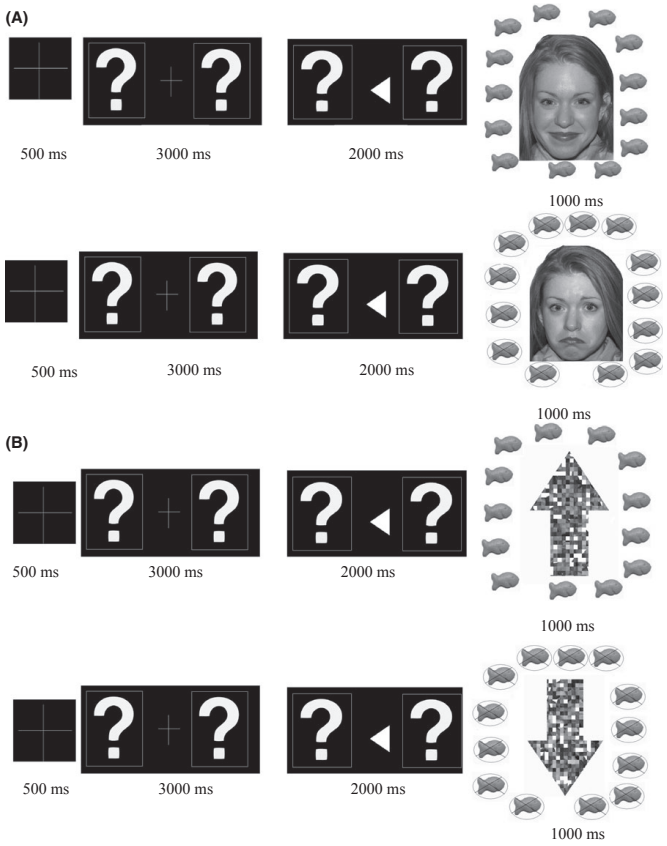

Figure 1 Stimulus presentation. (A) Schematic of the stimuli and timing for the social condition. (B) Schematic of the stimuli and timing for the nonsocial condition. Feedback for 'correct' answers is shown on top, and feedback for 'incorrect' answers is shown below

analyses for the SPN included 20 children with ASD, and 23 TD children, and our final analyses for the FRN includes 19 children with ASD and 23 TD children.

Results

Data were analyzed using JMP (version 10.0). We used repeated-measures analysis of variance (ANOVA) to test for differences between groups, conditions, hemisphere, and caudality (anterior-posterior scalp locations). Greenhouse-Geisser corrected degrees of freedom are reported to account for violations of sphericity.

Behavior

No significant differences were found between groups on children's Likert ratings of liking the game, $F(1,39) = .72$ ns, or perception of generating correct answers, $F(1,39) = .95$, ns. As expected, significant differences were found between groups on the SRS-2 social subscale, $F(1,41) = 64.27$, $p < .001$, and the repetitive behavior subscale, $F(1,41) = 38.23$, $p < .001$, with children with ASD scoring significantly higher on both subscales compared to TD children. Means and standard deviations for both groups on the SRS-2 are shown in Table 1.

Event-related-potential

Stimulus preceding negativity. The mean amplitude of the SPN was measured between −210 and −10 ms, prior to feedback onset, as defined in previous research (Kotani, Hiraku, Suda, & Aihara, 2001). Electrode sites F3/F4, C3/C4, P3/P4, and T5/T6, which are typically maximum amplitude sites for SPN (Kotani et al., 2003), were analyzed. Grand average waveforms for the face and arrow conditions for TD children and those with ASD are plotted in Figure 2.

A 2(Group) × 2(Conditions) × 2(Hemisphere) × 4 (Electrode location) was conducted. No effects of hemisphere were found in either group or condition. We then conducted a 2 (Group) x 2 (Condition) x 4 (Electrode location) that was collapsed across hemispheres. This ANOVA showed a significant group x condition interaction, $F(1, 41.05) = 7.19$, $p = .01$. Pair-wise comparisons revealed a significant group difference for social stimuli, 95% CI [−13.18 to −.48] $F(1, 78.97) = 4.4$, $p = .038$. SPN amplitude was greater in the social condition for TD participants versus participants with ASD. There was a significant difference between the social versus nonsocial conditions for the TD group, 95% CI [−11.42 to −.275] $F(1,41.52) = 4.19$, $p = .046$, with TD participants showing a larger SPN to the social versus nonsocial conditions. Children in the ASD group demonstrated the opposite pattern – a larger SPN response to arrows versus faces – however, this difference within the ASD group did not reach significance ($p = .09$). There was no significant group difference for nonsocial stimuli ($p > .05$). There was a significant main effect of electrode position, $F(3, 123.1) = 3.15$, $p = .027$, with parietal and central electrodes eliciting larger SPNs than frontal or temporal electrodes, but Tukey's HSD test revealed no significant differences between individual electrode positions. Figure 3 shows topographic maps of mean ERP amplitude between −210 and −10 ms in the face and arrow conditions for TD and ASD children.

Trial numbers for each group in both the face and arrow conditions are shown in Table 2. No significant differences for trial numbers between groups were found in the social condition, $p > .1$. Significant differences in trial numbers between groups were found in the nonsocial condition $F(1,41) = 7.44$, $p < .01$. Due to this difference, we analyzed data from a subset of participants who were matched on number of trials (criteria for matching was within 4 trials). Thirteen children in each group were successfully matched. Comparisons of numbers of trials for each condition between groups were nonsignificant (all ps > .5). The group by condition interaction remained significant, $F(1,24.17) = 4.45$, $p = .045$ such that TD children had a larger SPN to social versus nonsocial stimuli, and children with ASD showed the opposite pattern.

Feedback related negativity. Previous literature has examined the FRN between 275–375 ms (Bress, Smith, Foti, Klein, & Hajcak, 2012). However, visual inspection of our waveforms revealed that our FRN occurred between 300–450 ms. Therefore, we used this time window for analysis. The FRN was measured separately for correct and incorrect trials as mean amplitude between 300–450 ms after feedback onset in frontal electrodes Fz, FCz, and Cz. Figure 4 shows grand averaged waveforms for electrodes Fz, Cz, and Cz for the TD and ASD groups.

A 2(Group) × 2(Condition) × 2(Correct/incorrect) × 3(Electrode) ANOVA was conducted. An interaction that approached statistical significance occurred between group, condition, and correctness, $F(1, 33.36) = 3.94$, $p = .055$ such that TD children had a larger FRN to correct versus incorrect answers in the face condition, but in the arrows condition their incorrect answers elicited a larger FRN compared to correct answers. For children with ASD, the pattern was reversed. That is, children with ASD had a larger FRN to correct versus incorrect answers in the arrow condition, but in the face condition their incorrect answers elicited a larger FRN. Pairwise comparisons revealed only marginal effects of specific contrasts by group or condition. These effects reached traditional significance (at the .05 level), but correction for multiple comparisons yielded a critical p-value of .0083, and by this criterion, none of the pairwise comparisons were significant. Figure 3 shows topographic maps of mean amplitude of ERP amplitude

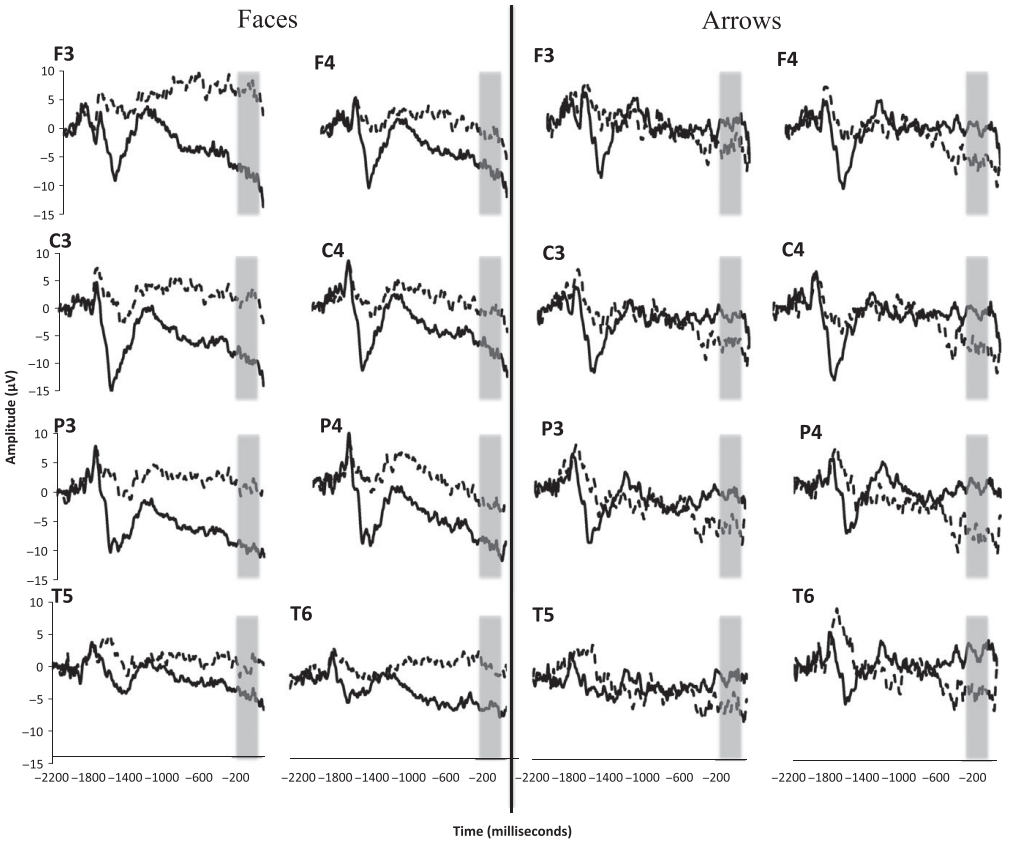

Figure 2 Grand averaged waveforms for TD children and those with ASD from the Stimulus Preceding Negativity (SPN) in response to social/faces (left) and nonsocial/arrows (right). TD children are represented by a solid line, and children with ASD with a dashed line. The area between −210 and −10 ms, used for statistical analysis, is highlighted with a gray box

between 300–450 ms for the face and arrow conditions in both the TD and ASD groups.

Previous literature has also investigated incorrect minus correct difference waves in the FRN (Bress et al., 2012; McPartland et al., 2012). Therefore, we conducted a 2(Group) × 2(Condition) × 3(Electrode) analysis of the mean amplitude between 300 and 450 ms of the incorrect minus correct difference wave for each participant using a repeated-measures ANOVA. Consistent with our results when correct and incorrect answers were analyzed separately, there was a group by condition interaction for the difference wave. Children with ASD had a larger FRN difference wave than TD children to social stimuli, and TD children had a larger FRN difference wave than those with ASD to nonsocial stimuli, $F(1, 33.36) = 3.94$, $p = .055$. No pairwise comparisons were significant (all ps > .05). Note that we calculated an incorrect minus correct difference wave, and TD children demonstrated *larger* FRNs to correct versus incorrect responses in the social condition while children with ASD had the opposite pattern.

Trial numbers for both groups are displayed in Table 2. Due to differences in trial numbers between groups in the nonsocial condition – $F(1,40) = 7.42$, $p < .01$ for nonsocial correct, $F(1,40) = 7.64$, $p < .01$ for nonsocial incorrect – we analyzed data from a subset of participants who were matched on number of trials (criteria for matching was within four trials). Ten children per group were successfully matched. Analysis of number of trials for each condition between groups of matched participants were all nonsignificant (all ps > .1). The previous condition by group by correct interaction was highly significant $F(1,17.68) = 9.15$, $p = .007$.

To examine latency differences between groups and conditions, we used a 2(Group) × 2(Condition) × 3 (Electrode) × 2(Correct) ANOVA to examine fractional peak latency. Fractional peak latency, defined as the point in the waveform where the

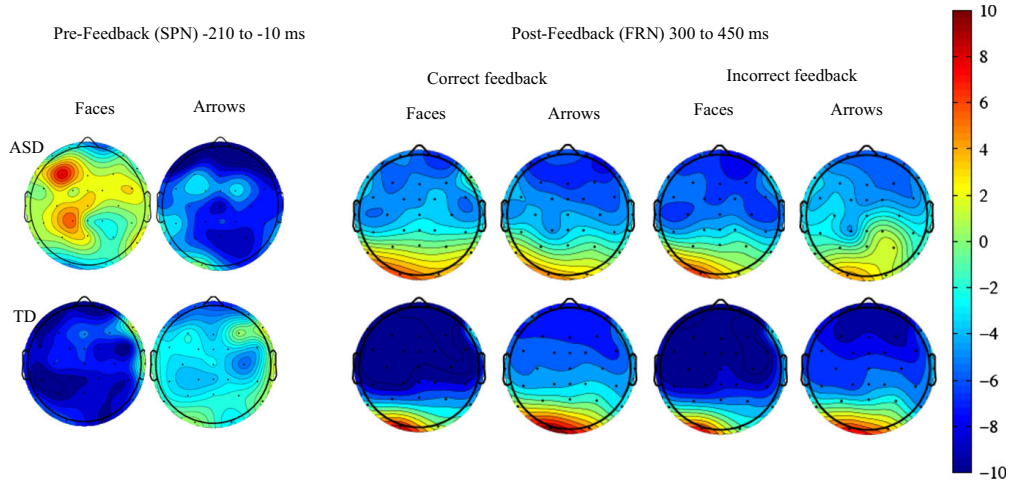

Figure 3 Topographic maps of mean amplitude between −210 and −10 ms (SPN), and 300 and 450 ms (FRN) for children with ASD (top), and TD children (bottom). Both the SPN and FRN are negative waveforms, thus darker (blue) areas indicate greater activation

area under the curve is 50% of the total, is thought to be the most rigorous measure of the timing of ERP activity, because it is less influenced by noise than latency to the peak (Luck, 2005; Woodman, 2010). Latency was measured between 300–450 ms for correct and incorrect trials separately. An interaction between condition and correct answers that approached significance was found, $F(1, 41.11) = 3.89$, $p = .055$, such that for both groups, the FRN was faster for faces versus arrows during incorrect feedback, but faster for arrows versus faces during correct feedback.

Discussion

This study investigated brain correlates of social versus nonsocial feedback on both reward anticipation and processing in young children with TD and ASD using a paradigm that controlled for both rewards and physical stimulus properties. The paradigm has general applicability in studies of TD children and the development of the reward system and its role in children's social-cognitive functioning. It also has applicability in other atypically developing populations, such as in children with Williams Syndrome, who may have abnormally high social motivation, and in whom learning is also affected. These results add significantly to our understanding of reward systems, in that previous investigations of social motivation in ASD have not controlled for tangibility of rewards between conditions.

SPN: Differences between social stimuli in TD children versus children with ASD

The current results extend our previous finding that TD children exhibit larger SPNs when anticipating social versus nonsocial stimuli (Stavropoulos & Carver, 2013a) by showing that TD children have larger SPNs when anticipating social stimuli compared to children with ASD. Importantly, the results also suggest that children with ASD have anticipatory reward deficits for social stimuli, as opposed to global deficits in reward anticipation. No differences were observed between TD individuals and those with ASD in the *non*social condition, suggesting that reward anticipation is blunted in ASD for social stimuli alone – anticipation for nonsocial stimuli is intact.

Our results are largely consistent with previous studies examining reward anticipation in this population (Groen et al., 2008; Kohls et al., 2011). One previous study utilized a probabilistic learning task with nonsocial stimuli, and found that children with ASD and ADHD showed equivalent SPN activations when anticipating negative feedback, but enhanced SPN when anticipating positive feedback (Groen et al., 2008). While it is important to note that our task differed from this previous investigation (because participants could not predict whether upcoming feedback would be positive or negative), we also found that TD children and those with ASD elicited a statistically equivalent SPN response to *non*social feedback. Our results are consistent with findings by Kohls et al. (2011), who reported that children with ASD have an attenuated anticipatory P300 response to trials indicative of social rewards. Our results differ with regards to TD children, however, because we found that TD children elicited a larger SPN response to social versus nonsocial stimuli, whereas Kohls et al. (2011) found the opposite pattern. Our use of a tangible reward (goldfish crackers) for both social and nonsocial blocks may explain these differences. It is possible that both TD

Table 2 Descriptive statistics of trial numbers and amplitude for typically developing (TD) individuals in the top row, and those with autism spectrum disorder (ASD) on the bottom row for each condition separately

Group	FRN: Correct faces	FRN: Incorrect faces	FRN: Correct arrows	FRN: Incorrect arrows	SPN: Faces	SPN: Arrows
TD	Trials: $M = 27.56$	Trials: $M = 26.26$	Trials: $M = 27.56$	Trials: $M = 28.56$	Trials: $M = 47.54$	Trials: $M = 45.26$
	$SD = 6.65$	$SD = 6.60$	$SD = 7.20$	$SD = 6.42$	$SD = 12.90$	$SD = 16.57$
	Amplitude: $M = -8.72$	Amplitude:	Amplitude: $M = -4.80$	Amplitude: $M = -5.02$	Amplitude: $M = -7.15$	Amplitude: $M = -1.31$
	$SD = 7.80$	$M = -6.86 SD = 9.26$	$SD = 7.62$	$SD = 7.05$	$SD = 12.53$	$SD = 8.93$
ASD	Trials: $M = 27.36$	Trials: $M = 25.21$	Trials: $M = 21.68$	Trials: $M = 22.68$	Trials: $M = 41.55$	Trials: $M = 31.75$
	$SD = 4.98$	$SD = 6.43$	$SD = 6.65$	$SD = 7.35$	$SD = 14.73$	$SD = 15.75$
	Amplitude: $M = -2.60$	Amplitude: $M = -4.51$	Amplitude: $M = -4.56$	Amplitude: $M = -3.42$	Amplitude: $M = -.33$	Amplitude: $M = -5.63$
	$SD = 9.49$	$SD = 6.44$	$SD = 8.05$	$SD = 7.08$	$SD = 11.10$	$SD = 8.93$

children and those with ASD show more reward anticipation when rewards are tangible, such as in the monetary condition of Kohls et al. (2011). Previous research suggests that neural activity when viewing faces is changed under different motivational conditions (Skelly & Decety, 2012). It is therefore possible that our results differed from previous investigations because we utilized a design in which the faces and arrows were incidental, rather than the central focus of the task. Future studies should attempt to clarify this point by directly comparing tangible versus intangible rewards within both social and nonsocial conditions.

FRN: Social stimuli and feedback in TD children versus children with ASD

Our results show that TD children and those with ASD are differentially affected by correct versus incorrect feedback and that this interacts with social versus nonsocial stimulus type. In our study, TD children have a larger FRN response to correct feedback when viewing social stimuli, but a larger FRN response to incorrect feedback when viewing nonsocial stimuli. Children with ASD show the opposite pattern (i.e., larger FRN to correct feedback during the nonsocial condition, and larger FRN to incorrect feedback during the social condition). In contrast to previous research using the FRN in children with ASD versus TD children (Larson et al., 2011; McPartland et al., 2012), we did not find a main effect of feedback type such that incorrect feedback elicited a larger FRN versus correct feedback. We found that TD participants' responses were larger to correct feedback in the social condition, but larger to incorrect feedback in the nonsocial condition. Thus, in the nonsocial condition, our results with TD children are consistent with previous findings. Previous FRN literature did not utilize social versus nonsocial stimuli, and it is possible that our results in the social condition may be due to the highly salient nature of viewing faces for TD children.

In the ASD group, results during the social condition were consistent with previous investigations (i.e., larger FRN to incorrect vs. correct feedback), but results in the nonsocial condition differ from previous studies. If we use analogous logic as with TD children, results from children with ASD point to nonsocial stimuli (arrows in this study) being highly salient, because the FRN to *nonsocial* stimuli in the ASD group was largely analogous to the FRN to *social* stimuli in the TD group. The current results suggest that future research on the FRN in both TD children and those with ASD should investigate how social and nonsocial rewards affect reward outcome processing.

Our latency results suggest that both TD children and those with ASD elicit a faster FRN response to faces versus arrows during incorrect feedback, and faster FRN response to arrows versus faces during

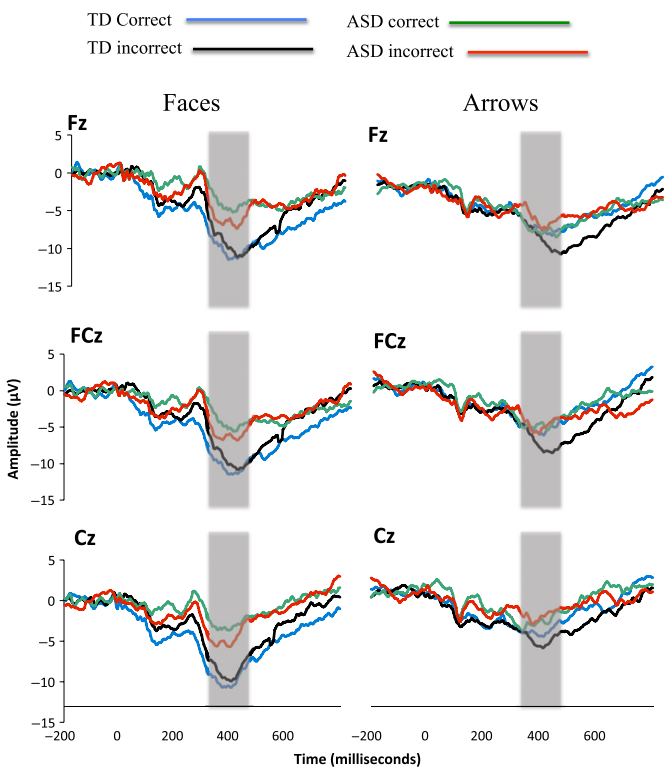

Figure 4 Grand averaged waveforms for TD children and those with ASD from the feedback related negativity (FRN) in response to social/faces (right) and nonsocial/arrows (left). The area between 300 and 450 ms, used for statistical analyses, is highlighted with a gray box

correct feedback. Our latency data indicate a later response than previous FRN studies (Larson et al., 2011; McPartland et al., 2012). This is likely explained by the fact that the current study utilized a younger population than previous studies, and younger children typically have longer latency ERP responses (Courchesne, 1978). In summary, the FRN results demonstrate that TD children are affected by correct versus incorrect feedback while viewing social versus nonsocial stimuli differently than those with ASD, which could point to higher salience of social stimuli for TD children (vs. nonsocial stimuli), and the opposite pattern obtains for children on the autism spectrum. Further research using the FRN may benefit by utilizing principle component analysis (PCA) in order to help tease apart the effects of viewing social stimuli versus nonsocial stimuli between groups.

Testing only high functioning children with ASD allowed us to match groups on IQ scores, however this means that the results cannot be immediately extrapolated to all individuals with ASD independent of severity, and because ASD is a developmental disorder, the current results cannot be extrapolated to younger individuals on the spectrum. Adaptation of the current paradigm would allow us to test both lower functioning children with ASD and younger children.

Conclusions

We examined reward processing of social and nonsocial stimuli in children using a paradigm that can be widely employed to study both typical and atypical populations. Our results comparing typically developing children and children with autism provide evidence of a social reward anticipation impairment in children with ASD. Reward processing evidence suggests that TD children may find social stimuli more salient than nonsocial stimuli, whereas children with ASD demonstrate the opposite pattern. It is interesting to consider, then, whether children with ASD may have increased motivation for nonsocial stimuli at the expense of social stimuli, rather than only a deficit in social motivation. While our study was not designed to examine this directly, future studies should investigate this further. Using two components of the ERP, we showed differences

between typically developing children and children with autism in reward anticipation (via the SPN component of the ERP), and reward processing (via the FRN component of the ERP), finding that both reward anticipation and reward processing are impaired in ASD in response to social stimuli. These findings increase our understanding of the nature of the reward system's response to social stimuli in typically developing children and the nature of deficits seen in children with autism.

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Key points

- Children with autism spectrum disorder demonstrate selective deficits in reward anticipation and processing for social stimuli.
- Children with autism spectrum disorder process reward feedback differently than typically developing children for social versus nonsocial stimuli.

References

Böcker, K.B.E., Brunia, C.H.M., & van den Berg-Lenssen, M.M.C. (1994). A spatiotemporal dipole model of the stimulus preceding negativity (SPN) prior to feedback stimuli. *Brain Topography*, *7*, 71–88.

van Boxtel, G.J.M., & Böcker, K.B.E. (2004). Cortical measures of anticipation. *Journal of Psychophysiology*, *18*, 61–76.

Bress, J., Smith, E., Foti, D., Klein, D., & Hajcak, G. (2012). Neural response to reward and depressive symptoms in late childhood to early adolescence. *Biological Psychology*, *89*, 156–162.

Brunia, C.H.M., Hackley, S.A., van Boxtel, G.J.M., Kotani, Y., & Ohgami, Y. (2011). Waiting to perceive: Reward or punishment? *Clinical Neurophysiology*, *122*, 858–868.

Charman, T., Swettenham, J., Baron-Cohen, S., Cox, A., Baird, G., & Drew, A. (1998). An experimental investigation of social-cognitive abilities in infants with autism: Clinical implications. *Infant Mental Health Journal*, *19*, 260–275.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E.S., & Schultz, R.T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*, 231–239.

Constantino, J.N., & Gruber, C.P. (2012). *Social responsiveness scale*, 2nd ed. Los Angeles: Western Psychological Services.

Courchesne, E. (1978). Neurophysiological correlates of cognitive development: Changes in long-latency event-related potentials from childhood to adulthood. *Electroencephalography and Clinical Neurophysiology*, *45*, 468–482.

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, *20*, 775–803.

Dawson, G., Carver, L., Meltzoff, A.N., Panagiotides, H., McPartland, J., & Webb, S.J. (2002). Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. *Child Development*, *73*, 700–717.

Dawson, G., Webb, S.J., Wijsman, E., Schellenberg, G., Estes, A., Munson, J., & Faja, S. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology*, *17*, 679–697.

Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., & Fiez, J.A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*, *84*, 3072–3077.

Delmonte, S., Balsters, J.H., McGrath, J., Fitzgerald, J., Brennan, S., Fagan, A.J., & Gallagher, L. (2012). Social and monetary reward processing in autism spectrum disorders. *Molecular Autism*, *3*, 7.

Dichter, G.S., Richey, J.A., Rittenberg, A.M., Sabatino, A., & Bodfish, J.W. (2012). Reward circuitry function in autism during face anticipation and outcomes. *Journal of Autism and Developmental Disorders*, *42*, 147–160.

Foti, D., Weinberg, A., Dien, J., & Hajcak, G. (2011). Event-related potential activity in the basal ganglia differentiates rewards from nonrewards: Temporospatial principal components analysis and source localization of the feedback negativity. *Human Brain Mapping*, *32*, 2267–2269.

Gaspar, P., Berger, B., Febvret, A., Vigny, A., & Henry, J.P. (1989). Catecholamine innervation of the human cerebral cortex as revealed by comparative immunohistochemistry of tyrosine hydroxylase and dopamine-beta-hydroxylase. *Journal of Comparative Neurology*, *279*, 249–271.

Grelotti, D., Gauthier, I., & Schultz, R.T. (2002). Social interest and the development of cortical face specialization: What

autism teaches us about face processing. *Developmental Psychobiology*, *40*, 213–225.
Groen, Y., Wijers, A.A., Mulder, L.J.M., Waggeveld, B., Minderaa, R.B., & Althaus, M. (2008). Error and feedback processing in children with ADHD and children with autistic spectrum disorder: An EEG event-related potential study. *Clinical Neurophysiology*, *119*, 2476–2493.
Hajcak, G., Moser, J.S., Holroyd, C.B., & Simons, R.F. (2006). The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. *Biological Psychology*, *71*, 148–154.
Holroyd, C.B., & Coles, M.G.H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*, 679–709.
Jones, E.A., & Carr, E.G. (2004). Joint attention in children with autism: Theory and intervention. *Focus on Autism & Other Developmental Disabilities*, *19*, 13–26.
Kampe, K.W., Frith, C.D., Dolan, R.J., & Frith, U. (2001). Reward value of attractiveness and gaze. *Nature*, *413*, 589.
Kohls, G., Chevallier, C., Troiani, V., & Schultz, R.T. (2012). Social "wanting" dysfunction in autism: Neurobiological underpinnings and treatment implications. *Journal of Neurodevelopmental Disorders*, *4*, 10.
Kohls, G., Peltzer, J., Schulte-Rüther, M., Kamp-Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., & Konrad, K. (2011). Atypical brain responses to reward cues in autism as revealed by event-related potentials. *Journal of Autism and Developmental Disorders*, *41*, 1523–1533.
Kohls, G., Schulte-Rüther, M., Nehrkorn, B., Müller, K., Fink, G.R., Kamp-Becker, I., … & Konrad, K. (2013). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *8*, 565–572.
Kotani, Y., Hiraku, S., Suda, K., & Aihara, Y. (2001). Effect of positive and negative emotion on stimulus-preceding negativity prior to feedback stimuli. *Psychophysiology*, *38*, 873–878.
Kotani, Y., Kishida, S., Hiraku, S., Suda, K., Ishii, M., & Aihara, Y. (2003). Effects of information and reward on stimulus-preceding negativity prior to feedback stimuli. *Psychophysiology*, *40*, 818–826.
Kuhl, P.K., Tsao, F.-M., & Liu, H.-M. (2003). Foreign-language experience in infancy: Effects of short-term exposure and social interaction on phonetic learning. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 9096–9101.
Larson, M.J., South, M., Krauskopf, E., Clawson, A., & Crowley, M.J. (2011). Feedback and reward processing in high-functioning autism. *Psychiatry Research*, *187*, 198–203.
Lord, C., Rutter, M., DiLavore, P.C., Risi, S., Gotham, K., & Bishop, S.L. (2012). *ADOS-2: autism diagnostic observation schedule*. Los Angeles: Western Psychological Services.
Luck, S.J. (2005). *An Introduction to the Event-Related Potentials*. Caimbridge, MA: MIT Press.
Lopez-Calderon, J., & Luck, S.J. (2014). ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*, *8*, 1–14.
Mattox, S.T., Valle-Inclán, F., & Hackley, S.A. (2006). Psychophysiological evidence for impaired reward anticipation in Parkinson's disease. *Clinical Neurophysiology*, *117*, 2144–2153.
McPartland, J.C., Crowley, M.J., Perszyk, D.R., Mukerji, C.E., Naples, A.J., Wu, J., & Mayes, L.C. (2012). Preserved reward outcome processing in ASD as revealed by event-related potentials. *Journal of Neurodevelopmental Disorders*, *4*, 16.
McPartland, J., Dawson, G., Webb, S.J., Panagiotides, H., & Carver, L.J. (2004). Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, *45*, 1235–1245.
Mundy, P., Sigman, M., Ungerer, J., & Sherman, T. (1986). Defining the social deficits of autism: The contribution of non-verbal communication measures. *Journal of Child Psychology and Psychiatry*, *27*, 657–669.
Nieuwenhuis, S., Slagter, H.A., von Geusau, N.J.A., Heslenfeld, D.J., & Holroyd, C.B. (2005). Knowing good from bad: Differential activation of human cortical areas by positive and negative outcomes. *The European Journal of Neuroscience*, *21*, 3161–3168.
Richey, J.A., Rittenberg, A., Hughes, L., Damiano, C.R., Sabatino, A., Miller, S., … & Dichter, G.S. (2014). Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Social Cognitive and Affective Neuroscience*, *9*, 367–377.
Schultz, R.T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience*, *23*, 125–141.
Scott-Van Zeeland, A.A., Dapretto, M., Ghahremani, D.G., Poldrack, R.A., & Bookheimer, S.Y. (2010). Reward processing in autism. *Autism Research*, *3*, 53–67.
Skelly, L.R., & Decety, J. (2012). Passive and motivated perception of emotional faces: Qualitative and quantitative changes in the face processing network. *PLoS ONE*, *7* (6), e40371.
Stavropoulos, K.K.M., & Carver, L.J. (2013a). Research review: Social motivation and oxytocin in autism-implications for joint attention development and intervention. *Journal of Child Psychology and Psychiatry*, *54*, 603–618.
Stavropoulos, K.K.M., & Carver, L.J. (2013b). Reward sensitivity to faces versus objects in children: An ERP study. *Social Cognitive and Affective Neuroscience*. [Epub ahead of print].
Tottenham, N., Tanaka, J.W., Leon, A.C., McCarry, T., Nurse, M., Hare, T.A., … & Nelson, C. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*, *168*, 242–249.
Tsukamoto, T., Kotani, Y., Ohgami, Y., Omura, K., Inoue, Y., & Aihara, Y. (2006). Activation of insular cortex and subcortical regions related to feedback stimuli in a time estimation task: An fMRI study. *Neuroscience Letters*, *399*, 39–44.
Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence*. San Antonio, TX: Pearson.
Whalen, C., & Schreibman, L. (2003). Joint attention training for children with autism using behavior modification procedures. *Journal of Child Psychology and Psychiatry*, *44*, 456–468.
Woodman, G.F. (2010). A brief introduction to the use of event-related potentials in studies of perception and attention. *Attention, Perception, & Psychophysics*, *72*, 2031–2046.

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Chapter 3

Effect of familiarity on reward anticipation in children with and without autism spectrum disorders

Effect of Familiarity on Reward Anticipation in Children with and without Autism Spectrum Disorders

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Abstract

Background: Previous research on the reward system in autism spectrum disorders (ASD) suggests that children with ASD anticipate and process social rewards differently than typically developing (TD) children—but has focused on the reward value of unfamiliar face stimuli. Children with ASD process faces differently than their TD peers. Previous research has focused on face processing of unfamiliar faces, but less is known about how children with ASD process familiar faces. The current study investigated how children with ASD anticipate rewards accompanied by familiar versus unfamiliar faces.

Methods: The stimulus preceding negativity (SPN) of the event-related potential (ERP) was utilized to measure reward anticipation. Participants were 6- to 10-year-olds with ($N = 14$) and without ($N = 14$) ASD. Children were presented with rewards accompanied by incidental face or non-face stimuli that were either familiar (caregivers) or unfamiliar. All non-face stimuli were composed of scrambled face elements in the shape of arrows, controlling for visual properties.

Results: No significant differences between familiar versus unfamiliar faces were found for either group. When collapsing across familiarity, TD children showed larger reward anticipation to face versus non-face stimuli, whereas children with ASD did not show differential responses to these stimulus types. Magnitude of reward anticipation to faces was significantly correlated with behavioral measures of social impairment in the ASD group.

Conclusions: The findings do not provide evidence for differential reward anticipation for familiar versus unfamiliar face stimuli in children with or without ASD. These findings replicate previous work suggesting that TD children anticipate rewards accompanied by social stimuli more than rewards accompanied by non-social stimuli. The results do not support the idea that familiarity normalizes reward anticipation in children with ASD. Our findings also suggest that magnitude of reward anticipation to faces is correlated with levels of social impairment for children with ASD.

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Introduction

Autism spectrum disorder (ASD) is a disorder defined by social-communicative deficits and repetitive and restricted behaviors. ASD is estimated to effect up to 1 in 68 children in the US (Centers for Disease Control and Prevention [CDC], 2014). Children with ASD have well documented difficulties in multiple aspects of social communication, including eye contact [1,2], language [3], and joint attention [1], in addition to having repetitive behaviors and restricted interests.

Several theories have emerged concerning why individuals with ASD are impaired relative to their neurotypical peers in social abilities. One is the social motivation hypothesis [4–9]. According to this idea, children with ASD are less intrinsically motivated to attend to and engage with others, which leads to downstream social deficits. The social motivation hypothesis might predict, then, that children with ASD need to be more motivated than TD children in order to find faces rewarding. In the current study, we tested the hypothesis that, although unfamiliar faces may not be rewarding for children with ASD, a socially important familiar face, such a caregiver's face, may have greater reward value than an unfamiliar face.

There is reason to believe that children with autism might respond differently to a caregiver's face than to other, unfamiliar faces. Previous literature has investigated how children with and without ASD react to their caregivers, and whether attachment relationships differ between the two groups. The attachment literature suggests that children with ASD show somewhat typical and secure attachment relationships to their caregivers [10,11], although a recent meta-analysis suggested that children with ASD are less likely to be securely attached compared to TD children and those with other developmental disorders [12]. Given the suggestion that children with ASD may react to their parents similarly to TD children despite their social impairments, it is possible that familiar faces may be particularly salient to children with ASD, and may "normalize" the neural responses of people

with ASD [13]. While this is an intriguing possibility, no prior study has directly investigated the effect of face familiarity on the brain's reward system in ASD. The current study was designed to investigate whether familiar faces would increase reward anticipation in children with ASD compared to their TD peers.

Previous literature has documented different neural responses in individuals with ASD compared to their TD peers when viewing unfamiliar faces [14–16]. The relatively small literature on the effect of familiarity in ASD has been limited to the effect of familiarity on face processing [13,17–25]. The studies on familiarity have varied results, likely due to inter-study differences in participants' age, methodologies, and stimuli. Previous literature on the reward system in ASD has also had mixed results, with some studies finding reward deficits in social rewards only, and others finding global reward deficits. One recent study has integrated these two lines of research and investigated familiar versus unfamiliar faces, as well as monetary rewards in a behavioral paradigm and found that both face and monetary rewards improved behavioral performance for individuals with and without ASD in a go/no-go task [26]. In order to setup and motivate the current study, we next briefly review the research on the reward system in ASD individuals using electrophysiology, functional neuroimaging, and combined methodologies, and then review previous research on the effect of familiar faces in ASD.

Reward System in ASD

Electrophysiological studies. Event-related potentials (ERP) are brain potentials recorded at the surface of the scalp. These recordings reflect synchronous firing of groups of synapses, and have been used to measure the time course of brain activity related to the anticipation or processing of specific discrete events.

ERPs have been used to study the reward system in ASD. Three studies have compared reward anticipation between TD individuals and those with ASD [27–29]. One study used a probabilistic learning task with monetary rewards and found that children with ASD and ADHD demonstrated larger neural responses than TD children when anticipating positive outcomes, but equivalent responses when anticipating negative outcomes [27]. A second study measured attentional ERP components in response to cues triggering trials with social vs. nonsocial rewards and found that TD children exhibited larger attentional components during reward versus non-reward conditions, but children with autism did not. In addition, children with autism exhibited smaller attentional components after cues initiating social reward anticipation trials [28]. A third study measured neural correlates of reward anticipation in a guessing game task with social and nonsocial rewards and found group differences such that children with ASD showed reduced brain activity when anticipating rewards accompanied by intact versus scrambled faces [29]. Taken together, ERP studies of social reward anticipation provide evidence that individuals with ASD elicit less brain activity when anticipating social rewards compared to their TD peers.

Previous ERP studies have also investigated electrophysiological correlates of reward processing in ASD. In studies examining reward processing in ASD, two studies have utilized a guessing game with monetary rewards. Both studies found similar activation patterns in children with ASD and TD [30,31], suggesting that children with ASD do not demonstrate deficits in reward feedback processing when the rewards are monetary. Our previous investigation of social versus non-social rewards revealed group differences in reward processing between TD children and those with ASD—especially for social stimuli [29].

Functional neuroimaging studies. Previous research on social versus nonsocial rewards in ASD has also utilized functional magnetic resonance imaging (fMRI). The fMRI literature on social versus nonsocial rewards in ASD vs. TD is mixed. Some studies have suggested that individuals with ASD may elicit reduced neural activation for monetary rewards compared to TD children, but have similar neural activation for social rewards [32]; others have found reduced brain activity in response to social rewards in ASD [33].

Behavioral studies. One recent study has investigated reward responsiveness to both familiar versus unfamiliar faces, as well as nonsocial rewards, in both TD children and those with ASD using a modified go/no-go task [26]. Children either received auditory or visual indicators of reward after successful response inhibition. The authors found that both monetary and social (both familiar and unfamiliar faces) rewards increased performance versus a control (no-reward) condition. The authors did not find evidence of decreased responsiveness to social rewards in children with ASD, but found that parents' practices with rewards and contingencies at home strongly predicted performance in the ASD group [26].

Effects of Familiarity in ASD

Electrophysiological studies. We now turn to previous research investigating the effects of familiarity on face processing in ASD. Several ERP studies have measured responses to familiar and unfamiliar faces. Some investigations have found that individuals with ASD are less responsive to familiar faces compared to their typically developing peers [18,25], yet others have found that responsiveness to familiarity may be typical, but delayed, in ASD [24], or may increase after exposure to social skills groups [17]. Conversely, other investigations found no differences between adults with and without ASD in responsiveness to familiar faces [23], or in children at high versus low risk for ASD [20,34]. The ERP literature on the effects of familiarity on face processing in ASD is widely varied, and likely depends on a variety of factors, including cognitive functioning, age of participants, and the tasks utilized.

Functional Neuroimaging Studies. Two studies have investigated recognition of face familiarity using functional neuroimaging with individuals with and without ASD [13,22]. In a study of adults, both typical and ASD groups showed increased neural activation in response to familiar versus unfamiliar faces. [22]. In a study of school-aged children with and without ASD, children with ASD demonstrated similar brain activity to their TD peers when viewing pictures of children or familiar adults, but reduced activation when viewing pictures of unfamiliar adults [13]. In contrast to these findings, many studies in which brain responses are elicited to novel faces suggest that people with ASD do not activate face-processing brain areas to the same degree that TD controls do [16,35]. Thus, the results of recent face processing studies that have manipulated familiarity using fMRI measures suggest that brain responses might be normalized when familiar faces are used as stimuli.

Summary

Previous research on the *reward* system in ASD has been mixed, likely due to the wide variety of methodologies and procedures utilized. However, several studies have found that individuals with ASD have differences in the neural correlates of the reward system compared to TD individuals. Similarly, previous investigations of *familiar faces* on face processing have met with mixed findings. While previous literature has investigated the effects of familiar faces on face processing, as well as the effects of social versus nonsocial stimuli on the reward system in ASD, only one study has directly investigated the effect of familiar faces on reward

responsiveness in ASD [26]. No previous studies have investigated the effects of familiarity on *neural correlates* of reward in TD versus ASD.

Current Study

The aim of the current study was to utilize electrophysiology to investigate the effect of familiarity on reward anticipation in response to faces versus non-faces in children with and without ASD. While previous studies have investigated the effects of familiarity on face processing, none have directly explored how the neural reward system is affected by familiarity in ASD. Specifically, we wanted to investigate reward anticipation for familiar versus unfamiliar faces, and scrambled versions of those images.

Previous investigations using electrophysiology to measure reward anticipation focused on the stimulus preceding negativity (SPN) component [29,36,37] The SPN is a component of the ERP that reflects brain activity occurring before expected feedback about one's performance [38]. SPN reflects the *expectation* of reward, and related activity of the dopaminergic reward system [39]. Our previous study of the SPN in children with ASD versus their TD peers revealed differences in how children with ASD anticipate social stimuli (pictures of faces) [29]. However, this previous study utilized a variety of unfamiliar faces.

The current study utilized one familiar and one unfamiliar face in order to determine whether familiar faces accompanying reward stimuli normalized reward anticipation in children with ASD. This design allowed us to gain information about both the effect of familiar faces on reward anticipation, and also whether the use of only one face in each condition may lead to habituation effects over time. In the current study, we also investigated whether brain activity and behavioral measures of ASD (via the SRS-2) were correlated, and whether children with more severe social impairments had reduced reward anticipation for face stimuli. We hypothesized that TD children would have an increased SPN response to face versus arrow stimuli—and that this effect would be most pronounced for familiar versus unfamiliar faces. We hypothesized that children with ASD would not have increased SPN responses to face versus arrow stimuli overall, but would have larger SPN responses to a familiar versus unfamiliar face. Lastly, we hypothesized that we would find a specific brain-behavior correlation—children with more severe social impairments (as measured with the SRS-2) would have decreased SPN amplitude to faces.

Methods

Participants

To estimate the needed sample size for the current study, we ran a power analysis on data from our previous study which used the same paradigm [29]. The resulting power value of .86 yielded a sample size of 26. Therefore, we recruited 28 participants for the current study: TD children ($N = 14$) and children with ASD ($N = 14$). Each child that was tested provided an adequate number of ERP trials for analysis and was included in the final sample. Exclusionary criteria for participants with ASD included history of seizures, brain injury, neurological disorders, genetic causes of ASD (e.g. Fragile X), or any concurrent psychiatric condition (other than ASD), based on parent report. Exclusionary criteria for TD participants included all of the above criteria, plus an immediate family history of ASD. None of the children in the TD group were taking psychoactive medications. One child in the ASD group was taking medication to improve concentration, and one was taking medication to decrease aggression and stabilize mood. Participants were recruited from a UC San Diego subject pool and through postings on websites for parents of children on the autism spectrum. All participants had normal hearing and normal or corrected to normal vision. Procedures were approved by the University of California, San Diego institutional review board, and written consent was obtained from caregivers. All children over 7 years of age signed an assent form.

Table 1 provides detailed participant information. IQ scores [40] were available for all participants. TD children were matched with children with ASD on mental age (full scale IQ/100 * chronological age). No differences were found between groups on mental age, $F(1,26) = .01$. Children in the ASD group had been previously diagnosed with ASD through various sources (e.g. formal evaluations through an autism center, or school diagnosis). Diagnosis was confirmed for the current study with Module 3 of the ADOS-2 [41]. The ADOS-2 was administered by an individual trained to research reliability on administration, scoring, and interpretation of the measure.

Behavioral Measures

Participants' caregivers completed the Social Responsiveness Scales (SRS-2) [42], which measures social responsiveness and behavior. We also tested for overt motivation or affective differences between groups for each condition. To accomplish this, children ($N = 9$ TD, 13 ASD) completed a 1–7 Likert rating scale of how much they enjoyed the game (1 = "I do not like this game", and 7 = "I love this game") after each block. This was used in order to gather more information about whether one group felt more or less motivated to engage in the task. Previous research suggests that the presence of reward versus no reward affects SPN amplitude—with greater SPN amplitude in reward versus no-reward conditions [43]—and we wished to assess whether both groups felt equally invested in the game. Participants also completed a 1–7 Likert scale about their perception of answering correctly (1 = "I never got correct answers", and 7 = "I always got correct answers"). In reality, the correct versus incorrect answers was predetermined, equated for individuals, and controlled by experimental design; the rating was used to verify that the groups did not differ in their perception that they were obtaining correct answers.

Stimuli and Task

The task was identical to that described in previous studies [29,37], but the stimuli differed in order to include different blocks of trials with a familiar or an unfamiliar face. The task was a guessing game that presented blocks of trials that used left and right visual stimuli (question marks). Participants were asked to indicate their guess via button press whether the left or right stimulus was "correct." After this choice, the left and right question marks were replaced with an arrow in the middle pointing towards whichever question mark the participant chose. This was done to reinforce the idea that participants had control over the task and their responses were being recorded.

There were four blocked feedback conditions: *familiar social*, *familiar nonsocial, unfamiliar social, and unfamiliar nonsocial*. The incidental stimulus in the familiar social condition was a picture of the child's caregiver that was smiling for "correct" answers and frowning for "incorrect" answers (photographs obtained via digital camera in our lab, and modeled after the NimStim stimulus set) [44]. The incidental stimulus in the unfamiliar social condition was a picture of another child's caregiver that was smiling for "correct" answers and frowning for "incorrect" answers. Incidental stimuli in the nonsocial conditions were composed of scrambled face elements from the social conditions formed into an arrow that pointed upwards for

Table 1. Participant characteristics including: IQ (WASI), chronological age, mental age (WASI/100 * chronological age), gender, SRS-2 T-score, and ADOS-2 severity scores for the ASD group.

Group	Participants	WASI (full-scale)	Chron. Age	Mental Age	Gender	SRS-2 SCI T-Score	SRS-2 RBB T-Score	ADOS-2 Severity Score
ASD	14	$M = 99.42_a$ $SE = 4.10$	$M = 8.85$ $SE = .39$	$M = 8.86$ $SE = .57$	11 M 3 F	$M = 77.50_b$ $SE = 1.94$	$M = 80.07_c$ $SE = 2.30$	$M = 7.14$ $SE = .46$
TD	14	$M = 112.64_a$ $SE = 4.10$	$M = 7.94$ $SE = .39$	$M = 8.96$ $SE = .57$	11 M 3 F	$M = 43.53_b$ $SE = 2.01$	$M = 46.38_c$ $SE = 2.39$	N/A

$^aP = .03$, 95% CI [−1.28 −25.14].
$^bP < .0001$, 95% CI [39.72 28.20].
$^cP < .0001$, 95% CI [40.52 26.84].
WASI Wechsler Abbreviated Scale of Intelligence, *SRS-2* Social Responsiveness Scale, second edition, *SCI* Social Communication and Interaction, *RBB* Restricted Interests and Repetitive Behavior, *ADOS-2* Autism Diagnostic Observation Schedule Second Edition.
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"correct" answers and downwards for "incorrect" answers (e.g. the stimulus in the familiar nonsocial condition was an arrow composed from the familiar social photograph, and stimulus in the unfamiliar nonsocial condition was an arrow composed from the unfamiliar social photograph). The face images and scrambled-face images were individually created from photographs taken in our lab with a digital camera. The face in the unfamiliar condition was chosen for each subject to match his or her caregiver's face on ethnicity, gender, and presence or absence of glasses. The use of scrambled faces to construct the arrow controlled for low-level visual features of the stimuli. Presented stimuli subtended a horizontal visual angle of 14.5 degrees, and a vertical visual angle of 10.67 degrees. The order in which children saw the four blocks of trials was counterbalanced between participants.

Participants were told that the reward for each correct answer was a goldfish cracker, or if they preferred, fruit snacks. They were told that if they guessed correctly, they would see a ring of intact goldfish crackers, and the goldfish would be crossed out for incorrect answers. Participants were told that the computer would sum their total of correct responses, and they would receive a goldfish cracker for each correct answer they gave, but would not lose any goldfish crackers for incorrect answers. Importantly, in both the familiar and unfamiliar social and nonsocial feedback trials, the face/arrow information was incidental. A computer program predetermined correct versus incorrect answers in pseudorandom order such that children got 50% "correct" and 50% "incorrect," with no more than three of the same answer in a row.

The four feedback conditions were tested in separate blocks, each composed of 60 trials. There were four conditions that composed the trials (familiar face/"familiar social"; unfamiliar face/"unfamiliar social"; familiar arrow/"familiar nonsocial"; and unfamiliar arrow/ "unfamiliar nonsocial" trials). Within each block of 60 trials, there were 10-s breaks every 15 trials. During breaks, participants were asked to relax, or move if they felt restless. Between blocks, a longer break (2–5 min.) was taken. To control for attentional effects, children were observed via webcam, and trials in which they were not attending to the stimulus were marked and discarded during analysis. Of the final sample, none of the children had any trials discarded for this reason.

EEG Recording

Participants wore a standard, fitted cap (Electrocap International) with 33 silver/silver-chloride (Ag/AgCl) electrodes placed according to the extended international 10–20 system. Continuous EEG was recorded with a NeuroScan 4.5 System with a reference electrode at Cz and re-referenced offline to the average activity at left and right mastoids. Electrode resistance was kept under 10 kOhms. Continuous EEG was amplified with a low pass filter (70 Hz), a directly coupled high pass filter (DC), and a notch filter (60 Hz). The signal was digitized at a rate of 250 samples per second via an Analog-to-Digital converter. Eye movement artifacts and blinks were monitored via horizontal electrooculogram (EOG) placed at the outer canthi of each eye and vertical EOG placed above and below the left eye. ERP trials were time locked to the onset of the feedback stimulus. The baseline period was −2200 to −2000 ms, and the data were epoched from −2200 to 100 ms. The interval between trials was varied between 1,800–2,000 ms. Trials with no behavioral response, or containing electrophysiological artifacts, were excluded from the averages.

Artifacts were removed via a four-step process. Data were visually inspected for drift exceeding +/−200 mV in all electrodes, high frequency noise visible in all electrodes larger than 100 mV, and flatlined data. Following inspection, data were epoched and

eyeblink artifacts were identified using independent component analysis (ICA). Individual components were inspected alongside epoched data, and blink components were removed. To remove additional artifacts, we utilized a moving window peak-to-peak procedure in ERPlab [45], with a 200 ms moving window, a 100 ms window step, and a 150 mV voltage threshold. Participants with less than 10 artifact-free trials in any block of testing were excluded ($N = 0$). Thus, our final analysis includes 14 children with ASD and 14 TD children.

Results

Data were analyzed using JMP (version 10.0). For our initial analysis, we separated familiarity (familiar, unfamiliar) from condition (face, arrow). We used mixed model (between and within subjects) analysis of variance (ANOVA) to test for differences between group, condition, familiarity, and caudality (anterior-posterior scalp locations).

Behavioral Measures

As expected, SRS-2 T-scores (which reflect more severe social impairments) were significantly higher for the ASD group than the TD group for the social communication subscale $F(1, 32) = 215$, $p<.0001$, and the repetitive and restricted behavior subscale $F(1,32) = 158.55$, $p<.0001$. Means and standard deviations between groups on the SRS-2 are shown in *Table 1*. No significant differences were found between groups on children's Likert ratings of liking the game for any of the four conditions, (all ps>.2), or perception of generating correct answers, (all ps>.1)

ERP

SPN. The mean amplitude of the SPN was measured between −210 and −10 ms, prior to feedback onset, as defined in previous research [29,37,46]. Electrode sites F3/F4, C3/C4, P3/P4, and T5/T6, which are typically maximum amplitude sites for SPN [43], were analyzed. Artifact-free trials were analyzed for each of the four conditions between groups. No significant differences were found between groups for any of the four conditions (all ps> .15). Mean amplitude and trial numbers for each group in all 4 conditions are shown in *Table 2*.

A 2 (Group) ×2 (Condition) ×2 (Familiarity) ×4 (Electrode location) ANOVA did not reveal a significant effect of familiarity, $F(1, 32.06) = .23$, *n.s*, or any interactions with familiarity and other variables of interest. It is possible that over the course of each block, children's response to the single repeated stimulus habituated. In order to explore this possibility, we analyzed the first and second half of each participant's accepted trials for all four blocks in a 2 (Time) ×2 (Group) 2 (Familiarity) ×2 (Condition) ×4 (Electrode location) ANOVA. There was a marginal main effect of time such that the first half of trials elicited a larger SPN than the second half, regardless of group or condition $F(25.9) = 3.72$, $p = .064$, 95% CI [−2.31 to 4.99]. No other interactions with time were significant.

Given previous reports of differences in brain responses to familiar versus unfamiliar faces in TD children, but not those with ASD we conducted a planned 4 (Condition) ×2 (Group) ×4 (Electrode location) ANOVA for faces. We found a significant effect of group × electrode. Subsequent pairwise comparisons were non-significant. In order to better understand the effects of the different conditions on each group, a 4 (Condition) ×4 (Electrode location) ANOVA was conducted for the TD group and ASD groups separately. For TD children there was a main effect of condition, $F(3, 37.55) = 2.76$, $p = .055$, such that the familiar and unfamiliar face conditions elicited larger responses

Table 2. Descriptive statistics of trial numbers and amplitude of the SPN for typically developing (TD) individuals and those with autism spectrum disorder (ASD).

Group	Familiar Faces		Unfamiliar Faces		Familiar Arrows		Unfamiliar Arrows	
	Trials	Amplitude	Trials	Amplitude	Trials	Amplitude	Trials	Amplitude
TD	30.15 (2.67)	−6.58 (2.97)	30.21 (2.72)	−3.91 (2.89)	29.92 (3.01)	−.28 (2.97)	30.14 (2.31)	−.12 (2.89)
ASD	25.07 (2.57)	−3.65 (2.89)	30.28 (2.72)	−3.74 (2.89)	28.14 (2.90)	−2.21 (2.89)	25.21 (2.31)	−5.73(2.89)

Means are displayed, followed by standard error in parentheses (SE). Amplitude is the average magnitude of the SPN over the last 200 ms before reward stimulus onset (measured in microvolts).

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than the familiar and unfamiliar arrow conditions. Follow-up contrasts between the familiar face condition and the other three conditions (alpha corrected = .016) revealed marginally significant differences between the familiar face condition and the unfamiliar arrow condition ($p = .018$, 95% CI [1.15 to 11.82]) as well as a marginally significant difference between the familiar face and unfamiliar arrow conditions ($p = .02$, 95% CI [.90 to 11.82]). No other pairwise comparisons were significant. For the ASD group, there was no effect of condition $F(3, 36.24) = .53$, *n.s*. *Figure 1* shows grand averages of all four conditions for each group.

Because there was no main effect of familiarity within or between groups, nor interactions involving familiarity, we collapsed across familiarity for each condition (face, arrow) separately and conducted a 2 (Group) ×2 (Condition) ×4 (Electrode location) ANOVA. This analysis resulted in a significant group × condition interaction, $F(1, 26.03) = 5.97$, $p = .021$. Pairwise comparisons (alpha corrected = .012) revealed a significant effect of condition for the TD group, such that faces elicited a larger SPN than arrows for TD children, $F(1, 25.75) = 8.36$, $p > .01$, 95% CI [1.70 to 8.75], but not for children with ASD. *Figure 2* shows grand averages of the face and arrow conditions for each group.

There was a significant effect of electrode position, $F(3, 77.28) = 2.72$, $p = .05$, such the SPN was larger over central and parietal electrodes than frontal or temporal electrode sites. Follow-up Tukey's HSD showed that central electrode sites showed a significantly larger SPN than frontal electrode sites ($p = .04$, 95% CI [.1 to 7.67]). No other pairs of electrode sites were significantly different. There was a Condition × Electrode interaction, $F(3, 75.59) = 2.72$, $p = .05$. Pairwise comparisons (alpha corrected = .008) revealed that the significant effect of electrode was largely driven by the face condition, $F(3, 140.7) = 4.31$, $p = .006$, such that faces elicited a larger SPN than arrows differentially over various electrode sites. Pairwise comparisons also revealed a significant effect of the parietal electrode position, $F(1, 76.74) = 8.53$, $p = .004$ 95% CI [1.29 9.20], such that the face condition elicited a larger SPN than the arrow conditions at this electrode site regardless of group. There was a Group × Condition × Electrode interaction, $F(3, 75.59) = 3.40$, $p = .02$. In order to investigate the Group × Condition interaction at each electrode site, we performed contrasts at all four electrode sites. These contrasts showed a significant Group × Condition interaction (alpha corrected = .012) at both the central, $F(1, 78.57) = 6.51$, $p = .012$, 95% CI [1.07 to 8.20], and frontal electrodes, $F(1, 78.57) = 11.24$, $p = .001$, 95% CI [2.53 to 9.66], such that for the TD group, faces elicited a larger SPN than arrows, whereas for the ASD group arrows elicited a larger SPN than faces.

Nc. Visual inspection of our waveforms in *Figure 1* suggested a potential difference between groups in anticipation of face stimuli in a middle latency negative component (similar to an Nc) that occurred about 400 ms after the stimulus that signaled the choice of the participant in the guessing game. The Nc is traditionally thought to reflect attention and salience in frontal and central midline electrodes, and has previously been described as a response to a presented stimulus [47,48]. Our waveforms suggest an *anticipatory* Nc that occurred prior to the onset of face stimuli, but after children made their response. To investigate this possibility, we conducted a 2 (Group) ×2 (Familiarity) ×3 (Electrode) ANOVA for face stimuli between −1700 and −1550 ms (before the reward stimulus onset) in electrodes Fz, FCz, and Cz. Children's responses via button pad occur at −2000 ms—suggesting that this component occurred around 300 to 450 ms after the response. This time-frame (300 to 450 ms after response) is consistent with the time course of the Nc in previous investigations [47]. The ANOVA revealed a marginally significant effect of electrode, $F(2, 52.47) = 3.10$, $p = .053$. However, Tukey HSD follow-up tests did not reveal any significant differences between electrode pairs. We found a significant main effect of group, $F(1, 26.06) = 4.91$, $p = .035$, 95% CI [2.50 to 10.81], such that the face stimulus elicited a larger Nc component for TD children compared to children with ASD. No significant effects of familiarity were found, $F(1, 25.66) = 1.8$, *n.s*. We re-ran the ANOVA collapsed across familiarity and our significant effects remained. Grand averages for both groups for the face condition are seen in *Figure 3*.

Brain-Behavior Correlations

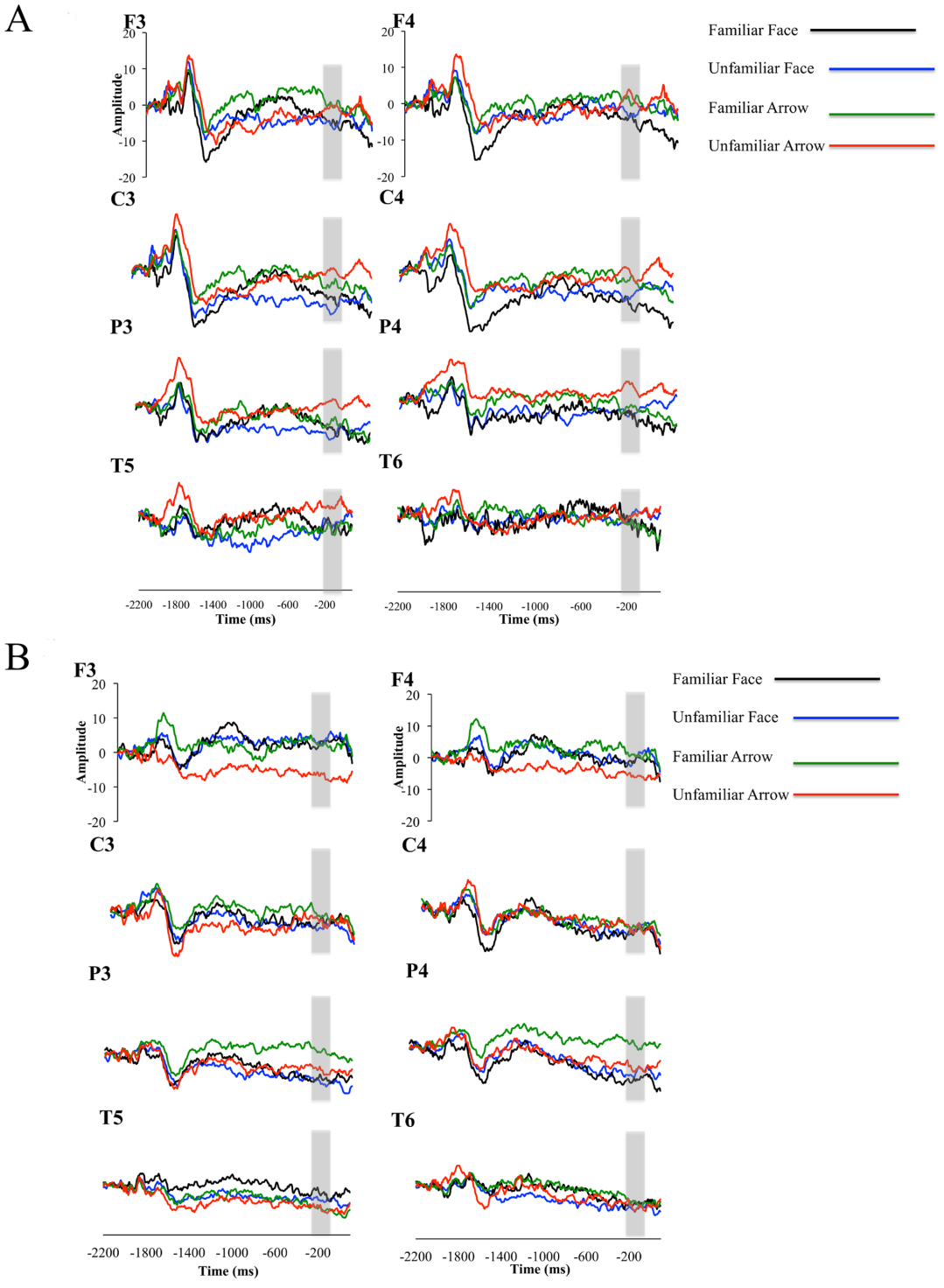
We also investigated the relationship between brain activity and behavioral measures of ASD. Specifically, we asked whether magnitude of autism symptoms in the ASD group, as measured by the SRS-2, could predict the magnitude of SPN ERP response in the face condition (collapsed across familiarity). We found a significant correlation between T-scores on the SRS-2 and magnitude of SPN in response to faces, such that children with lower T-scores (and thus less severe social impairments as reported by caregivers), showed larger SPNs in response to faces, $F(1, 12) = 6.95$, $p = .021$, Cohen's $f^2 = .577$. *Figure 4* shows a scatterplot of SRS-2 scores and amplitude in the face condition. However, it is can be noted that one subject elicited a particularly large SPN response, and thus may be considered an outlier, and when this subject was removed, the correlation no longer reached statistical significance, $F(1,11) = 1.5$, *n.s*.

Discussion

ERP

SPN. The current study suggests that there is not a significant difference in anticipation of a familiar versus an unfamiliar face for either children with ASD or their TD peers. However, TD children showed differences between conditions such that familiar faces elicited larger SPN compared to either of the arrow conditions, whereas unfamiliar faces were numerically larger (but not significantly different from) either arrow condition. This suggests that for TD children between the ages of 6–11 years old, familiar faces elicit a larger reward anticipation response compared to non-face stimuli. For children with ASD, we did not find any significant differences between conditions. Because we did not find the expected familiarity differences, we also explored whether the use of one repeated stimulus in each block would lead to habituation effects in either or both groups. We found a marginal effect of time, such that the first half of trials in each block elicited larger SPN responses than the second half, regardless of stimulus type or group. This suggests that although there is likely some habituation in the SPN response to a large number of repetitions of a single stimulus, it does not differ between groups or social versus nonsocial stimuli. Thus, it is unlikely that differences in the SPN response observed between groups are due to differences in how children with and without ASD habituate to stimuli, although habituation effects may explain the lack of familiarity effects in the present study.

Our results differ from several previous investigations [13,17,18,22,24,25]. Key differences in our task compared to previous studies may explain this. Whereas previous studies have utilized passive viewing tasks, or tasks in which participants attend directly to images and respond to a target stimulus, the current study was designed such that pictures of faces (and scrambled versions of those images) were incidental to the task. In other words, participants did not need to attend to the face or arrow


A
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Time (ms)
Familiar Face
Unfamiliar Face
Familiar Arrow
Unfamiliar Arrow
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C4
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Time (ms)
Familiar Face
Unfamiliar Face
Familiar Arrow
Unfamiliar Arrow

Figure 1. Grand averaged waveforms for the Stimulus Preceding Negativity (SPN). (A) Grand averaged waveforms for TD children from the Stimulus Preceding Negativity (SPN) prior to familiar faces, unfamiliar faces, familiar arrows, and unfamiliar arrows. (B) Grand averaged waveforms for children with ASD from the Stimulus Preceding Negativity (SPN) in ancitipation of familiar faces, unfamiliar faces, familiar arrows, and unfamiliar arrows. The area between −210 and −10 ms, used for statistical analysis, is highlighted with a grey box.
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stimulus in order to gain information about whether their responses were ''correct'' or ''incorrect.'' Although this paradigm allowed us to directly control for physical stimulus properties and tangibility between conditions, it is difficult to directly compare our results with those found in previous studies.

In previous research, one group of authors found that children with ASD showed differential neural activity in response to familiar versus unfamiliar faces [13], and another group of authors found that a small subset of children with ASD began to show differential neural activity in response to familiar face after social skills training [17]. One potential reason for this discrepancy in previous literature may be due to stimulus differences between studies. Previous studies used multiple familiar and unfamiliar faces (rather than just one familiar and one unfamiliar face) [13]. With the exception of [17], which investigated neural activation after social skills training, Pierce and Redcay [13] was the only study to find differences between familiar and unfamiliar faces in children with ASD. One possibility is that children with ASD are more likely to differentiate between familiar versus unfamiliar faces when viewing multiple exemplars from each category. The finding in the current study that there was a marginal tendency for children across groups to habituate to the repeated presentation of a single stimulus supports this idea. Previous research suggests the fusiform face area (FFA) may be involved in determining the identity of individual faces [49]—thus, presenting multiple different faces may activate the FFA to a greater degree than presentations of single faces. It is possible that in previous research, presentation of multiple different familiar faces was adequate to normalize brain responses to faces in ASD. This is an interesting direction for future research, and future studies may wish to compare within subjects whether children with ASD elicit differential neural activity when viewing multiple faces versus one face.

Importantly, although we did not find a main effect of familiarity or interactions between group and familiarity, when we collapsed across familiarity for both groups, we found a group by condition interaction such that TD children showed a larger SPN component in response to faces versus arrows, while children with ASD demonstrated the opposite pattern. This replicates our previous work [29] with a novel group of participants and novel stimuli. These results are in line with the social motivation hypothesis—that TD children are more rewarded by social versus nonsocial stimuli, while children with ASD do not demonstrate this pattern.

Our results are consistent with previous studies that examined reward anticipation in these populations [27,28], in that we found TD children and those with ASD elicited a statistically equivalent SPN response to *non*social feedback. Similarly, while the current study investigated reward anticipation of social versus nonsocial stimuli, and other ERP studies of the reward system in ASD have focused on reward processing of monetary stimuli only [30,31], our results are consistent with these investigations insofar as we found that children with ASD elicit similar reward anticipation to their TD peers for nonsocial stimuli. Our results differ with regards to TD children, however, because we found that TD children elicited a larger SPN response to social versus nonsocial stimuli, whereas [28] found the opposite pattern. Our results also differ from behavioral measures of response inhibition for social versus monetary rewards [26], as those authors found that both TD children and those with ASD have increased performance for all reward types. However, the authors also found no difference in performance for familiar versus unfamiliar social stimuli in either group, which is consistent with the current findings [26].

One important difference between our current and previous findings is that current pairwise comparisons did not reveal a significant difference between the ASD and TD [29] groups for face stimuli. That is, while TD children had a significantly larger SPN to faces versus non-faces, there was not a significant difference between TD children and those with ASD for the face stimuli. This differs from our previous findings, where in addition to differences between face and non-face stimuli, TD children also had larger SPN responses to faces than children with ASD. One potential reason for this is stimulus variation. In our previous study, children saw a variety of unfamiliar faces, whereas in the current study they saw just one unfamiliar and one familiar face. When comparing our current results to our previous findings, TD children have a smaller SPN response in the face condition, while children with ASD have a larger SPN response in the face condition. In contrast, for the arrow condition, both groups are largely unchanged between studies. This raises the possibility that while TD children show larger SPN responses when viewing multiple faces, children with ASD demonstrate the opposite pattern. The current study was not designed to investigate this, and thus these possibilities remain conjecture, but future studies could manipulate the number of faces in the stimulus set, and measure resulting effects on the SPN.

Nc. We found an Nc-like component after participant's response, but before feedback. This component differentiated TD children from those with ASD. The component occurred at about the time (~400 msec after the participant's button press) and had a similar scalp distribution (prominent at frontal electrode sites) as the Nc component that has typically been investigated in response to visual stimuli [50]. These findings provide novel information about the Nc component—in effect that the Nc can act as an anticipatory waveform. Previous findings have examined the Nc as a component related to salience and attention in response to a stimulus in infants and young children (e.g. [25]). Our findings, however, suggest that the Nc is also sensitive to anticipation of upcoming stimuli and/or the testing context (i.e., blocks of familiar and unfamiliar faces vs. arrows), and differentiates between diagnostic groups. It is important to note, however, that the current study was not designed to investigate anticipatory effects of the Nc component, as most studies on the Nc do not involve overt responses by the participant. Thus, while our results have interesting implications for the Nc, it is necessary for future studies to look directly at the effect of anticipation on the Nc between children with and without ASD.

Brain and Behavior Correlations

The present results provide evidence that magnitude of reward anticipation response to faces in children with ASD can be predicted by reported levels of social impairments (as measured by the social responsiveness scales). This provides evidence that is in line with the social motivation hypothesis, insofar as children with lower levels of reported social impairments showed larger reward anticipation responses to faces compared to children with higher

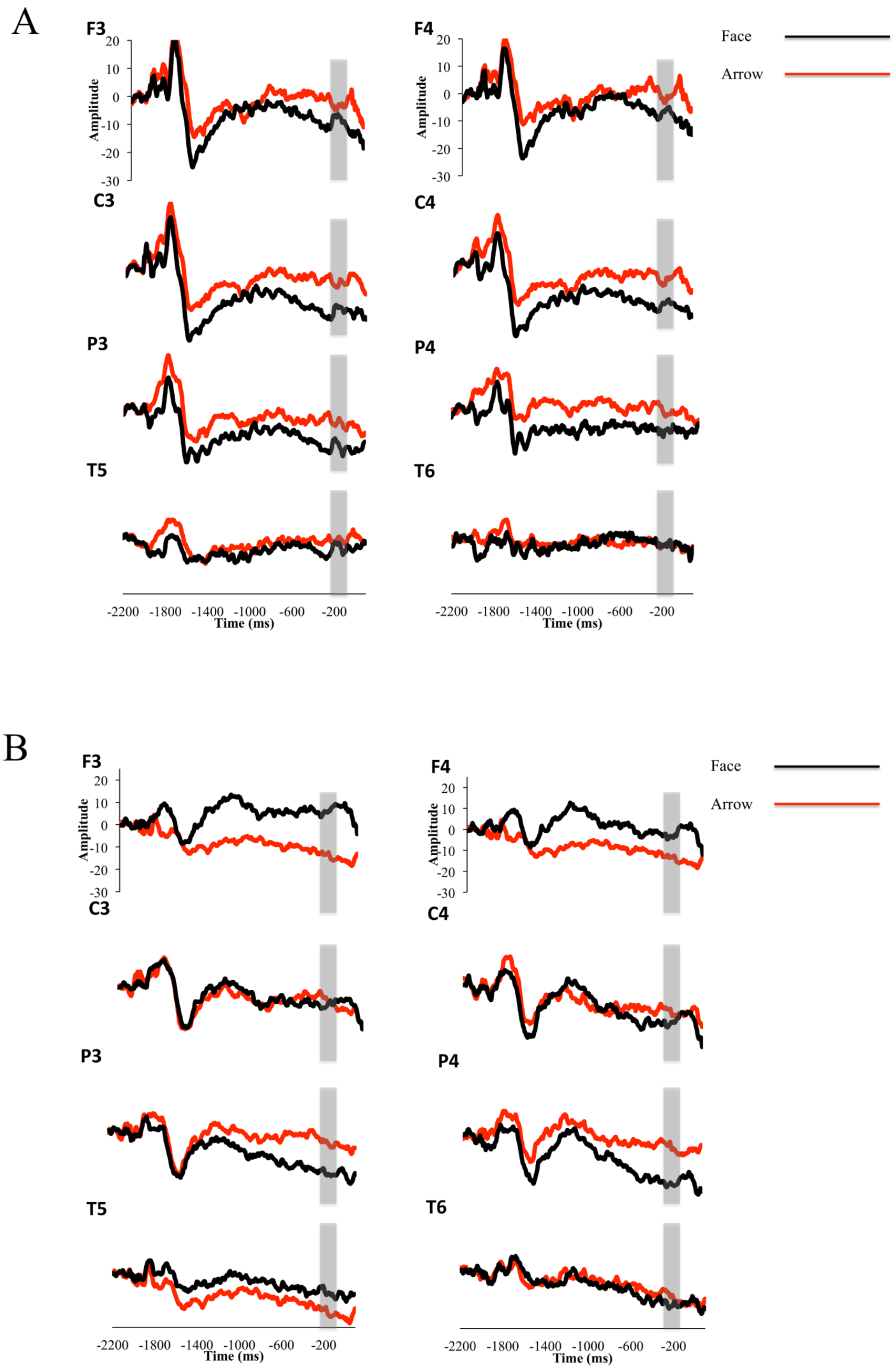

Figure 2. Grand averaged waveforms collapsed across familiarity. (A) Grand averaged waveforms for TD children from the Stimulus Preceding Negativity (SPN) prior to faces and arrows (collapsed across familiarity). The area between −210 and −10 ms, used for statistical analysis, is highlighted with a grey box. (B) Grand averaged waveforms for children with ASD from the Stimulus Preceding Negativity (SPN) prior to faces and arrows (collapsed across familiarity). The area between −210 and −10 ms, used for statistical analysis, is highlighted with a grey box.
doi:10.1371/journal.pone.0106667.g002

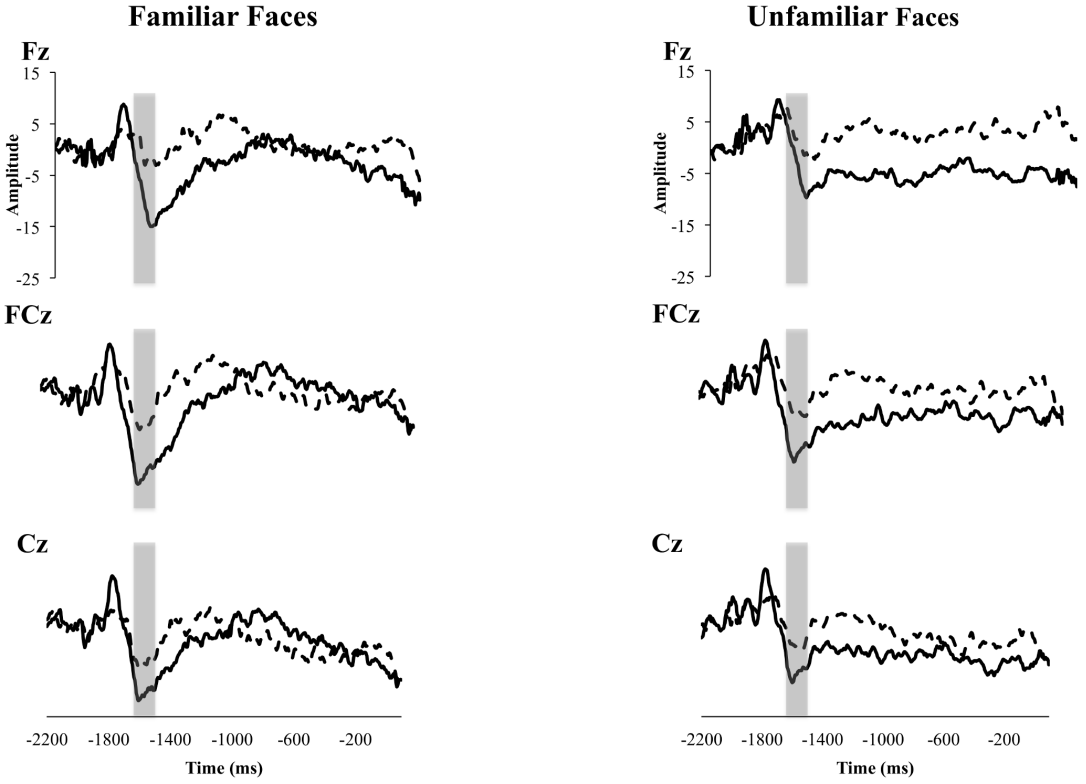

Figure 3. Grand averaged waveforms for both groups from the Nc component prior to familiar and unfamiliar faces. TD children are represented with a solid line, and children with ASD with a dashed line. The area between −1700 and −1550 ms, used for statistical analyses, is highlighted with a grey box.
doi:10.1371/journal.pone.0106667.g003

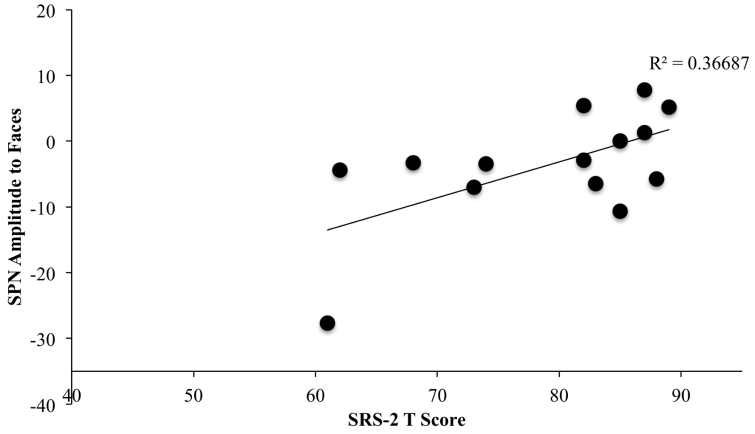

Figure 4. Scatter plot of SPN amplitude to faces (collapsed across familiarity) by SRS-2 T-score for children with ASD. Higher SRS-2 T-scores indicate more severe social impairments. As the SPN is a negative ERP component, more negative values indicate a larger response. Note that one participant had a particularly large SPN response and thus may be considered an outlier; and when this subject was removed, the correlation no longer reached statistical significance, $F(1,11) = 1.5$, *ns*.
doi:10.1371/journal.pone.0106667.g004

levels of reported impairments. We note, however, that this effect may have been driven by a single participant in the current study, so it is not advisable to draw large-scale conclusions from this analysis. Future studies should look into these types of correlations with a larger sample of children with ASD.

The current study has some limitations that should be noted. First, our sample size ($N = 14$ in each of the TD and ASD groups) is relatively small (although within the estimates provided by our power analysis). This makes it difficult to draw broad and generalized inferences. Further, we did not obtain information about treatment history from participants. Given previous findings about the effect of social skills training on face processing [17], as well as parent attitudes towards reward contingencies on behavioral sensitivity to rewards [26], this limitation should be taken into consideration when interpreting the current findings.

Conclusions and Broader Implications

We examined reward anticipation of incidental familiar versus unfamiliar faces and scrambled versions of those images in children with and without ASD. Although we did not find evidence for an effect of familiar versus unfamiliar faces in either group, the current study adds to the body of literature supporting the social motivation hypothesis, and replicates previous findings using different stimuli and participants. The current study also provides evidence that magnitude of reward anticipation to faces is significantly correlated with levels of parent-reported social impairments. This suggests that our paradigm is sensitive to social impairments as measured by questionnaires, which provides evidence that we are accurately capturing social motivation in children with ASD.

Our findings provide interesting implications for future work on the Nc-like component, which we observed as a measure of anticipation in children, and suggest that for TD children, anticipation of face stimuli elicits a larger Nc-like component than for children with ASD. While our study was not designed to directly address this question, we feel it is an important future direction. The current study also suggests intriguing areas for future research in regards to whether children with and without ASD are differentially affected by viewing one versus multiple unfamiliar faces. The current study and previous work suggest that perhaps TD children show larger reward anticipation for multiple unfamiliar faces, while children with ASD show the opposite pattern. However, because the current and previous studies utilized different participants and stimuli, we suggest this as an important future direction.

The current study suggests that social motivation deficits in ASD are not ameliorated by viewing familiar faces when face stimuli are incidental to the task. Future research is necessary to determine whether task specifications or number of faces within a stimulus set affects these findings. The current study provides further evidence for the social motivation hypothesis, and suggests that levels of social impairment in ASD are correlated with magnitude of reward anticipation to faces. This paradigm could be utilized as a biomarker of social motivation, and could be used before and after behavioral or pharmacological interventions designed to improve social motivation. In this way, individual children's levels of reward anticipation to faces could be tracked over time along with behavioral levels of social impairment, in order to see changes throughout the course of intervention.

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Author Contributions

Conceived and designed the experiments: KKMS LJC. Performed the experiments: KKMS. Analyzed the data: KKMS. Contributed reagents/materials/analysis tools: KKMS LJC. Contributed to the writing of the manuscript: KKMS LJC.

References

1. Mundy P, Sigman M, Ungerer J, Sherman T (1986) Defining the social deficits of autism: the contribution of non-verbal communication measures. J Child Psychol Psychiatry 27: 657–669. doi: 10.1111/j.1469-7610.1986.tb00190.x.
2. Walters AS, Barrett RP, Feinstein C (1990) Social relatedness and autism: current research, issues, directions. Res Dev Disabil 11: 303–326. doi: 10.1016/0891-4222(90)90015-Z.
3. Charman T, Swettenham J, Baron-Cohen S, Cox A, Baird G, et al. (1998) An experimental investigation of social-cognitive abilities in infants with autism: Clinical implications. Infant Ment Health J 19: 260–275. doi: 10.1002/(SICI)1097-0355(199822)19:2<260::AID-IMHJ12>3.0.CO;2-W.
4. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT (2012) The social motivation theory of autism. Trends Cogn Sci 16: 231–239. doi:10.1016/j.tics.2012.02.007.
5. Dawson G (2008) Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. Dev Psychopathol 20: 775–803. doi:10.1017/S0954579408000370.
6. Dawson G, Carver L, Meltzoff AN, Panagiotides H, McPartland J, et al. (2002) Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. Child Dev 73: 700–717. doi: 10.1111/1467-8624.00433.
7. Dawson G, Webb SJ, Wijsman E, Schellenberg G, Estes A, et al. (2005) Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: implications for a model of abnormal development of social brain circuitry in autism. Dev Psychopathol 17: 679–697. doi:10.1017/S0954579405050327.
8. Grelotti D, Gauthier I, Schultz RT (2002) Social Interest and the Development of Cortical Face Specialization: What Autism Teaches Us About Face Processing. Dev Psychobiol 40: 213–225. doi:10.1002/dev.10028.
9. Schultz RT (2005) Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int J Dev Neurosci 23: 125–141. doi:10.1016/j.ijdevneu.2004.12.012.
10. Sigman M, Mundy P (1989) Social attachments in autistic children. J Am Acad Child Adolesc Psychiatry 28: 74–81. doi: 10.1097/00004583-198901000-00014.
11. Sigman M, Ungerer JA (1984) Attachment behaviors in autistic children. J Autism Dev Disord 14: 231–244.
12. Rutgers AH, van Ijzendoorn MH, Bakermans-Kranenburg MJ, Swinkels SHN, van Daalen E, et al. (2007) Autism, attachment and parenting: a comparison of children with autism spectrum disorder, mental retardation, language disorder, and non-clinical children. J Abnorm Child Psychol 35: 859–870. doi:10.1007/s10802-007-9139-y.
13. Pierce K, Redcay E (2008) Fusiform function in children with an autism spectrum disorder is a matter of "who". Biol Psychiatry 64: 552–560. doi:10.1016/j.biopsych.2008.05.013.
14. McPartland J, Dawson G, Webb SJ, Panagiotides H, Carver LJ (2004) Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. J Child Psychol Psychiatry 45: 1235–1245. doi:10.1111/j.1469-7610.2004.00318.x.
15. Dawson G, Webb SJ, Carver L, Panagiotides H, McPartland J (2004) Young children with autism show atypical brain responses to fearful versus neutral facial expressions of emotion. Dev Sci 7: 340–359. doi: 10.1111/j.1467-7687.2004.00352.x.
16. Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, et al. (2000) Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch Gen Psychiatry 57: 331–340. doi: 10.1001/archpsyc.57.4.331.
17. Gunji A, Goto T, Kita Y, Sakuma R, Kokubo N, et al. (2013) Facial identity recognition in children with autism spectrum disorders revealed by P300 analysis: a preliminary study. Brain Dev 35: 293–298. doi:10.1016/j.braindev.2012.12.008.
18. Gunji A, Inagaki M, Inoue Y, Takeshima Y, Kaga M (2009) Event-related potentials of self-face recognition in children with pervasive developmental disorders. Brain Dev 31: 139–147. doi:10.1016/j.braindev.2008.04.011.

19. Key APF, Stone WL (2012) Processing of novel and familiar faces in infants at average and high risk for autism. Dev Cogn Neurosci 2: 244–255. doi:10.1016/j.dcn.2011.12.003.
20. Kylliäinen A, Wallace S, Coutanche MN, Leppänen JM, Cusack J, et al. (2012) Affective-motivational brain responses to direct gaze in children with autism spectrum disorder. J Child Psychol Psychiatry 53: 790–797. doi:10.1111/j.1469-7610.2011.02522.x.
21. Luyster RJ, Wagner JB, Vogel-Farley V, Tager-Flusberg H, Nelson CA (2011) Neural correlates of familiar and unfamiliar face processing in infants at risk for autism spectrum disorders. Brain Topogr 24: 220–228. doi:10.1007/s10548-011-0176-z.
22. Pierce K, Haist F, Sedaghat F, Courchesne E (2004) The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain 127: 2703–2716. doi:10.1093/brain/awh289.
23. Webb SJ, Jones EJH, Merkle K, Murias M, Greenson J, et al. (2010) Response to familiar faces, newly familiar faces, and novel faces as assessed by ERPs is intact in adults with autism spectrum disorders. Int J Psychophysiol 77: 106–117. doi:10.1016/j.ijpsycho.2010.04.011.
24. Webb SJ, Jones EJH, Merkle K, Venema K, Greenson J, et al. (2011) Developmental change in the ERP responses to familiar faces in toddlers with autism spectrum disorders versus typical development. Child Dev 82: 1868–1886. doi:10.1111/j.1467-8624.2011.01656.x.
25. Dawson G, Carver L, Meltzoff AN, Panagiotides H, McPartland J, et al. (2002) Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. Child Dev 73: 700–717. doi: 10.1111/1467-8624.00433
26. Pankert A, Pankert K, Herpertz-Dahlmann B, Konrad K, Kohls G (2014) Responsivity to familiar versus unfamiliar social reward in children with autism. J Neural Transm. doi:10.1007/s00702-014-1210-6.
27. Groen Y, Wijers AA, Mulder LJM, Waggeveld B, Minderaa RB, et al. (2008) Error and feedback processing in children with ADHD and children with Autistic Spectrum Disorder: an EEG event-related potential study. Clin Neurophysiol 119: 2476–2493. doi:10.1016/j.clinph.2008.08.004.
28. Kohls G, Peltzer J, Schulte-Rüther M, Kamp-Becker I, Remschmidt H, et al. (2011) Atypical brain responses to reward cues in autism as revealed by event-related potentials. J Autism Dev Disord 41: 1523–1533. doi:10.1007/s10803-011-1177-1.
29. Stavropoulos KKM, Carver LJ (2014) Reward anticipation and processing of social versus nonsocial stimuli in children with and without autism spectrum disorders. J Child Psychol Psychiatry. doi:10.1111/jcpp.12270.
30. McPartland JC, Crowley MJ, Perszyk DR, Mukerji CE, Naples AJ, et al. (2012) Preserved reward outcome processing in ASD as revealed by event-related potentials. J Neurodev Disord 4: 16. doi:10.1186/1866-1955-4-16.
31. Larson MJ, South M, Krauskopf E, Clawson A, Crowley MJ (2011) Feedback and reward processing in high-functioning autism. Psychiatry Res 187: 198–203. doi:10.1016/j.psychres.2010.11.006.
32. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW (2012) Reward circuitry function in autism during face anticipation and outcomes. J Autism Dev Disord 42: 147–160. doi:10.1007/s10803-011-1221-1.
33. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY (2010) Reward processing in autism. Autism Res 3: 53–67. doi:10.1002/aur.122.
34. Luyster RJ, Wagner JB, Vogel-Farley V, Tager-Flusberg H, Nelson CA (2011) Neural correlates of familiar and unfamiliar face processing in infants at risk for autism spectrum disorders. Brain Topogr 24: 220–228. doi:10.1007/s10548-011-0176-z.
35. Pierce K, Müller RA, Ambrose J, Allen G, Courchesne E (2001) Face processing occurs outside the fusiform "face area" in autism: evidence from functional MRI. Brain 124: 2059–2073. doi: 10.1093/brain/124.10.2059.
36. Ohgami Y, Kotani Y, Tsukamoto T, Omura K, Inoue Y, et al. (2006) Effects of monetary reward and punishment on stimulus-preceding negativity. Psychophysiology 43: 227–236. doi:10.1111/j.1469-8986.2006.00396.x.
37. Stavropoulos KKM, Carver LJ (2013) Reward sensitivity to faces versus objects in children: an ERP study. Soc Cogn Affect Neurosci. doi:10.1093/scan/nst149.
38. Brunia CHM, Hackley SA, van Boxtel GJM, Kotani Y, Ohgami Y (2011) Waiting to perceive: reward or punishment? Clin Neurophysiol 122: 858–868. doi:10.1016/j.clinph.2010.12.039.
39. Boxtel GJM Van, Böcker KBE (2004) Cortical Measures of Anticipation. J Psychophysiol 18: 61–76. doi:10.1027/0269-8803.18.2.
40. Wechsler D (1999) Wechsler Abbreviated Scale of Intelligence. San Antonio. TX: Pearson.
41. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K (2012) ADOS-2: autism diagnostic observation schedule. Los Angeles: Western Psychological Services.
42. Constantino JN, Gruber CP (2012) Social Responsiveness Scale, Second Edition. Los Angeles: Western Psychological Services.
43. Kotani Y, Kishida S, Hiraku S, Suda K, Ishii M, et al. (2003) Effects of information and reward on stimulus-preceding negativity prior to feedback stimuli. Psychophysiology 40: 818–826. doi: 10.1111/1469-8986.00082.
44. Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, et al. (2009) The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Res 168: 242–249. doi:10.1016/j.psychres.2008.05.006.
45. Lopez-Calderon J, Luck SJ (2014) ERPLAB: an open-source toolbox for the analysis of event-related potentials. Front Hum Neurosci 8: 1–14. doi:10.3389/fnhum.2014.00213.
46. Kotani Y, Hiraku S, Suda K, Aihara Y (2001) Effect of positive and negative emotion on 10.1111/j.1467-7687.2005.00452.x.
47. Courchesne E (1978) Neurophysiological correlates of cognitive development: Changes in long-latency event-related potentials from childhood to adulthood. Electroencephalogr Clin Neurophysiol 45: 468–482. doi: 10.1016/0013-4694(78)90291-2.
48. Webb SJ, Long JD, Nelson CA (2005) A longitudinal investigation of visual event-related potentials in the first year of life. Dev Sci 8: 605–616. doi: 10.1111/j.1467-7687.2005.00452.x.
49. Haxby JV, Hoffman EA, Gobbini MI (2000) The distributed human neural system for face perception. Trends Cogn Sci 4: 223–233. doi:10.1111/j.1467-7687.2005.00452.x.
50. De Haan M, Johnson MH, Halit H (2003) Development of face-sensitive event-related potentials during infancy: a review. Int J Psychophysiol 51: 45–58. doi:10.1016/S0167-8760(03)00152-1.

Chapter 3, in full, is a reprint of the material as it will appear in Effect of familiarity on reward anticipation in children with and without autism spectrum disorders in *PLOS ONE*. Savropoulos, Katherine K. M., Carver, Leslie J. (2014). The dissertation author was the primary investigator and author of this paper. Permission was obtained from PLOS ONE.

Chapter 4

Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention

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Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention

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Background and scope: The social motivation hypothesis (SMH) suggests that individuals with autism spectrum disorders (ASD) are less intrinsically rewarded by social stimuli than their neurotypical peers. This difference in social motivation has been posited as a factor contributing to social deficits in ASD. Social motivation is thought to involve the neuropeptide oxytocin. Here, we review the evidence for oxytocin effects in ASD, and discuss its potential role in one important social cognitive behavior. **Methods:** Systematic searches were conducted using the PsychINFO and MEDLINE databases and the search terms 'oxytocin' and 'autism'; the same databases were used for separate searches for 'joint attention', 'intervention', and 'autism', using the same inclusion criteria as an earlier 2011 review but updating it for the period 2010 to October 2012. **Findings:** Several studies suggest that giving oxytocin to both individuals with ASD and neurotypical individuals can enhance performance on social cognitive tasks. Studies that have attempted to intervene in joint attention in ASD suggest that social motivation may be a particular obstacle to lasting effects. **Conclusions:** The review of the evidence for the SMH suggests a potential role for oxytocin in social motivation deficits in ASD. Because of its importance for later communicative and social development, the focus here is on implications of oxytocin and social motivation in the development of and interventions in joint attention. Joint attention is a central impairment in ASD, and as a result is the focus of several behavioral interventions. In describing this previous research on joint attention interventions in ASD, we pay particular attention to problems encountered in such studies, and propose ways that oxytocin may facilitate behavioral intervention in this area. For future research, integrating behavioral and pharmacological interventions (oxytocin administration) would be a worthwhile experimental direction to improve understanding of the role of oxytocin in ASD and help optimize outcomes for children with ASD. **Keywords:** Autism spectrum disorders, behavioral interventions, social motivation hypothesis.

Introduction

Atypicalities in social behavior and social cognition are a central characteristic of autism spectrum disorders (ASD). Although it is clear that individuals with autism are impaired in multiple aspects of social behavior, the basis for these concerns has been the subject of debate. Effective strategies for intervening in social deficits in ASD can be improved by an understanding of the mechanisms behind the deficits, as well as effective behavioral treatments. Ideally, treatments would integrate knowledge that has proven effective in the lab, and our growing understanding of the neural basis of ASD.

The social motivation hypothesis (SMH) (Dawson, 2008; Dawson & Bernier, 2007; Dawson et al., 2002, 2005; Grelotti, Gauthier & Schultz, 2002) has been proposed as an explanation for social deficits in ASD. According to the SMH, children with ASD lack motivation to engage in social activities (joint attention, eye gaze) because they find these activities less rewarding than neurotypical individuals do. Brain reward circuits in neurotypical individuals are activated by social rewards such as faces (Kampe, Frith, Dolan & Frith, 2001; Vrtička, Andersson, Grandjean, Sander & Vuilleumier, 2008). In contrast, in ASD, reward centers are less activated for social stimuli than in controls (Kohls et al., 2012; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack & Bookheimer, 2010). It is not yet clear whether reward deficits in ASD are specific to social rewards, or reflect a general reward processing deficit (Dichter, Richey, Rittenberg, Sabatino & Bodfish, 2012; Dichter, Felder, et al., 2012). The SMH is the first theory to suggest that the lack of social motivation itself leads to later autism symptomology including abnormal brain responses to faces (McPartland, Dawson, Webb, Panagiotides & Carver, 2004), language and communication problems (Charman, 2003), and impaired joint attention ability (Charman, 2003; Mundy, 1995; Mundy, Sigman, Ungerer & Sherman, 1986), rather than that abnormal social brain function precedes and causes the symptoms of autism.

If there is a deficit in social motivation in ASD, a likely candidate mechanism is abnormality in the function of the neuropeptide oxytocin. Oxytocin has been implicated in several aspects of social behavior in animals (e.g. Liu & Wang, 2003) and humans (e.g. Guastella, Mitchell & Dadds, 2008), and likely plays a role in social reward systems (e.g. Baskerville & Douglas, 2010). Here, we examine the literature on the SMH in ASD, and the possible role of oxytocin in

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it. As a 'test case', we examine the putative role of oxytocin and social motivation in a specific social cognitive behavior, joint attention. Impairments in joint attention are one of the earliest and clearest signs of ASD. It is important to note that while this review will focus specifically on joint attention, there are many other problems in ASD that are relevant to social motivation. In a recent review, Dawson, Bernier and Ring (2012) discussed the role of oxytocin in a different facet of social behavior: social orienting.

First, we will describe the role of oxytocin in social motivation. Next, we will review the recent research on oxytocin levels and genetics in individuals with ASD. We next describe the effect of oxytocin administration in people with ASD and typical development. We will discuss how social motivation may contribute to the development of joint attention in both neurotypical individuals and those with ASD. Next, we describe behavioral interventions that have attempted to improve joint attention in individuals with ASD. This review will discuss behavioral interventions insofar as they relate to the SMH and the potential role of oxytocin. It is not written to evaluate clinical practice, but rather to review interventions that have attempted to improve joint attention, relate them to the SMH and oxytocin, and discuss implications of oxytocin findings for interventions.

Method

Systematic searches were conducted using the PsychINFO and MEDLINE databases and the search terms 'oxytocin' and 'autism'. The search was limited to empirical peer reviewed articles on human populations that were written in English. Forty studies fit these criteria. We examined the reference sections of the remaining studies to check for papers missed by the original search. Of these, we included ten papers that administered oxytocin to humans and measured social behaviors as a direct outcome. Papers that administered oxytocin but did not measure social behaviors (e.g. Kirsch et al., 2005) were not included.

For our discussion of joint attention and interventions targeting joint attention, searches were conducted using PsychINFO and MEDLINE with the search terms 'joint attention', 'intervention', and 'autism'. The search was limited to empirical peer-reviewed articles written in English. 76 peer reviewed articles remained for consideration. White et al. (2011) published an excellent and comprehensive review summarizing behavioral interventions that focused on joint attention in ASD up through 2010. The authors searched in multiple online databases, and used the following criteria for inclusion: papers must utilize an intervention for joint attention, use joint attention as a dependent variable, utilize experimental control, and have at least one child with ASD in the study. The authors found 27 articles that met the above criteria for review. The current review utilized the same inclusion criteria as White et al. (2011). To avoid redundancy with White et al. (2011), we included studies from 2010 to October 2012 (the time of manuscript submission), as well as studies from White et al. (2011) that were particularly relevant to the SMH and joint attention.

Oxytocin's role in social motivation

Although this review will focus on oxytocin and its role in social motivation, it is important to note that oxytocin does not work alone to modulate social behaviors. Gordon, Martin, Feldman and Leckman (2011) reviewed oxytocin's relation with the neuropeptide arginine vasopressin, and how both interact with sex hormones and the hypothalamic-pituitary-gonadal axis to affect sexual, maternal, and adult bonds. For the purposes of this review, we will focus on the neurochemical oxytocin and its interactions with dopamine in the putative social motivation system.

Dopamine is the primary neurotransmitter involved in the reward system (Schultz, 1998). Functional magnetic resonance imaging (fMRI) research has shown that areas involved in the dopamine reward pathway (e.g., the ventral striatum) are activated in neurotypical adults when pictures of faces are shown (Cacioppo, Norris, Decety, Montelone & Nusbaum, 2009). This suggests that the dopamine reward circuit responds to social stimuli. This study also measured brain activity of lonely participants compared to non-lonely participants, and found that lonely individuals show less activity of the ventral striatum reward pathway in response to faces compared to non-lonely individuals. Thus, social stimuli might be more rewarding for some people than for others. For example, if people who find social stimuli less rewarding may be more likely to become lonely (Cacioppo et al., 2009). Alternatively, of course, it may be that spending a great deal of time alone leads to a reduction in oxytocin levels. However, if low oxytocin levels lead to social isolation, this may explain one aspect of social function in ASD. Perhaps individuals with ASD find social stimuli less rewarding (because of differences in the reward pathways in the brain), and therefore are not motivated to seek out those interactions. This failure to find social stimuli rewarding could in turn contribute to symptoms of autism.

Bell, Nicholson, Mulder, Luty and Joyce (2006), measured plasma oxytocin levels of individuals with different personality traits. People with low levels of reward dependence, as assessed using the Temperament and Character Inventory, also had low levels of oxytocin. Another study found similar results for reward dependence, and found that women who were more likely to express and share emotions with friends showed higher oxytocin levels (Tops, Van Peer, Korf, Wijers & Tucker, 2007). These studies support the hypothesis that oxytocin plays an important role in social behaviors, and that oxytocin

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is related to variations in personal characteristics related to social rewards.

The dopamine reward system is activated in response to eye contact (Kampe et al., 2001) and smiling supportive faces (Vrtička et al., 2008). However, research involving nonhuman mammals has shown that dopamine alone might not account for social motivation. Oxytocin might be involved in social behavior and rewards via the mesocorticolimbic dopamine circuit (Dawson, 2008; Insel & Frenald, 2004; Neuhaus, Beauchaine & Bernier, 2010). Oxytocin is a peptide synthesized in the hypothalamus and released into the blood stream via the posterior pituitary (Insel, O'Brien & Leckman, 1999). Neuropeptides such as oxytocin might modulate the dopamine reward pathway when social interactions occur (Baskerville & Douglas, 2010; Young, Liu & Wang, 2008). In female prairie voles, blocking oxytocin receptors in the nucleus accumbens prevented partner preference induced by dopamine agonists. Conversely, blocking dopamine receptors in the nucleus accumbens prevented partner preference induced by oxytocin agonists (Liu & Wang, 2003). The animal literature suggests that an association between dopamine and oxytocin could also exist in humans.

There is an extensive literature on oxytocin in animals (Liu & Wang, 2003; Ferguson, Young, Hearn, Insel & Winslow, 2000; for a review see Modi & Young, 2012). As these studies examine oxytocin function in animals, they do not directly inform the question of how oxytocin dysfunction may be related to ASD. Thus, we will not discuss them further here. In addition, although this review will discuss oxytocin as it is relevant to social dysfunction in ASD, others have written excellent reviews on oxytocin and other aspects of social behavior, including parenting and romantic bonds (e.g. Feldman, 2012). This review will focus on oxytocin and its relationship to the reward system, but it is important to note that other neuropeptides, including vasopressin, have also gained attention as potentially important for social behavior in humans. For an in-depth review of studies that have administered either oxytocin or vasopressin and measured various aspects of social behavior, see Zink and Meyer-Lindenberg (2012).

We will next consider evidence that supports the hypothesis that oxytocin is deficient or different in individuals with ASD compared to neurotypical individuals.

Evidence for deficient/different oxytocin levels in ASD

Initial papers looking at oxytocin levels in individuals with ASD measured blood plasma levels of oxytocin. In a study of plasma oxytocin levels in children with autism and neurotypical peers, Modahl et al. (1998), found that children with autism had lower oxytocin levels than controls. The relationship between oxytocin levels and social functioning was different for neurotypical children than those with ASD. Neurotypical children who had higher oxytocin levels scored higher on social interaction scales, while children with ASD with higher oxytocin levels were more impaired in social and linguistic development (Modahl et al., 1998). However, plasma levels of oxytocin were measured, which are thought to provide a less direct measure of neuropeptide levels than cerebral spinal fluid (CSF). Furthermore, the ASD and control groups were not matched for verbal or nonverbal measures of IQ, or on measures of daily living, communication, or socialization. The control group scored significantly higher on these measures than the ASD group (Modahl et al., 1998). There was also large variability in oxytocin levels in the sample (e.g. there were children with ASD with high levels of oxytocin, and neurotypical children with low levels of oxytocin).

Individuals with ASD not only may have lower levels of oxytocin, they also show differences in an alternative peptide form of oxytocin (the extended form of oxytocin, oxytocin-X, with a three amino acid extension, Gainer, Lively & Morris, 1995). Oxytocin-X becomes oxytocin through enzymatic activity (Green et al., 2001). Individuals with ASD showed higher levels of oxytocin-X compared to neurotypical individuals, but lower levels of oxytocin, resulting in a large oxytocin-X/oxytocin ratio difference between the two groups (Green et al., 2001). In neurotypical children, oxytocin, but not oxytocin-X was positively associated with age. In contrast, there was a positive association between oxytocin-X and age in the sample of children with ASD. Although these studies are suggestive of a relation between the synthesis of oxytocin from oxytocin-X and ASD, they are very preliminary. Participants from Modahl et al. (1998) were used in this study, and, as described above, ASD participants were not matched with the comparison group on IQ, vocabulary, communication, socialization, and daily living abilities. Furthermore, as these studies used the same participants, one must consider their results as one piece of evidence rather than a replication of findings.

These results suggest that individuals with ASD have differences in the enzymatic activity that converts oxytocin-X to oxytocin in typical individuals, which could be the result of defects in the genes controlling oxytocin synthesis, the oxytocin gene itself, or genes that regulate developmental changes in activity. Although these studies must be interpreted with caution, they provided important preliminary evidence for differences in oxytocin between typical individuals and those with ASD, and have served to motivate later research on this topic.

Genetic studies

There are multiple studies that shed light on potential genetic mechanisms that may be responsi-

ble for the differences in oxytocin in individuals with ASD. Studies have largely focused on two genes, the oxytocin receptor gene (OXTR), and a gene hypothesized to be involved in oxytocin release (CD38) (Ebstein et al., 2009; Lerer et al., 2010; Munesue et al., 2010; Reibold et al., 2011).

Several studies investigating the relation between ASD and OXTR have found correlations between single nucleotide polymorphisms and ASD symptoms (Campbell et al., 2011; Ebstein et al., 2009; Jacob et al., 2007; Lerer et al., 2008; Liu et al., 2010; Walum et al., 2012; Wu et al., 2005; Ylisaukko-oja et al., 2006; Yrigollen et al., 2008; For a review of the relation between single nucleotide polymorphisms of the OXTR and various psychiatric disorders including ASD, depression, and anxiety, see Brüne, 2012). However, several studies that have found relations between ASD and OXTR alleles have not corrected for multiple comparisons, and one that did (e.g. Campbell et al., 2011) found that effects were not maintained after corrections were applied. As has been described by Sullivan (2007), there are risks of false positive significant results in genetic association studies where correction of the significance threshold to account for the number of tests conducted is not applied. Of the papers mentioned above, only Ebstein et al. (2009), Liu et al. (2010), and Yrigollen et al. (2008) adjusted *p*-values for multiple comparisons. Lerer et al. (2008, 2010), used a similar, albeit slightly less conservative technique of correcting for multiple comparisons but accounting for correlations between markers. As Lerer et al. (2010) point out, this technique increases power, but results should nevertheless be interpreted somewhat cautiously. Jacob et al. (2007) does not discuss correction for multiple comparisons, but because the authors only tested two a priori identified single nucleotide polymorphisms, this potential confound is likely not applicable to this study. Similarly, Reibold et al. (2011), examined CD38 expression, and a priori identified single nucleotide polymorphism, so the concerns about multiple comparisons likely do not apply. Campbell et al. (2011) undertook the largest-scale study of single nucleotide polymorphisms, observed phenotypes, and ASD. Although the authors found multiple nominally significant results, they point out that none of the results would survive corrections for multiple comparisons. The results of these studies can be interpreted as preliminary evidence for association between alterations in the OXTR gene and ASD, and provide useful future directions for research associating genetic results with observable phenotypes of ASD. Future studies should be careful to employ rigorous statistical controls to confirm this finding.

Not all studies find relations between single nucleotide polymorphisms and ASD (e.g. Tansey et al., 2010; Wermter et al., 2009). In independent samples from Portugal and the UK, Tansey et al. (2010) did not find a relation between any significant single nucleotide polymorphism on the OXTR gene and ASD that survived statistical correction for multiple comparisons. The authors suggest heterogeneity of participants as one reason for lack of replication from previous studies. The two samples did not utilize the same inclusion criteria, however, which might also have affected the outcome (Tansey et al., 2010).

Other studies have suggested that oxytocin genes are associated with reward dependence, and fMRI activation in response to social stimuli (Tost et al., 2010). Finally, a genetic study of ASD suggested that over methylation of OXTR could be responsible for gene silencing in some patients (Gregory et al., 2009). Although these genetic studies are by no means conclusive evidence that the OXTR or CD38 genes are causally related to ASD, they do suggest that it is important to study oxytocin in ASD. Given the diversity of genetic results, epigenetic approaches may be a beneficial avenue for future research in pharmacological treatment for ASD.

This section has briefly reviewed genetic studies concerning oxytocin and ASD. Other studies have investigated single nucleotide polymorphisms on oxytocin-related genes in neurotypical individuals (e.g. Chen & Johnson, 2011; Sauer, Wörner, Kirsch, Montag & Reuter, 2012; Walum et al., 2012), as well as genetic studies of arginine vasopressin and ASD. Those studies are outside the scope of the current review, but are discussed in other reviews (e.g. Ebstein, Knafo, Mankuta, Hong Chew & San Lai, 2012; Skuse & Gallagher, 2011)

Effects of oxytocin administration on social behavior

Studies of oxytocin levels and genetic studies suggest that deficits in oxytocin function should be considered as a possible contributor to social dysfunction in ASD. Table 1 summarizes the human oxytocin administration studies that measured social behaviors. In neurotypical individuals, several studies show that social behavior is enhanced under oxytocin administration. These include recognition of emotions (Domes, Heinrichs, Michel, Berger & Herpertz, 2007), gaze to the eye region of the face (Gamer, Zurowski & Büchel, 2010; Guastella, Mitchell, et al., 2008), the salience of positive social memories (Guastella, Mitchell & Mathews, 2008), and the effects of social reinforcement on learning (Hurlemann et al., 2010). Neurotypical individuals given oxytocin show increased trust during a social computer game (Kosfeld, Heinrichs, Zak, Fischbacher & Fehr, 2005). Oxytocin also decreases amygdala response to fearful scenes and faces (Gamer et al., 2010; Kirsch et al., 2005). These studies provide important information about the role of oxytocin in social behavior in neurotypical individuals. However, in neurotypical individuals, effects of oxytocin

Table 1 Studies that have examined effects of oxytocin on social behavior

Study authors	Population, sample size (*N*), age (mean, *M*)	Administration	Dependent variable(s)	Results of oxytocin administration	Effect size
Andari et al., 2010;	HFAD, AS (*N* = 13) TD (*N* = 13) *M* = 26 years	Intranasal	1. Cooperation with computer partners in a computer game 2. Gaze to regions of the face	1. Demonstrated preference for 'good' versus 'bad' computer partner 2. Increased gaze to eye region of the face	–[a] –[a]
Bartz et al., 2010;	TD *N* = 27 *M* = 26.8 years	Intranasal	Accuracy of emotional /empathetic recognition as a function of autism quotient (AQ) scores	Individuals with low AQ scores did well on the empathy task regardless of oxytocin; whereas individuals with high AQ scores improved after oxytocin	–[a]
Domes et al., 2007;	TD *N* = 30 *M* = 25 years	Intranasal	Reading the Mind in the Eyes Test (REMET)	Improvement on items rated as 'difficult'	–[a]
Gamer et al., 2010;	TD *N* = 46 *M* = 28 years	Intranasal	1. Fixation to regions of emotional faces 2. Amygdala activity in response to emotional faces	1. More gaze changes toward eye region regardless of facial emotion 2. Dampened amygdala response to fearful faces; enhanced response to happy/neutral faces	–[a] –[a]
Guastella et al., 2010;	HFAD, AS *N* = 16 *M* = 14.8 years	Intranasal	REMET	Improvement on items rated as 'easy'	–[a]
Guastella, Mitchell, et al., 2008	TD *N* = 52 *M* = 19.80 years	Intranasal	Looking time and fixation to regions of neutral faces	Longer gaze + more fixations to the eyes	Fixation count to eyes placebo versus oxytocin: ES = .88 Gaze time to eyes placebo versus oxytocin: ES = 1.20
Guastella, Mitchell, and Mathews 2008;	TD *N* = 69 *M* = 19.98 years	Intranasal	Making 'remember', 'know' or 'new' judgment for new and previously seen happy, neutral, and angry faces	More likely to make 'remember' and 'know' judgments for previously seen happy faces, but not for neutral or angry faces	'know' = .608[b] 'remember' = .421[b]
Hollander et al., 2007;	ASD, AS *N* = 15 *M* = 32 years	Intravenous	Ability to identify and comprehend affective speech	1. Improved ability to identify and comprehend affective speech 2. Improvements lasted to session 2 if session 1 was oxytocin versus placebo	–[a] *d* = .66
Hurlemann et al., 2010;	TD *N* = 48 *M* = 25.9 years	Intranasal	1. Learning task with either social or nonsocial feedback	1. Improved learning when feedback is social	.848 main effect of oxytocin[b]
Kosfeld et al., 2005	TD *N* = 58 *M* = 22 years	Intranasal	Trust in a partner during an investment game (willingness to invest)	Increased willingness to invest with partner	.249[c]

ASD, autism spectrum disorder; HFAD, high functioning autistic disorder; AS, Asperger's syndrome; TD, typical development; RTMET, Reading the Mind in the Eyes Test.
[a]Authors did not report effect sizes, and we are unable to calculate effect sizes accurately from the published information.
[b]Authors did not report effect sizes. We calculated them with the information provided in the results section. Whenever there were multiple interactions, we calculated the effect size for the main effect.
[c]Authors did not report effect sizes. We calculated them with the information provided in the results section. Note that these effect sizes were calculated from a Mann–Whitney *U*-test, and will not be directly comparable to the other effect sizes reported above (e.g., Cohen's *d*). An effect size calculated this way considers .3 as a moderate effect size.

administration are seen only on difficult versions of tasks (Domes et al., 2007). For example, in the Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001; Domes et al., 2007), intranasal doses of oxytocin improved neurotypical adults' performance, but only on items that had been identified in previous research as 'difficult' (Domes et al., 2007). There was no improvement on items identified as 'easy'. This is likely because the Reading the Mind through the Eyes Test was designed to measure severe impairments in mind reading (e.g. with individuals with ASD), and thus neurotypical adults already score highly on items rated as 'easy' (Domes et al., 2007).

Domes et al.'s (2007) results may be explained in part by changes in looking behavior to the face under oxytocin administration. Guastella, Mitchell, et al. (2008) administered intranasal oxytocin to neurotypical adults and measured both looking time and fixations to various regions of the face. Participants who received oxytocin had significantly longer gaze and more fixations to the eye region of the face compared to those who received placebo. Increased gaze to the eyes may have helped participants better identify ambiguous emotions in the Reading the Mind through the Eyes Test. Following the direction of eye gaze is an important preliminary component of joint attention (Scaife & Bruner, 1975). Because there is significant evidence that people with ASD tend to look less at eyes than neurotypical controls (Jones, Carr & Klin, 2008; Klin, Jones, Schultz, Volkmar & Cohen, 2002), results from the Guastella, Mitchell, et al. (2008) study have provocative implications for ASD, and particularly the joint attention deficits reported in children with ASD.

Administering oxytocin to individuals with ASD

Studies that have administered oxytocin to individuals with ASDs are relatively limited. Of those that exist, there is a range of procedures that have been utilized. In general, results of these studies suggest that oxytocin improves performance on social tasks relative to placebo. These tasks include: recognition of affective speech (Hollander, Bartz, Chaplin & Phillips, 2007), the Reading the Mind through the Eyes Test (Guastella et al., 2010), and social cooperation in an online computer game (Andari et al., 2010). Andari et al. (2010) had adult participants play a cooperative ball tossing game with fictitious partners who were programmed to have 'neutral', 'bad', or 'good' traits depending on the amount they cooperated (i.e. passing the ball back). In a baseline measure, participants with ASD or Asperger's syndrome did not distinguish between the characteristics of the partners, throwing the ball equally often to each of the players regardless of their programmed behavior. In contrast, control participants tended to throw the ball exclusively to cooperative partners by the end of the game. When participants with ASD or Asperger's syndrome were given intranasal doses of oxytocin, their performance became more comparable to neurotypical participants in that they preferred to interact with the good compared to bad partner (Andari et al., 2010). Participants with ASD or Asperger's syndrome also showed increased gaze fixation on socially relevant areas of the face (e.g. the eyes) after oxytocin administration. The results of this study suggest that, like controls, individuals with ASD or Asperger's syndrome improve on social tasks after oxytocin administration. However, even after oxytocin administration, individuals with ASD or Asperger's syndrome spent less time gazing at the face and eye region compared to neurotypical participants. Although oxytocin increased the time spent gazing at the face and eyes in individuals with ASD or Asperger's, performance was still different from controls. Furthermore, because the neurotypical participants were not tested with oxytocin, it is difficult to contextualize the improvements seen in individuals with ASD or Asperger's syndrome. For example, the results of the study cannot tell us how neurotypical individuals might perform on these tasks with oxytocin, and whether the groups would differ on eye gaze measures before and after oxytocin administration.

Guastella et al. (2010) had adolescents with ASD or Asperger's syndrome complete the Reading the Mind through the Eyes Test after taking either placebo or oxytocin. Participants showed significant improvement after oxytocin. Notably, this study was the first to administer oxytocin to young adolescents, and when analyses were restricted to individuals under 16 years of age, performance on the Reading the Mind through the Eyes Test still improved after oxytocin. However, when the items were separated into 'easy' and 'hard', improvements were significant only for 'easy' items. These results contrast with those of Domes et al. (2007), who found that while neurotypical adults showed significant improvement on the Reading the Mind through the Eyes Task after oxytocin, that improvement was significant only for items rated as 'hard'. As Domes et al. (2007) speculate, their result could be due to the fact that neurotypical adults are unlikely to improve further on items that they already perform extremely well on. Guastella et al. (2010), suggested that oxytocin might improve performance on tasks that are of medium difficulty (e.g. neither too hard nor too easy). One could speculate that because individuals with ASD or Asperger's syndrome find items rated as 'easy' to be somewhat difficult, and items rated as 'hard' to be extremely difficult, selective improvement could occur. Unfortunately, because Domes et al. (2007) only studied neurotypical adults, and Guastella et al. (2010) studied only adolescents with ASD or Asperger's syndrome, a direct comparison between the two studies is not possible.

In one within-subjects study, order effects were seen in an affective speech recognition task when

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adults were given oxytocin during one session (either session one or two), and placebo during the other session (Hollander et al., 2007). Individuals who received oxytocin first maintained high levels of performance even during the later placebo session. In contrast, participants who were administered placebo in the first session showed decreased performance during their second, oxytocin session. This finding suggests two noteworthy things: administration of placebo or oxytocin during the first session improved performance relative to baseline; and performance was improved as a result of the *expectation* of receiving treatment in the placebo condition. However, when the first session injection was placebo, the improvements did not last until the second session, whereas those seen from oxytocin maintained even after the delay. Thus, there appear to be effects of oxytocin on the ability to recognize and remember affective speech even above the placebo effect. These order effects suggest that oxytocin administration has the potential to facilitate improvements in the ability to recognize affective speech that last beyond a single testing session.

These results have important implications for ASD interventions. If oxytocin is given before a behavioral intervention, improvement might continue throughout the intervention – and thus oxytocin should be administered *prior* to behavioral interventions. The Hollander et al. (2007) results also suggest that oxytocin affects the ability of individuals with ASD to correctly identify affective speech – which is an important aspect of social cognitive functioning.

However, because the Hollander et al. (2007) study was done with adults, it is difficult to make assumptions about whether oxytocin administration would have equally long-lasting results in adolescents or children with ASD. In addition, therapeutic use of oxytocin would require repeated administration over time and early in development. Currently, little is known about the effects of repeated doses of oxytocin in development.

One recent animal study looked at the effects of repeated oxytocin administration. Bales et al. (in press), repeatedly administered intranasal oxytocin to prairie voles from weaning to sexual maturity. As expected, initial oxytocin administrations led to increases in social behaviors. However, long-term administration led to deficits in partner preference behavior (Bales et al., 2012). These results suggest that oxytocin administration might have unexpected negative results over time. Relatedly Bales and Perkeybile (2012) reviewed the animal literature, and suggested that oxytocin and vasopressin administration may change how social experiences affect development. Although these papers are relevant to the animal literature, they point out the need for further research into repeated exposures of oxytocin, as well as research that will shed light on effects of early or repeated oxytocin exposure in humans.

The aforementioned studies suggest that oxytocin might mediate some social cognitive deficits seen in ASD. However, it should be noted that there have only been three completed studies that investigate the effects of oxytocin on social deficits in individuals with ASDs, and of those three, two of them were with adults. It is likely that many other studies will be completed soon. The website *clinicaltrials.gov* lists eight active and one completed study investigating the effects of oxytocin on individuals with ASD. Of these, four involve recruiting adolescents or children, and the other four are recruiting adults. From the information on the website, it appears as though none of the listed studies are administering oxytocin concurrently with a behavioral intervention with ASD, but are either measuring brain or behavior after a single administration of oxytocin, or giving oxytocin over time and measuring behavior afterwards (Clinicaltrials.gov, 2012).

We have reviewed results of oxytocin administration on social behaviors in both neurotypical individuals and those with ASD. We have limited the discussed studies to those that explicitly measured social behaviors rather than including those that discuss how social information is processed. For a review of all studies concerning oxytocin administration and social information processing, see Graustella and MacLeod (2012). For a review of studies administering oxytocin or vasopressin and using imaging methods, please see Zink and Meyer-Lindenberg (2012).

We have not discussed studies that have administered oxytocin to individuals with disorders other than ASD. Oxytocin administration has been preliminarily helpful in treating symptoms of schizophrenia (e.g. Feifel et al., 2010; Pedersen et al., 2011). For a review of the literature on oxytocin administration and schizophrenia, see MacDonald and Feifel (2012). Of particular note, Pedersen et al. (2011) found that intranasal oxytocin improved measures of social cognition in patients with schizophrenia, including theory of mind and recognition of suspicious faces. These results suggest that intranasal oxytocin might be helpful for social deficits seen in a variety of disorders, not only ASD.

Potential issues in intranasal oxytocin administration

Some questions about the efficacy of intranasal oxytocin administration exist. It is not clear whether oxytocin and other neuropeptides cross the blood–brain barrier when administered intranasally, although there is recent evidence that intranasal oxytocin appears in saliva (Weisman, Zagoory-Sharon & Feldman, 2012) and blood (Andari et al., 2010) for a short time after intranasal administration. Weisman et al. (2012) demonstrated that in neurotypical adults, intranasal oxytocin administration increases the amount of oxytocin in saliva after

15 min, reaches a peak 45 min after administration, and still not does return to baseline after 4 hr. This has important implications for the appropriate timeline for conducting experiments concerning intranasal oxytocin and social behaviors. Nine of the 10 studies reported in Table 1 measured social behaviors 45–50 min after intranasal oxytocin administration. The only exception (Hollander et al., 2007), administered oxytocin intravenously, and measured comprehension of affective speech at five separate time points as the amount of oxytocin administered was increased. Thus, the majority of studies have measured social behavior at the time of peak levels of oxytocin.

Churchland and Winkielman (2012) adeptly point out the error in assuming oxytocin has passed through the blood brain barrier based solely on reports of increased peripheral concentration of the peptide (e.g. in blood plasma). However, other studies report that peripheral and CSF levels of neuropeptides closely related to oxytocin (e.g. arginine vasopressin) are correlated (Born et al., 2002; Riekkinen et al., 1987). Studies have suggested that intranasal administration of neuropeptides, such as vasopressin, caused CSF levels to increase within 10 min of administration, and continued to rise for 80 min after administration (Born et al., 2002).

A more general issue with measuring plasma or CSF levels of oxytocin is that the amount of oxytocin in the blood or brain does not necessarily reflect whether oxytocin has reached the appropriate binding sites in the brain. Even if oxytocin reaches the brain via intranasal administration, there have not been any studies investigating *where* it goes, and whether it reaches the appropriate receptors (see Churchland & Winkielman, 2012; for a more in-depth discussion of this issue). Plasma and CSF measures of oxytocin may not reflect efficient oxytocin binding. If oxytocin receptors are damaged or the genes that control them are mutated, and oxytocin is available in the brain but not binding correctly, plasma and CSF measurements would not accurately represent the success or failure of oxytocin to bind, but only represent the net amount available in the brain. Further research on the location, timing, and binding of oxytocin after intranasal administration is necessary (Churchland & Winkielman, 2012). Such research would likely be possible with nonhuman primates, where concentrations of oxytocin in the brain could be measured after intranasal administration. While all of these limitations concerning intranasal oxytocin administration must be considered carefully, evidence in sum suggests that intranasal oxytocin administration succeeds in increasing oxytocin levels.

Social motivation and joint attention in ASD

We turn now to a case of social behavior that is impaired in ASD, and for which oxytocin may have important treatment implications. Joint attention is a crucial developmental milestone for typical social-cognitive development, and is among the most commonly identified deficits in ASD. Joint attention occurs when two people share attention to an object, location, or event in space. Joint attention allows information to be effectively conveyed from one person to another about an object without using language. In typical development, joint attention is thought to emerge during the second half of the first year of life, and is important for both successful language learning and later social cognition (Baldwin, 1991; Bates, 1979; Brooks & Meltzoff, 2005, 2008; Bruner, 1983; Corkum & Moore, 1998; Mundy & Gomes, 1998; Sigman & Kasari, 1995; Tomasello & Farrar, 1986). For reasons we will expand upon below, joint attention is an especially interesting test case for the SMH. A typical example of joint attention is the following scenario: An infant looks to his mother, up at a passing airplane, and back to her as if to indicate, 'look at that unusual thing in the sky!' This triadic interaction involving self (infant), other (mother), and their shared object of attention toward an object (airplane) is the defining feature of joint attention (Bakeman & Adamson, 1984; Scaife & Bruner, 1975; Tomasello, 1995). According to the SMH, individuals with ASD have impairments in joint attention because they find social activities less rewarding than neurotypical individuals. Given the evidence reviewed above that oxytocin may play a significant role in social behavior and social motivation, interventions focusing on joint attention that are combined with administration of oxytocin in may increase intrinsic social motivation and improve outcomes from joint attention interventions.

Although joint attention is often mentioned as a unified concept, it can be separated into two distinct subtypes that likely develop separately (Mundy & Gomes, 1998; Mundy, Sullivan & Mastergeorge, 2009). This differentiation is important because being able to respond to joint attention (i.e. following another person's gaze) likely develops earlier than initiating joint attention (i.e. seeking to share attention with another person through gaze that you initiate, Dunham & Moore, 1995). Joint attention can also serve multiple communicative functions (Gomez, Sarria & Tamarit, 1993; Mundy, Sigman & Kasari, 1993). *Imperative* joint attention occurs if a child points or gazes toward an object with the intention of requesting that object. *Declarative* joint attention occurs if a child points or gazes at an object with the intention of sharing his interest in that object with an adult (Gomez et al., 1993; Mundy et al., 1993). Using these distinctions, one could respond to a joint attention bid from another person that is either imperative or declarative, and also initiate joint attention for either of these two functions. As we will see in a subsequent section, these distinctions between two types of joint attention and

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the two functions they serve are especially important when discussing joint attention difficulties in ASD.

Joint attention in children with ASD

Individuals with ASD are profoundly impaired in joint attention (Mundy, 1995; Mundy et al., 1986). This inability to share attention with another person is central to ASD and has been incorporated into the DSM-IV criteria for the disorder (American Psychiatric Association, 1994). Deficits in joint attention differentiate children with ASD from both neurotypical and other developmentally delayed children (Bacon, Fein, Morris & Waterhouse, 1998; Charman et al., 1998; Dawson, Meltzoff, Osterling & Rinaldi, 1998; Mundy et al., 1986; Sigman, Kasari, Kwon & Yirmiya, 1992).

However, individuals with ASD are not equally impaired in all aspects of joint attention. Initiating joint attention is more impaired, and predicts symptoms better, in ASD than responding to joint attention (Leekam, Lopez & Moore, 2000; Mundy et al., 1986, 1993, 2009; Sigman, Mundy, Sherman & Ungerer, 1986). Perhaps this is not surprising because responding to joint attention chiefly involves following another's gaze. One could argue that an object of another's attention is often rewarding on its own and that responding to joint attention therefore does not necessitate motivation that is purely social (Corkum & Moore, 1998). Initiating joint attention, on the other hand, requires one to be motivated to share something interesting with another individual – meaning that the motivation behind initiating joint attention is likely purely social in nature (Mundy, 1995; Mundy & Gomes, 1998; Tomasello, 1995).

Based on this reasoning, the SMH (Dawson, 2008; Dawson & Bernier, 2007; Dawson et al., 2002, 2005; Grelotti et al., 2002) emphasizes initiating joint attention more than responding to joint attention skills. Similarly, individuals with ASD are impaired in both declarative and imperative joint attention, but show more profound problems with the declarative type, which can also be characterized as involving social motivation (Baron-Cohen, 1989, 1993; Mundy et al., 1986, 1993).

Improving joint attention skills in individuals with ASD

Because of its importance for later social and linguistic development, joint attention has been a focus of a great deal of intervention research. Research suggests that children with ASD who engage in joint attention gain language skills more rapidly than their peers who do not engage in joint attention over equivalent time periods (Bono, Daley & Sigman, 2004; Siller & Sigman, 2002). Furthermore, several studies suggest that relatively good joint attention skills early in development in children with ASD predicts better language and social outcomes up to several years later (Charman, 2003; Mundy, Sigman & Kasari, 1990; Sigman & Ruskin, 1999). Interventions for children with ASD that focus on nonverbal social communication skills lead to improvements in language and social skills in these children (see White et al., 2011 for review).

Interventions designed to improve joint attention in individuals with ASD

Interventions have sought to train individuals with ASD to engage in joint attention behaviors through various behavior modification procedures (e.g. discrete trial training, pivotal response training). Such interventions use principles of positive and negative reinforcement to increase desired behavior. As mentioned above, White et al. (2011) provide a thorough review of these interventions conducted prior to 2010. Table 2 summarizes studies of interventions to improve joint attention in individuals with ASD since 2010, and this section will review papers from Table 2, as well as those from White et al. (2011) that are particularly relevant to the scope of the current review.

Kasari, Freeman and Paparella (2006) and Kasari, Gulsrud, Wong, Kwon and Locke (2010), had children engage in 5–8 min of discrete trial training designed to improve initiating and responding to joint attention. This structured intervention was immediately followed by child-directed floor time designed to improve targeted skills in a less structured setting. In interventions like this, children are extrinsically reinforced for responding to and initiating joint attention bids, and generally show marked improvements in joint attention skills. However, many intervention studies fail to conduct follow-up sessions to assess whether skills gained during intervention are maintained, and those that did varied in duration (e.g. Ferraioli & Harris, 2011; Kaale, Smith & Sponheim, 2012). Of studies that did assess improvement at follow-up, often initiating joint attention skills did not last over time (e.g. Whalen & Schreibman, 2003), or were not as successfully improved as other primary outcome measures (e.g. Schertz, Odom, Baggett, & Sideris, 2012; Kasari et al., 2010; Landa, Holman, O'Neill & Stuart, 2011). Dysfunction in social motivation may explain the finding that joint attention intervention effects often do not last to follow-up. Because of the lack of intrinsic social motivation, extrinsic rewards are used, and when these rewards are no longer available, joint attention regresses. Studies that have attempted to use more naturalistic reinforcers, or that have attempted to generate intrinsic social motivation have shown better success on follow-up (e.g. Ingersoll, 2012; Isaksen & Holth, 2009; Naoi et al., 2008). However, even some studies that follow this model still report mixed levels of success (e.g. Taylor & Hoch, 2008). Only a few studies have attempted to teach responding to or initiation joint

Table 2 Studies that have examined the effects of joint attention interventions on individuals with autism spectrum disorders since 2010 [updating the studies reviewed in White et al. (2011)]

Study authors	Sample size, Age (mean, *M*)	Focus of intervention	Length (weeks)	Sessions per week	Significant improvement (effect size)	Follow-up?	Follow-up duration (months)	Effects maintained at follow-up
Ferraioli & Harris, 2011;	4 *M* = 4.2 years	Sibling JA	7–8	–	RJA IJA (2 participants only)[a]	Y	3	RJA, IJA (2 participants only)
Ingersoll, 2012;	14 intervention 13 control *M* = 37.95 months	Imitation intervention	10	3	IJA (η^2_p = .16)	Y	2–3	IJA
Kaale et al., 2012;	61 *M* = 48.4 months	Preschool intervention	8	10	JE with mothers (*d* = .67) IJA with teachers (*d* = .44)	N	–	
Kasari et al., 2010;	19 intervention 19 control *M* = 30.83 months	Caregiver JA	8	3	JE (*d* = .87) RJA (*d* = .74)	Y	12	JE, RJA
Landa et al., 2011;	24 intervention 24 control *M* = 2 years	IJA, SPA	24	4	IJA (trend) (*d* = .89)	Y	6	IJA (trend) (*d* = 1.56)
Lawton & Kasari, 2012;	9 intervention 7 control *M* = 44.69 months	IJA	6	2	IJA for classroom observation only (*d* = 1.85)	N	–	
Lawton & Kasari, 2012	20 JA intervention 16 symbolic play intervention 16 control *M* = 42.01 months	JAPA, JAPAU	5–6	7	No significant improvement at exit	Y	6, 12	JAPA (6 months: ES = 1.36; 12 months: ES = 1.52), JAPAU (6 months: ES = 1.16; 12 months: ES = 1.75) For JA vs. control[b]
Schertz, Odom, Baggett, Sideris, 2012	11 intervention 12 control *M* = 26.11 months	IJA, RJA	16–56 (*M* = 28)	1	RJA (*d* = 1.39)	Y	1, 2	RJA (*d* = 1.18)

JA, joint attention; RJA, responding to joint attention; IJA, initiating joint attention; SPA, shared positive affect; JAPA, joint attention with positive affect; JAPAU, joint attention with positive affect and utterances; JE, joint engagement.

[a]Authors did not report effect size, and *N* was too small to calculate effect size.

[b]Authors did not report effect size. Effect size was calculated with information given by the authors in the results section of published work.

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attention without tangible extrinsic rewards, although Jones and Carr (2004), suggested it as a useful direction.

Isaksen and Holth (2009) attempted to deal with the problem of joint attention regression after interventions that utilize extrinsic motivation. They reinforced the smiling, nodding, and verbalization that typically occur after initiating joint attention behaviors. For example, an adult and a child with ASD were seated across from each other and various desirable toys were on the table. The adult's smiles and nods were used as a signal that the child could take a toy. When the adult was not smiling or nodding, any attempts to take a toy were blocked. In this way, the experimenters paired natural adult behavior with a rewarding activity. These types of social reinforcements motivate neurotypical children to engage in initiating joint attention behaviors (Isaksen & Holth, 2009; Jones & Carr, 2004; Whalen & Schreibman, 2003), are naturalistic, and will continue to be present after the intervention. Isaksen & Hoth measured joint attention behaviors after a 1-month follow-up interval and found that initiating joint attention skills maintained or improved for all four participants.

In summary, intervention studies demonstrate that children with ASD can improve their response to joint attention skills. However, initiating joint attention is much more challenging, most likely for motivational reasons. Studies such as those of Ingersoll (2012), Isaksen and Holth (2009), Naoi et al., (2008), and Taylor and Hoch (2008) are useful in their attempts to improve initiating joint attention without using extrinsic motivators, but their varied success underscores the difficulty of reinforcing social interactions for children with ASD. Finding a way to intrinsically motivate children with ASD to engage in initiating joint attention behaviors while they participate in interventions is important for long-term success.

Conclusions

This review has examined literature in the context of the SMH, including: oxytocin and ASD, administration of oxytocin and social behaviors, joint attention and ASD, and behavioral interventions to improve joint attention in ASD.

Although multiple neurotransmitters and neuropeptides have been implicated as candidates for improving intrinsic motivation for social interaction, oxytocin has consistently been seen as important for social motivation, interaction, and memory. Most of the literature linking oxytocin and social behavior derives from animal research, but there is a growing literature examining oxytocin administration in humans. Data from studies in which oxytocin has been administered to humans have strengthened the argument that oxytocin is important for social interaction. Because of the link between oxytocin and social behavior that has begun to emerge, oxytocin has begun to be used in interventions to improve social recognition in individuals with ASD.

Individuals with ASD have well-documented deficits in joint attention (Bacon et al., 1998; Charman et al., 1998; Dawson et al.,1998; Mundy et al., 1986; Sigman et al., 1992). Improving joint attention deficits is important for improving social and linguistic functioning of individuals with ASD (Bono et al., 2004; Charman, 2003; Koegel, 2000; Lord, 2000; Rogers & Lewis, 1989; Siller & Sigman, 2002), and therefore has been a focus of multiple behavioral interventions (e.g. see White et al., 2011; Table 2). Although these interventions have been somewhat successful in improving joint attention, one key underlying issue has been individuals with ASD's lack of intrinsic motivation to initiate joint attention and other social interactions (Jones & Carr, 2004; Whalen & Schreibman, 2003). Extrinsic rewards are often necessary for behavioral interventions to succeed, and when those are removed, individuals with ASD are no longer motivated to engage in joint attention behaviors, resulting in a failure of effects to maintain over the long term. Some theorists have proposed that increasing intrinsic motivation for social interaction might be a key component in improving symptoms of ASD (Dawson, 2008; Dawson & Bernier, 2007; Dawson et al., 2002, 2005; Grelotti et al., 2002).

However, one piece missing from the literature is integrating behavioral interventions and oxytocin administration in individuals with ASD. Behavioral interventions are important for increasing social behaviors, especially in young children with ASD. Oxytocin has been used experimentally to attempt to change social behaviors in ASD, but to our knowledge has not yet been used in a controlled treatments study, nor has it been used in combination with other intervention methods. By adding oxytocin administration to behavioral interventions, one important problem (lack of intrinsic motivation) that seems to hinder long-term success might be diminished. Interventions that combine behavioral interventions and oxytocin administration are crucial to long-term and generalized improvement of joint attention behaviors in young individuals with ASD (Dawson et al., 2012).

Experimental tests of such interventions would advance our understanding of how oxytocin mediates social symptoms of ASD in both the short and long term. Such experiments would need to be well-controlled, double-blind, and compare interventions plus oxytocin versus the same interventions with placebo. One issue would be when to administer oxytocin during the intervention, as well as what type of intervention to utilize. Multiple meta-analyses have emphasized the effectiveness of early intensive behavioral interventions (i.e. young children with ASD receiving 30–40 hr per week of structured behavioral interventions for over 2 years,

e.g. Reichow, 2012; Eldevik et al., 2009). Although these interventions require a large time investment, they are highly successful in improving a variety of behavioral skills, as well as improving IQ. To utilize oxytocin for behavioral interventions, however, it would likely be more practical to administer a more short-term intervention similar to those reported by White et al., 2010 and in Table 2.

Based on previous animal studies (Ferguson, Aldag, Insel & Young, 2001) as well as studies of the time course of oxytocin in saliva (Weisman et al., 2012) and order effects (Hollander et al. (2007), intervention should administer oxytocin about 45 min before each intervention session (rather than after or during sessions).

Directions for future research

We propose that two highly studied and important areas (behavioral intervention and studies on oxytocin administration) should be integrated to achieve optimal outcomes for children with ASD. Combining behavioral and pharmacological interventions has been highly successful in the alleviation of symptoms in other disorders (Hoffman et al., 2006; Ressler et al., 2004).

In the case of ASD, this novel approach to improving joint attention skills with both pharmacological and behavioral intervention is a necessary and worthwhile experimental direction. Theoretically, oxytocin administration will heighten patients' *intrinsic* motivation to engage in social interactions, and the behavioral interventions will facilitate and teach social interactions. By improving intrinsic motivation to engage in social interactions, behavioral interventions can use *only* social rewards, and cease using any extrinsic motivators. Because the rewards will be entirely social, and intrinsic motivation will be improved (via oxytocin), interventions should have long-lasting effects. Using behavioral interventions in combination with oxytocin administration should increase the chances of long-term success and an improved understanding of the role of oxytocin in ASD.

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Key points

- The social motivation hypothesis posits that individuals with autism spectrum disorders (ASDs) are less motivated to engage in social behaviors than their neurotypical peers, and this lack of motivation leads to later atypicalities in social behavior and cognition.
- The neurochemical oxytocin has received attention as a potential mechanism for social atypicalities in ASD.
- Administering oxytocin to individuals with and without ASD has been effective at improving social cognition.
- We propose that future studies should combine oxytocin administration and behavioral interventions to optimize outcomes for various social cognitive behaviors in autism spectrum disorder.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th edn). Washington, DC: Author.

Andari, E., Duhamel, J.R., Zalla, T., Herbrecht, E., Leboyer, M., & Sirigu, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 4389–4394.

Bacon, A.L., Fein, D., Morris, R., & Waterhouse, L. (1998). The responses of autistic children to the distress of others. *Journal of Autism and Developmental Disorders*, *28*, 129–142.

Bakeman, R., & Adamson, L.B. (1984). Coordinating attention to people and objects in mother-infant and peer-infant interaction. *Child Development*, *55*, 1278–1289.

Baldwin, D.A. (1991). Understanding the link between joint attention and language. In C. Moore & P.J. Dunham (Eds.), *Joint Attention: its origins and role in development* (pp. 131–158). Hillsdale, NJ: Lawrence Erlbaum.

Bales, K.L., & Perkeybile, A.M. (2012). Developmental experiences and the oxytocin receptor system. *Hormones and Behavior*, *61*, 313–319.

Bales, K.L., Perkeybile, A.M., Conley, O.G., Lee, M.H., Guoynes, C.D., Downing, G.M., … & Mendoza, S.P. (in press). Chronic intranasal oxytocin causes long-term impairments in partner preference formation in male prairie voles. *Biological Psychiatry*. doi: 10.1016/j.biopsych.2012.08.025.

Baron-Cohen, S. (1989). Perceptual role-taking and protodeclarative pointing in autism. *British Journal of Developmental Psychology*, *7*, 113–127.

Baron-Cohen, S. (1993). From attention–goal psychology to belief–desire psychology: The development of a theory of mind and its dysfunction. In S. Baron-Cohen, H. Tager-Flusberg & D. Cohen (Eds.), *Understanding other minds:*

doi:10.1111/jcpp.12061

Perspectives from autism (pp. 59–82). New York, NY: Oxford University Press.

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "reading the mind in the eyes" test revised version: A study with normal adults, and adults with Asperger syndrome and high-functioning autism. *Journal of Child Psychological Psychiatry*, *42*, 241–251.

Bartz, J.A., Zaki, J., Bolger, N., Hollander, E., Ludwig, N.N., Kolevzon, A., & Ochsner, K.N. (2010). Oxytocin selectively improves empathic accuracy. *Psychological Science*, *21*, 1426–1428.

Baskerville, T.A., & Douglas, A.J. (2010). Dopamine and oxytocin interactions underlying behaviors: Potential contributions to behavioral disorders. *CNS Neuroscience and Therapeutics*, *16*, 92–123.

Bates, E. (1979). *The emergence of symbols: Cognition and communication in infancy*. New York, NY: Academic Press.

Bell, C.J., Nicholson, H., Mulder, R.T., Luty, S.E., & Joyce, P.R. (2006). Plasma oxytocin levels in depression and their correlation with the temperament dimension of reward dependence. *Journal of Psychopharmacology*, *20*, 656–660.

Bono, M.A., Daley, Y.T., & Sigman, N.M. (2004). Relations among joint attention, amount of intervention and language gain in autism, *Journal of Autism and Developmental Disorders*, *34*, 495–505.

Born, J., Lange, T., Kern, W., McGregor, G.P., Bickel, U., & Fehm, H.L. (2002). Sniffing neuropeptides: A transnasal approach to the human brain. *Nature Neuroscience*, *5*, 514–616.

Brooks, R., & Meltzoff, A.N. (2005). The development of gaze following and its relation to language. *Developmental Science*, *8*, 535–543.

Brooks, R., & Meltzoff, A.N. (2008). Infant gaze following and pointing predict accelerated vocabulary growth through two years of age: A longitudinal, growth curve modeling study. *Journal of Child Language*, *35*, 207–220.

Brüne, M. (2012). Does the oxytocin receptor (OXTR) polymorphism (rs2254298) confer 'vulnerability' for psychopathology or 'differential susceptibility'? Insights from evolution. *BMC Medicine*, *10*, 38.

Bruner, J. (1983). *Child's talk*. New York, NY: Norton.

Cacioppo, J.T., Norris, C.J., Decety, J., Montelone, G., & Nusbaum, H. (2009). In the eye of the beholder: Individual differences in perceived social isolation predict regional brain activation to social stimuli. *Journal of Cognitive Neuroscience*, *21*, 83–92.

Campbell, D.B., Datta, D., Jones, S.T., Batey Lee, E., Sutcliffe, J.S., Hammock, E.A., & Levitt, P. (2011). Association of oxytocin receptor (OXTR) gene variants with multiple phenotype domains of autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, *2*, 101–112.

Charman, T. (2003). Why is joint attention a pivotal skill in autism? *Philosophical Transaction of the Royal Society B*, *358*, 315–324.

Charman, T., Swettenham, J., Baron- Cohen, S., Cox, A., Baird, G., & Drew, A. (1998). An experimental investigation of social-cognitive abilities in infants with autism: Clinical implications. *Infant Mental Health Journal*, *19*, 260–275.

Chen, F.S., & Johnson, S.C. (2011). An oxytocin receptor gene variant predicts attachment anxiety in females and autism-spectrum traits in males. *Social Psychological and Personality Science*, *3*, 93–99.

Churchland, P.S., & Winkielman, P. (2012). Modulating social behavior with oxytocin: How does it work? What does it mean? *Hormones and Behavior*, *61*, 392–399.

Clinicaltrials.gov. (2012). Oxytocin AND autism [Search]. Available from: http://www.clinicaltrials.gov/ct2/results?term=oxytocin+AND+autism&Search=Search. [last accessed 1 November 2012].

Corkum, V., & Moore, C. (1998). The origins of joint visual attention in infants. *Developmental Psychology*, *34*, 28–38.

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, *20*, 775–803.

Dawson, G., & Bernier, R. (2007). Development of social brain circuitry in autism. In D. Coch, G. Dawson & K.W. Fischer (Eds.), *In: Human behavior, learning, and the developing brain: Atypical development* (pp. 28–56). New York, NY: Guilford Press.

Dawson, G., Bernier, R., & Ring, R.H. (2012). Social attention: A possible early indicator of efficacy in autism clinical trials. *Journal of Neurodevelopmental Disorders*, *4*, 11.

Dawson, G., Carver, L., Meltzoff, A.N., Panagiotides, H., McPartland, J., & Webb, S.J. (2002). Neural correlates of face and object recognition in young children with autism spectrum disorder, developmental delay, and typical development. *Child Development*, *73*, 700–717.

Dawson, G., Meltzoff, A.N., Osterling, J., & Rinaldi, J. (1998). Neuropsychological correlates of early symptoms of autism. *Child Development*, *69*, 1276–1285.

Dawson, G., Webb, S.J., Wijsma, E., Schellenberg, G., Estes, A., Munson, J., & Faja, S. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology*, *17*, 679–697.

Dichter, G.S., Felder, J.N., Green, S.R., Rittenberg, A.M., Sasson, N.J., & Bodfish, J.W. (2012). Reward circuitry function in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, *7*, 160–172.

Dichter, G.S., Richey, A.J., Rittenberg, A.M., Sabatino, A., & Bodfish, J.W. (2012). Reward circuitry function in autism during face anticipation and outcomes. *Journal of Autism and Developmental Disorders*, *42*, 147–160.

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S.C. (2007). Oxytocin improves "mind-reading" in humans. *Biological Psychiatry*, *61*, 731–733.

Dunham, P.J., & Moore, C. (1995). Current themes in research on joint attention. In C. Moore & P.J. Dunham (Eds.), *Joint attention: Its origins and role in development* (pp. 15–28). Hillsdale, NJ: Erlbaum.

Ebstein, R.P., Israel, S., Lerer, E., Uzefovsky, F., Shalev, I., Gritsenko, I., … & Yirmiya, N. (2009). Arginine vasopressin and oxytocin modulate human social behavior. *Annals of the New York Academy of Sciences*, *1167*, 87–102.

Ebstein, R.P., Knafo, A., Mankuta, D., Hong Chew, S., & San Lai, P. (2012). The contributions of oxytocin and vasopressin pathway genes to human behavior. *Hormones and Behavior*, *61*, 359–379.

Eldevik, S., Hastings, R.P., Hughes, C.J., Jahr, E., Eikesth, S., & Cross, S. (2009). Meta-analysis of early intensive behavioral intervention for children with autism. *Journal of Clinical Child & Adolescent Psychology*, *38*, 439–450.

Feifel, D., Macdonald, K., Nguyen, A., Cobb, P., Warlan, H., Galangue, B., … & Hadley, A. (2010). Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biological Psychiatry*, *68*, 678–680.

Feldman, R. (2012). Oxytocin and social affiliation in humans. *Hormones and Behavior*, *61*, 380–391.

Ferguson, J.N., Aldag, J.M., Insel, T.R., & Young, L.J. (2001). Oxytocin in the medial amygdala is essential for social recognition in the mouse. *Journal of Neuroscience*, *21*, 8278–8285.

Ferguson, J.N., Young, L.J., Hearn, E., Insel, T.R., & Winslow, J. (2000). Social amnesia in mice lacking the oxytocin gene. *Nature Genetics*, *25*, 284–288.

Ferraioli, S.J., & Harris, S.L. (2011). Teaching joint attention to children with autism through a sibling-mediated behavioral intervention. *Behavioral Interventions*, *26*, 261–281.

Gainer, H., Lively, M.O., & Morris, M. (1995). Immunological and related techniques for studying neurohypophyseal peptide-processing pathways. *Journal of Neuroscience Methods*, *23*, 195–207.

Gamer, M., Zurowski, B., & Büchel, C. (2010). Different amygdala subregions mediate valence related and attentional effects of oxytocin in humans. *Proceedings of the National Academy of Science of the United States of America*, *107*, 9400–9405.

Gomez, J.C., Sarria, E., & Tamarit, J. (1993). The comparative study of early communication and theories of mind: Ontogeny, phylogeny and pathology. In S. Baron-Cohen, H. Tager-Flusberg & D. Cohen (Eds.), *Understanding other minds: perspectives from autism* (pp. 397–426). New York, NY: Oxford University Press.

Gordon, I., Martin, C., Feldman, R., & Leckman, J.F. (2011). Oxytocin and social motivation. *Developmental Cognitive Neuroscience*, *1*, 471–492.

Graustella, A.J., & MacLeod, C. (2012). A critical review of the influence of oxytocin nasal spray on social cognition in humans: Evidence and future directions. *Hormones and Behavior*, *61*, 410–418.

Green, L.A., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., & Morris, M. (2001). Oxytocin and autistic disorder: Alternations in peptide forms. *Biological Psychiatry*, *50*, 609–613.

Gregory, S.G., Connelly, J.J., Towers, A.J., Johnson, J., Biscocho, D., Markunas, C.A., … & Pericak-Vance, M.A. (2009). Genomic and epigenetic evidence for oxytocin receptor deficiencies in autism. *BMC Medicine*, *7*, 62.

Grelotti, D., Gauthier, I., & Schultz, R. (2002). Social interest and the development of cortical face specialization; what autism teaches us about face processing. *Developmental Psychobiology*, *40*, 213–225.

Guastella, A.J., Einfeld, S.L., Gray, K.M., Rinehart, N.J., Tonge, B.J., Lambert, T.J., & Hickie, I.B. (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry*, *67*, 692–694.

Guastella, A.J., Mitchell, P.B., & Dadds, M.R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*, *63*, 3–5.

Guastella, A.J., Mitchell, P.B., & Mathews, F. (2008). Oxytocin enhances the encoding of positive social memories in humans. *Biological Psychiatry*, *64*, 256–258.

Hoffman, S.G., Meuret, A.E., Smits, J.A.J., Simon, N.M., Pollack, M.H., … & Otto, M.W. (2006). Augmentation of exposure therapy with D-Cycloserine for social anxiety disorder. *Archives of General Psychiatry*, *63*, 298–304.

Hollander, E., Bartz, J.A., Chaplin, W., & Phillips, A. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry*, *61*, 498–503.

Hurlemann, R., Patin, A., Onur, O.A., Cohen, M.X., Baumgartner, T., Metzler, S., … & Kendrick, K.M. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *The Journal of Neuroscience*, *30*, 4999–5007.

Ingersoll, B. (2012). Brief report: Effect of a focused imitation intervention on social functioning in children with autism. *Journal of Autism and Developmental Disorders*, *42*, 1768–1773.

Insel, T.R., & Frenald, R.D. (2004). How the brain processes social information: Searching for the social brain. *Annual Review of Neuroscience*, *27*, 697–722.

Insel, T.R., & Hulihan, T.J. (1995). A gender-specific mechanism for pair bonding: Oxytocin and partner-preference formation in monogamous voles. *Behavioral Neuroscience*, *109*, 782–789.

Insel, T.R., O'Brien, D.J., & Leckman, J.F. (1999). Oxytocin, vasopressin, and autism: Is there a connection? *Biological Psychiatry*, *45*, 145–157.

Isaksen, J., & Holth, P. (2009). An operant approach to teaching joint attention skills to children with autism. *Behavioral Interventions*, *24*, 215–236.

Jacob, S., Brune, C.W., Carter, C.S., Leventhal, B.L., Lord, C., & Cook, E.H., Jr (2007). Deletion of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neuroscience Letters*, *417*, 6–9.

Jones, E., & Carr, E. (2004). Joint attention in children with autism: Theory and intervention. *Focus on Autism and Other Developmental Disabilities*, *19*, 13–26.

Jones, W., Carr, K., & Klin, A. (2008). Absence of preferential looking to the eyes of approaching adults predicts social disability in two-year-old toddlers with autism spectrum disorder. *Archives of General Psychiatry*, *65*, 946–954.

Kaale, A., Smith, L., & Sponheim, E. (2012). A randomized controlled trial of preschool-based joint attention intervention for children with autism. *Journal of Child Psychology and Psychiatry*, *53*, 97–105.

Kampe, K.K., Frith, C.D., Dolan, R.J., & Frith, U. (2001). Reward value of attractiveness and gaze. *Nature*, *413*, 589–602.

Kasari, C., Freeman, S., & Paparella, T. (2006). Joint attention and symbolic play in young children with autism: A randomized controlled intervention study. *Journal of Child Psychology and Psychiatry*, *47*, 611–620.

Kasari, C., Gulsrud, A.C., Wong, C., Kwon, S., & Locke, J. (2010). Randomized controlled caregiver mediated joint engagement intervention for toddlers with autism. *Journal of Autism and Developmental Disorders*, *40*, 1045–1056.

Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., … & Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans, *The Journal of Neuroscience*, *25*, 11489–11493.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry*, *59*, 809–816.

Koegel, L.K. (2000). Interventions to facilitate communication in autism. *Journal of Autism and Developmental Disorders*, *30*, 383–391.

Kohls, G., Schulte-Ruther, M., Nehrkorn, B., Muller, K., Fink, G.R., Kampe-Becker, I., … & Konrad, K.. (2012). Reward system dysfunction in autism spectrum disorders. *Social Cognitive and Affective Neuroscience*, 1–8. Advanced access published 11 April 2012. doi:10.1093/scan/nss033.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*, 673–676.

Landa, R.J., Holman, K.C., O'Neill, A.H., & Stuart, E.A. (2011). Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: A randomized control trial. *Journal of Child Psychology and Psychiatry*, *52*, 13–21.

Lawton, K., & Kasari, C. (2012). Brief report: Longitudinal improvements in the quality of joint attention in preschool children with autism. *Journal of Autism and Developmental Disorders*, *42*, 307–312.

Leekam, S.R., Lopez, B., & Moore, C. (2000). Attention and joint attention in preschool children with autism. *Developmental Psychology*, *36*, 261–273.

Lerer, E., Levi, S., Israel, S., Yaari, M., Nemanov, L., Mankuta, D., … & Ebstein, R.P. (2010). Low CD38 expression in lymphoblastoid cells and haplotypes are both associated with autism in a family-based study. *Autism Research*, *3*, 293–302.

Lerer, E., Levi, S., Salomon, S., Darvasi, A., Yirmiya, N., & Ebstein, R.P. (2008). Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. *Molecular Psychiatry*, *13*, 980–988.

Liu, X., Kawamura, Y., Shimada, T., Otowa, T., Koishi, S., Sugiyama, T., … & Sasaki T. (2010). Association of the oxytocin receptor (OXTR) gene polymorphisms with autism

doi:10.1111/jcpp.12061

spectrum disorder (ASD) in the Japanese population. *Journal of Human Genetics*, *55*, 137–141.
Liu, Y., & Wang, Z.X. (2003). Nucleus accumbens dopamine and oxytocin interact to regulate pair bond formation in female prairie voles. *Neuroscience*, *121*, 537–544.
Lord, C. (2000). Commentary: Achievements and future directions for intervention in communication and autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *30*, 393–398.
MacDonald, K., & Feifel, D. (2012). Oxytocin in schizophrenia: A review of evidence for its therapeutic effects. *Acta Neuropsychiatrica*, *24*, 130–146.
McPartland, J., Dawson, G., Webb, S.J., Panagiotides, H., & Carver, L.J. (2004). Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. *Journal of Child Psychological Psychiatry*, *45*, 1235–1245.
Modahl, C., Green, L.A., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., & Levin H. (1998). Plasma oxytocin levels in autistic children. *Biological Psychiatry*, *43*, 270–277.
Modi, M.E., & Young, L.J. (2012). The oxytocin system in drug discovery for autism: Animal models and novel therapeutic strategies. *Hormones and Behavior*, *61*, 340–350.
Mundy, P. (1995). Joint attention and social-emotional approach behavior in children with autism. *Developmental Psychopathology*, *7*, 63–82.
Mundy, P., & Gomes, A. (1998). Individual differences in joint attention skill development in the second year. *Infant Behavior and Development*, *21*, 469–482.
Mundy, P., Sigman, M., & Kasari, C. (1990). A longitudinal study of joint attention and language development in autistic children. *Journal of Autism and Developmental Disorders*, *20*, 115–128.
Mundy, P., Sigman, M., & Kasari, C. (1993). The theory of mind and joint attention in autism. In S. Baron-Cohen, H. Tager-Flusberg & D. Cohen (Eds.), *Understanding other minds: perspectives from autism* (pp. 181–203). New York, NY: Oxford University Press.
Mundy, P., Sigman, M., Ungerer, J., & Sherman, T. (1986). Defining the social deficits of autism: the contribution of non-verbal communication measures. *Journal of Child Psychology and Psychiatry*, *27*, 657–669.
Mundy, P., Sullivan, L., & Mastergeorge, A.M. (2009). A parallel and distributed-processing model of joint attention, social cognition and autism. *Autism Research*, *2*, 2–21.
Munesue, T., Yokoyama, S., Nakamura, K., Anitha, A., Yamada, K., Hayashi, K., … & Higashida, H. (2010). Two genetic variants of CD38 in subjects with autism spectrum disorder and controls. *Neuroscience Research*, *67*, 181–191.
Naoi, N., Tsuchiya, R., Yamaoto, J.I., & Nakamura, K. (2008). Functiona training for initiating joint attention in children with autism. *Research in Developmental Disabilities*, *29*, 595–609.
Neuhaus, E., Beauchaine, T.P., & Bernier, R. (2010). Neurobiological correlates of social functioning in autism. *Clinical Psychology Review*, *30*, 733–748.
Pedersen, C.A., Gibson, C.M., Rau, S.W., Salimi, K., Smedley, K.L., Casey, R.L., … & Penn, D.L. (2011). Intranasal oxytocin reduces psychotic symptoms and improves theory of mind and social perception in schizophrenia. *Schizophrenia Research*, *132*, 50–53.
Reibold, M., Mankuta, D., Lerer, E., Israel, S., Zhong, S., Nemanov, L., … & Ebstein, R.P. (2011). All-trans retinoic acid upregulates reduced CD38 transcription in lymphoblastoid cell lines from autism spectrum disorder. *Molecular Medicine, , 7-8*, 799–806.
Reichow, B. (2012). Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *42*, 512–520.
Ressler, K.J., Rothbaum, B.O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., … & Davis, M. (2004). Use of D-Cycloserine in phobic individuals to facilitate extinction of fear. *Archive of General Psychiatry*, *61*, 1136–1144.
Riekkinen, P., Legros, J.J., Sennef, C., Jolkkonen, J., Smitz, S., & Soininen, H. (1987). Penetration of DGAVP (Org 5667) across the blood-brain barrier in human subjects. *Peptides*, *8*, 261–265.
Rogers, S., & Lewis, H. (1989). An effective day treatment model for young children with pervasive developmental disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *28*, 207–214.
Sauer, C., Wörner, C., Kirsch, P., Montag, C., & Reuter, M. (2012). Effects of a common variant in the CD38 gene on social processing in an oxytocin challenge study: possible links to autism. *Neuropsychopharmacology*, *37*, 1474–1482.
Scaife, M., & Bruner, J. (1975). The capacity for joint visual attention in the infant. *Nature*, *253*, 255–256.
Schertz, H.H., Odom, S.L., Baggett, K.M., & Sideris, J.H. (2013). Effects of joint attention mediated learning for toddlers with autism spectrum disorders: an initial randomized control study. *Early Childhood Research Quarterly*, *28*, 249–258.
Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology*, *80*, 1–27.
Scott-Van Zeeland, A.A., Dapretto, M., Ghahremani, D.G., Poldrack, R.A., & Bookheimer, S.Y. (2010). Reward processing in autism. *Autism Research*, *3*, 53–67.
Sigman, M., & Kasari, C. (1995). Joint attention across contexts in normal and autistic children. In C. Moore & P.J. Dunham (Eds.), *Joint attention: Its origins and role in development* (pp. 189–203). Hillsdale, NJ: Lawrence Erlbaum.
Sigman, M., Kasari, C., Kwon, J., & Yirmiya, N. (1992). Responses to the negative emotions of others by autistic, mentally retarded and normal children. *Child Development*, *63*, 796–807.
Sigman, M., Mundy, P., Sherman, T., & Ungerer, J. (1986). Social interactions of autistic, mentally retarded and normal children and their caregivers. *Journal of Child Psychology and Psychiatry*, *27*, 647–656.
Sigman, M., & Ruskin, E. (1999). Continuity and change in the social competence of children with autism, Down syndrome and developmental delays. *Monograph of the Society for Research on Child Development*, *64*, 1–114.
Siller, M., & Sigman, M. (2002). The behaviors of parents of children with autism predict the subsequent development of their children's communication. *Journal of Autism and Developmental Disorders*, *32*, 77–89.
Skuse, D.H., & Gallagher, L. (2011). Genetic influences on social cognition. *Pediatric Research*, *69*, 85R–91R.
Sullivan, P.F. (2007). Spurious genetic associations. *Biological Psychiatry*, *61*, 1121–1126.
Tansey, K.E., Brookes, K.J., Hill, M.J., Cochrane, L.E., Gill, M., Skuse, D., … & Anney, R.J.L. (2010). Oxytocin receptor (OXTR) does not play a major role in the aetiology of autism: Genetic and molecular studies. *Neuroscience Letters*, *474*, 163–167.
Taylor, B.A., & Hoch, H. (2008). Teaching children with autism to respond to and initiate bids for joint attention. *Journal of Applied Behavior Analysis*, *41*, 377–391.
Tomasello, M. (1995). Joint attention as social cognition. In C. Moore & P.J. Dunham (Eds.), *Joint attention: Its origins and role in development* (pp. 103–130). Hillsdale, NJ: Lawrence Erlbaum Associates.
Tomasello, M., & Farrar, M.J. (1986). Joint attention and early language. *Child Development.*, *57*, 1454–1463.
Tops, M., Van Peer, J.M., Korf, J., Wijers, A.A., & Tucker, D.M. (2007). Anxiety, attachment, and cortisol predict plasma oxytocin. *Psychophysiology*, *44*, 444–449.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B.A., … & Meyer-Lindenberg, A. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of the National Academy of Sciences*, *107*, 13936–13941.

Vrtička, P., Andersson, F., Grandjean, D., Sander, D., & Vuilleumier, P. (2008). Individual attachment style modulates human amygdala and striatum activation during social appraisal. *PLoS One*, *3*, e2868.

Walum, H., Lichtenstein, P., Neiderhiser, J.M., Reiss, D., Ganiban, J.M., Spotts, E.L., … & Westberg, L. (2012). Variation in the oxytocin receptor gene is associated with pair-bonding and social behavior. *Biological Psychiatry*, *71*, 419–426.

Weisman, O., Zagoory-Sharon, O., & Feldman, R. (2012). Intranasal oxytocin administration is reflected in human saliva. *Psychoneuroendocrinology*, *37*, 1582–1586.

Wermter, A.K., Kamp-Becker, I., Hesse, P., Schulte-Körne, G., Strauch, K., & Remschmidt, H. (2009). Evidence for the involvement of genetic variation in the oxytocin receptor gene (OXTR) in the etiology of autistic disorders on high-functioning level. *American Journal of Medical Genetics Part B*, *153*, 629–639.

Whalen, C., & Schreibman, L. (2003). Joint attention training for children with autism using behavior modification procedures. *Journal of Child Psychology and Psychiatry*, *44*, 456–468.

White, P.J., O'Reilly, M., Streusand, W., Levine, A., Sigafoos, J., & Lancioni Agular, J. (2011). Best practices for teaching joint attention: A systematic review of the intervention literature. *Research in Autism Spectrum Disorders*, *5*, 1283–1295.

Wu, S., Jia, M., Ruan, Y., Liu, J., Guo, Y., Shuang, M., … & Zhang, D. (2005). Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. *Biological Psychiatry*, *58*, 74–77.

Ylisaukko-oja, T., Alarcon, M., Cantor, R.M., Auranen, M., Vanhala, R., Kempas, E., … & Peltonen, L. (2006). Search for autism loci by combined analysis of autism genetic resource exchange and Finnish families. *Annals of Neurology*, *59*, 145–155.

Young, K.A., Liu, Y.Y., & Wang, Z. (2008). The neurobiology of social attachment: A comparative approach to behavioral, neuroanatomic, and neurochemical studies. *Comparative Biochemistry, and Physiology, Part C*, *148*, 401–410.

Yrigollen, C.M., Han, S.S., Kochetkova, A., Babitz, T., Chang, J.T., Volkmar, F.R., … & Grigorenko, E.L. (2008). Genes controlling affiliative behavior as candidate genes for autism. *Biological Psychiatry*, *63*, 911–916.

Zink, C.F., & Meyer-Lindenberg, A. (2012). Human neuroimaging of oxytocin and vasopressin in social cognition. *Hormones and Behavior*, *61*, 400–409.

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GENERAL DISCUSSION

The goal of this set of experiments was to empirically test the social motivation hypothesis in children with autism spectrum disorders (ASD). Through these investigations, I hoped to provide a better understanding of factors that contribute to social deficits in ASD. This research provides evidence in favor of the social motivation hypothesis, and enhances our understanding of the conditions under which social motivation is impaired in ASD. The final chapter suggests future directions for research combining pharmacological and behavioral interventions in order to improve social motivation in ASD.

In Chapter 1, we were interested in how social motivation occurs in typically developing (TD) 6- to 8-year-old children. We created a new event-related potential (ERP) paradigm to investigate reward anticipation in TD children for social versus nonsocial stimuli while keeping reward properties and physical stimulus characteristics controlled between conditions. Children played a guessing game for a food reward (goldfish crackers), and social versus nonsocial stimuli were incidental to the task. Incidental stimuli in the social condition were a smiling face for correct responses and a frowning face for incorrect responses. Incidental stimuli in the nonsocial condition were pictures from the social condition scrambled into an upwards-facing arrows for correct responses and downwards facing arrows for incorrect responses. Importantly, “correct” versus “incorrect” responses were predetermined by the computer. Results from Chapter 1 suggest that TD children have increased reward anticipation for rewards accompanied by an incidental social stimulus versus an incidental nonsocial stimulus.

In Chapter 2, we compared a subset of TD children from Chapter 1 (matched on gender and IQ score) with a group of children with ASD on the task developed in Chapter 1. Additionally, we measured both reward anticipation (via the stimulus preceding negativity, SPN), and reward processing (via the feedback related negativity, FRN). The results suggest that children with ASD have differences both anticipating and processing rewards accompanied by social stimuli versus their TD peers.

Results from the SPN suggest that children with ASD have intact reward anticipation for nonsocial stimuli, but significantly less reward anticipation for social stimuli compared to TD children. Results from the FRN were more complex, but suggest that TD children and children with ASD are differentially affected by correct versus incorrect feedback for social versus nonsocial stimuli. Results from the FRN provide further evidence that these two groups of children elicit differential reward processing for social versus nonsocial stimuli.

Taken together, the results from the SPN and FRN provide evidence in favor of the social motivation hypothesis insofar as children with ASD seem to have smaller reward responses (both in anticipation and processing) for rewards accompanied by social stimuli compared to TD children. Interestingly, the results provide evidence that reward deficits in ASD are specific to social stimuli, rather than a more global reward deficit in this population.

The experiment in Chapter 3 investigated whether deficits in social motivation are present for all faces, or only for certain types of face stimuli. Specifically, I was

interested in whether children with ASD show increased reward anticipation for familiar faces (e.g., caregiver) versus an unfamiliar face (e.g., stranger). The novel task that was originally developed in Chapter 1 was used with a new group of children with and without ASD. Rather than being limited to two conditions (social versus nonsocial), the experiment systematically tested four conditions (familiar social, unfamiliar social, familiar nonsocial, and unfamiliar nonsocial). Familiar faces were pictures of a caregiver, and unfamiliar faces were pictures of another child's caregiver, matched on gender, hair and eye color, and presence or absence of glasses.

Results from Chapter 3 suggest a lack of reward anticipation difference between familiar versus unfamiliar stimuli for both TD children and those with ASD. When we collapsed across the familiar and unfamiliar stimuli, we found that we replicated results from Chapter 2 for reward anticipation. That is, TD children have increased reward anticipation for social versus nonsocial stimuli, while children with ASD do not.

Another finding from Chapter 3 was the presence of an Nc-like component in anticipation of social and nonsocial stimuli for both children with and without ASD. Previous work on the Nc has used passive viewing paradigms, and has only examined the Nc as it occurs in *response* to stimuli. We found an Nc component that occurred prior to the onset of social and nonsocial stimuli. The Nc differed between groups for social stimuli, with TD children having a larger Nc component prior to social stimuli compared to children with ASD (for both familiar and unfamiliar faces). This provides

evidence that the Nc may occur as an *anticipatory* component, and suggests that future studies should attempt to elicit an anticipatory Nc during passive viewing.

Chapter 4 suggests how future research might increase social motivation pharmacologically with the neuropeptide oxytocin, and reviews previous research on oxytocin and social behavior. Chapter 4 uses a core social deficit, joint attention, as a test case to understand how oxytocin could be beneficial in conjunction with behavioral interventions. This chapter discusses how joint attention has been historically difficult to intervene upon with behavioral methods alone, because it requires social motivation. If children with ASD have impaired social motivation, behavioral interventions may not be enough to increase joint attention. However, if a pharmacological agent, such as oxytocin, could increase baseline levels of social motivation, behavioral intervention would likely be more successful. That is, if oxytocin prior to each individual session of intervention increases social motivation, each session would likely be more successful at increasing joint attention.

Taken together, Chapters 1 and 2 provide novel empirical evidence in support of the social motivation hypothesis, and suggest that children with ASD have specific reward impairments for social stimuli. Chapter 3 extends this work in order to explore whether especially salient social stimuli, such as a caretaker's face, can ameliorate deficits in social motivation in ASD. While Chapter 3 did not find evidence that familiar faces improve social reward deficits in ASD, the results replicated the findings from Chapters 1 and 2, and moreover, the results suggest novel applications of the Nc as a potential anticipatory component.

In summary, Chapters 1-3 provide novel neuroscience evidence for the social motivation hypothesis, and Chapter 4 makes suggestions for future research into the combination of pharmacology and behavioral interventions in order to improve social deficits in ASD that rely on social motivation. This dissertation expands upon previous investigations of the reward system in ASD, and is the first group of studies to measure reward anticipation and processing for social versus nonsocial stimuli while controlling for reward and stimulus properties.