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Unlocking Clinical Outcomes: Exploring Individual Differences, Intervention Strategies, and Neural Reward Systems in Autistic Children and Adolescents

A Dissertation submitted in partial satisfaction
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by

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ABSTRACT OF THE DISSERTATION

Unlocking Clinical Outcomes: Exploring Individual Differences, Intervention Strategies, and Neural Reward Systems in Autistic Children and Adolescents

by

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University of California, Riverside, September 2024
Dr. Katherine Meltzoff, Chairperson

This dissertation examines event-related potentials (ERPs), measured from electroencephalogram (EEG) recordings, of social and nonsocial reward processing in a predominantly Latinx group of autistic children and teens before and after intervention. Additionally, this investigation proposes using objective, neuroscientific techniques to measure clinical trial effects of oxytocin administration, a neuropeptide associated with social behaviors.

Chapter 1 investigates neural response and attenuation of social and nonsocial rewards via the reward positivity component (RewP) in autistic and non-autistic adolescents before and after participation in the Program for the Education and Enrichment of Relational Skills (PEERS) intervention. Increased reward sensitivity was observed during the first half of trials in the autistic group after intervention. Neural correlates of reward also predicted improvements in social behavior. This suggests that participating in PEERS increases reward system sensitivity in autistic teens and that

PEERS may be most effective for teens who have “room to grow” in their social reward responsivity.

Chapter 2 examines individual differences in anticipation of and response to rewards in autistic and non-autistic teens before and after PEERS. Older adolescents and those with lower parent-reported social motivation prior to participation in PEERS displayed increased social reward anticipation (more robust stimulus-preceding negativity; SPN) from pre- to post-intervention. Participants who displayed more parent-reported social motivation before intervention and were more actively engaged in the PEERS intervention, evidenced by increased social reward processing (more robust RewP) from pre- to post-intervention. Findings support a ‘precision model’ approach to autism intervention with an emphasis on brain-based outcomes.

Chapter 3 reviews the therapeutic effects of oxytocin on social behaviors in autistic individuals, focusing on functional outcomes from neuroimaging investigations. Additionally, this chapter proposes a model for clinical trials that includes simultaneous behavioral intervention and oxytocin administration and the hypothesized role of the neural reward system on intervention outcomes.

In sum, this dissertation examines neural measures of reward-related brain activity as an outcome measure of intervention in autistic populations and proposes methods for future studies examining combined treatment effects of behavioral and oxytocin interventions.

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Introduction

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by unconventional social behaviors and the presence of repetitive and restricted behaviors (American Psychiatric Association, 2022). The Social Motivation Hypothesis proposes that the brain's reward centers process social stimuli differently in autistic versus neurotypical populations (Chevallier et al., 2012; Clements et al., 2018), which may have downstream impacts on social development across the lifespan. For example, a reduction in social interactions with peers and classmates may result in further challenges in social skills or disruptions in social learning. As such, reward processing is an important area of study in ASD (Supekar et al., 2018). Demonstration of the Social Motivation Hypothesis often relies on the use of brain-based methods, including neural and neuropsychological markers of reward processing (Bottini, 2018).

Neural Evidence of Social Motivation

Reward centers of the brain include the mesolimbic dopamine system, comprised of the midbrain (via the ventral tegmental area) and striatum (via the nucleus accumbens) (Haber & Knutson, 2010; Supekar et al., 2018). The mesolimbic dopamine circuit is activated by rewarding stimuli and is associated with desire, wanting, and excitement (Depue & Morrone-Strupinsky, 2005; Neuhaus et al., 2010).

Past studies have suggested that autistic individuals demonstrate dampened or atypical reward-related brain activity compared to neurotypical peers in response to social stimuli (i.e., faces) (Dichter, Richey, et al., 2012). Differences in social motivation

may also be impacted by individual differences in reward processing, including characteristics such as cognitive ability, symptom severity, age, and the varied nature of autism profiles. The Social Motivation Hypothesis may identify or inform interventions that incorporate rewarding stimuli into social situations or environments to enhance reward responses, particularly interventions with reinforcement principles.

An updated view of reward processing in ASD suggests autistic individuals display lower activation in the reward system in response to various stimulus types, including social and nonsocial inputs (e.g., dollars, money) (Dichter, Felder, et al., 2012; Kohls et al., 2014). As such, a modified assumption of the Social Motivation Hypothesis may include domain-general altered responses to rewards (Bottini, 2018). Taken together, a more nuanced measure of individual differences and aberrant reward processing in ASD may elucidate intervention effectiveness.

Measuring Intervention Outcomes

Behavioral interventions have been designed to improve social communication skills in ASD by augmenting interactions with others and helping autistic individuals form meaningful relationships (Dawson & Burner, 2011; Reichow et al., 2016). Interventions using behavioral principles have been effective at improving language skills and social behaviors, as well as reducing anxiousness and aggression (Dawson & Burner, 2011). Studies that have integrated behavioral and brain-based methods of outcome demonstrate altered brain activity after behavioral intervention, though findings may be mixed in this emerging field (for review, see Stavropoulos, 2017).

For example, Van Hecke et al. (2015) found that after participating in the Program for the Education and Enrichment of Relational Skills (PEERS) social skills intervention, autistic teens displayed increased left-dominant gamma asymmetry (which is associated with increased motivation and affect), such that their brain activity appeared similar to that of neurotypical teens. Additionally, autistic teens who (a) demonstrated greater knowledge of PEERS concepts, (b) had more get-togethers during intervention, and (c) had improved social skills after intervention displayed a greater degree of relative left-hemisphere dominant EEG activity in the gamma band (Van Hecke et al., 2015). Taken together, these findings provide evidence that participation in PEERS may lead to autistic adolescents being more willing to engage with peers, as evidenced by increased social approach and motivation reflected by EEG and behavioral findings.

With the use of neuroscientific methodologies, it may be possible to predict individual outcomes of intervention that advance a "precision medicine" approach (e.g., predict who is most likely to benefit from a specific intervention). Moreover, neural changes in the reward system after intervention may provide an empirical basis for determining who may benefit most from particular interventions and inform how interventions may be tailored to improve outcomes.

Oxytocin

Aligned with the Social Motivation Hypothesis, deficits in dopamine systems may alter reward responses. Oxytocin, a neuropeptide, plays a role in modulating dopamine activity in social engagement (Dawson & Bernier, 2007). Studies have shown that oxytocin modulates behaviors in autistic individuals by enhancing social processes,

including facial perception, social learning, theory of mind, and social perception (Baumgartner et al., 2008; Domes et al., 2007; Guastella et al., 2008; Korisky et al., 2022; Parker et al., 2017; Petrovic et al., 2008). However, some investigations have not found clinical efficacy of oxytocin administration in autistic individuals, such that no changes in social behaviors or social functioning were identified (Daniels et al., 2023; Guastella et al., 2015; Sikich et al., 2021). This may be due to the heterogeneity of effects and individual differences in autistic individuals or may be a result of measures of social behaviors that may not be sensitive to change.

Simultaneous exposure to oxytocin administration and behavioral intervention may augment long-term social communication outcomes beyond that observed with either single-dose oxytocin administration or behavioral intervention in isolation. As such, if oxytocin increases social responses and attention to the social environment in some autistic individuals, behavioral intervention may be implemented after oxytocin administration to leverage these temporary neural changes (Stavropoulos & Baker, 2021). It remains unclear if behavioral interventions lead to better outcomes compared to behavioral intervention or oxytocin alone. Given the heterogeneity of ASD and the varied effectiveness of oxytocin, empirical investigations combining treatment modalities to augment long-term social communication outcomes may be warranted.

Chapters

Chapter 1 investigates neural responses and attenuation of social and nonsocial rewards in teens with and without ASD before and after participation in the PEERS intervention. Reward response was measured using the reward positivity component

(RewP), an event-related potential (ERP) characterized by positivity in response to gains versus losses (Holroyd et al., 2008; Proudfit, 2015). The purpose of this study was to understand processes of habituation and sensitization to social stimuli among adolescents with ASD by examining patterns of reward-related neural across an ERP task (e.g., activity in the first versus the second half of a task). The ERP task utilized was a reward-based guessing game in which participants were presented with rewards accompanied by incidental face or nonface stimuli.

Chapter 2 examines individual differences in anticipation of and response to rewards in teens with autism before and after PEERS. The stimulus-preceding negativity (SPN) component measures brain activity prior to stimulus presentation and serves as a measure of anticipation (van Boxtel & Böcker, 2004). Anticipation of and response to rewards involve separate cognitive processes, and both processes should be investigated (Meyer et al., 2021) to understand the entirety of how the reward system functions in individuals with and without ASD. This study measured how changes in reward-related brain activity before and after intervention relate to individual factors (i.e., social skills).

Chapter 3 reviews therapeutic effects of oxytocin on social behaviors in individuals with ASD, focusing on functional outcomes from neuroimaging investigations. Additionally, this chapter proposes a suggested model for clinical trials that includes simultaneous behavioral intervention and oxytocin administration and the hypothesized role of the neural reward system on intervention outcomes.

In sum, this dissertation examines neural measures of reward-related brain activity as an outcome measure of intervention in autistic populations and proposes

methods for future studies examining combined treatment effects of behavioral and oxytocin interventions.

References

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). American Psychiatric Publishing.

Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., & Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, *58*(4), 639–650. https://doi.org/10.1016/j.neuron.2008.04.009

Bottini, S. (2018). Social reward processing in individuals with autism spectrum disorder: A systematic review of the social motivation hypothesis. *Research in Autism Spectrum Disorders*, *45*, 9–26. https://doi.org/10.1016/j.rasd.2017.10.001

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*(4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007

Clements, C. C., Zoltowski, A. R., Yankowitz, L. D., Yerys, B. E., Schultz, R. T., & Herrington, J. D. (2018). Evaluation of the social motivation hypothesis of autism: A systematic review and meta-analysis. *JAMA Psychiatry*, *75*(8), 797. https://doi.org/10.1001/jamapsychiatry.2018.1100

Daniels, N., Moerkerke, M., Steyaert, J., Bamps, A., Debbaut, E., Prinsen, J., Tang, T., Van der Donck, S., Boets, B., & Alaerts, K. (2023). Effects of multiple-dose intranasal oxytocin administration on social responsiveness in children with autism: A randomized, placebo-controlled trial. *Molecular Autism*, *14*(1), 16. https://doi.org/10.1186/s13229-023-00546-5

Dawson, G., & Bernier, R. (2007). Development of social brain circuitry in autism. In D. Coch, G. Dawson, & K. Fischer (Eds.), *Human behavior and the developing brain* (2nd ed.). Guilford Press.

Dawson, G., & Burner, K. (2011). Behavioral interventions in children and adolescents with autism spectrum disorder: A review of recent findings. *Current Opinion in Pediatrics*, *23*(6), 616–620. https://doi.org/10.1097/MOP.0b013e32834cf082

Depue, R. A., & Morrone-Strupinsky, J. V. (2005). A neurobehavioral model of affiliative bonding: Implications for conceptualizing a human trait of affiliation. *The Behavioral and Brain Sciences*, *28*(3), 313–350; discussion 350-395. https://doi.org/10.1017/S0140525X05000063

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*(2), 160–172. https://doi.org/10.1093/scan/nsq095

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*(2), 147–160. https://doi.org/10.1007/s10803-011-1221-1

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007). Oxytocin improves "mind-reading" in humans. *Biological Psychiatry*, *61*(6), 731–733. https://doi.org/10.1016/j.biopsych.2006.07.015

Guastella, A. J., Gray, K. M., Rinehart, N. J., Alvares, G. A., Tonge, B. J., Hickie, I. B., Keating, C. M., Cacciotti-Saija, C., & Einfeld, S. L. (2015). The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: A randomized controlled trial. *Journal of Child Psychology and Psychiatry*, *56*(4), 444–452. https://doi.org/10.1111/jcpp.12305

Guastella, A. J., Mitchell, P. B., & Dadds, M. R. (2008). Oxytocin increases gaze to the eye region of human faces. *Biological Psychiatry*, *63*(1), 3–5. https://doi.org/10.1016/j.biopsych.2007.06.026

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*(1), 4–26. https://doi.org/10.1038/npp.2009.129

Holroyd, C. B., Pakzad-Vaezi, K. L., & Krigolson, O. E. (2008). The feedback correct-related positivity: Sensitivity of the event-related brain potential to unexpected positive feedback. *Psychophysiology*, *45*(5), 688–697. https://doi.org/10.1111/j.1469-8986.2008.00668.x

Kohls, G., Thönessen, H., Bartley, G. K., Grossheinrich, N., Fink, G. R., Herpertz-Dahlmann, B., & Konrad, K. (2014). Differentiating neural reward responsiveness in autism versus ADHD. *Developmental Cognitive Neuroscience*, *10*, 104–116. https://doi.org/10.1016/j.dcn.2014.08.003

Korisky, A., Goldstein, A., & Gordon, I. (2022). The dual neural effects of oxytocin in autistic youth: Results from a randomized trial. *Scientific Reports*, *12*(1), Article 1. https://doi.org/10.1038/s41598-022-19524-7

Meyer, G. M., Marco-Pallarés, J., Boulinguez, P., & Sescousse, G. (2021). Electrophysiological underpinnings of reward processing: Are we exploiting the full potential of EEG? *NeuroImage*, *242*, 118478. https://doi.org/10.1016/j.neuroimage.2021.118478

Neuhaus, E., Beauchaine, T. P., & Bernier, R. (2010). Neurobiological correlates of social functioning in autism. *Clinical Psychology Review*, *30*(6), 733–748. https://doi.org/10.1016/j.cpr.2010.05.007

Parker, K. J., Oztan, O., Libove, R. A., Sumiyoshi, R. D., Jackson, L. P., Karhson, D. S., Summers, J. E., Hinman, K. E., Motonaga, K. S., Phillips, J. M., Carson, D. S., Garner, J. P., & Hardan, A. Y. (2017). Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. *Proceedings of the National Academy of Sciences*, *114*(30), 8119–8124. https://doi.org/10.1073/pnas.1705521114

Petrovic, P., Kalisch, R., Singer, T., & Dolan, R. J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(26), 6607–6615. https://doi.org/10.1523/JNEUROSCI.4572-07.2008

Proudfit, G. H. (2015). The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology*, *52*(4), 449–459. https://doi.org/10.1111/psyp.12370

Reichow, B., Boyd, B. A., Barton, E. E., & Odom, S. L. (2016). *Handbook of early childhood special education*. Springer Science+Business Media.

Sikich, L., Kolevzon, A., King, B. H., McDougle, C. J., Sanders, K. B., Kim, S.-J., Spanos, M., Chandrasekhar, T., Trelles, M. D. P., Rockhill, C. M., Palumbo, M. L., Witters Cundiff, A., Montgomery, A., Siper, P., Minjarez, M., Nowinski, L. A., Marler, S., Shuffrey, L. C., Alderman, C., … Veenstra-VanderWeele, J. (2021). Intranasal oxytocin in children and adolescents with autism spectrum disorder. *New England Journal of Medicine*, *385*(16), 1462–1473. https://doi.org/10.1056/NEJMoa2103583

Stavropoulos, K. K. M. (2017). Using neuroscience as an outcome measure for behavioral interventions in autism spectrum disorders (ASD): A review. *Research in Autism Spectrum Disorders*, *35*, 62–73. https://doi.org/10.1016/j.rasd.2017.01.001

Stavropoulos, K. K. M., & Baker, E. (2021). Priming the pathway: Combining oxytocin and behavioral intervention to improve outcomes in autism spectrum disorder. In W. Wu (Ed.), *IntechOpen*. https://doi.org/10.5772/intechopen.96859

Supekar, K., Kochalka, J., Schaer, M., Wakeman, H., Qin, S., Padmanabhan, A., & Menon, V. (2018). Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism. *Brain*, *141*(9), 2795–2805. https://doi.org/10.1093/brain/awy191

van Boxtel, G. J. M., & Böcker, K. B. E. (2004). Cortical measures of anticipation. *Journal of Psychophysiology*, *18*, 61–76. https://doi.org/10.1027/0269-8803.18.23.61

Van Hecke, A. V., Stevens, S., Carson, A. M., Karst, J. S., Dolan, B., Schohl, K., McKindles, R. J., Remmel, R., & Brockman, S. (2015). Measuring the plasticity of social approach: A randomized controlled trial of the effects of the PEERS intervention on EEG asymmetry in adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *45*(2), 316–335. https://doi.org/10.1007/s10803-013-1883-y

Chapter 1

Increased neural reward responsivity in adolescents with ASD after social skills intervention

Increased Neural Reward Responsivity in Adolescents with ASD after Social Skills Intervention

Baker, E., Veytsman, E., Martin, A. M., Blacher, J. & Stavropoulos, K. K. M. Increased neural reward responsivity in adolescents with ASD after social skills intervention**.** *Brain Sciences, 10*(6), 1–11. https://doi.org/10.3390/brainsci10060402

Abstract

The reward system has been implicated as a potential neural mechanism underlying social-communication deficits in individuals with autism spectrum disorder (ASD). However, it remains unclear whether the neural reward system in ASD is sensitive to behavioral interventions. The current study measured the reward positivity (RewP) in response to social and nonsocial stimuli in seven adolescents with ASD before and after participation in the Program for the Education and Enrichment of Relational Skills (PEERS®) intervention. This study also included seven neurotypical adolescents who were tested at two time points but did not receive intervention. We examined the RewP across the course of a task by comparing brain activity during the first versus second half of trials to understand patterns of responsivity over time. Improvements in social skills and decreased social-communication impairments for teens with ASD were observed after PEERS®. Event-related potential (ERP) results suggested increased reward sensitivity during the first half of trials in the ASD group after intervention.

Adolescents with ASD who exhibited less reward-related brain activity before intervention demonstrated the greatest behavioral benefits from the intervention. These findings have implications for how neuroscience can be used as an objective outcome measure before and after intervention in ASD.

Introduction

The cognitive process of habituation can be conceptualized in a variety of ways, but is generally considered a decreased response to stimuli after repeated exposure [1]. Individuals with autism spectrum disorder (ASD), defined by social communication deficits and the presence of restricted interests and repetitive behaviors [2], display altered rates of habituation. Specifically, individuals with ASD do not habituate to social information at the same rate as neurotypical controls, as evidenced through amygdala activation to faces over time [3–7]. In individuals with ASD, repeated presentation of social information elicits activation rates similar to that of novel stimuli for neurotypical subjects [8]. In neurotypical individuals, habituation tends to occur at a lower rate for stimuli that are more salient, intense, or stimulating [1,9]. Salient information may cause sensitization to stimuli, such that heightened responses can be observed over time [1,10]. One explanation for slowed habituation rates in response to faces is that individuals with ASD find processing social information more challenging than their neurotypical peers and thus must employ more cognitive resources. Alternatively, lack of habituation could reflect sensitization in this population.

Beyond reflecting the allocation of cognitive resources, habituation is also an indicator of learning. Reinforcement learning is facilitated by the goal of maximizing

rewards and satisfying desired outcomes. The reward system has been discussed at length in relation to the core symptoms of ASD. According to the social motivation hypothesis, individuals with ASD experience social interactions as less rewarding than their neurotypical peers, which may lead to reduced social initiation during critical periods of social development [11]. Investigations utilizing electroencephalography (EEG) to measure reward-specific event-related potentials (ERPs) suggest that children with ASD tend to find nonsocial stimuli more salient than social stimuli, and that children with ASD have less reward-related brain activity than that of their neurotypical peers in response to faces [12]. Thus, it is not that the reward system in ASD populations is under-active in response to all stimulus types, but that it is selectively functioning for some categories and not others [13]. However, the literature is mixed on whether the reward system is globally hypoactive in individuals with ASD [14,15]. If the reward system is selectively functioning in ASD, this system might be malleable, and behavioral intervention strategies that focus on social reinforcement might increase brain activity in response to social stimuli in this population. This hypothesis is supported by previous literature demonstrating neural changes in participants with ASD from pre- to post-intervention [16–22].

Social skills interventions for individuals with ASD often implement strategies of reinforcement learning, including applied behavior analysis and social skills training [23–25]. The goal of many interventions is to provide training for independent skill acquisition, ranging from a reduction in maladaptive behavior to increasing social engagement at school. Considerations of habituation or sensitization before and after such

interventions are pertinent to not only the effectiveness of intervention but also the interpretation of outcomes.

Understanding how reward-related brain activity changes across the course of a task for individuals with and without ASD can increase our understanding of whether habituation or sensitization occurs at a similar rate across populations, and whether such activity is affected by participation in a social skills intervention. One method for measuring change in brain activity across a task is analyzing brain activity during the first and second halves of a task separately. In the current study, we sought to understand processes of habituation and sensitization to social stimuli among adolescents with ASD by examining patterns of reward-related neural responses to social versus nonsocial stimuli across a task (e.g., activity in the first versus second half of a task), before and after participation in a social skills intervention. The ERP task utilized was a reward-based guessing game in which participants were presented with rewards accompanied by incidental face or nonface stimuli.

Methods

Participants

Participants included seven adolescents with ASD, and seven age- and gender-matched neurotypical (TD) adolescents. Detailed information about participant demographics can be found in Table 1. No significant differences in age or IQ were observed between groups (*p's* > 0.70).

Table 1. Descriptive characteristics of the autism spectrum disorder (ASD) and neurotypical (TD) groups.

Variable	ASD	TD
Gender	6 male, 1 female	6 male, 1 female
Age in years, *M (SD), Range*	13.88 (2.21), 11.26–16.98	13.46 (2.29), 10.10–17.10
IQ, *M (SD), Range*	104.14 (17.36), 77–129	102.50 (17.96), 79–128
White *n*	2	1
Latino *n*	4	4
Mixed Race *n*	1	2
Maternal Education Level		
Less Than College	5	2
College and Above	2	3
Missing Data	0	2
Household Income		
Up to $50,000	3	1
$50,001–$100,000	2	1
Over $100,001	2	2
Missing Data	0	3

For both the ASD and TD groups, exclusionary criteria included a history of seizures/epilepsy, a history of brain injury or disease, or a diagnosis of intellectual disability. For the TD group, immediate family history of ASD or developmental disabilities, or any psychiatric diagnosis for the adolescent was exclusionary. For the ASD group, a diagnosis of ASD was required, though commonly co-occurring disorders were not exclusionary (e.g., ADHD). For the ASD group, history of serious psychiatric illness (e.g., schizophrenia, bipolar disorders) or a recent (within 6 months) psychiatric hospitalization were exclusionary.

The study took place in inland Southern California with a large Latinx population [26]. Participant families were recruited via flyers posted online and via local community organizations. Those who expressed interest were contacted for an initial phone screen.

At the initial intake appointment, informed consent and assent (from adolescents) were obtained.

Behavioral Intervention (Program for the Education and Enrichment of Relational Skills, (PEERS®) [27–30])

PEERS® is a manualized intervention designed to help adolescents make and keep friends (see [31] for intervention details). PEERS® consists of 16 weekly 1.5 h group sessions with concurrent but separate adolescent and parent groups. Parents learn how to support their adolescents in practicing and maintaining skills outside of the group. All groups were run by PEERS® certified providers.

Measures

Cognitive abilities were assessed using the 2-subtest Wechsler Abbreviated Scales of Intelligence [32] (WASI-II); an IQ under 70 was exclusionary for both groups. For adolescents with ASD, diagnosis was confirmed using the Autism Diagnostic Observation Schedule, Second Edition [33] (ADOS-2), and motivation to learn how to make and keep friends was assessed using the Mental Status Checklist [27]. Trained study staff performed these assessments. As these measures were used to confirm eligibility, they were only completed prior to the intervention.

Questionnaires

Data reported here are part of a larger-scale study. Caregivers completed the Social Responsiveness Scale, Second Edition [34] (SRS-2) and the Social Skills Improvement System [35] (SSIS) both before the intervention began (Time 1), and immediately after intervention completion (Time 2). Times 1 and 2 were approximately 4

months apart. Neurotypical adolescents (TD participants) did not receive PEERS®, but had lab visits at Times 1 and 2, where each visit was four months apart. In addition, all adolescents completed the Test of Adolescent Social Skills Knowledge, Revised [28] (TASSK-R) at both Time 1 and Time 2, which measures acquisition of the concepts taught in PEERS®.

Electrophysiology Stimuli and Task

The stimuli and task are described in detail in previously published manuscripts [12,36,37]. Briefly, the task was a guessing game in which participants saw a left and right visual stimulus (question marks), and 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.

In previously published manuscripts utilizing this task, participants were told that the reward for each correct answer was a small snack; here, the food reward was an Oreo cookie, or if preferred, fruit snacks or goldfish crackers. Participants were told that if they guessed correctly, they would see a ring of intact Oreo cookies, and the cookies would be crossed out for incorrect answers. There were two blocked feedback conditions: Social versus nonsocial. Importantly, in both the social and nonsocial feedback trials, the face/arrow information was incidental (e.g., the face/arrow image was not part of the overt task). Thus, differences in brain activity between social and nonsocial conditions were not due to differences in tangible rewards or differences in task structure. Incidental

stimuli in the social condition were faces obtained from the NimStim database [38] that were smiling for “correct” answers and frowning for “incorrect” answers. 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 order of social versus nonsocial blocks was counterbalanced between participants.

A computer program predetermined correct versus incorrect answers in a pseudorandom order, such that children got 50% “correct” and 50% “incorrect,” with no more than three of the same answer-type in a row. The two feedback conditions (face/“social” trials and arrow/“nonsocial” trials) were tested in separate blocks, each composed of 50 trials.

EEG Recording

Participants wore a standard, fitted cap (Brain Products ActiCap) with 32 silver/silver-chloride (Ag/AgCl) electrodes placed in accordance with the extended international 10–20 system. Continuous EEG was recorded using a Brain Vision Recorder with a reference electrode at Cz, and re-referenced offline to the average activity at left and right mastoids. Electrode resistance was kept under 50 kOhms. Continuous EEG was amplified with a directly coupled high pass filter (DC), and notch filter (60 Hz). The signal was digitized at a rate of 500 samples per second. 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. Trials were time locked to the onset of the feedback stimulus. To measure reward

processing, the baseline period was −100–0 ms, and the data were epoched from −100 to 800 ms. Trials with no behavioral response, or containing electrophysiological artifacts, were excluded.

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 [39], with a 200 ms moving window, a 100 ms window step, and a 150 mV voltage threshold.

For both conditions (face, arrow) and both feedback types (correct, incorrect), mean brain activity was calculated between 275 and 425 ms after feedback onset. The reward positivity (RewP) was defined as a difference wave, wherein brain activity in response to "incorrect" feedback was subtracted from brain activity in response to "correct" feedback. For statistical analysis, mean amplitude of the RewP between 275 and 425 ms was utilized. To compare reward-related brain activity during the first half and second half of trials, the first half and last half of all accepted trials (e.g., trials that were not removed through any of the processes mentioned above) were extracted for each of the two conditions (e.g., faces, arrows). Comparing brain activity during the first and second halves of trials allowed us to better understand patterns of reward-related brain

activity throughout the task. To be included in statistical analysis, participants had to have a minimum of 6 trials in each half of each condition.

Results

All analyses were conducted using SPSS (version 26). Prior to analysis, Pearson correlations between ERP amplitude, age, and IQ were conducted. No significant relationships were observed (*p's* > 0.421).

ERP Results

An independent samples t-test was conducted to ensure no significant differences in the number of acceptable trials were present between groups (all p's > 0.638).

A 2 (group) × 2 (condition) × 2 (time) × 2 (half) repeated measure analysis of variance (ANOVA) was run. Condition (social, nonsocial), time (pre-intervention, Time 1; post-intervention, Time 2), and half (RewP amplitude during the first and second halves of the task) were within-subjects variables, and group (TD, ASD) was used as a between-subjects variable. A significant 3-way interaction was found between time, half, and group; $F(12, 20.76) = 5.20$, $p = 0.042$, $\eta_p^2 = 0.30$. Pairwise comparisons revealed a significant effect of group, such that the ASD group had significantly larger RewP amplitude compared to that of the TD group in the first half of trials at Time 2; $F(12, 27.04) = 4.83$, $p = 0.048$. Thus, regardless of condition, the ASD group had larger reward-related brain activity in the first half of presented trials at Time 2 (post-intervention) compared to that of the TD group. No other significant main effects or interactions were observed. See Figure 1 for grand average waveforms at Time 2.

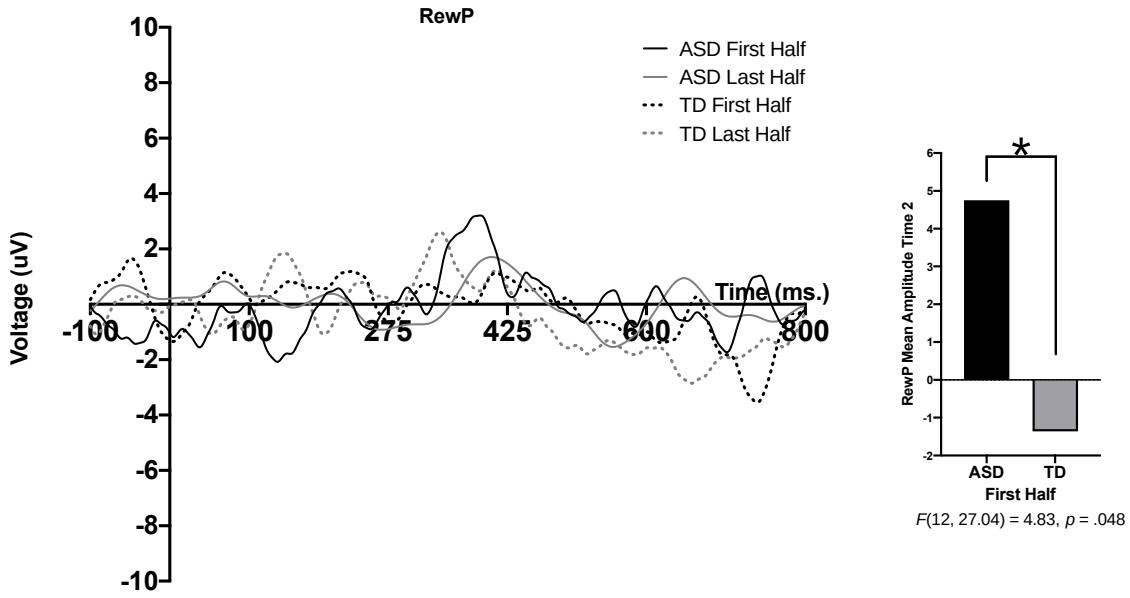

Figure 1. Grand average waveforms during the first and second halves of trials in participants with and without ASD at Time 2 (post-intervention). Significant differences were observed between the ASD and TD groups during the first half of trials at Time 2 (post-intervention). Note that for the purposes of this figure, the ERP was filtered using a 25 Hz low-pass filter.

Behavioral Results

To understand how behavioral measures changed over time for each group, 2 (group) × 2 (time) repeated measure ANOVAs were conducted on measures of autism symptoms (SRS-2), social skills (SSIS social skills subscale), and PEERS®-specific knowledge (TASSK-R).

For the SRS-2, a main effect of group was observed, $F(1,12) = 9.51$, $p = 0.009$, $\eta_p^2 = 0.96$, such that the TD group had significantly lower SRS-2 scores than those of the ASD group. Lower SRS-2 scores indicate less severe social impairments. An interaction between group and time approached significance, $F(1, 12) = 4.56$, $p = 0.054$. Post-hoc

follow-up tests using Bonferroni corrections revealed a significant difference between groups on the SRS-2 at Time 1 (pre-intervention), such that the TD group had lower scores than those of the ASD group ($p = 0.001$). The difference between the two groups was no longer significant at Time 2 (post-intervention). Pairwise comparisons revealed a trend-level effect of time for the ASD group, such that SRS-2 scores decreased from pre- to post-intervention ($p = 0.07$), whereas no effect of time was observed for the TD group.

For the SSIS social skills subscale, an interaction between group and time approached significance, $F(1,12) = 4.20$, $p = 0.063$. Post-hoc follow-up tests using Bonferroni corrections revealed a significant effect of time for the ASD group, such that SSIS social skills subscale scores increased from pre- to post-intervention ($p = 0.035$), whereas no effect of time was observed for the TD group. Higher scores on the SSIS social skills subscale indicate better social skills. Pairwise comparisons also revealed a trend-level difference between groups on the SSIS social skills subscale at Time 1 (pre-intervention) such that the TD group had higher scores than those of the ASD group ($p = 0.071$), whereas the difference between groups was not significant at Time 2 (post-intervention).

For the TASSK-R, a main effect of group was observed, $F(1,12) = 5.4$, $p = 0.038$, $\eta_p^2 = 0.31$, such that adolescents with ASD had higher scores on the TASSK-R compared to neurotypical teens. Higher scores on the TASSK-R indicate more understanding of PEERS®-specific skills. A significant effect of time was observed, $F(1,12) = 45.82$, $p < 0.001$, $\eta_p^2 = 0.79$, such that TASSK-R scores increased from Time 1 (pre-intervention) to Time 2 (post-intervention). A significant interaction between time and group was

observed, $F(1,12) = 25.78$, $p < 0.001$, $\eta_p^2 = 0.68$. Post-hoc follow-up tests using Bonferroni corrections revealed a significant effect of time for the ASD group, such that scores on the TASSK-R increased from pre- to post-intervention ($p < 0.001$). No effect of time was observed for the TD group. Pairwise comparisons also revealed a significant difference between groups on the TASSK-R at Time 2 (post-intervention), such that the ASD group had higher scores on the TASSK-R compared to those of the TD group ($p = 0.001$), whereas the difference between groups was not significant at Time 1 (pre-intervention). Please refer to Table 2 for behavioral measures at each timepoint.

Table 2. Behavioral measures for Time 1 and Time 2 in ASD and TD groups.

Variable	ASD	TD
Time 1 *M (SD), Range*		
SRS-2	69.14 (14.18), 47–90	44.00 (4.55), 39–52
SSIS Social Skills	85.86 (25.13), 41–121	106.71 (11.93), 94–125
TASSK-R	14.29 (3.09), 10–9	14.57 (3.69), 10–21
Time 2 *M (SD), Range*		
SRS-2	61.43 (14.89), 45–88	48.00 (14.46), 39–80
SSIS Social Skills	93.57 (22.78), 51–120	105.00 (9.27), 96–119
TASSK-R	24.29 (4.61), 17–29	16.00 (2.65), 14–21

Brain and Behavior Correlations

Within the ASD group, Pearson correlations were conducted to examine how change on the behavioral measures from pre- to post-intervention related to ERP results. Difference scores were calculated for the SRS-2, SSIS social skills subscale, and TASSK-R by subtracting post-intervention scores from pre-intervention scores. A significant negative correlation was observed between the SRS-2 difference score and RewP amplitude in the last half of the social condition at Time 1 ($r = -0.77$, $p = 0.044$),

such that participants with ASD who had less reward-related brain activity in response to social stimuli at Time 1 (pre-intervention) displayed larger improvements on the SRS-2 compared to individuals with more robust social reward-related brain activity at Time 1. See Figure 2a.

A positive correlation was observed between RewP amplitude in the last half of the social condition at Time 1 (pre-intervention) and SSIS social skills subscale difference score ($r = 0.78$, $p = 0.038$), such that adolescents with ASD who displayed less social reward-related brain activity during the last half of trials in the social condition at Time 1 exhibited greater improvements in social skills from pre- to post-intervention compared to those who displayed more robust reward-related brain activity prior to intervention. See Figure 2b.

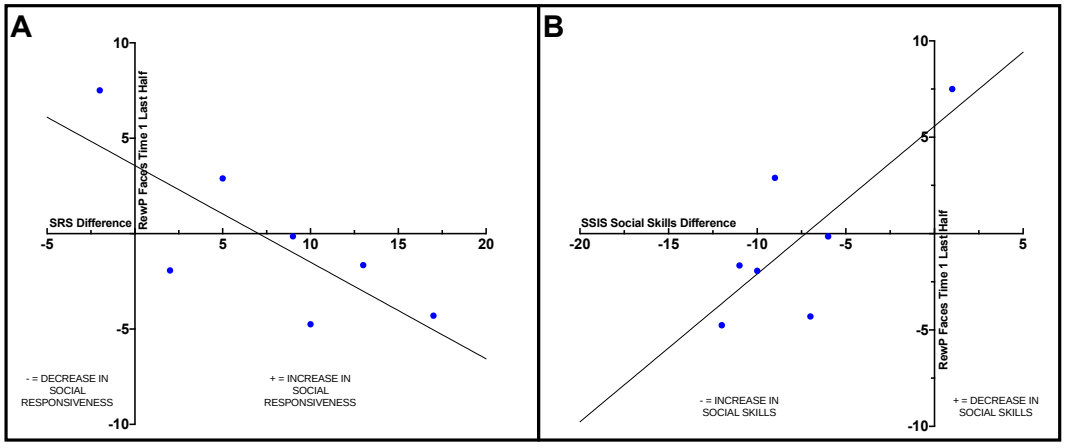

Figure 2. (a) Correlation between SRS-2 difference score before and after intervention in the ASD group and reward positivity (RewP) mean amplitude in the last half of the social condition at Time 1 ($r = -0.77$, $p = 0.04$). **(b)** Correlation between SSIS social skills difference score before and after intervention in the ASD group and RewP mean amplitude in the last half of the social condition at Time 1 ($r = 0.78$, $p = 0.04$).

Finally, a negative correlation was found between the TASSK-R difference score and RewP amplitude in the last half of the social condition at Time 2 (post-intervention) ($r = -0.79$, $p = 0.035$), such that participants with ASD who demonstrated larger increases in their knowledge of intervention-specific knowledge displayed larger social reward-related brain activity in response during the second half of trials compared to participants who had smaller increases in intervention-specific knowledge from pre- to post-intervention.

No significant correlations were observed between behavioral measures and reward-related brain activity in the nonsocial (arrow) condition.

Discussion

This study investigated the effect of the PEERS® social skills intervention on both neural correlates of reward processing and social behaviors in adolescents with ASD. Specifically, we sought to understand how reward-related brain activity changed throughout the course of a task by comparing brain activity during the first and second halves of trials.

Prior to the start of the intervention, patterns of reward-related brain activity did not differ between participants with ASD and their neurotypical peers. However, after intervention, participants with ASD were more sensitive or responsive to all reward types (both social and nonsocial) during the first half of the ERP paradigm. Increased brain activity related to reward processing indicated increased reward responsivity in adolescents with ASD, irrespective of stimulus type, after participating in a social skills intervention. A larger reward response is similar to what Kohls and colleagues [14] have

described as a “liking” response involving the consumption of rewards that are salient. Initial sensitivity to rewards (e.g., during the first half of trials) may have been heightened after exposure to frequent reinforcement strategies that were utilized throughout the intervention to encourage participant engagement.

Although lack of significant differences in brain activity between groups at Time 1 (pre-intervention) is in contrast with some previous intervention literature utilizing neuroscience methods, e.g., [16], and changes in brain activity from pre- to post-intervention in individuals with ASD has been reported previously [17,18,20,21]. Notably, previous research measuring brain activity before and after intervention in individuals with ASD either did not utilize a neurotypical control group, e.g., [17,18,20,21], or had a neurotypical group but did not test children with ASD and the TD group at two timepoints (e.g., pre- and post-intervention for the ASD group) [16,22]. Collecting data from both teens with ASD and their neurotypical peers, as well as utilizing neuroscience paradigms that are hypothesized to capture changes directly relevant to the intervention itself, are both important strategies when measuring neural correlates of change after an intervention (for a review, see [40]). In the current study, we hypothesized that increased reward-related brain activity would be observed across the course of the ERP task after teens with ASD underwent an intervention that utilized social positive reinforcement principles to increase success in making and keeping friends. To our knowledge, this is the first investigation of brain activity of both neurotypical teens and those with ASD before and after participation in an intervention

(or, in the case of the TD group, before and after a delay in which no intervention took place).

Contrary to our hypotheses, brain activity did not differ in response to condition (e.g., social, nonsocial) for either group. This contrasts with previous findings using this paradigm with young children with and without ASD [12,36]. However, this is the first time that this ERP paradigm has been utilized with adolescents. Thus, differences between the current study and previous research might reflect developmental changes. It is plausible that adolescents with and without ASD are less overtly motivated by food rewards as they would be by other reward types (e.g., monetary), and thus may have found the paradigm less engaging/rewarding than younger children. Future studies should consider utilizing this paradigm in a cross-sectional design with different age groups to better understand the effects of age on reward responsivity.

As expected, at Time 1 (pre-intervention), the ASD group had more severe social-communication impairments associated with ASD (measured by the SRS-2) and poorer social skills (measured by the SSIS social skills subscale) than the TD group. Adolescents with ASD improved on both measures after intervention (Time 2), which mirrors previously reported findings of the effectiveness of the PEERS® social skills intervention [30,31]. No differences were observed from Time 1 to Time 2 in the TD group. This was expected, as the neurotypical teens did not participate in the intervention. Importantly, only one ASD participant remained in the range for clinical concern on both the overall SRS-2 score and SSIS social skills subscale score following intervention. This is important as it suggests that change from Time 1 to Time 2 was not only statistically

significant, but also clinically meaningful. Further, no significant differences were observed between groups on the SRS-2 or SSIS social skills subscale at Time 2 (post-intervention), suggesting that both social-responsiveness symptoms and social skills in our sample of adolescents with ASD began to resemble social behaviors observed in our neurotypical participants.

One of the most interesting findings of our investigation was that ASD participants who demonstrated less robust social reward-related brain activity in the second half of trials prior to the intervention (Time 1) evidenced the biggest gains from Time 1 to Time 2 in both social responsivity and social skills. This suggests that perhaps the adolescents who benefitted the most from PEERS® were those who had the most "room to improve" in terms of social reward response. This also provides initial evidence that the neural characteristics of reward responsiveness prior to intervention may serve as an indicator of treatment response. That is, it might be possible to utilize neural correlates of social reward responsivity to predict which individuals with ASD might benefit the most from participating in PEERS®. To further investigate this potential predictor of intervention efficacy, future research with a larger sample size and a randomized control group should be conducted.

Limitations

This study is part of a larger investigation of a social skills intervention, and this report serves as an initial analysis. Thus, the current study had a small number of participants. It is important to interpret differences in behavioral measures that were approaching significance with caution. Additionally, randomization of treatment was not

performed (i.e., a waitlist control group was not utilized) and ASD participants were aware of their enrollment in the social skills intervention (i.e., parent rating forms were not completed "blind," as parents were actively participating in the PEERS® intervention with their teen). Thus, we cannot rule out the possibility that improvements in parent ratings in the ASD group were due to the expectation of improvements. Finally, findings from this study cannot be generalized to all individuals with ASD, as one of the criteria for participation was that the adolescent was motivated to participate in PEERS® and wanted help making and keeping friends. Thus, this sample consisted of adolescents who were highly motivated to learn social skills.

Conclusions

The results of our study have important implications for intervention outcomes in adolescents with ASD. First, these findings add to the existing literature on the efficacy of PEERS® for adolescents with ASD. Second, we found evidence for increased reward sensitivity in adolescents with ASD (compared to their neurotypical peers) after participation in the intervention. This suggests that participating in PEERS® increases reward system sensitivity in teens with ASD. Finally, we found that teens who benefitted the most from the intervention (i.e., had the largest gains in social skills and largest decrease in social-communicative impairments) were those with less reward-related brain activity in response to faces prior to the intervention. This relationship between symptom improvement and brain activity prior to the intervention suggests that PEERS® might be most effective for teens with ASD who have "room to grow" in their social reward responsivity, whereas teens with ASD who already have higher levels of social reward

responsivity might benefit less. Finally, neuroscience measures may be reliable predictors of teens' responsiveness to treatment because they are independent of potentially biased parent ratings.

References

1. Thompson, R.F.; Spencer, W.A. Habituation: A Model Phenomenon for the Study of Neuronal Substrates of Behavior. *Psychol. Rev.* **1966**, *73*, 16, doi:10.1037/h0022681.

2. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association, Ed.; American Psychiatric Publishing: Washington, DC, USA, 2013.

3. Tam, F.I.; King, J.A.; Geisler, D.; Korb, F.M.; Sareng, J.; Ritschel, F.; Steding, J.; Albertowski, K.U.; Roessner, V.; Ehrlich, S. Altered Behavioral and Amygdala Habituation in High-Functioning Adults with Autism Spectrum Disorder: An FMRI Study. *Sci. Rep.* **2017**, *7*, 1–9, doi:10.1038/s41598-017-14097-2.

4. Swartz, J.R.; Wiggins, J.L.; Carrasco, M.; Lord, C.; Monk, C.S. Amygdala Habituation and Prefrontal Functional Connectivity in Youth with Autism Spectrum Disorders. *J. Am. Acad. Child Adolesc. Psychiatry* **2013**, *52*, 84–93, doi:10.1016/j.jaac.2012.10.012.

5. Webb, S.J.; Jones, E.J.H.; Merkle, K.; Namkung, J.; Toth, K.; Greenson, J.; Murias, M.; Dawson, G. Toddlers with Elevated Autism Symptoms Show Slowed Habituation to Faces. *Child Neuropsychol.* **2010**, *16*, 255–278, doi:10.1080/09297041003601454.

6. Kaartinen, M.; Puura, K.; Himanen, S.-L.; Nevalainen, J.; Hietanen, J.K. Autonomic Arousal Response Habituation to Social Stimuli Among Children with Asd. *J. Autism Dev. Disord.* **2016**, *46*, 3688–3699, doi:10.1007/s10803-016-2908-0.

7. Kleinhans, N.M.; Johnson, L.C.; Richards, T.; Mahurin, R.; Greenson, J.; Dawson, G.; Aylward, E. Reduced Neural Habituation in the Amygdala and Social Impairments in Autism Spectrum Disorders. *AJP* **2009**, *166*, 467–475, doi:10.1176/appi.ajp.2008.07101681.

8. Vivanti, G.; Hocking, D.R.; Fanning, P.A.J.; Uljarevic, M.; Postorino, V.; Mazzone, L.; Dissanayake, C. Attention to Novelty versus Repetition: Contrasting Habituation Profiles in Autism and Williams Syndrome. *Dev. Cogn. Neurosci.* **2018**, *29*, 54–60, doi:10.1016/j.dcn.2017.01.006.

9. Rankin, C.H.; Abrams, T.; Barry, R.J.; Bhatnagar, S.; Clayton, D.F.; Colombo, J.; Coppola, G.; Geyer, M.A.; Glanzman, D.L.; Marsland, S.; et al. Habituation Revisited: An Updated and Revised Description of the Behavioral Characteristics of Habituation. *Neurobiol. Learn. Mem.* **2009**, *92*, 135–138, doi:10.1016/j.nlm.2008.09.012.

10. McSweeney, F.K.; Murphy, E.S. Sensitization and Habituation Regulate Reinforcer Effectiveness. *Neurobiol. Learn. Mem.* **2009**, *92*, 189–198, doi:10.1016/j.nlm.2008.07.002.

11. Chevallier, C.; Kohls, G.; Troiani, V.; Brodkin, E.S.; Schultz, R.T. The Social Motivation Theory of Autism *Trends. Cogn. Sci.* **2012**, *16*, 231–239, doi:10.1016/j.tics.2012.02.007.

12. Stavropoulos, K.K.M.; Carver, L.J. Reward Anticipation and Processing of Social versus Nonsocial Stimuli in Children with and without Autism Spectrum Disorders. *J. Child Psychol. Psychiatry* **2014**, *55*, 1398–1408, doi:10.1111/jcpp.12270.

13. McPartland, J.C.; Crowley, M.J.; Perszyk, D.R.; Mukerji, C.E.; Naples, A.J.; Wu, J.; Mayes, L.C. Preserved Reward Outcome Processing in ASD as Revealed by Event-Related Potentials. *J. Neurodev. Disord.* **2012**, *4*, 16, doi:10.1186/1866-1955-4-16.

14. Kohls, G.; Chevallier, C.; Troiani, V.; Schultz, R.T. Social 'Wanting' Dysfunction in Autism: Neurobiological Underpinnings and Treatment Implications. *J. Neurodev. Disord.* **2012**, *4*, 10, doi:10.1186/1866-1955-4-10.

15. Kohls, G.; Schulte-Rüther, M.; Nehrkorn, B.; Müller, K.; Fink, G.R.; Kamp-Becker, I.; Herpertz-Dahlmann, B.; Schultz, R.T.; Konrad, K. Reward System Dysfunction in Autism Spectrum Disorders. *Soc. Cogn. Affect. Neurosci.* **2013**, *8*, 565–572, doi:10.1093/scan/nss033.

16. Van Hecke, A.V.; Stevens, S.; Carson, A.M.; Karst, J.S.; Dolan, B.; Schohl, K.; McKindles, R.J.; Remmel, R.; Brockman, S. Measuring the Plasticity of Social Approach: A Randomized Controlled Trial of the Effects of the PEERS Intervention on EEG Asymmetry in Adolescents with Autism Spectrum Disorders. *J. Autism Dev. Disord.* **2015**, *45*, 316–335, doi:10.1007/s10803-013-1883-y.

17. Yang, Y.J.D.; Allen, T.; Abdullahi, S.M.; Pelphrey, K.A.; Volkmar, F.R.; Chapman, S.B. Neural Mechanisms of Behavioral Change in Young Adults with High-Functioning Autism Receiving Virtual Reality Social Cognition Training: A Pilot Study. *Autism Res.* **2018**, *11*, 713–725, doi:10.1002/aur.1941.

18. Yang, D.; Pelphrey, K.A.; Sukhodolsky, D.G.; Crowley, M.J.; Dayan, E.; Dvornek, N.C.; Venkataraman, A.; Duncan, J.; Staib, L.; Ventola, P. Brain Responses to Biological Motion Predict Treatment Outcome in Young Children with Autism *Transl. Psychiatry* **2016**, *6*, e948, doi:10.1038/tp.2016.213.

19. Ventola, P.; Friedman, H.E.; Anderson, L.C.; Wolf, J.M.; Oosting, D.; Foss-Feig, J.; McDonald, N.; Volkmar, F.; Pelphrey, K.A. Improvements in Social and Adaptive

Functioning Following Short-Duration PRT Program: A Clinical Replication. *J. Autism Dev. Disord.* **2014**, *44*, 2862–2870, doi:10.1007/s10803-014-2145-3.

20. Venkataraman, A.; Yang, D.Y.-J.; Dvornek, N.; Staib, L.H.; Duncan, J.S.; Pelphrey, K.A.; Ventola, P. Pivotal Response Treatment Prompts a Functional Rewiring of the Brain among Individuals with Autism Spectrum Disorder. *Neuroreport* **2016**, *27*, 1081–1085, doi:10.1097/WNR.0000000000000662.

21. Voos, A.C.; Pelphrey, K.A.; Tirrell, J.; Bolling, D.Z.; Vander Wyk, B.; Kaiser, M.D.; McPartland, J.C.; Volkmar, F.R.; Ventola, P. Neural Mechanisms of Improvements in Social Motivation after Pivotal Response Treatment: Two Case Studies. *J. Autism Dev. Disord.* **2013**, *43*, 1–10, doi:10.1007/s10803-012-1683-9.

22. Dawson, G.; Jones, E.J.H.; Merkle, K.; Venema, K.; Lowy, R.; Faja, S.; Kamara, D.; Murias, M.; Greenson, J.; Winter, J.; et al. Early Behavioral Intervention Is Associated With Normalized Brain Activity in Young Children With Autism *J. Am. Acad. Child Adolesc. Psychiatry* **2012**, *51*, 1150–1159, doi:10.1016/j.jaac.2012.08.018.

23. Eikeseth, S.; Smith, T.; Jahr, E.; Eldevik, S. Outcome for Children with Autism Who Began Intensive Behavioral Treatment between Ages 4 and 7: A Comparison Controlled Study. *Behav. Modif.* **2007**, *31*, 264–278, doi:10.1177/0145445506291396.

24. Virués-Ortega, J. Applied Behavior Analytic Intervention for Autism in Early Childhood: Meta-Analysis, Meta-Regression and Dose–Response Meta-Analysis of Multiple Outcomes. *Clin. Psychol. Rev.* **2010**, *30*, 387–399, doi:10.1016/j.cpr.2010.01.008.

25. Laugeson, E.A.; Frankel, F. *Social Skills for Teenagers with Developmental and Autism Spectrum Disorders: The PEERS Treatment Manual*; Routledge: Abingdon, UK, 2011.

26. Bureau USC Quick Facts: Riverside County, California. Available online: https://www.census.gov/quickfacts/fact/table/riversidecountycalifornia/RHI725216—viewtop.

27. Laugeson, E.A.; Frankel, F. *Social Skills for Teenagers with Developmental and Autism Spectrum Disorders: The PEERS Treatment Manual*; Routledge: Abingdon, UK, 2011.

28. Laugeson, E.A.; Frankel, F.; Mogil, C.; Dillon, A.R. Parent-Assisted Social Skills Training to Improve Friendships in Teens with Autism Spectrum Disorders. *J. Autism Dev. Disord.* **2009**, *39*, 596–606, doi:10.1007/s10803-008-0664-5.

29. Laugeson, E.A. *The PEERS Curriculum for School-Based Professionals*, 1 Ed.; Routledge: New York, NY, USA, 2013.

30. Laugeson, E.A.; Gantman, A.; Kapp, S.K.; Orenski, K.; Ellingsen, R. A Randomized Controlled Trial to Improve Social Skills in Young Adults with Autism Spectrum Disorder: The UCLA PEERS® Program. *J. Autism Dev. Disord.* **2015**, *45*, 3978–3989, doi:10.1007/s10803-015-2504-8.

31. Laugeson, E.A.; Frankel, F.; Gantman, A.; Dillon, A.R.; Mogil, C. Evidence-Based Social Skills Training for Adolescents with Autism Spectrum Disorders: The UCLA PEERS Program. *J. Autism Dev. Disord.* **2012**, *42*, 1025–1036, doi:10.1007/s10803-011-1339-1.

32. Wechsler, D. *Wechsler Abbreviated Scale of Intelligence*, 2nd ed.; Pearson: London, UK, 2011.

33. Lord, C.; Rutter, M. *Autism Diagnostic Observation Schedule*^{TM}, 2nd ed.; WPS: 2012.

34. Constantino, J.N. *Social Responsiveness Scale*, 2nd Ed.; WPS: 2012.

35. Gresham, F.M.; Elliott, S.N. *Social Skills Improvement System Rating Scales*; Pearson: London, UK, 2008.

36. Stavropoulos, K.K.M.; Carver, L.J. Reward Sensitivity to Faces versus Objects in Children: An ERP Study. *Soc. Cogn. Affect. Neurosci.* **2014**, *9*, 1569–1575, doi:10.1093/scan/nst149.

37. Stavropoulos, K.K.M.; Carver, L.J. An Electrophysiology Protocol to Measure Reward Anticipation and Processing in Children. *J. Vis. Exp.* **2018**, doi:10.3791/58348.

38. Tottenham, N.; Tanaka, J.W.; Leon, A.C.; McCarry, T.; Nurse, M.; Hare, T.A.; Marcus, D.J.; Westerlund, A.; Casey, B.; Nelson, C. The NimStim Set of Facial Expressions: Judgments from Untrained Research Participants. *Psychiatry Res.* **2009**, *168*, 242–249, doi:10.1016/j.psychres.2008.05.006.

39. Lopez-Calderon, J.; Luck, S.J. ERPLAB: An Open-Source Toolbox for the Analysis of Event-Related Potentials. *Front. Hum. Neurosci.* **2014**, *8*, 213, doi:10.3389/fnhum.2014.00213.

40. Stavropoulos, K.K.M. Using Neuroscience as an Outcome Measure for Behavioral Interventions in Autism Spectrum Disorders (ASD): A Review. *Res. Autism Spectr. Disord.* **2017**, *35*, 62–73, doi:10.1016/j.rasd.2017.01.001.

Chapter 2

Investigating changes in reward-related neural correlates after PEERS intervention in adolescents with ASD: Preliminary evidence of a "precision medicine" approach

Investigating changes in reward-related neural correlates after PEERS intervention in adolescents with ASD: Preliminary evidence of a "precision medicine" approach

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Abstract

The Social Motivation Hypothesis proposes that individuals with autism spectrum disorder (ASD) experience social interactions as less rewarding than their neurotypical (TD) peers, which may lead to reduced social initiation. Existing studies of the brain's reward system in individuals with ASD report varied findings for anticipation of and response to social rewards. Given discrepant findings, the anticipation of and response to social rewards should be further evaluated, particularly in the context of intervention outcome. We hypothesized that individual characteristics may help predict neural changes from pre- to post-intervention.

Thirteen adolescents with ASD received the Program for the Education and Enrichment of Relational Skills (PEERS) intervention for 16 weeks; reward-related EEG was collected before and after intervention. Fourteen TD adolescents were tested at two timepoints but did not receive intervention. Event-related potentials were calculated to

measure anticipation of (stimulus-preceding negativity; SPN) and response to (reward-related positivity; RewP) social and nonsocial rewards. Additionally, measures of social responsiveness, social skills, and intervention-engagement were collected. Group differences were analyzed as well as individual differences using prediction models.

Parent-reported social responsiveness and social skills improved in adolescents with ASD after participation in PEERS. ASD adolescents displayed marginally decreased anticipation of social rewards at post-intervention compared to pre-intervention. Regression models demonstrated that older adolescents and those with *lower* parent-reported social motivation prior to participation in PEERS displayed marginally increased social reward anticipation (more robust SPN) from pre- to post-intervention. Participants who displayed more parent-reported social motivation before intervention and were more actively engaged in the PEERS intervention evidenced increased social reward processing (more robust RewP) from pre- to post-intervention.

Findings suggest that there may be differences in saliency between wanting/anticipating social rewards versus liking/responding to social rewards in individuals with ASD. Our findings support the hypothesis that identification of individual differences may predict which adolescents are poised to benefit the most from particular interventions. As such, reported findings set the stage for the advancement of 'precision medicine.' This investigation is a critical step forward in our ability to understand and predict individual response to interventions in individuals with ASD.

Introduction

There is a current lack of universally accepted terminology for describing autism (1) and as such, several terms are used in this paper to describe adolescents with autism. We used both person-first language and identity-first language in an effort to be inclusive of numerous current perspectives on appropriate terminology.

Autism and social motivation.

Children with autism spectrum disorder (ASD) have reduced preferences toward social information compared to their neurotypical or typically developing (TD) peers (2,3). The Social Motivation Hypothesis proposes that the brain's reward centers are related to early impairments in social attention due to social stimuli being less rewarding, thus setting a series of negative developmental consequences in motion (4). This may result in a reduction in social orienting, social interaction, and social skills—all of which may lead to broader deficits in social behaviors. (4). Demonstration of the social motivation hypothesis often relies on the use of brain-based methods, including neural and neuropsychological markers of reward processing (5). Reward centers of the brain include mesolimbic dopamine system, comprised of the midbrain (via the ventral tegmental area) and striatum (via the nucleus accumbens) (6,7).

Social motivation and neural response.

Though some research suggests that children with ASD have less reward-related brain activity than their neurotypical peers in response to faces (8,9), other work suggests that individuals with ASD evidence hypoactivity in the reward system in response to all stimulus types (10).

One way to approach mixed findings is by examining differences in reward-related brain activity by evaluating the difference between *anticipating* versus *processing* rewards. Anticipation is linked to cues of reward and may become reinforced when the reward is more attractive or salient. Similarly, response to reward (i.e., reward processing) is enhanced if the reward is preferred but dampened if the reward is non-preferred. Anticipation of and response to rewards involve separate cognitive processes and both processes should be investigated in order to understand the entirety of how the reward system functions in individuals with and without ASD. Moreover, metrics of anticipation tend to be overlooked in paradigms designed to measure reward processing (11), which may contribute to mixed neural findings. A meta-analysis of functional magnetic resonance imaging (fMRI) studies examining anticipation of and response to rewards suggests that reward differences in ASD may apply to both social and nonsocial stimuli (12). Specifically, the caudate, nucleus accumbens, and anterior cingulate gyrus were hypoactive during anticipation of and in response to social and nonsocial rewards (12). These findings expand upon initial theories of disrupted reward systems more broadly.

Electroencephalographic (EEG) methods may serve to further elucidate the complexity of reward processing in ASD, as high temporal resolution is a notable feature and thus complements the high spatial resolution of fMRI. Additionally, EEG is a relatively inexpensive, non-invasive technique that is well-tolerated across the psychiatric spectrum. Using event-related potentials (ERPs), the stimulus-preceding negativity (SPN) component measures brain activity prior to stimulus presentation and may serve as a

measure of anticipation. The reward-related positivity (RewP) ERP measures response to rewards and reflects the evaluation of rewards (i.e., determining if a reward is 'liked' or 'disliked') by comparing losses to gains (13,14). There is evidence to suggest that the SPN and RewP support the social motivation hypothesis, as children with ASD with less severe social impairments display larger reward anticipation (SPN) (15) and reward response (RewP) to faces (16).

Behavioral interventions for ASD.

Behavioral interventions have been designed to improve social communication skills in ASD—by augmenting interactions with others and helping individuals with ASD form meaningful relationships; for reviews see (17,18). The Program for the Education and Enrichment of Relational Skills (PEERS) intervention is a manualized, evidence-based group intervention designed to provide adolescents with ASD skills to both make and keep friends; see methods section for additional details (19–21). PEERS is efficacious in increasing social skills, frequency of social get-togethers, and friendships (20,22).

Objective outcome measures for intervention.

Objective measures, including brain-based measures, may identify factors that result in favorable intervention outcomes. To our knowledge, less than ten studies have been published using measures of neural response as either an outcome measure or predictor of response to empirically supported behavioral intervention in individuals with ASD (16,23–30). Of these studies, four used fMRI, and five used EEG methodology (16,23,24,29,30). Seven measured brain activity both before and after interventions

(16,24–27,29,30), five of which found increased brain activity in response to social stimuli (e.g., while viewing faces or in response to point-light displays of biological motion) (16,25–27,29). A majority of these investigations were done in children under five years, leaving much to be learned regarding adolescents' neural response to intervention.

As such, there is a pressing need for biomarkers that can detect meaningful intervention outcomes. Biomarkers may also address the heterogeneity of ASD through the identification of homogeneous subgroups of individuals based on biological factors. The N170, a neural measure of face processing and perception, is currently the only psychiatric biomarker for ASD approved by the Food and Drug Administration (31). It has been shown to be a sensitive measure of change due to the effects intervention while also identifying groups of individuals with ASD who have similar pathophysiology (23,29,31). Social difficulties in autism are underscored by aberrant processing of social information, as evidenced by a slower response (longer N170 latency) to faces compared to TDs (32–34), including in response to emotional faces (35). Given that the N170 is also closely associated with social communication challenges in ASD, it is a biomarker grounded in core ASD symptomatology.

Use of neural response before and after PEERS.

Of the aforementioned papers using measures of neural response as an intervention outcome measure, two looked at brain activity before and after participation in PEERS. Van Hecke and colleagues measured resting state EEG before and after PEERS (24). The authors found that after participating in PEERS, teens with ASD

displayed increased left-dominant gamma asymmetry, such that their brain activity appeared similar to that of neurotypical teens (24). Left-hemisphere dominance is associated with increased motivation and affect, while right-hemisphere dominance is associated with withdrawal and negative emotional style (36,37). Additionally, Van Hecke and colleagues (24) found that after intervention, teens with ASD who (a) displayed fewer symptoms of ASD, (b) had more get-togethers with other adolescents during the intervention, and (c) displayed greater understanding of PEERS-specific concepts showed the greatest relative left-hemisphere dominant EEG activity in the gamma band. Therefore, it appears that individual characteristics seem related to the degree of left-dominant pattern of hemispheric asymmetry post-intervention.

In a second investigation of brain activity before and after PEERS (16), there was evidence of enhanced reward processing (as measured by the RewP) in teens with ASD after completion of PEERS. These findings suggest a malleability of social motivation in adolescents with ASD after social skills training. Additionally, the investigators found that adolescents with ASD who displayed less robust social reward processing prior to intervention made the most gains in social responsiveness, social skills, and PEERS-specific knowledge after intervention (16). That is, teens with ASD who displayed *less* response to social rewards prior to PEERS appeared to benefit the most from intervention. Thus, it appears critical to measure the contribution of unique individual factors to identify which individuals stand to benefit the most from intervention.

One such individual factor that remains unexplored is teen engagement in behavioral intervention. Motivation to participate in intervention, by way of active

participation within sessions, may predispose adolescents to receive more benefits compared to those who are less engaged. PEERS was originally validated in children and teens ages 11 to 16 years (22), a developmental period from late childhood through adolescence characterized by increased social demands (33). As such, age should be considered as a potential moderator to the effects of intervention. Age is also relevant in brain-based studies of reward processing, as younger individuals (e.g., early adolescents) with ASD appear to show greater variability in striatal activation during social reward tasks compared to older individuals with ASD, which may contribute to differences in anticipation versus response processes in ASD (12).

Current Study

The current study, which is a preliminary model of using a 'precision medicine' approach to intervention, was designed to answer the following questions:

1. How does reward-related brain activity, both anticipation (SPN) and processing (RewP), to social and nonsocial stimuli change from pre- to post- PEERS intervention in a sample of adolescents with ASD?
2. How does brain activity related to anticipation of and response to social and nonsocial rewards differ across time between adolescents with ASD receiving PEERS versus typically developing (TD) adolescents not receiving PEERS?
3. Does change in reward-related brain activity before and after intervention relate to individual factors? That is, can individual change in reward anticipation and processing from pre- to post- PEERS intervention be predicted by individual characteristics (e.g., age, social skills)?

To our knowledge, this is the first study to: (A) measure electrophysiological correlates of both anticipation of and response to social and nonsocial stimuli in teens with ASD before and after participation in PEERS, and (B) compare brain activity of teens with ASD before and after PEERS to brain activity of TD teens across time. Exploratory analyses on the N170 were performed after visual inspection of the ERP data; see Methods for details.

Methods

Participants

Participants included 13 adolescents with ASD and 14 sex-, age-, IQ-, and race-matched TD adolescents; see Table 1. A total of 17 ASD participants were initially enrolled in the study. However, four dropped out for reasons including: difficulty with transportation, psychiatric hospitalization, and the adolescent no longer wanting to attend sessions. Thus, 13 ASD participants were included in the final sample. The 14 TD participants were not enrolled in the PEERS intervention and instead were seen at two timepoints, 16 weeks apart. Though the sample size is modest, a majority of participants in the current study identified as Latinx. Much intervention research is carried out with White, monolingual English-speakers. This is one of the first studies to investigate the effect of PEERS in a diverse sample in which the intervention was carried out in a language-inclusive environment in both English and Spanish, see below.

Table 1. Descriptive characteristics of the autism spectrum disorder (ASD) and neurotypical (TD) groups at Time 1.

Characteristics	ASD n = 13	TD n = 14
Sex	10 male, 3 female	12 male, 2 female
Age *(M (SD), Range)*	14.17 (2.09), 11.3 – 17.1	13.22 (1.63), 11.1 – 17.1
IQ, M (SD), Range	99.54 (15.62), 77 – 129	106.14 (15.49), 79 -131
Race (n)		
White n	3	4
Latinx n	9	8
Mixed Race/Other n	1	2
Maternal Education Level (n)		
Less than College	10	5
College and Above	3	9
Household Income (n)		
Up to $50,000	4	4
$50, 001-$100,000	5	4
Over $100,001	4	5
Missing Data	--	1

Note: The ASD and TD samples are well matched on sex, age, IQ, race, and household income. However, we note that maternal education is lower in the ASD group compared to the TD group.

Flyers with study details were posted at community centers and events. Interested families with adolescents between the ages of 11 to 18 years were contacted via phone or email. Exclusionary criteria for the ASD and TD groups included: an IQ below 70, history of seizures/epilepsy, history of brain injury/disease, and a diagnosis of intellectual disability. Commonly co-occurring disorders were not exclusionary in the ASD group, though a history of serious psychiatric illness (e.g., schizophrenia, bipolar disorder) or a recent (within 6 months) psychiatric hospitalization was exclusionary. Additional

exclusionary criteria for the TD group included a psychiatric diagnosis of any kind and immediate family history of ASD.

All participants in the ASD group had diagnosis confirmed with the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) (38). The ADOS-2 was performed by research-reliable graduate students who had at least five years of experience working with individuals with ASD. ASD adolescents needed to have English as a primary language to be included in the intervention. Parents could speak either English or Spanish as parent groups were delivered in a bilingual format. A third timepoint set for four months later was scheduled to measure lasting impacts of intervention; however, COVID-19 prevented participants from returning to the lab to complete the EEG follow-up visit. This study was approved by the Institutional Review Board at the University of California, Riverside. Caregivers provided informed consent, and adolescents provided assent.

Procedures, Assessments, and Questionnaires

Cognitive abilities were tested using the 2-subtest Wechsler Abbreviated Scales of Intelligence, 2nd edition (WASI-II) (39). Composite scores were combined to create a full-scale IQ-2 (FSIQ-2). For adolescents with ASD, diagnosis was confirmed using the ADOS-2 (38). ADOS-2 consists of five modules based upon the individual's language ability and age. In this study, Modules 3 and 4 were used for participants with ASD. Willingness to participate the intervention was assessed in ASD participants using the Mental Status Checklist (21). These measures were used to confirm eligibility and therefore were not repeated.

Caregivers completed the Social Responsiveness Scale, Second Edition (SRS-2) (40), and the Social Skills Improvement System (SSIS) (41) before the intervention began (Time 1) and immediately after intervention completion (Time 2). Times 1 and 2 were approximately 4 months apart, as the duration of the PEERS intervention is 16 weeks. The same EEG task was completed by adolescents in both groups at Time 1 and Time 2.

The SRS-2 is a standardized 65-item parent-report rating scale used to assess the severity of autism symptoms and social responsiveness in children ages 4 to 18 (40). A Total Score is calculated from five subscales: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior.

The SSIS is a standardized 79-item parent-report measure of social and behavioral functioning for children ages 3 to 18 (41). The measure is designed to assess treatment-related changes in social skills (subscale: Social Skills) and problem behaviors (subscale: Problem Behaviors).

Teen engagement in intervention sessions was measured by tallying the number of times adolescents actively participated (e.g. asking questions, making comments, reporting on homework assignments). The tallies were recorded by the interventionist during active sessions. A sum of participation across 16 sessions was calculated. This metric is referred to below as "Teen Participation." See Table 2 for SRS-2, SSIS, and Teen Participation means.

Table 2. Mean scores on behavioral measures in TD and ASD participants at Time 1 and Time 2. Please note: higher SRS-2 scores indicate greater severity, while lower SSIS scores indicate greater severity.

	TD		ASD	
	Time 1 *M (SD)*	Time 2 *M (SD)*	Time 1 *M (SD)*	Time 2 *M (SD)*
SRS-2 Total T-score	45.29 (6.33)	44.07 (6.38)	74.85 (12.84)	68.85 (15.06)
SRS-2 Social Motivation T-score	49.21 (8.83)	47.43 (9.23)	75.15 (14.97)	70.77 (17.76)
SSIS Social Skills Standard Score	105.64 (11.89)	105.21 (12.59)	81.62 (19.19)	87.85 (19.05)
Teen Participation	---		256.31 (91.38), range: 165 – 469	

Social Skills Intervention: PEERS

PEERS is a 16-week, outpatient, manualized intervention to help adolescents make and keep friends (19–22,42). The PEERS intervention consists of weekly, 1.5-hour group sessions for parents and teens. Parent groups are conducted in a separate room from adolescent groups. Adolescent group sessions focused on teaching social skills specific to making and keeping friends and handling peer conflict and rejection. Skills were taught using didactic instruction which included role-play demonstrations, behavioral rehearsal activities with reinforcement and corrective feedback, and weekly homework assignments (43). Parent group sessions were provided in a bilingual format. All written parent materials were available in Spanish and English. Each group was led by a trained interventionist. All procedures were supervised by a licensed psychologist.

EEG

EEG Task

The EEG task was completed by ASD and TD participants at Time 1/pre-intervention and Time 2/post-intervention. The EEG task included two blocks of 50 trials,

each comprised of one of two conditions (social or nonsocial). In both blocks, at the beginning of each trial, a fixation cross appeared on the screen for 500 milliseconds (ms). After the fixation cross, two boxes, each containing a question mark, were displayed. Participants were instructed to indicate their guess via a button pad regarding whether the left or right stimulus was "correct." The boxes were displayed until participants made a choice—up to 3000 ms. If participants did not make a choice after 3000 ms the trial ended and the next trial began. After participants indicated their choice, an arrow appeared pointing in the direction of the box they picked for 3000 ms. After 3000 ms, feedback appeared to indicate if the participant guessed correctly or incorrectly (displayed for 1000 ms).

In the social condition, feedback was an image of a smiling face from the 'NimStim' database (44) surrounded by intact Oreo cookies for correct answers or an image of a frowning face surrounded by crossed out Oreo cookies for incorrect answers. In the nonsocial condition, feedback was an image of an upward arrow surrounded by Oreo cookies for correct answers or an image of a downward arrow surrounded by crossed out Oreo cookies for incorrect answers. Arrow stimuli were composed of scrambled face elements from the social condition. A computer program predetermined correct versus incorrect answers in semi-random order such that participants got 50% "correct" and 50% "incorrect," with no more than three of the same feedback in a row. Each trial was marked to be correct vs. incorrect regardless of the participant's response.

Participants were verbally told that the reward for correct answers was Oreo cookies (or an equivalent snack). 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 their response was correct. Participants were told that correct vs. incorrect responses were signaled by whether the Oreo cookies were intact or crossed out. Whether individuals viewed the social versus nonsocial block first was counterbalanced. See Figure 1.

EEG Recording and Processing

Participants wore a standard, fitted cap (Brain Products ActiCap) with 32 silver/silver-chloride (Ag/AgCl) electrodes placed according to the extended international 10-20 system. Continuous EEG was recorded using Brain Vision Recorder with a reference electrode at Cz and re-referenced offline to average activity at left and right mastoids. Electrode resistance was kept under 50 kOhms. Continuous EEG was amplified with a directly coupled high pass filter (DC) and notch filter (60Hz). The signal was digitized at a rate of 500 samples per second. 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.

Trials with no behavioral response, or containing electrophysiological artifacts, were excluded. 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 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.

SPN. Baseline was -3200 to -3000 ms, and the data were epoched from -3200 to 100 ms (time-locked to the onset of feedback stimuli). SPN mean amplitude between -210 and -10ms was calculated for social and nonsocial conditions. Electrode locations included F3/F4, C3/C4, P3/P4, and T7/T8. See Figure 2 for electrode locations.

RewP. Baseline was set to -100 to 0 ms, and the data were epoched from -100 to 800 ms. RewP mean amplitude was calculated for each condition from the frontocentral electrode, Fz (46,47). For both conditions (face, arrow) and both feedback types (correct, incorrect), mean brain activity was calculated between 275 and 425 ms after feedback onset. The RewP was defined as a difference wave where brain activity in response to "incorrect" feedback was subtracted from brain activity in response to "correct" feedback.

N170. Upon visual inspection of grand average EEG data files, a negative-going deflection was observed after stimulus presentation, particularly in the social condition. Though the EEG stimuli in the current investigation were designed to elicit reward anticipation and response, exploratory analyses of the N170 are included. Only social and nonsocial trials with correct feedback (i.e., smiling faces and upwards-facing arrows) were analyzed. Incorrect trials were excluded from N170 analyses to eliminate confounds related to processing negative emotional valences (48) (i.e., frowning faces). The baseline period was set to -100 to 0 ms and data were epoched from -100 to 800 ms. Peak

amplitude and latency were calculated between 150 and 250 ms in CP5/CP6 and P7/P8 electrodes (33,49).

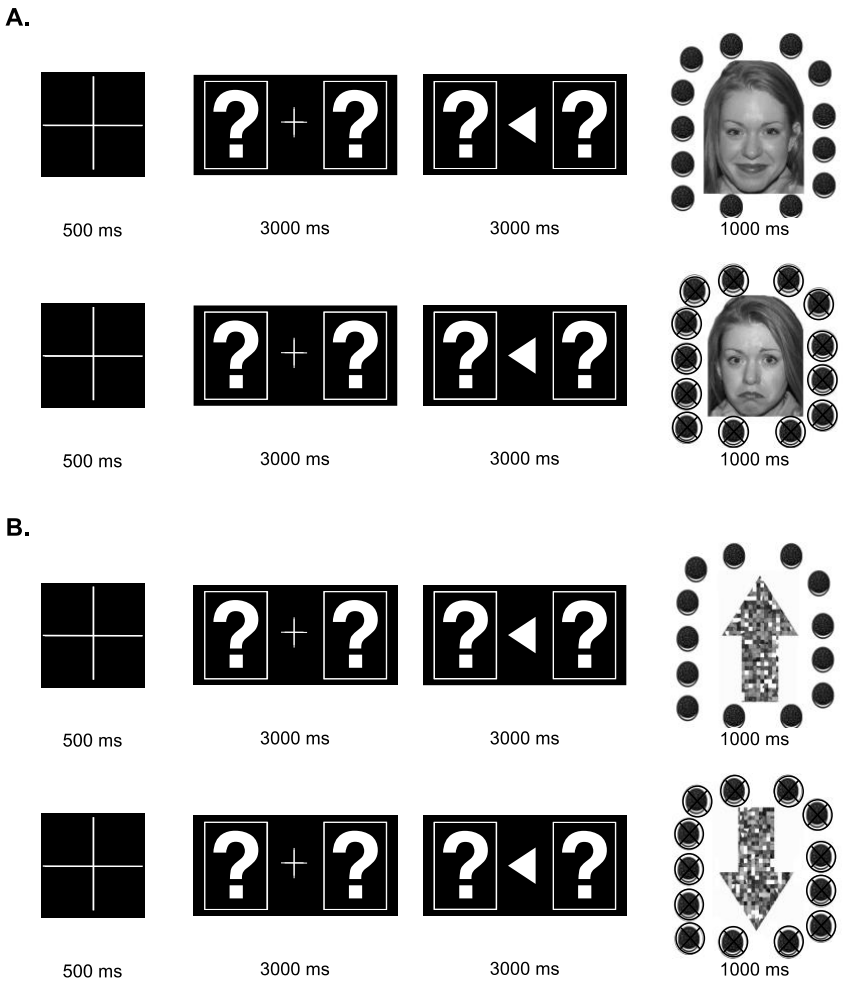

Figure 1. Stimulus presentation: **(A)** Stimuli and presentation timing for the social condition. **(B)** Stimuli and presentation timing for the nonsocial condition. Correct feedback is shown on top (intact Oreos); incorrect feedback is shown on the bottom (crossed-out Oreos).

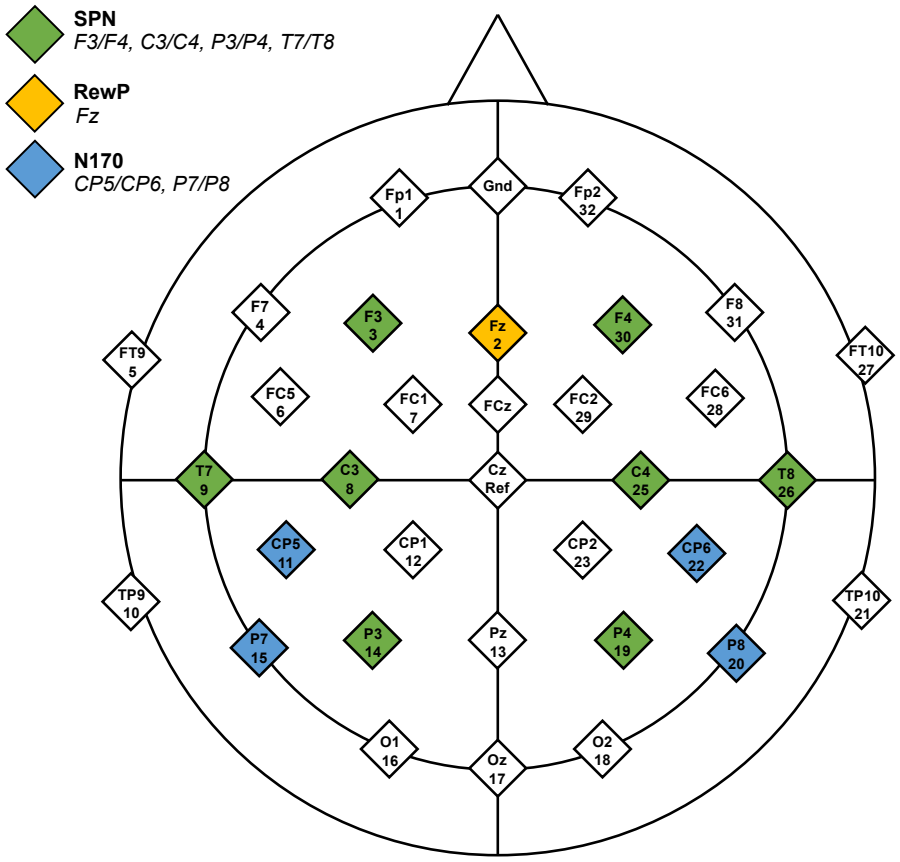

Figure 2. Headmap of electrode positions displaying regions of interest for the SPN, RewP, and N170 components.

EEG Data Retention

Of the 13 ASD participants included in this investigation, 12 participants provided a minimum of 10 trials in the social and nonsocial conditions at Time 1 and Time 2. Thus, 12 ASD participants were included in analyses of the SPN, RewP, and N170.

All 14 TD were included in RewP and N170 analyses, as each participant provided a minimum of 10 trials per condition at each timepoint. For SPN analyses, four TD participants did not provide the necessary 10 trials per condition at both timepoints, resulting in a total of 10 TD participants included in SPN analyses.

Statistical Analyses

All analyses were conducted using SPSS Version 27 (2020). Repeated-measures analyses of variance (ANOVAs) were conducted to test the effects of condition (social, nonsocial), time (pre-, post-intervention), and group (ASD, TD) on SPN mean amplitude, RewP mean amplitude, and N170 peak amplitude and latency. ANOVAs were conducted with Age at Time 1 as a covariate.

Repeated-measures ANOVAs were conducted to test the effects of group and time on behavioral measures of interest (i.e., SRS-2, SSIS, and Teen Engagement). Pearson correlations were conducted to test which pre-intervention measures were significantly associated with change in ERPs after intervention in the ASD group. Change in SPN and RewP was calculated as a difference score by subtracting pre-intervention mean amplitudes from post-intervention mean amplitudes within social and nonsocial conditions, respectively. Though there are some methodological concerns surrounding the use of change scores (e.g., reliability), they were used in this investigation due to their robustness against non-randomized designs, particularly when change scores are included as a dependent variable in regression analyses (50). Pearson correlations between behavioral variables of interest at Time 1 (pre-intervention) and ERP difference scores in the ASD group from Time 1 (pre-intervention) to Time 2 (post-intervention) were conducted to determine which variables to include in linear regression models. Finally, separate linear regressions were conducted in the ASD group based on the results of the correlations between behavioral measures at Time 1 and changes in brain activity from Time 1 to Time 2. The number of independent variables included in a

multivariate regression is often determined using a 20:1 ratio, such that there should be 20 subjects for each independent variable (51,52). Given the small sample size in this investigation, separate univariate regressions were conducted as to not violate basic principles. No prediction models including the N170 were conducted, as these analyses were exploratory.

Results

ERP

SPN

Prior to running ANOVAs to test the effect of intervention and group on SPN amplitude, differences by hemisphere and electrode position were conducted using a 2 (hemisphere: left, right) x 2 (time) x 4 electrode position (Frontal, Central, Parietal, Temporal) ANOVA. No significant main effects or interactions were found. As such, ANOVAs were collapsed across hemisphere and electrode position, similar to prior investigations using the same ERP paradigm (9,53). Note that some of these values are at the margin of statistical significance; analyses were reported for hypothesis-generating purposes and to inform future research.

A significant 2-way interaction was found between time and condition; $F(1,19) = 6.07$; $p = .02$, $\eta_p^2 = .24$. A marginally significant 3-way interaction was found between time, condition, and group; $F(1,19) = 4.09$, $p = .057$, $\eta_p^2 = .18$. Pairwise comparisons revealed a marginally significant effect of time in the ASD group, such that participants had marginally smaller SPN magnitude in the social condition at post-intervention compared to pre-intervention; $F(1,19) = 4.14$, $p = .056$. Pairwise comparisons also

revealed a marginal effect of condition at Time 2 in the TD group such that TD participants displayed a marginally more robust SPN to faces versus arrows at time 2; $F(1,19) = 3.34$, $p = .083$. No other main effects or interactions were observed. See Figure 3A and 3B.

RewP

A main effect of condition was found; $F(1,23) = 5.15$, $p = .03$, $\eta_p^2 = .18$ such that all participants, regardless of time, had a more robust RewP mean amplitude in response to social versus nonsocial stimuli. No other main effects or interactions were observed. See Figure 4A and 4B.

Exploratory Analysis: N170 Peak Amplitude

See note above; some of these values are at the margin of statistical significance. A significant 3-way interaction was found between time, hemisphere, and group; $F(1,23) = 13.35$, $p = .045$, $\eta_p^2 = .16$. A 4-way interaction was found between time, condition, hemisphere, and group; $F(1,23) = 14.19$, $p = .027$, $\eta_p^2 = .195$. Pairwise comparisons revealed that in the right hemisphere at Time 1, the ASD group had a more robust N170 than the TD group in the social condition; $F(1,23) = 5.14$, $p = .033$. In the ASD group there was a marginal effect of time such that in the right hemisphere there was a more robust N170 in the social condition at Time 2 (post-intervention) compared to Time 1 (pre-intervention); $F(1,23) = 3.99$, $p = .058$. In the TD group at Time 1, a more robust N170 was found in the nonsocial compared to the social condition in both left ($F(1,23) = 6.08$, $p = .022$) and right hemispheres ($F(1,23) = 4.57$, $p = .043$). Additionally, a marginally significant effect of hemisphere was observed in the TD group at Time 1 in

the social condition such that a more robust N170 was observed in the right versus left hemisphere; $F(1,23) = 3.86$, $p = .062$. See Figure 5.

N170 Latency

A main effect of hemisphere was observed, $F(1,23) = 5.802$, $p = .024$, $\eta_p^2 = .20$, such that the left hemisphere had a shorter N170 latency than the right hemisphere. No other main effects or interactions were observed.

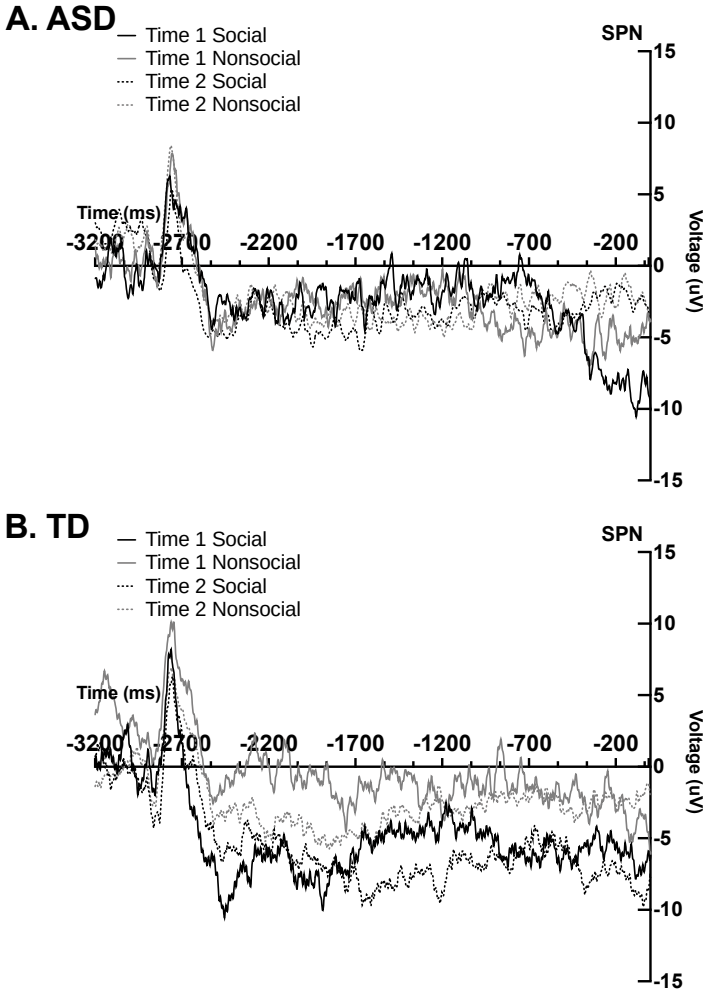

Figure 3. Grand average waveforms in the social and nonsocial conditions at Time 1 and Time 2 from the Stimulus Preceding Negativity (SPN) in **(A)** ASD participants and **(B)** TD participants.

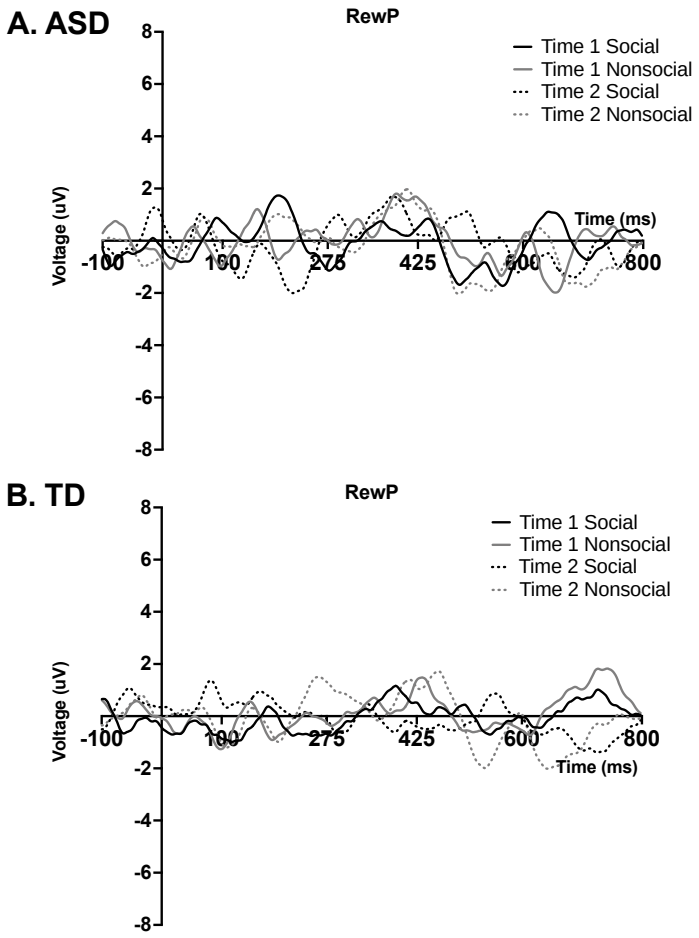

Figure 4. Grand average waveforms in the social and nonsocial conditions at Time 1 and Time 2 from Reward Positivity (RewP) ERP in **(A)** ASD participants and **(B)** TD participants. Note that for this figure, ERPs were filtered using a 25 Hz low-pass filter.

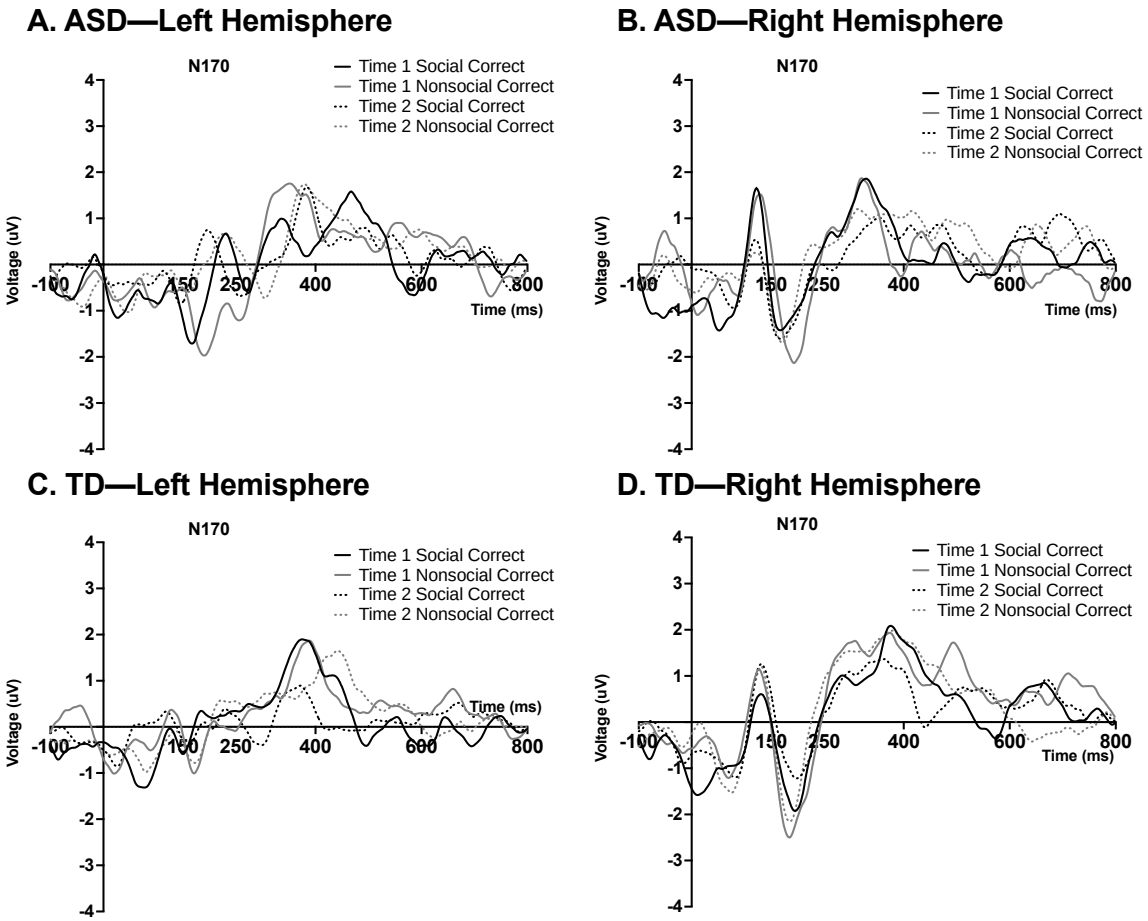

Figure 5. Grand average waveforms in the social and nonsocial conditions at Time 1 and Time 2 for the N170 ERP in **(A)** ASD participants in the left hemisphere, **(B)** ASD participants in the right hemisphere, **(C)** TD participants in the left hemisphere, and (**D**) TD participants in the right hemisphere. Note that for this figure, ERPs were filtered using a 25 Hz low-pass filter.

Behavioral Results: Repeated Measures ANOVA

Three 2 (group) x 2 (time) repeated measures ANOVAs were conducted to measure changes in SRS-2 Total score, SRS-2 Social Motivation, and SSIS Social Skills from Time 1 to Time 2. For the SRS-2 Total score, there was a main effect of time; $F(1,25) = 9.66$, $p < .01$, $\eta_p^2 = .28$; and a significant interaction between time and group;

$F(1,25) = 4.25$, $p = .05$, $\eta_p^2 = .15$. Pairwise comparisons revealed ASD participants had significantly higher SRS-2 Total scores at Time 1; $F(1,25) = 58.94$, $p < .01$, $\eta_p^2 = .70$); and Time 2; $F(1,25) = 31.84$, $p < .01$, $\eta_p^2 = .56$; compared to TD participants. ASD SRS-2 Total scores decreased from Time 1 to Time 2; $F(1,25) = 12.88$, $p < .01$, $\eta_p^2 = .34$, while TD scores remained the same across time, $F(1,25) = .59$, $p = .49$. A main effect of group was observed for the SRS-2 Social Motivation subscale; $F(1,25) = 27.26$, $p < .001$, $\eta_p^2 = .52$, and SSIS Social Skills subscale, $F(1,25) = 12.88$, $p < .01$, $\eta_p^2 = .34$, such that TDs had lower Social Motivation T-scores and higher Social Skills Standard Scores than ASD participants, regardless of time. Note that for the SRS-2, lower scores indicate fewer symptoms of ASD, whereas on the SSIS, higher sores indicate fewer social skills impairments. Refer to Table 2 for mean values.

ERP and Behavior: Correlations and Linear Regressions

Correlations

Note that some of these values are at the margin of statistical significance. The SPN social condition mean amplitude change was marginally correlated with pre-intervention age ($r = -.56$, $p = .059$) and pre-intervention SRS-2 Social Motivation scores ($r = -.57$, $p = .055$). Thus, increased magnitude of the SPN from Time 1 to Time 2 (note that the SPN more negative change scores reflect more robust reward anticipation) was correlated with older ages and worse social motivation prior to the start of intervention. Two additional correlations with the SPN social condition mean amplitude change trended towards significance. SPN mean amplitude change was negatively correlated

with SRS-2 Total (r = -.53, p = .079) and positively correlated with SSIS Social Skills (r = .54, p = .069).

The RewP social condition mean amplitude change was negatively correlated with SRS-2 Social Motivation scores pre-intervention (r = -.67, p = .02), such that an increased reward response to social stimuli was correlated with better social motivation scores before the start of intervention. RewP social condition difference score was positively correlated with Teen Participation (r = .70, p = .01), such that increased reward response to social stimuli from Time 1 to Time 2 was correlated with more intervention engagement. See Table 3 for a summary of correlation and linear regression results.

Table 3. Results of correlations and linear regressions in the ASD Group only. SPN social condition change and RewP social condition change are each outcome variables; all regressions were run separately.

SPN Social Condition Change	Correlation		Linear Regression				
	r	*p*	*B*	*SE B*	*β*	*t*	*p*
Age T 1	-.56	.059	-3.27	1.53	-.56	-2.133	.059
SRS-2 Social Motivation T 1	-.57	.055	-.484	.22	-.57	-2.17	.055
SRS-2 Total T 1	-.53	.079	-	-	-	-	-
SSIS Social Skills T 1	.54	.069	-	-	-	-	-
RewP Social Condition Change	Correlation		Linear Regression				
	r	*p*	*B*	*SE B*	*β*	*t*	*p*
SRS-2 Social Motivation T 1	-.67	.02	-.32	.11	-.67	-2.85	.02
Teen Participation	.70	.01	.05	.02	.70	3.10	.01

Linear Regressions

As stated above, some of these values are at the margin of statistical significance. Two linear regressions were conducted to test if age at the start of intervention and pre-intervention SRS-2 Social Motivation scores predicted change in SPN social condition

mean amplitude. Thirty-two percent of the variance of the change in anticipation of social reward was accounted for by SRS-2 Social Motivation pre-intervention scores, β = -.57*;* $F(1,10) = 4.71$, $p = .055$. Thirty-one percent of the variance in change in anticipation of social reward was accounted for by age at the start of intervention, β = -.56*;* $F(1,10) = 4.55$, $p = .059$.

Two linear regressions were conducted in the ASD group to test if pre-intervention SRS-2 Social Motivation scores and Teen Participation predicted change in RewP social condition mean amplitude. Results revealed that 44.9% of the variance of the change in social reward responsivity (RewP mean amplitude in response to faces) was accounted for by SRS-2 Social Motivation pre-intervention scores, β = -.67*;* $F(1,10) = 8.14$, $p = .02$. Similarly, 49% of the variance of the change in social reward responsivity was accounted for by Teen Participation, $\beta = .70$; $F(1,10) = 9.60$, $p = .01$.

Discussion

Social behaviors were improved in adolescents with ASD in the areas of social responsiveness and social skills, such that a reduction in autism symptomatology was observed after participation in PEERS. In addition to behavioral improvements, changes in neural correlates of reward were detected. The primary aim of this study was to investigate anticipation of and response to reward-related brain activity before and after completion of PEERS and to examine the ways in which individual factors impacted outcomes. As such, this preliminary study is one of the first to examine reward-related brain activity before and after intervention with a group of teens with ASD. Additionally, this investigation included a majority Latinx sample, a historically underrepresented

group. The inclusion of minority groups in intervention and in measures of neural response advances the representation of such groups and improves generalizability of findings.

Anticipation

Participants with ASD displayed marginally less anticipation (less robust SPN) to social rewards at post-intervention compared to pre-intervention. Though contrary to our hypotheses, it is possible that increased comfort and familiarity with social situations may explain these findings. That is, increased familiarity and experiences in social settings and/or in social interactions may have dampened anticipation of social information, as social behaviors became routine throughout the course of intervention. In contrast, TD participants did not evidence differences in reward anticipation across time. However, marginal differences between social and nonsocial conditions were observed at Time 2 such that TD adolescents evidenced more anticipatory brain activity in response to social versus nonsocial stimuli. Our findings suggest that participation in PEERS leads to changes in anticipation of social stimuli for adolescents with ASD, whereas time does not lead to equivalent changes for TD adolescents.

Individual variability of change in neural correlates of social anticipation from pre- to post-intervention was predicted by age and parent-reported social motivation at the beginning of the intervention. Older adolescents and those with *less* reported social motivation prior to PEERS displayed increased neural anticipation for faces from pre- to post-intervention. It will be important for future research to explore potential effects of age on PEERS efficacy, as the intervention is inclusive of a large age range. Our finding

that teens with less social motivation prior to PEERS displayed increased social reward anticipation after PEERS is a critical step forward in our ability to understand why some participants may benefit more from intervention than others.

Processing

In all participants, response to rewards was greater (more robust RewP) to social compared to nonsocial stimuli. Though previous work has reported hypoactivation in reward-related brain areas to social stimuli (54), findings in the current study provide an alternative account. It is possible that social deficits unique to ASD may not be reliably detected at the neural level in all children/adolescents, indicating that behavioral and objective measures of social response may not always be aligned. This is an important consideration when using objective measures of neural activity and emphasizes the need to examine individual variables in addition to group differences. It is important to keep in mind that one of the criteria for participation in PEERS is that teens with ASD be motivated to make and keep friends; as such, teens in the current study were distinctly socially motivated. Consequently, future studies measuring neural changes before and after intervention in adolescents and/or adults with ASD should consider participant motivation, as it is often required in these groups.

Although between-group differences were not observed, within-group variability of adolescents with ASD shed light on individual differences that affect social reward responsivity after intervention. Individual change in neural correlates of response to social reward was predicted by parent-reported social motivation before intervention and active engagement during the program. Participants who were *more* actively engaged in

PEERS and who displayed *more* social motivation prior to the start of intervention made the biggest gains in neural response to social rewards from pre- to post-intervention. Findings related to teen participation during intervention underscore the importance of engagement during behavioral intervention.

The effect of parent-reported social motivation prior to PEERS on changes in brain activity related to reward processing is the opposite of what we observed for social reward anticipation. That is, adolescents who had *lower* levels of parent-reported social motivation prior to PEERS displayed *greater* increases in neural correlates of social anticipation after PEERS, yet adolescents who had *higher* levels of parent-reported social motivation before PEERS displayed *increased* neural correlates of social reward responsivity after PEERS. This underscores the importance of dissociating social reward anticipation from social reward processing when considering individual response to intervention, as these constructs likely represent different neural processes. It may be that there are differences in saliency between wanting/anticipating social rewards versus liking/responding to social rewards (55,56) within the brain's reward system in individuals with ASD. These distinct cognitive processes offer a unique understanding of the Social Motivation Theory in adolescents with ASD who are driven to make and keep friends, suggesting that both motivation and reward systems may moderate intervention effects.

Exploratory N170 findings

Exploratory analyses were performed on the N170. A more robust N170 response approached significance at post-intervention compared to pre-intervention in the ASD

group within the right hemisphere. This indicates an enhancement of facial processing after intervention that mirrors findings in neurotypical populations (32). It is important to note that the stimuli and ERP paradigm used in the current investigation were not designed to elicit N170 responses and thus differ from traditional measurements of the N170 (e.g. facial stimuli were positive in valence and contained additional reward-related information). Thus, findings from the N170 should be interpreted with caution.

Limitations

Some limitations must be considered when interpreting results. Our sample size is small, and thus may have been underpowered to detect between-group differences. Inclusion of an ASD wait-list control group would have improved the experimental design of the investigation and may have allowed for the effects of the "natural passage of time" versus "intervention" to be disentangled in the ASD group. However, inclusion of a TD group established, in-part, that change was not solely due to the passage of time. Change scores were used in this investigation instead of alternative methods of pre- and post-test analyses, which may have influenced results. A clustered design was not utilized in this design and this may have impacted our statistical power and effect size of intervention effects (57). Additionally, a small sample size reduces our ability to generalize our findings to larger groups of adolescents with ASD. Given the cognitive demands of PEERS and the EEG procedures, participants were required to have cognitive abilities in the average range to be eligible for the current study (i.e., IQ greater than or equal to 70). Another requirement was for teens with ASD to be motivated to make and keep friends and for both parents and teens to be able to attend weekly 90-minute

intervention sessions for 16 weeks. Given these considerations, it is likely that participants in the current study represent a subset of adolescents with ASD. In the future, it will be important to clarify which of these factors may affect the efficacy of PEERS.

Conclusion

To our knowledge, this is the first study to measure neural correlates of both social reward anticipation and processing in adolescents with ASD before and after the PEERS intervention. Findings supported our hypothesis that change in neural correlates of social reward anticipation and processing can be predicted by individual characteristics prior to intervention. Although traditional conceptualizations of social motivation define this construct as the desire or intention to engage and interact with others, our findings reinforce previous work that reward anticipation and reward processing are dissociable constructs (56,58). Our findings suggest that for individuals with ASD who may have lower levels of intrinsic motivation to interact with others, PEERS may enhance their desire to approach others, commonly known as approach motivation, or 'wanting' to interact (as indicated by increased neural reward anticipation to faces; SPN). However, for those who are already motivated to interact with others, completion of the PEERS program may further reinforce social interactions as pleasant (as indicated by increased neural reward processing of faces, RewP).

In ASD intervention research, there remains a lack of validated biomarkers that can be used to predict intervention outcomes (59). Future studies with larger samples should attempt to both replicate these findings and further parse these constructs to move

closer to ‘precision medicine’ efforts to individualize intervention and predict which adolescents are most likely to benefit from PEERS.

References

1. Kenny L, Hattersley C, Molins B, Buckley C, Povey C, Pellicano E. Which terms should be used to describe autism? Perspectives from the UK autism community. Autism. 2016 May 1;20(4):442–62.

2. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. Arch Gen Psychiatry. 2008 Aug;65(8):946–54.

3. Pierce K, Marinero S, Hazin R, McKenna B, Barnes CC, Malige A. Eye tracking reveals abnormal visual preference for geometric images as an early biomarker of an autism spectrum disorder subtype associated with increased symptom severity. Biol Psychiatry. 2016 Apr 15;79(8):657–66.

4. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. Trends Cogn Sci. 2012 Apr;16(4):231–9.

5. Bottini S. Social reward processing in individuals with autism spectrum disorder: A systematic review of the social motivation hypothesis. Research in Autism Spectrum Disorders. 2018 Jan 1;45:9–26.

6. Haber SN, Knutson B. The reward circuit: Linking primate anatomy and human imaging. Neuropsychopharmacol. 2010 Jan;35(1):4–26.

7. Supekar K, Kochalka J, Schaer M, Wakeman H, Qin S, Padmanabhan A, et al. Deficits in mesolimbic reward pathway underlie social interaction impairments in children with autism. Brain. 2018 Sep 1;141(9):2795–805.

8. Kohls G, Antezana L, Mosner MG, Schultz RT, Yerys BE. Altered reward system reactivity for personalized circumscribed interests in autism. Molecular Autism. 2018 Jan 30;9(1):9.

9. Stavropoulos KKM, Carver LJ. Reward anticipation and processing of social versus nonsocial stimuli in children with and without autism spectrum disorders. Journal of Child Psychology and Psychiatry. 2014;55(12):1398–408.

10. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. J Autism Dev Disord. 2012 Feb 1;42(2):147–60.

11. Meyer GM, Marco-Pallarés J, Boulinguez P, Sescousse G. Electrophysiological underpinnings of reward processing: Are we exploiting the full potential of EEG? NeuroImage. 2021 Nov;242:118478.

12. Clements CC, Zoltowski AR, Yankowitz LD, Yerys BE, Schultz RT, Herrington JD. Evaluation of the social motivation hypothesis of autism: A systematic review and meta-analysis. JAMA Psychiatry. 2018 Aug 1;75(8):797.

13. Holroyd CB, Pakzad-Vaezi KL, Krigolson OE. The feedback correct-related positivity: Sensitivity of the event-related brain potential to unexpected positive feedback. Psychophysiology. 2008 Sep;45(5):688–97.

14. Proudfit GH. The reward positivity: From basic research on reward to a biomarker for depression. Psychophysiology. 2015;52(4):449–59.

15. Stavropoulos KKM, Carver LJ. Effect of familiarity on reward anticipation in children with and without autism spectrum disorders. PLOS ONE. 2014 Sep 3;9(9):e106667.

16. Baker E, Veytsman E, Martin AM, Blacher J, Stavropoulos KKM. Increased neural reward responsivity in adolescents with ASD after social skills intervention. Brain Sciences. 2020 Jun;10(6):402.

17. Dawson G, Burner K. Behavioral interventions in children and adolescents with autism spectrum disorder: A review of recent findings. Curr Opin Pediatr. 2011 Dec;23(6):616–20.

18. Reichow B, Boyd BA, Barton EE, Odom SL. Handbook of early childhood special education. New York, NY: Springer Science+Business Media; 2016.

19. Laugeson EA. The PEERS curriculum for school-based professionals. New York, NY: Routledge; 2013. 480 p.

20. Laugeson EA, Frankel F, Gantman A, Dillon AR, Mogil C. Evidence-based social skills training for adolescents with autism spectrum disorders: The UCLA PEERS program. J Autism Dev Disord. 2012 Jun 1;42(6):1025–36.

21. Laugeson EA, Frankel F. Social skills for teenagers with developmental and autism spectrum disorders: The PEERS treatment manual. Routledge; 2011. 446 p.

22. Laugeson EA, Frankel F, Mogil C, Dillon AR. Parent-assisted social skills training to improve friendships in teens with autism spectrum disorders. J Autism Dev Disord. 2009 Apr 1;39(4):596–606.

23. Dawson G, Jones EJH, Merkle K, Venema K, Lowy R, Faja S, et al. Early behavioral intervention is associated with normalized brain activity in young

children with autism. J Am Acad Child Adolesc Psychiatry. 2012 Nov;51(11):1150–9.

24. Van Hecke AV, Stevens S, Carson AM, Karst JS, Dolan B, Schohl K, et al. Measuring the plasticity of social approach: A randomized controlled trial of the effects of the PEERS intervention on EEG asymmetry in adolescents with autism spectrum disorders. Journal of Autism and Developmental Disorders. 2015;45(2):316–35.

25. Venkataraman A, Yang DYJ, Dvornek N, Staib LH, Duncan JS, Pelphrey KA, et al. Pivotal response treatment prompts a functional rewiring of the brain among individuals with autism spectrum disorder. Neuroreport. 2016 Sep 28;27(14):1081–5.

26. Ventola P, Yang DYJ, Friedman HE, Oosting D, Wolf J, Sukhodolsky DG, et al. Heterogeneity of neural mechanisms of response to pivotal response treatment. Brain Imaging Behav. 2015 Mar;9(1):74–88.

27. Voos AC, Pelphrey KA, Tirrell J, Bolling DZ, Vander Wyk B, Kaiser MD, et al. Neural mechanisms of improvements in social motivation after pivotal response treatment: Two case studies. J Autism Dev Disord. 2013 Jan;43(1):1–10.

28. Yang D, Pelphrey KA, Sukhodolsky DG, Crowley MJ, Dayan E, Dvornek NC, et al. Brain responses to biological motion predict treatment outcome in young children with autism. Transl Psychiatry. 2016 15;6(11):e948.

29. Kala S, Rolison MJ, Trevisan DA, Naples AJ, Pelphrey K, Ventola P, et al. Brief report: Preliminary evidence of the N170 as a biomarker of response to treatment in autism spectrum disorder. Front Psychiatry [Internet]. 2021 [cited 2021 Jul 7];12. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.709382/full

30. Key AP, Corbett BA. The unfulfilled promise of the N170 as a social biomarker. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2020 Mar 1;5(3):342–53.

31. McPartland JC, Bernier RA, Jeste SS, Dawson G, Nelson CA, Chawarska K, et al. The autism biomarkers consortium for clinical trials (ABC-CT): Scientific context, study design, and progress toward biomarker qualification. Front Integr Neurosci. 2020;14:16.

32. Kang E, Keifer CM, Levy EJ, Foss-Feig JH, McPartland JC, Lerner MD. Atypicality of the N170 event-related potential in autism spectrum disorder: A

meta-analysis. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2018 Aug;3(8):657–66.

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

34. Webb SJ, Dawson G, Bernier R, Panagiotides H. ERP evidence of atypical face processing in young children with autism. J Autism Dev Disord. 2006 Oct;36(7):881–90.

35. O'Connor K, Hamm JP, Kirk IJ. The neurophysiological correlates of face processing in adults and children with Asperger's syndrome. Brain and Cognition. 2005 Oct 1;59(1):82–95.

36. Miskovic V, Schmidt LA, Georgiades K, Boyle M, Macmillan HL. Adolescent females exposed to child maltreatment exhibit atypical EEG coherence and psychiatric impairment: Linking early adversity, the brain, and psychopathology. Dev Psychopathol. 2010 May;22(2):419–32.

37. Mitchell AM, Pössel P. Frontal brain activity pattern predicts depression in adolescent boys. Biological Psychology. 2012 Feb 1;89(2):525–7.

38. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop SL. Autism Diagnostic Observation Schedule. 2nd ed. WPS; 2012.

39. Wechsler D. Wechsler Abbreviated Scale of Intelligence. 2nd ed. Pearson; 2011.

40. Constantino JN. Social Responsiveness Scale. 2nd ed. WPS; 2012.

41. Gresham FM, Elliott SN. Social Skills Improvement System Rating Scales. Pearson; 2008.

42. Laugeson EA, Gantman A, Kapp SK, Orenski K, Ellingsen R. A randomized controlled trial to improve social skills in young adults with autism spectrum disorder: The UCLA PEERS program. J Autism Dev Disord. 2015 Dec 1;45(12):3978–89.

43. Ellingsen R, Bolton C, Laugeson E. Evidence-based social skills groups for individuals with autism spectrum disorder across the lifespan. In: Leaf JB, editor. Handbook of social skills and autism spectrum disorder [Internet]. Cham: Springer International Publishing; 2017 [cited 2020 Oct 20]. p. 343–58. (Autism

and Child Psychopathology Series). Available from: http://link.springer.com/10.1007/978-3-319-62995-7_20

44. Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, et al. The NimStim set of facial expressions: Judgments from untrained research participants. Psychiatry Research. 2009 Aug 15;168(3):242–9.

45. Lopez-Calderon J, Luck SJ. ERPLAB: An open-source toolbox for the analysis of event-related potentials. Front Hum Neurosci. 2014;8:213.

46. Hajcak G, Moser JS, Yeung N, Simons RF. On the ERN and the significance of errors. Psychophysiology. 2005;42(2):151–60.

47. Hajcak G, Moser JS, Holroyd CB, Simons RF. The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. Biol Psychol. 2006 Feb;71(2):148–54.

48. Blau VC, Maurer U, Tottenham N, McCandliss BD. The face-specific N170 component is modulated by emotional facial expression. Behavioral and Brain Functions. 2007 Jan 23;3(1):7.

49. Dawson G, Webb SJ, McPartland J. Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Dev Neuropsychol. 2005;27(3):403–24.

50. Allison PD. Change scores as dependent variables in regression analysis. Sociological Methodology. 1990;20:93–114.

51. Green SB. How many subjects does it take to do a regression analysis. Multivariate Behavioral Research. 1991 Jul;26(3):499–510.

52. Tabachnick BG, Fidell LS. Using multivariate statistics. Harper & Row; 1989. 774 p.

53. Stavropoulos KKM, Carver LJ. Reward sensitivity to faces versus objects in children: An ERP study. Soc Cogn Affect Neurosci. 2014 Oct;9(10):1569–75.

54. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY. Reward processing in autism. Autism Research. 2010;3(2):53–67.

55. Kohls G, Schulte-Rüther M, Nehrkorn B, Müller K, Fink GR, Kamp-Becker I, et al. Reward system dysfunction in autism spectrum disorders. Soc Cogn Affect Neurosci. 2013 Jun 1;8(5):565–72.

56. Berridge KC, Robinson TE, Aldridge JW. Dissecting components of reward: 'liking', 'wanting', and learning. Current Opinion in Pharmacology. 2009 Feb 1;9(1):65–73.

57. Lopata C, Donnelly JP, Rodgers JD, Thomeer ML. Systematic review of data analyses and reporting in group-based social skills intervention RCTs for youth with ASD. Research in Autism Spectrum Disorders. 2019 Mar;59:10–21.

58. Kohls G, Chevallier C, Troiani V, Schultz RT. Social 'wanting' dysfunction in autism: Neurobiological underpinnings and treatment implications. Journal of Neurodevelopmental Disorders. 2012 Jun 27;4(1):10.

59. McCracken JT, Anagnostou E, Arango C, Dawson G, Farchione T, Mantua V, et al. Drug development for autism spectrum disorder (ASD): Progress, challenges, and future directions. European Neuropsychopharmacology. 2021 Jun;48:3–31.

Chapter 3

The effects of oxytocin administration on individuals with ASD: Neuroimaging and behavioral evidence

The effects of oxytocin administration on individuals with ASD: Neuroimaging and behavioral evidence

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and the presence of restricted interests and repetitive behaviors. Although behavioral interventions are numerous, there are no Federal Drug Administration approved pharmacological treatments for the core symptoms of ASD. The neuropeptide oxytocin has been studied in animals for decades, and is involved in pair bonding and social affiliation. Given oxytocin's involvement in social communication in animals, researchers have begun exploring whether oxytocin administration in humans affects social behaviors and attachment. Particular attention has been paid to whether oxytocin has therapeutic benefits for improving social behaviors in individuals with ASD. Research on oxytocin administration in ASD has utilized both behavioral and brain-based outcomes. This chapter reviews the effects of oxytocin administration in ASD, with a focus on functional outcomes from neuroimaging investigations. Evidence of potential therapeutic benefits are reviewed, as well as

limitations of extant research. A proposed model for future research into the therapeutic benefits of oxytocin includes combining pharmacological (e.g. oxytocin) and behavioral (e.g. evidence-based behavioral interventions) techniques to improve social communication skills in ASD.

Introduction

It is estimated that 1 in 59 children in the United States has a diagnosis of Autism Spectrum Disorder (ASD),[1] which is characterized by life-long social communication deficits and the presence of restricted interests and repetitive behaviors.[2] In the first few years of life, commonly observed social communication deficits include poor imitation skills, reduced social orienting, and limited joint attention.[3,4] As children get older, challenges exist in maintaining social interactions and sustained conversations with their peers.[5,6] Restricted and repetitive interests, including resistance to change, repetitive motor movements, and strong interests in unusual topics (e.g. traffic lights, drain pipes), may further complicate and hinder social behaviors.[7,8] Despite shared core symptoms, ASD covers a wide spectrum and behavioral manifestations are varied between individuals to produce a heterogenous phenotype.

Given the heterogenous behavioral manifestations of ASD, it is unsurprising that multiple behavioral interventions have been developed to improve social communication and decrease challenging behaviors.[9–11] In terms of "treatments" for ASD, behavioral intervention is currently one of the most effective methods for improving social-communication skills. In contrast to other conditions in which both behavioral and medical treatments are supported by empirical evidence, no medication is currently

approved to improve core symptoms of ASD. Although two pharmaceutical medications, risperidone and aripiprazole, have been approved by the Federal Drug Administration for use in ASD, they do not address core symptoms. Rather, they have been approved to treat ancillary symptoms of ASD, such as aggression and irritability.[12]

Many challenges exist in both the production and efficacy-testing of novel pharmaceutical medications, particularly in children.[13] For example, methodologies necessary to test treatment efficacy within clinical trials may require invasive techniques, such as blood samples, which may not be well-tolerated by children. Alternatives to blood samples, such as urine testing, tend to be less reproduceable, thus weakening the potential to identify significant outcomes. Additionally, unintended psychological harm may exist during active clinical trials or long after the trial has be completed that may be difficult to detect in children.[14,15] Risk monitoring should be implemented in any clinical trial involving pediatric populations in order to continually assess well-being of the sample. This requires specialist-level training and experience with children. These specialists are often under-utilized in clinical trials with children, making the detection and assessment of well-being and psychological state more difficult.[15]

Due to the lack of pharmacological interventions to address the core symptoms of ASD, there has been a focus on compounds that may affect social communication directly. Though many have been discussed, one that has received considerable attention in recent decades is oxytocin, a hormone associated with prosocial behaviors in humans and animals.[16,17] Given oxytocin's role in prosocial behaviors, exogenous administration of the neuropeptide has potential noteworthy therapeutic benefits in ASD.

Oxytocin

Oxytocin, a neuropeptide produced in the hypothalamus,[18] has been extensively studied and utilized for its effects on social cognition and prosocial behaviors.[19–21] During childbirth, oxytocin is critical for uterine contractions and is necessary for the production of milk.[22,23] Oxytocin is developmentally regulated and its receptors are malleable, particularly in response to parent-child interactions.[24,25] Colloquially referred to as the "love hormone," oxytocin has been implicated in a variety of species, including rats and prairie voles, to be at increased levels during mating and pair-bonding.[26,27] In rats, development appears to play a significant role in both the number and location of oxytocin receptors. Two periods of development have been recognized as important for oxytocin expression: the week which precedes weaning, and puberty.[28] There is evidence that some brain areas which contain high densities of oxytocin binding sites in early life (e.g. cingulate and retrosplenial cortex, and regions of both the basal ganglia and limbic system), have low numbers of binding sites in the adult rat. The contrary has been found as well: some brain areas which do not contain high densities of oxytocin binding sites in early life begin to contain high densities of binding sites around puberty. Though studies of oxytocin binding sites in rats cannot be generalized to humans, this work sheds light on both the complexity of the oxytocin system, and the role that development plays in the maturation of the oxytocin receptors.[29]

In humans, oxytocin can be safely administered exogenously either intranasally or intravenously. Traces of oxytocin that are administered peripherally (e.g. intravenously) are found in cerebrospinal fluid, though uncertainty remains regarding the extent to

which oxytocin is able to cross the blood-brain barrier.[30,31] A study in rhesus macaques provided evidence that intranasal oxytocin was detectable in cerebrospinal fluid, however this investigation included only six nonhuman primates who were given a higher dosage of oxytocin than is usually administered in humans.[32] Administration of oxytocin is able to pass the blood-brain barrier, though measurable effects may diminish over time.[33] In healthy individuals, increases in pro-social behaviors are seen after administration of oxytocin, including improved emotion-identification of human faces, increased attention to the eye-region of faces, and enhanced theory of mind abilities.[19,34–37] In the section below, we briefly review studies using neuroscience methodology that investigate both brain and behavioral effects of oxytocin in neurotypical participants.

Brain-based studies of oxytocin administration in neurotypical individuals

A seminal neuroimaging study examined neural mechanisms of prosocial behaviors that have widely been observed in behavioral investigations of oxytocin administration.[37] Results showed reduced amygdala activation in response to threatening stimuli after oxytocin administration compared to placebo in healthy adults.[37] This response modulation provided the first evidence that increased prosocial behaviors observed after oxytocin administration may be a result of reduced amygdala response. Neuroimaging methods provide evidence that oxytocin administration consistently dampens amygdala activation in response to emotional stimuli. For example, Domes and colleagues [19] found that intranasal oxytocin administration in adult males attenuated amygdala activity to emotional faces, including angry, fearful, and happy faces. Thus, amygdala activation was globally reduced despite the faces' emotional valence.[36]

Using electrophysiological methods, a recent study in neurotypical adults provided evidence that oxytocin administration also affects brain activity related to imitation and social action perception. The authors observed enhanced mu rhythm suppression in response to both performing and viewing tasks of social biological motion compared to non-social motion.[38] As such, the mirror neuron system underlying imitation and action perception, which are thought to be impaired in social-communicative disorders such as ASD, appear to be more readily engaged after oxytocin administration. Prosocial effects of oxytocin administration can both elucidate neural mechanisms underlying social behavior and have implications for treatment of psychiatric disorders that are characterized by social deficits, such as ASD.[39] The subsequent section will review previous work related to oxytocin in ASD.

Oxytocin and ASD

Early theories about the relation between oxytocin and ASD began in the late twentieth century.[40,41] Modahl and colleagues were the first to provide evidence of reduced levels of oxytocin in children with ASD. Specifically, the authors found that compared to their neurotypical peers, oxytocin does not increase prior to the onset of puberty in individuals with ASD. This suggests that oxytocin is less available to individuals with ASD during development.[42] Our understanding of oxytocin in individuals with ASD has since been shaped by research that suggests deficits in oxytocin may reveal the pathogenesis of ASD. No known mechanistic pathway exists to form a substantial link between the neuropeptide and development of ASD, but studies support

that lower concentrations of oxytocin are strongly related to social impairments.[43] As such, oxytocin administration may enhance social communication in ASD.

Measurement of oxytocin levels in individuals with ASD continues to be explored, as binding sites, receptor function, and the production of oxytocin are challenging to study in humans, given limitations of in-vivo neurometabolic investigation. Oxytocin-related genes have been implicated in ASD, to the extent that polymorphisms in the oxytocin receptor genes are related to symptom severity.[44–46] Early studies of the endocrine system have found that oxytocin release occurs differently in children with ASD compared to their neurotypical peers, suggesting that oxytocin may be disrupted early in development.[47] Oxytocin blood plasma levels increase throughout neurotypical development, while children with ASD exhibit lower levels of plasma oxytocin[48] that are stable over time.[42] Therefore, disruptions of the oxytocin system may possibly occur early in life in individuals with ASD, resulting in cascading consequences.

An investigation of early life effects of oxytocin found that when oxytocin was administered to human mothers to induce labor, no negative effects were identified in offspring 20 years later.[49] Specifically, oxytocin exposure early in life did not influence behavioral problems or symptoms of ASD. However, levels of plasma oxytocin are positively correlated with social behaviors in individuals with ASD, their neurotypical siblings, and neurotypical controls.[44] Parker and colleagues found that oxytocin levels were largely heritable between individuals with ASD and their siblings, providing further evidence of oxytocin's role in the biology of social behavior and its heritability.[44] That is, low oxytocin levels are observed in siblings of individuals with ASD compared to

neurotypical children. This is particularly important, as approximately twenty percent of siblings of children with ASD will meet criteria for ASD by age three[50] and these siblings are at a significantly higher risk of developmental delay and general social deficits, even if they do not meet criteria for ASD.[51] Thus, first-degree relatives of siblings with ASD appear to also have reduced oxytocin levels compared to individuals who have siblings without ASD.

Sex differences and comorbidities should also be considered when measuring oxytocin levels in ASD, as oxytocin serum concentrations in females with both ASD and Intellectual Disabilities (ID) have been shown to be positively correlated with increased nonverbal skills and repetitive behaviors.[52] Conversely, in males with ASD and ID, oxytocin concentration has been shown to be negatively correlated with measures of repetitive behaviors.[52] Previous work suggests that males with ASD and ID exhibit greater restricted and repetitive interests than females with ASD and ID,[53] though this may be modulated by oxytocin concentration between sexes. Endogenous oxytocin levels may serve as a potential biomarker for later behavioral manifestations of ASD in females who also have ID and may act as a protective factor in males. That is, additional levels of oxytocin may not always contribute to decreased symptoms of ASD when individual characteristics, such as sex and cognitive ability, are considered. A recent investigation showed that increased variants in the oxytocin receptor gene were associated with greater connectivity between the brain regions related to reward and social cognition (including the nucleus accumbens and frontal pole, superior frontal gyrus, frontal medial and orbital cortex, paracingulate and cingulate cortex, caudate, and putamen) within females with

ASD.[54] This investigation highlights the relationship between genetic risk specific to the oxytocin receptor and brain connectivity in females. Interesting, the authors also found that the reward network connectivity with frontal brain regions in females with ASD is similar to that of neurotypical males.[54] This underscores the complexity of oxytocin within individuals with ASD.

It is important to note that findings from studies of oxytocin in ASD tend to be inconsistent. Recent studies with larger samples report no differences in levels of plasma oxytocin between individuals with ASD and neurotypical controls.[44,55,56] Unique findings across studies may relate to how plasma oxytocin is measured and whether examinations of the peripheral or central nervous system influence measurement.[57,58] Using a pharmacologically optimized approach to measure oxytocin receptor binding with postmortem human brains, individuals with ASD were found to have more oxytocin binding receptor sites in the nucleus basalis of Meynert (NBM), but reduced binding receptor sites in the ventral pallidum compared to neurotypical controls.[59] The NBM is located within the basal forebrain and is involved in the regulation of visual attention, gaze, and memory. As individuals with ASD have more binding sites in the NBM than expected, this may lead to atypical attentional allocation to social stimuli.[60] The ventral pallidum is located within the basal ganglia and is associated with the reward system in humans. A dearth of binding sites (e.g. lower density of binding sites) in brain areas associated with the reward system may account for why individuals with ASD have disruptions in social communication, which has implications for how social stimuli are processed.

According to the social motivation hypothesis, individuals with ASD may experience social interactions as less rewarding than their neurotypical peers, which leads to reduced social initiation.[61] Accordingly, it has been hypothesized that the reward system in individuals with ASD is less responsive to social stimuli compared to individuals without ASD (though it is important to note that research findings related to the neural reward system in ASD are mixed). Given oxytocin's role in social affiliation and bonding, it is not entirely surprising that this neuropeptide has been hypothesized to be relevant to potential disruptions in the reward system in individuals with ASD.[62,63] As refined methodologies are developed to locate and identify altered oxytocin receptors in ASD, the field moves closer to understanding the etiology of ASD and how behavior represents the presentation of biological aberrances. Particular attention should be paid to the distribution and density of oxytocin receptors in the reward system in both individuals with and without ASD, as this may clarify the role of oxytocin in the reward system more broadly. Given the hypothesized relation between oxytocin levels and symptoms of ASD, investigators have studied whether oxytocin administration improves social behaviors in this population.

Oxytocin Administration in Individuals with ASD

Behavioral findings of oxytocin administration in individuals with ASD

Though research on oxytocin in ASD is relatively new, literature on the topic has grown significantly in recent years. The earliest empirical studies of oxytocin administration in individuals with ASD occurred in the early twenty-first century, when Hollander and colleagues were the first to show that repetitive behaviors were reduced

after intravenous oxytocin administration.[64] Subsequent studies noted that oxytocin is generally well tolerated amongst individuals with ASD with few side-effects,[see65–67] though some negative side-effects have been observed.[68] For example, three participants in an oxytocin trial experienced hyperactivity and aggression, though side-effects ceased once administration was terminated.[68] Outcomes of oxytocin administration in individuals with ASD include increased sustained eye gaze and inferring emotion, social cooperation, improved emotion recognition, and a decrease in symptom severity.[48,69–71] These findings are critical, as the aforementioned behaviors (e.g. eye gaze, ability to infer emotions of others) set the stage for high-order social interactions. These findings are promising, though improvements in social behaviors in isolation may not impact functional social communication skills that make up core deficits of ASD, including the ability to integrate verbal and nonverbal communication skills to effectively socialize with others. In addition to findings related to social behaviors, reductions in repetitive behaviors have been observed after long-term intranasal oxytocin administration (4-6 weeks, once to twice a day) in adults with ASD compared to placebo.[67,72] Interestingly, some of the aforementioned studies failed to observe improvements in social communication after oxytocin administration compared to placebo[61,66]. In both of those studies, oxytocin administration decreased repetitive behaviors but did not have the hypothesized effects on social communicative behaviors.

It is important to note that some studies have failed to observe any significant benefits of oxytocin administration compared to placebo for participants with ASD. For example, Dadds and colleagues[66] conducted a double-blind randomized control trial with

38 male youths with ASD (7-16 years old) during which participated were given either oxytocin or placebo one per day for four consecutive days during parent—child interaction training sessions. Compared to placebo, oxytocin did not improve emotion recognition or social interaction abilities. Similarly, Guastella and colleagues[65] conducted a double-blind placebo-controlled trial in which participants with ASD (12-18 years old) received either oxytocin or placebo twice daily for 8 weeks. Participants were assessed before, during, and after treatment, as well as at a 3-month follow-up. No benefits of oxytocin were observed following treatment. Notably, parents who believed their children received oxytocin reported greater improvements on parent-rating scales compared to those who believed their child received placebo. This has important implications for how open-label trials should be interpreted and provides strong evidence that studies of oxytocin versus placebo should utilize double-blind designs whenever possible.

Several factors must be considered when evaluating the clinical impact of oxytocin administration, including the heterogeneity observed in ASD, comorbid disorders, and participant age.[73,74] Additionally, it is challenging to ascertain the behavioral effects of oxytocin in ASD given the variety of outcome measures that are utilized. Many measures exist to evaluate symptoms of ASD, including questionnaires, surveys, and interviews, though few studies utilize the same measures both before and after oxytocin administration. The use of objective and sensitive measures both before and after oxytocin administration can further our ability to measure the effects and utility of oxytocin in individuals with ASD. Investigations can be supplemented by including

neuroimaging findings to guide both future clinical trials and neurobiological studies, respectively.[55,75,76]

Brain-based findings of oxytocin administration in individuals with ASD

This section will summarize existing studies that have examined the effects of oxytocin on brain function in individuals with ASD (see Table 1). The use of neuroscience measures may not only elucidate the neural basis of neuropeptidergic functioning, but can also serve as a sensitive measure of the effects of oxytocin administration, as brain-based measures are objective and less susceptible to bias than self-report or caregiver-report.

The first investigation of the neural effects of oxytocin administration in ASD was conducted by Domes and colleagues.[77] Participants saw pictures of both neutral faces and houses, and were asked to determine whether the images were the same or different. Though no behavioral changes were observed in response to oxytocin administration, fMRI findings indicated increased activity in the right posterior amygdala in response to faces. The authors posit that amygdala activation may reflect stimulation of a social saliency network in ASD in response to facial images.[77] Thus, amygdala activation is not solely based on the emotional valence of the stimuli, but in individuals with ASD, increased response in this region may reflect increased attentional allocation to social stimuli more broadly. Alternatively, amygdala activation may represent oversensitivity to faces in general, such that neutral faces may be perceived with heightened emotion in individuals with ASD after oxytocin administration. Interestingly, this is in contrast with previous findings on the effects of oxytocin in neurotypical individuals.[19,37,78] That is,

neuroscience studies with neurotypical individuals demonstrate that oxytocin administration causes a decrease in amygdala activity in response to emotional stimuli, whereas results from Domes and colleagues found evidence that oxytocin administration enhanced amygdala activation to faces in individuals with ASD. Though these findings appear at odds with one another, it is possible that activation patterns relate to differences between tasks and/or stimuli.

A later study measured brain activity in both a cooperative social game (ball tossing with fair and unfair fictitious computer players) and a face or shape matching task.[79] In the face matching task, participants with ASD who had received oxytocin compared to placebo demonstrated enhanced activity in the inferior occipital gyrus and fusiform gyrus. During the social cooperation game, increased activity in the anterior orbito-frontal cortex (OFC), and reduced activity in the amygdala and hippocampus were observed in participants with ASD after receiving oxytocin.[79] The dampening of these two brain structures may reflect a stress-reducing effect of oxytocin when individuals with ASD are faced with social stimuli.[79] Thus, reduced activation found in brain areas associated with stress maintenance (e.g., the amygdala and the hippocampus) may facilitate improved social communication within certain social contexts. However, as noted above, other findings show increased activation of both right posterior and left amygdala to social stimuli after oxytocin treatment, indicating heightened emotional arousal.[77,80] As previously mentioned, these mixed findings may relate to task variation between studies (e.g. viewing neutral faces versus memory for whether a face is novel or familiar), or to sample characteristics.[81] Additionally, it is important to note that oxytocin

administration does not always result in measurable brain-based differences. An electrophysiological investigation of oxytocin's effects in ASD did not differ from placebo in response to neutral, pleasant, and unpleasant images that displayed social and nonsocial information.[82,83]

During the Reading the Mind in the Eyes Test (RMET)—a task which involves "reading" other people's emotions based solely on their eyes—participants with ASD who had been given oxytocin displayed enhanced activity in areas of the brain associated with reward processing (dorsal and ventral striatum) and areas of social attention and perception (premotor cortex, posterior cingulate, inferior parietal lobule, posterior superior temporal sulcus) compared to placebo controls.[84] Though no differences were observed in behavioral accuracy on the RMET between individuals who received oxytocin and those in the placebo group, individuals who received oxytocin displayed increased activation within the medial prefrontal cortex, which is closely associated with the ability to detect and decode information about mental states.[84] This finding underscores the utility of measuring both brain activity and behavior in oxytocin studies, as neural measures may be more sensitive to subtle changes that are undetected with behavioral measures alone.

An fMRI task of social judgement—known as Friend or Foe—requires participants to judge emotions of a human actor who displayed verbal (positive or negative word) and nonverbal (positive or negative facial expression) information in congruent and incongruent conditions.[85] Enhanced activation in the anterior cingulate cortex (ACC) and dorsomedial prefrontal cortex (dmPFC) was positively correlated with

improvements in behavioral performance after oxytocin administration compared to placebo.[85] In a previous investigation using a similar task but without oxytocin administration, the ACC and dmPFC were not activated in individuals with ASD.[86] Therefore, both behavioral performance and brain activation can be enhanced after oxytocin administration during a task requiring sophisticated social communication skills.

Using ^{1}H-magnetic resonance spectroscopy (H-MRS), investigators provided evidence of a possible mechanistic pathway underlying ACC and ventromedial prefrontal cortex (vmPFC) activation after oxytocin administration.[87] Independent of the fMRI task, neuronal energy, measured by N-acetylaspartate (NAA) level, was positively correlated with both ACC and vmPFC activity.[87] A path analysis further supported the authors' hypothesis that increased NAA levels likely lead to observed increases in brain activity in the ACC and vmPFC during fMRI tasks. The path analysis also suggested that increases in brain activity observed during fMRI relate to observable changes in behavior. Overall, it appears that increased NAA levels lead to increased activation in the ACC and vmPFC during social-cognitive tasks, which then results in observed behavioral improvements on such tasks.[87] This finding is critical, as it is the first to shed light on plausible neural mechanisms underlying changes in both brain activity and behavior in ASD after oxytocin administration.

Explorations into functional connectivity have also been utilized to further understand neurobiological effects of oxytocin administration. Functional connectivity methods can assess the strength of neural connections between brain regions and increase our understanding of how brain regions communicate with one another. Both increases in

endogenous and exogenous levels of oxytocin have been shown to be associated with reduction in amygdala-hippocampal connectivity during resting state fMRI.[88] This is consistent with the fMRI findings from Andari and colleagues described above,[70] as they observed decreased activation in both the amygdala and hippocampal regions in individuals with ASD after oxytocin administration. Taken together, both the fMRI and functional connectivity findings suggest that hyperactive connectivity in the amygdala-hippocampal pathway contributes to attenuated social responses seen in individuals with ASD.[see89] It is important to note that decreased activation in these areas was evidenced by two different fMRI circumstances: resting-state and an task-dependent, which may suggest that brain-based findings are reflective of the testing environment.

Previous research suggests that oxytocin also affects brain regions associated with both learning and reward sensitivity. In a probabilistic reinforcement learning task with adult males with ASD, oxytocin administration increased activity in the nucleus accumbens (NAcc) during social feedback compared to non-social feedback.[62] Effects of oxytocin are not limited to social stimuli, but also extend to nonsocial stimuli. During an incentive delay task, where participants received social (smiling face) or nonsocial (money) rewards, both increased and decreased connectivity were observed in nonsocial conditions.[90] Decreased functional connectivity in individuals with ASD was observed in response to nonsocial feedback (between left ACC, bilateral postcentral gyrus, left inferior front gyrus, left precentral gyrus, and left medial frontal gyrus) and increased functional connectivity during anticipation of nonsocial feedback (between the right NAcc and the right FP).[90] This highlights the role of the mesocorticolimbic system as a

possible mediator between social stimuli, nonsocial stimuli, and neurobiological function within socially impaired populations.

The anterior insula, a brain area known for its role in social cognition,[91] is less activated in individuals with ASD in response to social stimuli compared to neurotypical controls.[see92] Aoki and colleagues found that oxytocin administration enhanced activity in the right anterior insula and the ability to make social-emotional inferences during a Sally-Ann theory of mind task[93] in individuals with ASD.[94] The anterior insula appears sensitive to oxytocin across participant populations, as performance in this task is also enhanced in neurotypical controls after oxytocin administration.[35,78,95] This provides notable evidence that social deficits in ASD can be augmented both behaviorally and through brain activation with exogenous oxytocin treatment.

Brain activity in ASD can even resemble observed brain activity in neurotypical controls after oxytocin administration. For instance, Gordon and colleagues[96] measured brain function in children and teens with ASD in response to biological motion. After oxytocin administration, the participants with ASD displayed more activation in the right posterior temporal sulcus when viewing human motion compared to scrambled motion.[96] Such activation has also been observed in neurotypical populations.[97] Participants with ASD also displayed increased connectivity between the NAcc and primary auditory cortex when listening to happy voices; similar connectivity and activation levels have been observed in neurotypical adults when listening to preferred sounds.[98] Thus, augmentation of the mesolimbic pathway has been observed in individuals with ASD

after oxytocin administration, and these changes resemble brain activity observed in neurotypical participants.

The mesolimbic pathway forms the basis the dopaminergic reward pathway. It appears that oxytocin affects this pathway in individuals with ASD.[99] Although mechanistic adaptations of neural structures, brain function, and brain connectivity remain unknown, there is evidence that oxytocin can facilitate reward responses in ASD. This is not to say that brain function is "normalized" after oxytocin administration, but rather that the brain may be more readily able to process social information. Overall, neuroimaging studies have accelerated our understanding of how oxytocin can bolster social behaviors in ASD and have provided key insights into how brain areas function in response to this neuropeptide.

Discussion

Much remains unknown about how to effectively measure the effects of oxytocin in the human brain. In order to better understand the effects of oxytocin administration, it is crucial to both understand how endogenous levels of oxytocin relate to social behavior, and to obtain more accurate information about dosing and timing of oxytocin administration. In ASD, individual variability exists in oxytocin levels, processing, and receptor sites. Some of this variability may stem from genetic alterations or may be the result of disrupted development. Future studies should attempt to clarify the origins of such variability.

It may be the case that oxytocin administration in ASD is effective once the dose exceeds endogenous levels (e.g. once the dose is greater than the amount of oxytocin

available naturally). The bioavailability of oxytocin is quite short and is likely influenced by the dosage of oxytocin. Given the individual variability of oxytocin levels in those with ASD, future research should attempt to create more personalized dosing "schedules" to maximize effectiveness. As more is uncovered about both the development and processing of oxytocin in the brain, we can begin to identify specific neural mechanisms that may relate to the ASD endophenotype. Additionally, once neural mechanisms are better understood, more precise trials of exogenous oxytocin administration can be implemented with specific neural targets. The development of personalized treatments based on genetics, neurobiology, behavior, and the environment can then be developed.[100–102]

Importantly, other factors must be taken into consideration when evaluating current research into the benefits of oxytocin in ASD. It has become common practice to allot 45 minutes between oxytocin administration and experimental tasks.[77,79,80,84] However, this time delay is largely based on literature of neurotypical individuals rather than those with ASD.[see103] It will be important for future studies to measure levels of oxytocin in participants with ASD before administration, after administration, and after a time delay in order to clarify both the level of oxytocin that is available after administration and the rate at which oxytocin concentration declines over time. This is important, as the time between oxytocin administration and experimental tasks, length of experimental task, and the amount of oxytocin that successfully crosses the blood-brain barrier may influence outcome measures. A current barrier to generalizing findings related to oxytocin and brain activity in ASD is between-study differences in task length.

For example, if Lab A gives each participant 24 IU of oxytocin, waits 45 minutes, and then has participants complete a 10 minute fMRI task, and Lab B uses the same dosage and time delay but has participants complete a 45 minute fMRI task, comparing results between studies is problematic. It is likely that the concentration of oxytocin in a given participant at the end of Lab A's fMRI task is significantly higher than the concentration in a participant of oxytocin at the conclusion of Lab B's paradigm.

Furthermore, differences in age, ASD symptom severity, and individual oxytocin-related pathophysiology should be considered in future studies. Future studies should implement a data-driven approach to determine the appropriate dosage and time between administration and behavioral or neuroscientific measurement. Factors such as sex, BMI, medication-use, and comorbid disorders must be taken into account when considering treatment effectiveness and the potential for adverse-events.

Future Directions

Much promise exists in the potential therapeutic use of oxytocin in ASD. Future research should move beyond attempting to improve specific social behaviors (e.g. eye contact) after a one-time oxytocin administration, and instead combine oxytocin administration with behavioral intervention. Initial investigations have begun to take this approach, by pairing oxytocin administration with behavioral intervention,[66] though it is not yet clear whether combining oxytocin and behavioral interventions leads to better outcomes compared to behavioral intervention or oxytocin alone. Dadds and colleagues paired oxytocin administration with Parent-Child Interaction Training over the course of four days in children with ASD, such that oxytocin was given before each training

session.[66] No differences between the oxytocin and placebo groups were observed on measures of emotion recognition or social skills. However, the timing between oxytocin administration and behavioral training differed across treatment days and nearly half the sample also had attention-deficit/hyperactivity disorder.[66]

We posit that there is a potential to augment long-term social communication outcomes beyond that observed with either single-dose oxytocin administration or behavioral intervention in isolation. We hypothesize that outcomes will be enhanced when combining pharmacological (e.g. oxytocin administration) and behavioral (e.g. evidence-based behavioral interventions) techniques. Although novel in ASD research, the idea of combining medication and therapy to improve outcomes is not novel in research on psychological disorders more broadly. For example, individuals with anxiety or depression often experience the greatest clinical gains when medication is prescribed in conjunction with evidence-based therapy.[104] The studies reviewed above suggest that oxytocin bolsters social behavior by altering the function of specific brain structures, including the amygdala and NAcc. If oxytocin allows individuals with ASD to find social stimuli more rewarding and increase attention to the social environment, behavioral intervention can be implemented after oxytocin administration to leverage these temporary neural changes. Timing behavioral interventions to coincide with neural enhancements of social reward in individuals with ASD might produce the greatest benefits. Figure 1 demonstrates a suggested model of how such research may be conducted.

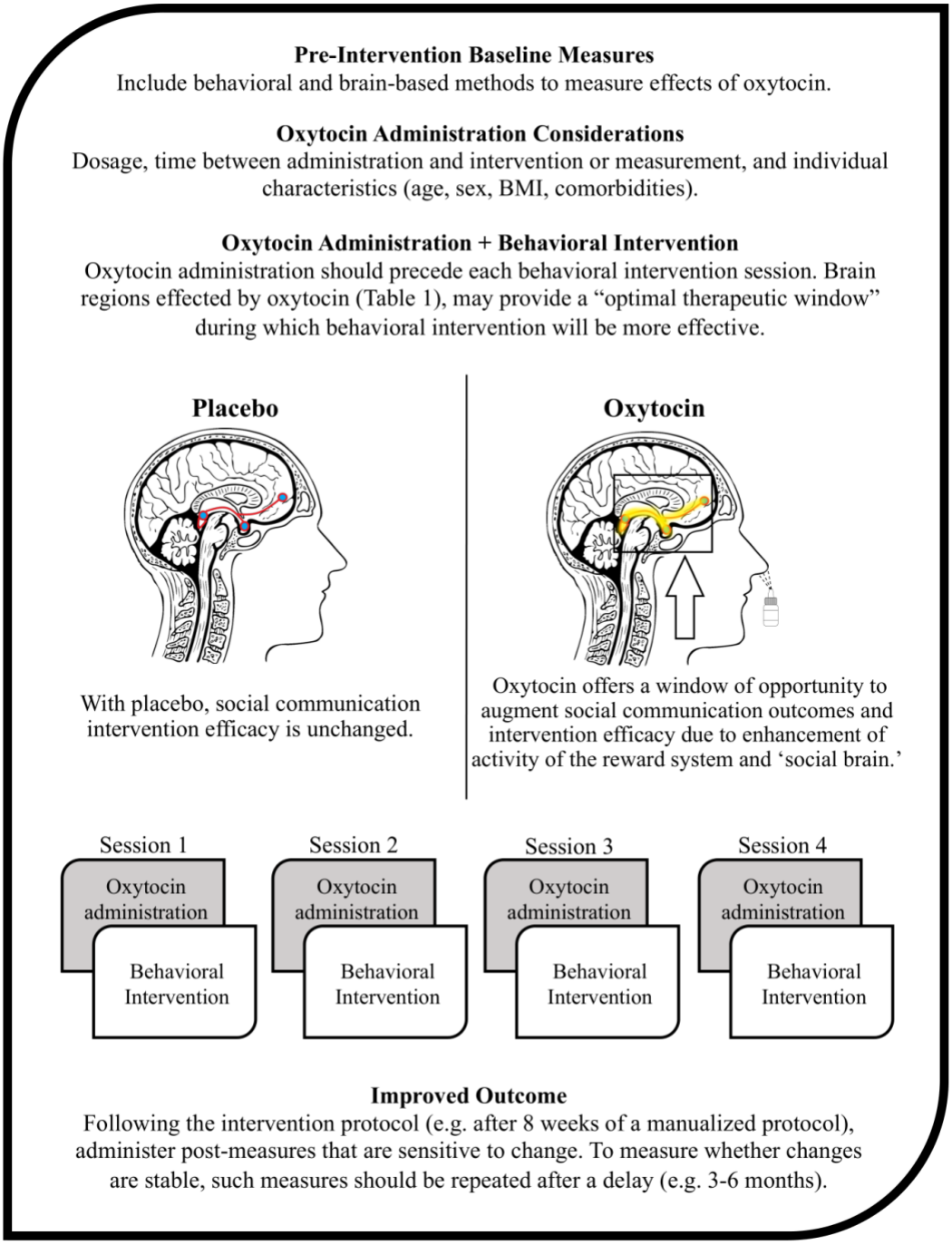

Figure 1. Suggested model for study design that includes simultaneous behavioral intervention and oxytocin administration. Hypothesized role of the neural reward system on intervention outcomes are shown.

Conclusions

In sum, both behavioral and brain-based studies of oxytocin administration in individuals with ASD provide evidence for biological changes related to the enhanced processing of social information. Integrating genetic, neuroscientific, and behavioral investigations will further contribute to the characterization of the ASD endophenotype. With more nuanced information about how oxytocin affects neural circuitry related to social cognition and the brain's reward systems, treatment outcomes in ASD may be improved by leveraging a window of opportunity during which the brain is primed to more efficiently process social information.

Table 1. Summary of published neuroimaging studies, main findings on the effects of oxytocin administration in individuals with autism spectrum disorder (ASD). (IU = International Units)

References	Participants	Oxytocin Administration	Stimuli/Paradigm	Time delay & Task Length	Major Findings
Domes et al., 2013	14 males with Asperger syndrome □ M_{age} = 24.0 yrs., SD_{age} = 6.9 yrs. 14 male neurotypical controls □ M_{age} = 24.3 yrs., SD_{age} = 5.4 yrs.	Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU. Placebo was administered in the same dosage and contained same ingredients except for the peptide.	fMRI. 36 black and white still images of neutral faces with direct or averted gaze.36 black and white images of houses, presented frontally or averted at 45 degrees. Images were paired within each condition. Participants indicated if the pictures of faces or houses were the same or different.	45 minutes between oxytocin administration and fMRI procedure; 45 minutes in the scanner; Task was roughly 8.20 minutes long.	Behavior: No effect of oxytocin on face matching in ASD Brain: Increased activity in the right posterior amygdala in ASD in response to faces.
Gordon et al., 2013	21 children and adolescents (3 females; 18 males) with ASD □ M_{age} = 13.2 yrs., SD_{age} = 2.7 yrs.	Intranasally. Older participants (16 – 19 yrs.) received a dose of 24 IU (4 puffs per nostril); 15 yr olds received 18 IU (3 puffs per nostril); Younger participants (7 - 11 yrs.) received 12 IUs, (1 puff per nostril); or placebo. Testing was repeated on consecutive study visits.	fMRI. Reading the Mind in the Eyes Test (RMET). Participants were instructed to label the mental state of each facial picture, or label the category of automobile images.	45 minutes between oxytocin administration and fMRI procedure; fMRI task was 5.1 minutes in length.	Social condition: Enhanced activity in the dorsal and ventral striatum, premotor cortex, posterior cingulate, inferior parietal lobule, and posterior STS in response to oxytocin.
Domes et al., 2014	14 males with Asperger syndrome □ M_{age} = 24.0 yrs., SD_{age} = 6.9 yrs. 14 male neurotypical controls □ M_{age} = 23.6 yrs., SD_{age} = 5.4 yrs.	Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU. Placebo was administered in the same dosage and contained	fMRI. Black and white still images of eyes or mouths of males and females displaying six facial emotions (anger, fear, disgust, happiness, sadness, and surprise). A correct or incorrect	45 minutes between oxytocin administration and fMRI procedure; 45 minutes in the scanner.	Behavior: Improved emotional labeling after oxytocin administration. Brain: Oxytocin administration increased left amygdala activation.

		same ingredients except for the peptide.	emotion label appeared after the images. Participants were instructed to indicate label accuracy.		
Aoki et al., 2014	*Experiment 1*: 17 males with ASD □ M_{age} = 29.6 yrs., □ SD_{age} = 8.0 yrs. 17 male neurotypical controls □ M_{age} = 30.4 yrs., □ SD_{age} = 5.6 yrs. *Experiment 2*: 20 males with ASD □ M_{age} = 30.8 yrs., SD_{age} = 6.0 yrs.	*Experiment 1*: No oxytocin was administered. *Experiment 2:* Intranasal administration: 24 IU of oxytocin (Syntocinon) or placebo. Participants were seen again one week after the first study visit. Placebo or oxytocin was randomized at the first visit and participants received the opposite nasal spray at the second visit.	*Experiment 1*: Performed Sally-Ann task (Baron-Cohen, Leslie, & Frith, 1985) to infer social emotions and beliefs of others during fMRI. *Experiment 2*: Same fMRI task, but performed after oxytocin or placebo administration on two study visits.	*Experiment 1*: n/a *Experiment 2*: 45 minutes between oxytocin administration and fMRI procedure; Sally-Ann task length was 16 minutes.	*Experiment 1*: Lower accuracy at inferring social emotions of others. Lower activation in right anterior insula and superior temporal sulcus during social emotional conditions. Decreased activity was seen in the dorsomedial prefrontal cortex when inferring beliefs of others. *Experiment 2*: Improved ability to infer social emotions of others without the presence of emotional cues and enhanced activity in the right anterior insula in individuals with ASD after oxytocin administration.
Wantanabe et al., 2014	40 males with ASD □ M_{age} = 28.5 yrs., SD_{age} = 5.9 yrs.	Intranasally. 24 IU of oxytocin (Syntocinon) or placebo containing the same inactive ingredients.	fMRI. Friend or Foe judgment task. Congruent condition: Positive facial/Positive vocal expression or Negative facial/Negative vocal expression. Incongruent condition: Facial and vocal expressions of opposite the opposite valence were paired.	40 minutes between oxytocin administration and fMRI procedure.	Behavior: Increased response time to both conditions after oxytocin administration. Brain: Oxytocin enhanced activation in the anterior cingulate cortex (ACC) and dorsomedial prefrontal cortex (dmPFC). Coordinated activity between the ACC and dmPFC mediated the effects of oxytocin on behavioral deficits.
Aoki et al., 2015	31 males with ASD □ M_{age} = 28.8 yrs., SD_{age} = 6.0 yrs.	Intranasally. 24 IU of oxytocin (Syntocinon) or placebo containing the same inactive ingredients.	fMRI task & ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS; proton nuclear) to	40 minutes between oxytocin administration and fMRI procedure. The ^{1}H-MRS scan	N-acetylaspartate level, which represents neuronal energy demands, reliably predicted activation of the ventromedial prefrontal cortex (vmPFC) and ACC after oxytocin

			measure N-acetylaspartate. Task: Friend or Foe judgment task, see Wantanabe et al., 2014.	followed the fMRI; time elapsed between oxytocin administration and ^{1}H-MRS scan was 87.5 minutes on average.	administration. This finding was independent of fMRI task demands.
Althaus et al., 2015	32 males with ASD M_{age} = 22.7 yrs., SD_{age} = 4.8 yrs. 30 male neurotypical controls M_{age} = 22.6 yrs., SD_{age} = 3.2 yrs.	Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU. Nostrils were alternated between puffs. Placebo was a saline solution.	Event-related potential (ERP) and concurrent electrocardiogram (ECG). Participants viewed images from the International Affective Picture System (IAPS, Lang et al., 2008).	60 minutes between oxytocin administration and start of ERP task. IAPS task was 45 minutes in length.	No oxytocin treatment effects were found between ASD and TD groups, such that ERP responses to images did not differ between groups.
Gordon et al., 2016	20 participants with ASD (3 females) M_{age} = 13.2 yrs., SD_{age} = 2.8 yrs.	Intranasally. Older participants (16 – 19 yrs.) received a dose of 24 IU (4 puffs per nostril); 15 yr olds received 18 IU (3 puffs per nostril); Younger participants (7 - 11 yrs.) received 12 IUs, (1 puff per nostril); or placebo. Testing was repeated on consecutive study visits. Placebo or oxytocin was randomized at the first visit and participants received the opposite nasal spray at the second visit.	fMRI. Participants passively viewed a biological motion paradigm (human motion and scrambled motion) and listened to a vocal affect perception paradigm (angry voices and happy voices).	45 minutes between oxytocin administration and start of fMRI scan.	Biological motion condition: enhanced response in the right posterior superior temporal sulcus (pSTS) after oxytocin administration. Negative vocal affect condition: Enhanced activation in right brainstem and right amygdala after oxytocin administration.
Andari et al., 2016	20 participants with ASD (1 female, 19 males) M_{age} = 26.4 yrs., SD_{age} = 8.5 yrs.	Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU, or placebo.	fMRI. 1. Cooperative social ball-tossing task (with fair and unfair fictious players).	40-45 minutes between oxytocin administration and start of fMRI scan. Social-ball task was 13 minutes in length;	Cooperative game: Increased activation in the anterior OFC. Reduced activation in the amygdala and hippocampus for participants with ASD who received oxytocin. Recognition of social unjustness led to activation of the right insula.

			2. Face-matching task (some of the faces were observed by participants previously and some were novel. Geometric shapes were also presented).	face-matching task was 8 minutes in length.	Face matching: Increased activation in the inferior occipital gyrus and fusiform gyrus after oxytocin in the ASD group..
Greene et al., 2018	28 children and adolescents with ASD (2 females, 26 males) M_{age} = 13.4 yrs., SD_{age} = 2.4 yrs.	Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU, or placebo containing the same inactive ingredients. Nostrils were alternated between puffs over the course of several minutes.	fMRI. Incentive delay task: nonsocial (money) or social rewards (smiling face).	Time between oxytocin administration and fMRI scan was not reported. Incentive delay task was 32 minutes in length.	Anticipation of nonsocial reward: Increased activity in right nucleus accumbens (NAcc), right frontal pole, left ACC, left superior frontal cortex, bilateral orbital frontal cortex (OFC) after oxytocin administration. Increased functional connectivity during nonsocial reward anticipation (between the right NAcc and the right FP). Nonsocial reward outcome: Decreased frontostriatal functional connectivity between left ACC, bilateral postcentral gyrus, left inferior front gyrus, left precentral gyrus, and left medial frontal gyrus.
Kruppa et al., 2019	15 males with ASD M_{age} = 21.8 yrs., SD_{age} = 2.6 yrs. 24 male neurotypical controls M_{age} = 22.1 yrs., SD_{age} = 1.9 yrs.	Intranasally. 10 puffs for a total of 20 IU (Syntocinon) or placebo.	fMRI. Probabilistic social reinforcement learning task. Participants were instructed to categorize learning targets. Social and nonsocial feedback was provided.	Average of 48 minutes between oxytocin administration and start of fMRI scan. Task length was 45 minutes.	Behavior: Improvement of social learning in the participants with ASD during social feedback after oxytocin administration. Brain: Positive correlation between reward prediction error (RPE) signal and NAcc activation during social feedback was found.
Alaerts et al., 2019	38 males with ASD M_{age} = 24.4 yrs., SD_{age} = 5.2 yrs.	Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU. Or placebo (saline natrium-chloride solution).	fMRI. resting state to measure amygdala-hippocampal connectivity fMRI was performed before nasal spray (oxytocin or placebo) and after nasal spray administration.	30 minutes between oxytocin administration and start of fMRI scan. Resting state lasted 7 minutes.	Negative correlation between endogenous oxytocin and functional connectivity between amygdala and hippocampal regions; administration of oxytocin reduced amygdala-hippocampal connectivity even further in individuals with ASD.

References

1. Christensen DL, Braun KVN, Baio J, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2012. *MMWR Surveill Summ*. 2018;65(13):1-23. doi:10.15585/mmwr.ss6513a1

2. American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.

3. Dawson G, Toth K, Abbott R, et al. Early social attention impairments in autism: Social orienting, joint attention, and attention to distress. *Developmental Psychology*. 2004;40(2):271-283. doi:10.1037/0012-1649.40.2.271

4. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *Int J Dev Neurosci*. 2005;23(2-3):143-152. doi:10.1016/j.ijdevneu.2004.05.001

5. Whitehouse AJO, Durkin K, Jaquet E, Ziatas K. Friendship, loneliness and depression in adolescents with Asperger's Syndrome. *J Adolesc*. 2009;32(2):309-322. doi:10.1016/j.adolescence.2008.03.004

6. Bauminger N, Kasari C. Loneliness and friendship in high-functioning children with autism. *Child Dev*. 2000;71(2):447-456. doi:10.1111/1467-8624.00156

7. Honey E, Leekam S, Turner M, McConachie H. Repetitive behaviour and play in typically developing children and children with autism spectrum disorders. *J Autism Dev Disord*. 2007;37(6):1107-1115. doi:10.1007/s10803-006-0253-4

8. Loftin RL, Odom SL, Lantz JF. Social interaction and repetitive motor behaviors. *J Autism Dev Disord*. 2008;38(6):1124-1135. doi:10.1007/s10803-007-0499-5

9. Eldevik S, Hastings RP, Hughes JC, Jahr E, Eikeseth S, Cross S. Meta-analysis of early intensive behavioral intervention for children with autism. *Journal of Clinical Child & Adolescent Psychology*. 2009;38(3):439-450. doi:10.1080/15374410902851739

10. Kasari C, Lawton K. New directions in behavioral treatment of autism spectrum disorders. *Curr Opin Neurol*. 2010;23(2):137-143. doi:10.1097/WCO.0b013e32833775cd

11. Dawson G, Rogers S, Munson J, et al. Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model. *Pediatrics*. 2010;125(1):e17-e23. doi:10.1542/peds.2009-0958

12. LeClerc S, Easley D. Pharmacological therapies for autism spectrum disorder: A review. *P T*. 2015;40(6):389-397.

13. Pica N, Bourgeois F. Discontinuation and nonpublication of randomized clinical trials conducted in children. *Pediatrics*. 2016;138(3). doi:10.1542/peds.2016-0223

14. Sammons H. Ethical issues of clinical trials in children: A European perspective. *Archives of Disease in Childhood*. 2009;94(6):474-477. doi:10.1136/adc.2008.149898

15. Sammons HM, Starkey ES. Ethical issues of clinical trials in children. *Pediatrics and Child Health*. 2012;22(2):47-50. doi:10.1016/j.paed.2011.04.011

16. Green JJ, Hollander E. Autism and oxytocin: New developments in translational approaches to therapeutics. *Neurotherapeutics*. 2010;7(3):250-257. doi:10.1016/j.nurt.2010.05.006

17. Guastella AJ, Hickie IB. Oxytocin treatment, circuitry, and autism: A critical review of the literature placing oxytocin into the autism context. *Biological Psychiatry*. 2016;79(3):234-242. doi:10.1016/j.biopsych.2015.06.028

18. Gainer H, Altstein M, Whitnall MH. The cell biology and development of vasopressinergic and oxytocinergic neurons. *Prog Brain Res*. 1987;72:153-161. doi:10.1016/s0079-6123(08)60204-6

19. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves “mind-reading” in humans. *Biological Psychiatry*. 2007;61(6):731-733. doi:10.1016/j.biopsych.2006.07.015

20. Hurlemann R, Patin A, Onur OA, et al. Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J Neurosci*. 2010;30(14):4999-5007. doi:10.1523/JNEUROSCI.5538-09.2010

21. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature*. 2005;435(7042):673-676. doi:10.1038/nature03701

22. Zingg HH, Laporte SA. The oxytocin receptor. *Trends in Endocrinology & Metabolism*. 2003;14(5):222-227. doi:10.1016/S1043-2760(03)00080-8

23. Caldeyro-Barcia R, Poseiro JJ. Oxytocin and contractility of the pregnant human uterus. *Annals of the New York Academy of Sciences*. 1959;75(2):813-830. doi:10.1111/j.1749-6632.1959.tb44593.x

24. Shapiro LE, Insel TR. Ontogeny of oxytocin receptors in rat forebrain: A quantitative study. *Synapse*. 1989;4(3):259-266. doi:10.1002/syn.890040312

25. Krol KM, Moulder RG, Lillard TS, Grossmann T, Connelly JJ. Epigenetic dynamics in infancy and the impact of maternal engagement. *Science Advances*. 2019;5(10):eaay0680. doi:10.1126/sciadv.aay0680

26. Magon N, Kalra S. The orgasmic history of oxytocin: Love, lust, and labor. *Indian J Endocrinol Metab*. 2011;15(Suppl3):S156-S161. doi:10.4103/2230-8210.84851

27. Carter CS, Porges SW. The biochemistry of love: An oxytocin hypothesis. *EMBO reports*. 2013;14(1):12-16. doi:10.1038/embor.2012.191

28. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. *Physiol Rev*. 2001;81(2):629-683. doi:10.1152/physrev.2001.81.2.629

29. Tribollet E, Dubois-Dauphin M, Dreifuss JJ, Barberis C, Jard S. Oxytocin Receptors in the Central Nervous System. *Annals of the New York Academy of Sciences*. 1992;652(1):29-38. doi:10.1111/j.1749-6632.1992.tb34343.x

30. Mens WB, Witter A, van Wimersma Greidanus TB. Penetration of neurohypophyseal hormones from plasma into cerebrospinal fluid (CSF): Half-times of disappearance of these neuropeptides from CSF. *Brain Res*. 1983;262(1):143-149. doi:10.1016/0006-8993(83)90478-x

31. Kang YS, Park JH. Brain uptake and the analgesic effect of oxytocin--its usefulness as an analgesic agent. *Arch Pharm Res*. 2000;23(4):391-395. doi:10.1007/bf02975453

32. Lee MR, Scheidweiler KB, Diao XX, et al. Oxytocin by intranasal and intravenous routes reaches the cerebrospinal fluid in rhesus macaques: determination using a novel oxytocin assay. *Molecular Psychiatry*. 2018;23(1):115-122. doi:10.1038/mp.2017.27

33. Landgraf R, Neumann ID. Vasopressin and oxytocin release within the brain: A dynamic concept of multiple and variable modes of neuropeptide communication. *Frontiers in Neuroendocrinology*. 2004;25(3):150-176. doi:10.1016/j.yfrne.2004.05.001

34. Guastella AJ, Mitchell PB, Dadds MR. Oxytocin increases gaze to the eye region of human faces. *Biol Psychiatry*. 2008;63(1):3-5. doi:10.1016/j.biopsych.2007.06.026

35. Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*. 2008;58(4):639-650. doi:10.1016/j.neuron.2008.04.009

36. Petrovic P, Kalisch R, Singer T, Dolan RJ. Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *J Neurosci*. 2008;28(26):6607-6615. doi:10.1523/JNEUROSCI.4572-07.2008

37. Kirsch P, Esslinger C, Chen Q, et al. Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci*. 2005;25(49):11489-11493. doi:10.1523/JNEUROSCI.3984-05.2005

38. Festante F, Ferrari PF, Thorpe SG, Buchanan RW, Fox NA. Intranasal oxytocin enhances EEG mu rhythm desynchronization during execution and observation of social action: An exploratory study. *Psychoneuroendocrinology*. October 2019:104467. doi:10.1016/j.psyneuen.2019.104467

39. Liu Y, Li S, Lin W, et al. Oxytocin modulates social value representations in the amygdala. *Nat Neurosci*. 2019;22(4):633-641. doi:10.1038/s41593-019-0351-1

40. Modahl C, Fein D, Waterhouse L, Newton N. Does oxytocin deficiency mediate social deficits in autism? *J Autism Dev Disord*. 1992;22(3):449-451. doi:10.1007/BF01048246

41. Waterhouse L, Fein D, Modahl C. Neurofunctional mechanisms in autism. *Psychological Review*. 1996;103(3):457-489. doi:10.1037/0033-295X.103.3.457

42. Modahl C, Green L, Fein D, et al. Plasma oxytocin levels in autistic children. *Biol Psychiatry*. 1998;43(4):270-277. doi:10.1016/s0006-3223(97)00439-3

43. Parker KJ, Oztan O, Libove RA, et al. Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. *PNAS*. 2017;114(30):8119-8124. doi:10.1073/pnas.1705521114

44. Parker KJ, Garner JP, Libove RA, et al. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. *PNAS*. 2014;111(33):12258-12263. doi:10.1073/pnas.1402236111

45. Wu S, Jia M, Ruan Y, et al. Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. *Biol Psychiatry*. 2005;58(1):74-77. doi:10.1016/j.biopsych.2005.03.013

46. Campbell DB, Datta D, Jones ST, et al. Association of oxytocin receptor (OXTR) gene variants with multiple phenotype domains of autism spectrum disorder. *J Neurodev Disord*. 2011;3(2):101-112. doi:10.1007/s11689-010-9071-2

47. Green L, Fein D, Modahl C, Feinstein C, Waterhouse L, Morris M. Oxytocin and autistic disorder: Alterations in peptide forms. *Biological Psychiatry*. 2001;50(8):609-613. doi:10.1016/S0006-3223(01)01139-8

48. Andari E, Duhamel J-R, Zalla T, Herbrecht E, Leboyer M, Sirigu A. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *PNAS*. 2010;107(9):4389-4394. doi:10.1073/pnas.0910249107

49. Guastella AJ, Cooper MN, White CRH, White MK, Pennell CE, Whitehouse AJO. Does perinatal exposure to exogenous oxytocin influence child behavioural problems and autistic-like behaviours to 20 years of age? *Journal of Child Psychology and Psychiatry*. 2018;59(12):1323-1332. doi:10.1111/jcpp.12924

50. Ozonoff S, Young GS, Carter A, et al. Recurrence risk for autism spectrum disorders: A baby siblings research consortium study. *Pediatrics*. 2011;128(3):e488-e495. doi:10.1542/peds.2010-2825

51. Charman T, Young GS, Brian J, et al. Non-ASD outcomes at 36 months in siblings at familial risk for autism spectrum disorder (ASD): A baby siblings research consortium (BSRC) study: Non-ASD outcomes at 36 months in high-risk siblings. *Autism Research*. 2017;10(1):169-178. doi:10.1002/aur.1669

52. Aita C, Mizoguchi Y, Yamamoto M, et al. Oxytocin levels and sex differences in autism spectrum disorder with severe intellectual disabilities. *Psychiatry Research*. 2019;273:67-74. doi:10.1016/j.psychres.2018.12.139

53. Hattier MA, Matson JL, Tureck K, Horovitz M. The effects of gender and age on repetitive and/or restricted behaviors and interests in adults with autism spectrum disorders and intellectual disability. *Research in Developmental Disabilities*. 2011;32(6):2346-2351. doi:10.1016/j.ridd.2011.07.028

54. Hernandez LM, Lawrence KE, Padgaonkar NT, et al. Imaging-genetics of sex differences in ASD: distinct effects of OXTR variants on brain connectivity. *Translational Psychiatry*. 2020;10(1):1-12. doi:10.1038/s41398-020-0750-9

55. Miller M, Bales KL, Taylor SL, et al. Oxytocin and vasopressin in children and adolescents with autism spectrum disorders: Sex differences and associations with symptoms. *Autism Res*. 2013;6(2):91-102. doi:10.1002/aur.1270

56. Taurines R, Schwenck C, Lyttwin B, et al. Oxytocin plasma concentrations in children and adolescents with autism spectrum disorder: Correlation with autistic symptomatology. *Atten Defic Hyperact Disord*. 2014;6(3):231-239. doi:10.1007/s12402-014-0145-y

57. Leng G, Ludwig M. Intranasal oxytocin: Myths and delusions. *Biological Psychiatry*. 2016;79(3):243-250. doi:10.1016/j.biopsych.2015.05.003

58. Leng G, Sabatier N. Measuring oxytocin and vasopressin: Bioassays, immunoassays and random numbers. *J Neuroendocrinol*. 2016;28(10). doi:10.1111/jne.12413

59. Freeman SM, Palumbo MC, Lawrence RH, Smith AL, Goodman MM, Bales KL. Effect of age and autism spectrum disorder on oxytocin receptor density in the human basal forebrain and midbrain. *Translational Psychiatry*. 2018;8(1):1-11. doi:10.1038/s41398-018-0315-3

60. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. *Arch Gen Psychiatry*. 2008;65(8):946-954. doi:10.1001/archpsyc.65.8.946

61. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The Social Motivation Theory of Autism. *Trends Cogn Sci*. 2012;16(4):231-239. doi:10.1016/j.tics.2012.02.007

62. Kruppa JA, Gossen A, Weiß EO, et al. Neural modulation of social reinforcement learning by intranasal oxytocin in male adults with high-functioning autism spectrum disorder: A randomized trial. *Neuropsychopharmacology*. 2019;44(4):749-756. doi:10.1038/s41386-018-0258-7

63. Stavropoulos KKM, Carver LJ. Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention. *Journal of Child Psychology and Psychiatry*. 2013;54(6):603-618. doi:10.1111/jcpp.12061

64. Hollander E, Novotny S, Hanratty M, et al. Oxytocin infusion reduces repetitive behaviors in adults with autistic and asperger's disorders. *Neuropsychopharmacol*. 2003;28(1):193-198. doi:10.1038/sj.npp.1300021

65. Guastella AJ, Gray KM, Rinehart NJ, et al. The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: A randomized controlled trial. *Journal of Child Psychology and Psychiatry*. 2015;56(4):444-452. doi:10.1111/jcpp.12305

66. Dadds MR, MacDonald E, Cauchi A, Williams K, Levy F, Brennan J. Nasal oxytocin for social deficits in childhood autism: A randomized controlled trial. *J Autism Dev Disord*. 2014;44(3):521-531. doi:10.1007/s10803-013-1899-3

67. Yamasue H, Okada T, Munesue T, et al. Effect of intranasal oxytocin on the core social symptoms of autism spectrum disorder: A randomized clinical trial. *Mol Psychiatry*. June 2018:1-10. doi:10.1038/s41380-018-0097-2

68. Yatawara CJ, Einfeld SL, Hickie IB, Davenport TA, Guastella AJ. The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: A randomized clinical crossover trial. *Molecular Psychiatry*. 2016;21(9):1225-1231. doi:10.1038/mp.2015.162

69. Hollander E, Bartz J, Chaplin W, et al. Oxytocin increases retention of social cognition in autism. *Biological Psychiatry*. 2007;61(4):498-503. doi:10.1016/j.biopsych.2006.05.030

70. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry*. 2010;67(7):692-694. doi:10.1016/j.biopsych.2009.09.020

71. Anagnostou E, Soorya L, Chaplin W, et al. Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: A randomized controlled trial. *Molecular Autism*. 2012;3(1):16. doi:10.1186/2040-2392-3-16

72. Bernaerts S, Boets B, Bosmans G, Steyaert J, Alaerts K. Behavioral effects of multiple-dose oxytocin treatment in autism: A randomized, placebo-controlled trial with long-term follow-up. *Molecular Autism*. 2020;11(1):6. doi:10.1186/s13229-020-0313-1

73. Wang Y, Wang M-J, Rong Y, He H-Z, Yang C-J. Oxytocin therapy for core symptoms in autism spectrum disorder: An updated meta-analysis of randomized controlled trials. *Research in Autism Spectrum Disorders*. 2019;64:63-75. doi:10.1016/j.rasd.2019.03.007

74. Higashida H, Munesue T, Kosaka H, Yamasue H, Yokoyama S, Kikuchi M. Social interaction improved by oxytocin in the subclass of autism with comorbid intellectual disabilities. *Diseases*. 2019;7(1):24. doi:10.3390/diseases7010024

75. Insel TR. The challenge of translation in social neuroscience: A review of oxytocin, vasopressin, and affiliative behavior. *Neuron*. 2010;65(6):768-779. doi:10.1016/j.neuron.2010.03.005

76. Yamasue H, Domes G. Oxytocin and autism spectrum disorders. In: Hurlemann R, Grinevich V, eds. *Behavioral Pharmacology of Neuropeptides: Oxytocin*. Current Topics in Behavioral Neurosciences. Cham: Springer International Publishing; 2018:449-465. doi:10.1007/7854_2017_24

77. Domes G, Heinrichs M, Kumbier E, Grossmann A, Hauenstein K, Herpertz SC. Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. *Biological Psychiatry*. 2013;74(3):164-171. doi:10.1016/j.biopsych.2013.02.007

78. Striepens N, Scheele D, Kendrick KM, et al. Oxytocin facilitates protective responses to aversive social stimuli in males. *PNAS*. 2012;109(44):18144-18149. doi:10.1073/pnas.1208852109

79. Andari E, Richard N, Leboyer M, Sirigu A. Adaptive coding of the value of social cues with oxytocin, an fMRI study in autism spectrum disorder. *Cortex*. 2016;76:79-88. doi:10.1016/j.cortex.2015.12.010

80. Domes G, Kumbier E, Heinrichs M, Herpertz SC. Oxytocin promotes facial emotion recognition and amygdala reactivity in adults with asperger syndrome. *Neuropsychopharmacology*. 2014;39(3):698-706. doi:10.1038/npp.2013.254

81. Bartz JA, Zaki J, Bolger N, Ochsner KN. Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences*. June 2011:S1364661311000830. doi:10.1016/j.tics.2011.05.002

82. Althaus M, Groen Y, Wijers AA, Noltes H, Tucha O, Hoekstra PJ. Oxytocin enhances orienting to social information in a selective group of high-functioning male adults with autism spectrum disorder. *Neuropsychologia*. 2015;79:53-69. doi:10.1016/j.neuropsychologia.2015.10.025

83. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Technical manual and affective ratings. *Technical Report*. 2008.

84. Gordon I, Wyk BCV, Bennett RH, et al. Oxytocin enhances brain function in children with autism. *PNAS*. 2013;110(52):20953-20958. doi:10.1073/pnas.1312857110

85. Watanabe T, Abe O, Kuwabara H, et al. Mitigation of sociocommunicational deficits of autism through oxytocin-induced recovery of medial prefrontal

activity: A randomized trial. *JAMA Psychiatry*. 2014;71(2):166-175. doi:10.1001/jamapsychiatry.2013.3181

86. Watanabe T, Yahata N, Abe O, et al. Diminished medial prefrontal activity behind autistic social judgments of incongruent information. *PLoS ONE*. 2012;7(6):e39561. doi:10.1371/journal.pone.0039561

87. Aoki Y, Watanabe T, Abe O, et al. Oxytocin's neurochemical effects in the medial prefrontal cortex underlie recovery of task-specific brain activity in autism: a randomized controlled trial. *Mol Psychiatry*. 2015;20(4):447-453. doi:10.1038/mp.2014.74

88. Alaerts K, Bernaerts S, Vanaudenaerde B, Daniels N, Wenderoth N. Amygdala–hippocampal connectivity is associated with endogenous levels of oxytocin and can be altered by exogenously administered oxytocin in adults with autism. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2019;4(7):655-663. doi:10.1016/j.bpsc.2019.01.008

89. Sweeten TL, Posey DJ, Shekhar A, McDougle CJ. The amygdala and related structures in the pathophysiology of autism. *Pharmacology Biochemistry and Behavior*. 2002;71(3):449-455. doi:10.1016/S0091-3057(01)00697-9

90. Greene RK, Spanos M, Alderman C, et al. The effects of intranasal oxytocin on reward circuitry responses in children with autism spectrum disorder. *Journal of Neurodevelopmental Disorders*. 2018;10(1):12. doi:10.1186/s11689-018-9228-y

91. Carr L, Iacoboni M, Dubeau M-C, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *PNAS*. 2003;100(9):5497-5502. doi:10.1073/pnas.0935845100

92. Di Martino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP. Functional brain correlates of social and nonsocial processes in autism spectrum disorders: An activation likelihood estimation meta-analysis. *Biological Psychiatry*. 2009;65(1):63-74. doi:10.1016/j.biopsych.2008.09.022

93. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind" ? *Cognition*. 1985;21(1):37-46. doi:10.1016/0010-0277(85)90022-8

94. Aoki Y, Yahata N, Watanabe T, et al. Oxytocin improves behavioural and neural deficits in inferring others' social emotions in autism. *Brain*. 2014;137(11):3073-3086. doi:10.1093/brain/awu231

95. Wittfoth-Schardt D, Gründing J, Wittfoth M, et al. Oxytocin modulates neural reactivity to children's faces as a function of social salience. *Neuropsychopharmacology*. 2012;37(8):1799-1807. doi:10.1038/npp.2012.47

96. Gordon I, Jack A, Pretzsch CM, et al. Intranasal oxytocin enhances connectivity in the neural circuitry supporting social motivation and social perception in children with autism. *Sci Rep*. 2016;6(1):35054. doi:10.1038/srep35054

97. Pelphrey KA, Morris JP. Brain mechanisms for interpreting the actions of others from biological-motion cues. *Curr Dir Psychol Sci*. 2006;15(3):136-140. doi:10.1111/j.0963-7214.2006.00423.x

98. Salimpoor VN, Bosch I van den, Kovacevic N, McIntosh AR, Dagher A, Zatorre RJ. Interactions between the nucleus accumbens and auditory cortices predict music reward value. *Science*. 2013;340(6129):216-219. doi:10.1126/science.1231059

99. Love TM. Oxytocin, motivation and the role of dopamine. *Pharmacology Biochemistry and Behavior*. 2014;119:49-60. doi:10.1016/j.pbb.2013.06.011

100. Geschwind DH, State MW. Gene hunting in autism spectrum disorder: On the path to precision medicine. *The Lancet Neurology*. 2015;14(11):1109-1120. doi:10.1016/S1474-4422(15)00044-7

101. Loth E, Murphy DG, Spooren W. Defining precision medicine approaches to autism spectrum disorders: Concepts and challenges. *Front Psychiatry*. 2016;7. doi:10.3389/fpsyt.2016.00188

102. Sahin M, Sur M. Genes, circuits, and precision therapies for autism and related neurodevelopmental disorders. *Science*. 2015;350(6263). doi:10.1126/science.aab3897

103. Bethlehem RAI, van Honk J, Auyeung B, Baron-Cohen S. Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies. *Psychoneuroendocrinology*. 2013;38(7):962-974. doi:10.1016/j.psyneuen.2012.10.011

104. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: A meta-analysis. *FOC*. 2014;12(3):347-358. doi:10.1176/appi.focus.12.3.347

General Discussion

Together, these three chapters utilize the theories underlying the Social Motivation Hypothesis to understand social communication challenges, changes in neurobiological markers of reward processing after intervention, and how unique approaches to behavioral intervention impact neural response and behavioral changes in autistic individuals.

Chapter 1 investigated changes to neural reward response before and after the PEERS behavioral intervention in a group of seven autistic teens aged 11 to 17. Reward positivity (RewP) was measured in response to social and nonsocial stimuli across the course of an ERP task by comparing brain activity during the first versus the second half of trials to understand patterns of responsivity over time. Improvements in social skills were observed in autistic teens after PEERS. ERP results demonstrated increased reward sensitivity during the first half of trials in the autistic ASD group after intervention compared to before intervention. Adolescents with ASD who exhibited less reward-related brain activity before intervention demonstrated the greatest behavioral benefits from the intervention. In sum, Chapter 1 demonstrated that reward response may change over time and that individual differences should be considered to better understand the variability of neural responses.

Chapter 2 investigated neural reward anticipation and response before and after the PEERS behavioral intervention in a group of 13 autistic teens. Anticipation of (stimulus-preceding negativity; SPN) and response to (RewP) social and non-social rewards were measured. Autistic adolescents showed improvement in their social

responsiveness and skills, according to parent-report. However, compared to pre-intervention, autistic adolescents demonstrated a slight decrease in anticipating social rewards after the intervention. All participants, both autistic and neurotypical teens, displayed a bigger reward response to social stimuli. Regression models indicated that older adolescents and those with less reported social motivation prior to PEERS displayed increased neural anticipation for faces from pre- to post-intervention. In addition, participants who were more actively engaged in PEERS and who displayed more social motivation prior to the start of intervention made the biggest gains in neural response to social rewards from pre- to post-intervention. In sum, Chapter 2 discusses the potential implications of brain-based neural correlates of reward to inform precision medicine approaches to creating tailored interventions based on individual needs and characteristics.

Chapter 3 explores the potential of oxytocin, a hormone known to play a role in social bonding, as a viable therapeutic benefit for autistic individuals. The paper presents a review of studies investigating the effects of oxytocin administration on both brain function and behavior in autistic individuals. Key findings from studies are reported, including that oxytocin administration may improve social cognition, reduce repetitive behaviors, and increase neural activation in brain regions associated with social processing. The paper also discusses the potential limitations of the studies, such as small sample sizes and variability in study design. Taken together, findings suggest that oxytocin may improve social behaviors and the discussion proposes the potential

enhanced outcomes when combining oxytocin and evidence-based behavioral intervention.

Social Motivation Hypothesis

While the basis of Chapter 3 utilizes principles of the Social Motivation Hypothesis, Chapters 1 and 2 test portions of the hypothesis. Given the expanded definition of the Social Motivation Hypothesis, which underscores dampened reward processing in autistic individuals to include both social and nonsocial stimuli, these chapters highlight intact processing that resembles neurotypical neural responses. Chapter 1 demonstrated that autistic and neurotypical teens had similar levels of reward response to both stimulus types before the autistic group began intervention. To further examine reward processing, Chapter 2 examined anticipation of rewards in a larger group of teens. Similarly, prior to intervention, autistic and neurotypical teens did not differ in their anticipation of rewards. Moreover, Chapter 2 provided evidence that response to social rewards was larger compared to nonsocial rewards in both autistic and non-autistic teens. Thus, the Social Motivation Hypothesis is not fully supported by this research. Instead, these findings help establish baseline levels of reward processing in autistic adolescents and suggest the malleability of reward processing after intervention, as evidenced by correlations between behavioral and neural correlates.

Moreover, the research presented in Chapters 1 and 2 underscores the importance of measuring nuanced constructs of reward, including anticipation and response. Studying both anticipation and response is essential when studying brain-based correlates

of reward because they play complementary roles in understanding the complex nature of reward processing.

Anticipation of and Response to Rewards

Anticipation of rewards involves neural mechanisms related to predicting and expecting rewards based on cues or contextual information. Additionally, the anticipation of receiving rewards is connected to the desire for the reward and therefore influences the motivation to attain something that is anticipated to be desirable. It activates regions such as the prefrontal cortex, ventral striatum, and amygdala, which are involved in decision-making, motivation, and emotional processing. Studying anticipation may help elucidate how the brain processes and represents reward-related information, and how anticipation of rewards may motivate or influence certain behaviors.

Response to rewards involves the brain's reactions to received stimuli and is associated with the degree to which the reward reinforces and satiates desires. Highly rewarding stimuli trigger the release of reward-related neurotransmitters, such as dopamine, involved in neurological reward signaling. This response activates regions such as the ventral striatum, nucleus accumbens (NAcc), and orbitofrontal cortex, which are associated with pleasure, reinforcement, and valuation of rewards. Studying response to rewards helps researchers understand how the brain reacts to rewarding outcomes, how it reinforces behavior, and how it influences future decision-making and motivation. In sum, by examining both anticipation and response, a comprehensive understanding of the neural mechanisms underlying reward processing can be established.

In Chapter 2, the investigation of neural *anticipation* and *response* to rewards showed that within-group individual differences played a role in changes in neural activation and their strength. Group-level analysis revealed that after intervention, autistic teens displayed decreased *anticipation* of social stimuli compared to before intervention, whereas non-autistic teens showed marginally more robust anticipation of social stimuli over time. In the autistic group, individual differences revealed a case of the "poor get richer," as older teens with lower levels of perceived social motivation displayed a more negative (i.e., stronger) SPN component after intervention. These findings suggest that maturity and reduced social inclination, as rated by parents, were significant factors in the change in expectation of social reinforcement. However, it is essential to note that given the change in SPN magnitude for the typically developing group who did not participate in intervention, SPN magnitude may be less stable in adolescence and should be further explored.

Regarding response to rewards in Chapter 2, all teens, both autistic and non-autistic, exhibited increased activation to social stimuli, regardless of time. Exploration of within-group variance revealed that autistic teens with the largest change in magnitude of the RewP component across time began the intervention with high parent ratings of social motivation and were more engaged during intervention sessions. Thus, reward *response* to social stimuli was a case of the "rich get richer," indicating that autistic teens who were perceived to have more social motivation and were more active during intervention sessions incurred larger increases in RewP magnitude to social stimuli. This heightened

increase in reward satiation, which implies positive reward valuation, was more apparent for autistic teens who were already motivated or "primed" to learn social skills.

Oxytocin and Reward

Similarly, neuroimaging studies have accelerated our understanding of how oxytocin can bolster social behaviors in ASD and have provided key insights into how brain areas function in response to this neuropeptide. Reward enhancements have been found in after oxytocin administration, as evidenced by augmentation of the mesolimbic pathway, including areas such as the ventral tegmental area (VTA) and the NAcc. The mesolimbic pathway forms the basis of the dopaminergic reward pathway, which is involved in neural responses to rewarding stimuli and is associated with motivation, reinforcement, and the experience of reward.

The relationship between the dopaminergic reward pathway and oxytocin in autistic individuals is complex and not fully understood. More research is needed to understand how these systems interact and their role in the behavioral expression of autism. Moreover, autism is a complex condition with diverse presentations, and not all individuals will have the same alterations in their neurochemical biology. As such, individual differences and variability should be incorporated to determine who may benefit from oxytocin administration, as this may enable the brain to process social information more readily, though remains unclear how such measures of social behavior translate to meaningful social interaction.

Neurodiversity

In the 5-year timespan (2018 to 2023) between the time the data from these chapters were collected, analyzed, and published, much has changed in the field of autism research regarding the language used to describe autistic individuals. The traditional deficit model has been rejected in place of identity-affirming and inclusive terminology that respects the volition and humanity of autistic individuals. Some of the chapters included in this dissertation contain terms such as "deficit" or "impairment." The author has since committed to working with autistic advocates better to understand the diverse perspectives within the autistic advocacy movement and to acknowledge the importance of stakeholders' voices in research. Beyond incorporating the sentiment "nothing about us without us," the author also recognizes the limitations and societal constraints on social behavior which may burden autistic individuals.

Furthermore, it's crucial to understand the fine line between masking and enhancing social skills when considering the role of intervention in the lives of autistic people. Enhancement implies improvement, which can unintentionally suggest previous inadequacies or shortcomings. On the other hand, masking refers to hiding or concealing certain characteristics to conform to normative social expectations. These nuances highlight the complexity of navigating social skills interventions in the context of autism research and advocacy. Such complexities have been reflected upon to strive for a balanced and inclusive approach that respects the diverse perspectives and experiences of autistic individuals and extends respect to their personhood. The aim of the intervention research provided in this dissertation was not to alter the traits or characteristics of

participating autistic teens, nor was the goal to change participants' neurotype. Rather, teens who participated in the PEERS intervention provided assent and stated their desire to learn social skills in order to form friendships.

In sum, the author notes the outdated language used in published work presented here and acknowledges the use of ableist language. Autistic characteristics should not be muted, nor should societal demands be placed upon autistic children in which they are forced to mask themselves. Rather, authentic selves and individual differences should be embraced so that children are supported in areas of strength, as well as in areas they want help in, and which will improve their quality of life. Such goals should be developed collaboratively between clinical researchers running studies and autistic individuals. In closing, the following lines from Hartman et al. (2023) exemplify the importance of identify-first language and the acceptance of human variation:

> Being Autistic is the neurological foundation from where each Autistic person grows. Being Autistic is not a **part** of a person, or in any way detachable or an impediment to be removed. Being Autistic **is** a naturally occurring neurology. (p 19)

Limitations

The data presented in this dissertation are not universally applicable to all autistic children and adolescents. For example, small sample sizes limit the ability to make stronger inferences about the larger clinical population. Additionally, participation in the studies reported on in Chapters 1 and 2 required an IQ score above 70, which restricts the generalizability of findings, and may not apply to autistic individuals with intellectual

disabilities. Furthermore, non-speaking autistic teens were not included in the studies, which implies that the findings and conclusions are solely based on verbal autistic teens with average cognitive abilities. Also, the research designs would have been improved by including a waitlist-control group of autistic teens to measure natural fluctuations of behavior and electrophysiology across time, regardless of intervention.

In terms of participant assent and selection for the empirical chapters, it was a requirement that autistic teens express explicit interest and motivation to make and keep friends. Therefore, participants may represent a unique subset of individuals with an autistic neurotype or profile.

Finally, a limitation of Chapter 3 is that specific guidelines around concerns of minor assent were not provided. As the effects, benefits, or consequences of oxytocin in children and teens are not yet fully understood, they should be fully aware of the known and unknown responses to treatment and explicitly confirm their willingness to participate in such research.

Conclusion and Future Directions

Overall, these papers suggest that social skills interventions, oxytocin administration, and a precision medicine approach can all have positive impacts on social motivation and related behaviors in autistic individuals. Future clinical guidelines may include tailoring interventions to the individual based on their unique needs and characteristics. Research designs should also investigate rich and varied individual data in addition to examining group-level aggregated differences and similarities to capture rich and varied behavior and neurological characteristics of autism.