Can Perception Affect Cognition? A Study of the Social Brain in Autism

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Abstract

While many theories have been proposed to explain the neuroscience of autism-spectrum disorders (ASD), few have been conclusively proven or disproven. In this paper, we set out to test a closely related set of theories which claim that the roots of ASD in the brain are primarily perceptual in nature. To do so, we gathered fMRI data on a sample of children with ASD and typically developing controls while they watched videos of children playing with toys either together or apart. We then performed psychophysiological interaction analysis (PPI) to determine if connectivity between superior temporal sulcus (a region implicated in social perception) and ventromedial pre-frontal cortex (a region involved in theory of mind) in the social condition differed across groups. Additionally, eyetracking data was gathered while participants viewed the videos, and was analyzed along with neuroimaging data in a post-hoc multiple regression analysis. While no difference in STS-vmPFC connectivity was found in our data, interesting patterns of activation involving the mirror neuron system and the amygdala were found in both our PPI and post-hoc analyses. Interpretations of our findings and possible directions for future research are discussed.

Introduction

Autism is a developmental disability characterized by significant impairment in social functioning and language acquisition and the presence of repetitive, stereotyped behaviors. (American Psychiatric Association, 2000). Individuals with autism-spectrum disorders (an umbrella of diagnoses which includes autism, Asperger Syndrom, and the catch-all Pervasive Developmental Disorder – Not Otherwise Specified) tend to have an extremely difficult time connecting with others and functioning in social situations; many people with more severe forms of the disorder are totally unable to function in daily life without significant, lifelong assistance. There is no known cure for any autism-spectrum disorder – though targeted behavioral intervention (especially early in childhood) can lead to significant improvements in functioning, the disorder itself persists across the lifespan. Furthermore, autism-spectrum disorders are far from uncommon; recent studies have found that as many as 1 in 88 children in North America have been diagnosed. In fact, diagnoses of autism-spectrum disorders (or ASD) have skyrocketed in the past decade, with the prevalence rate of the disorder estimated at 1 in 150 just ten years
ago (Centers for Disease Control and Prevention, 2012).

Fortunately, the massive rise in diagnoses of autism-spectrum disorders has been met with an explosion of research on causes, progression, and treatment. This research has taken many forms over the years. Since Leo Kanner first described the disorder in the 1940s (Kanner, 1943), early studies of autism focused almost entirely on understanding the disorder from a psychological perspective, often inspired by psychodynamic theories of personality development. For instance, many researchers in the 50s and 60s believed that autism was caused by a cold, distant parenting style on the part of the child’s mother (the so-called – and now debunked – ‘Refrigerator Mother’ theory of autism; Bettleheim, 1959). More recently, however, psychologists have come to realize that autism-spectrum disorders are extremely complex, and are characterized by numerous genetic and neurological differences that cannot be traced to any one purely psychological factor. ASD is now generally thought to have its roots in a complex interplay of environmental, genetic, psychological, and neurological factors, which combine to produce the cluster of symptoms that make up the disorder.

This has given researchers a wealth of approaches from which to study autism-spectrum disorders – from genetics to neuroscience to psychology – and any number of theoretical perspectives within these. In this paper, we will focus primarily on a cognitive neuroscientific approach to understanding the disorder, by attempting to untangle specific neural correlates of the social deficits seen in autism. Such an approach has several advantages. First and foremost, by comparing the neural deficits that underlie the social issues seen in autism to the functioning of the brain in typically developing individuals, researchers may be able to form a more complete
picture of the precise nature of these deficits. In order to do so, researchers must first have a strong understanding of what, exactly, these deficits are – an understanding that studies such as this one can contribute to.

The second advantage of a cognitive neuroscientific approach to studying autism is purely pragmatic, and is tied to treatment of the disorder. Research on treatments for autism has demonstrated overwhelmingly that the earlier treatment begins, the more profound an effect it can have on the overall functioning of individuals with autism. In fact, even a few years’ difference in beginning treatment can lead to huge reductions in the symptoms of the disorder (Corsello, 2005). That being said, how early in the lifespan interventions can take place is currently limited by the fact that autistic symptoms do not become apparent until a child is two or three years old. If techniques can be devised to allow for the detection of autism even earlier, they could have a great effect on treatments for the disorder. The more we learn about the role of the brain in autism, the more likely it is that we may find some marker that can be detected in infancy, allowing for extremely early interventions.

In this paper, we will examine and attempt to test one prominent thread present in many theoretical approaches to the neuroscience of autism. Over the last decade, several researchers have argued that the deficits in social functioning seen in children with autism may be inherently linked to more basic deficits in social perception. While the particulars of these theories vary greatly, they share one common view of the roots of autism-spectrum disorders; namely, that they are strongly mediated by perceptual processes. Though this claim is not without its detractors and counter-arguments, it is a fairly common idea that has been used as the basis for a
great deal of research in the field. We will start by discussing prior research examining particular regions of the brain that may be implicated in this connection, both in social perception in particular and in broader patterns of social cognition. We will also explore previous research related to this particular view of autism. Finally, we propose to test this idea by using fMRI analysis to examine connectivity between perceptual and social-cognitive regions of the brain (specifically regions implicated in a process known as theory of mind) in children with and without autism.

**Background**

*Autism and Perception*

Over the last few years, many theories concerning the neurobiological correlates of ASD have been proposed. Several of these theories focus primarily on certain perceptual deficits which are present in autism, and argue that these issues lead to the many social deficits linked to the disorder. In other words, according to this view some factor present in individuals with autism creates deficits in social perception. These deficits then cause a sort of ripple effect, creating the constellation of social symptoms seen in patients with autism. This is not to say that autism itself is caused by perceptual deficits, but rather that whatever combination of genes and environmental factors is responsible for autism-spectrum disorders causes perceptual issues, which then lead to social deficits.

This is quite a significant and far-reaching claim, and one that is difficult to test effectively. That being said, certain elements of this idea – especially concerning how individuals with autism perceive faces – have been researched extensively. Numerous studies have found that
when people with autism are shown images of faces they show diminished activation, compared to typically developing controls, in a region of the fusiform gyrus known as the fusiform face area (FFA), which has been found to activate in response to faces in typically developing individuals. This was first demonstrated in 2000 by two research groups, who independently found that subjects with high-functioning autism, when shown images of human faces in fMRI studies, demonstrate decreased activation of the fusiform gyrus, particularly in the fusiform face area, compared to controls (Critchley et. al., 2000; Schultz et. al., 2000). These findings have been replicated numerous times in the years since (Schultz, 2005 cites nine such studies, and several more have been published since then, such as Bolte et. al., 2006, and Kleinhans, et. al., 2008).

As Schultz (2005) points out in a later review of the literature on the fusiform gyrus in autism, part of what makes this pattern of deficits so intriguing is that it seems, ultimately, to be perceptual in nature. The patterns of FFA hypoactivation shown by research participants with ASD seem to suggest that they do not place the same importance on faces as typically developing individuals, which prevents them from perceiving faces the same way. This interpretation is supported by a case study finding that one child with autism who did not show FFA activation when shown images of faces, did in fact show increased FFA activation when shown images of (non-human) characters from a cartoon that he displayed a great deal of interest in. Additionally, the researchers found that that a single child without ASD, when shown characters from a cartoon series that he enjoyed, did not show this abnormal pattern of FFA activation (Grelotti et. al., 2003).
Koshino et. al. (2008) posit a mechanism for the unique patterns of activation seen in the FFA of individuals with autism. They found that in an n-back task testing memory for faces in subjects both with and without ASD, while individuals with ASD performed as well as controls on the task, they showed decreased FFA activation (as one might expect based on prior findings) while performing the task. Koshino and colleagues also, however, found that subjects with autism showed greater activation of posterior regions implicated in low-level perception (including the right medial frontal cortex, right lateral premotor area, and right superior parietal lobe) than controls. Based on these findings, Koshino and colleagues argue that individuals with autism perceive faces as a collection of objects than as a single unified whole. This would explain why the participants with autism did not show any deficits on the facial memory task despite showing decreased FFA activation.

While the deficits seen in the FFA may be perceptual in nature, some evidence suggests that the FFA may itself be an integral part of systems of social cognition, and that the diminished FFA activation seen in ASD leads to decreased performance within this system as a whole, giving rise to broader social deficits. Schultz (2005) argues “seeing a face [may] automatically and involuntarily activate FFA-based semantic knowledge about people and in some sense primes the observer for a social interaction” (page 137). Several findings support this theory, such as Kriegstein and Giraud (2004), who found that neurotypical individuals asked to identify people by their voices showed activation in the FFA in addition to areas generally recognized as involved in socially-relevant auditory processing, such as the superior temporal sulcus. Another such finding is a paper by Schultz et. al. (2003), who found that the FFA, among other areas, was
activated in neurotypical individuals who were shown animated geometric figures and asked if the figures were “friendly”, as opposed to when they were asked about non-social features (such as if the figures were “heavy”). Based on these and similar findings, Schultz argues that the FFA (along with the amygdala) is involved in a broader system of social cognition within the brain, in which the FFA is involved in not only perceiving faces, but encoding social information about the individuals represented by those faces.

While these findings are interesting, it seems to be a bit of a stretch to claim that they in and of themselves provide evidence for any broader perceptual claims about autism, clustered as they are around one specific region (the FFA) and type of social perception (faces). That being said, while much of the research on perceptually-based theories of autism has focused on this area, some researchers have examined whether these findings ultimately fall in to a larger pattern of deficits. The idea that the FFA deficits seen in autism indicate a larger pattern of perceptual deficits was formalized in a 2005 paper by Dakin and Frith. Based on extant literature on social perception in autism, the researchers concluded that the FFA deficits seen in autism were linked to core deficits in perceptual processing. They attributed this to abnormalities in a region of the brain called the superior temporal sulcus, a finding that we will discuss in more detail later.

This claim was further tested by Behrmann et. al. (2006), who demonstrated both that individuals with ASD were slower at discriminating faces than typically developing control subjects, and that they showed deficiencies in their general ability to perceive a global whole made up of smaller parts. Participants performed two tasks, one with compound letters and another with geometric shapes. In the first task, participants viewed a large letter made up of
smaller letters, which were either the same or different than the global letter. Neurotypical subjects identified the global letter faster than the local letters, and, when the two letters were incongruent, showed significant interference from the global letter in identifying the local letter. Participants with ASD showed no difference for reaction time or accuracy in the congruent condition, but showed significantly increased reaction time for identifying the local letters in the incongruent condition.

The second experiment used an experimental task known as the ‘primed matching paradigm’, in which participants are shown a prime followed by two probes, each of which consist of a geometric shape made up of other geometric shapes (a pattern known as a Navon stimulus), and are asked to rate if the probes are the same or different. While typically developing subjects tend to process the larger shape first and show no delay if the larger shape is made up of incongruent smaller shapes, individuals with ASD show an opposite pattern of results. Based on these findings, Behrmann et. al. concluded that the participants with ASD had lessened ability to recognize a global configuration of local objects and that deficits seen in face perception and processing are a result of this, rather than a processing deficit unique to the perception of faces (Behrmann et. al., 2006).

This claim has proven somewhat controversial, and other researchers have attempted to demonstrate that it may be inaccurate (for instance, Nishimura et. al., 2008, demonstrates that this pattern is not seen in individuals with Asperger syndrome). Despite this opposition, several other studies seem to suggest that Behrmann et. al.’s conclusions regarding configural processing may be accurate. For instance, the Koshino et. al. study discussed earlier (which found object
perception regions active during facial perception in autism) lends credence to this theory by providing further evidence that individuals with autism perceive faces as a collection of objects. Evidence from electrophysiologial studies supports this interpretation as well: for instance, Grice et. al. (2001), discuss a particular event-related potential seen in EEG that occurs when typical individuals perform tasks that involve putting disparate elements together in to a whole, and find that this pattern is abnormal in individuals with autism. In one literature review, Happe & Frith (2006) found that across 42 studies of configural processing in ASD, an overwhelming number found strong support for local biases in visual perception in individuals with autism-spectrum disorders. As Behrmann et. al. demonstrated, these perceptual differences are not limited to faces. Thus, while it is possible that they all originate in the FFA (as it has been argued that FFA is responsible for general holistic processing, and that faces are simply the most common holistically-processed stimulus), we must also consider the idea that some broader deficit in global processing drives the deficits in facial perception discussed earlier. If this is the case, then while this deficit is expressed in the FFA, it may well have its roots elsewhere in the brain. As was mentioned previously, Dakin and Frith (2005) argue that the superior temporal sulcus is primarily responsible for driving these deficits – a claim that we will now examine in more detail.

Superior Temporal Sulcus

The superior temporal sulcus, or STS, is an area located between the superior and middle temporal gyrii that has long been associated with perception. The first article to demonstrate this pattern was published in 1969, and found that monkeys with lesions to STS showed deficits in
audition compared to neurologically intact monkeys (Dewson et al., 1969). Since then, continuing research has demonstrated that STS does more than simply play a role in perception – it does much to drive the perception of socially-relevant versus non-socially-relevant stimuli. While this finding would be intriguing on its own, research has also uncovered significant STS deficits in people with autism, giving us a prime opportunity to better understand social perception in the autistic brain.

A great deal of research in neurotypical individuals has demonstrated that STS is activated when individuals perceive biological motion. Vaina et al. (1990) first argued that biological motion perception was handled by a specialized area of the brain based on a study of a patient, L.M., who after suffering bilateral lesions to the brain (including visual pathways) demonstrated severely lessened performance on several visual tasks, but showed normal performance on a point-light biological motion stimulus (presented as a group of points of light arranged against a black background in the shape of a moving human figure). This was further demonstrated by Howard et al. (1996), who found that when subjects watched a similar point-light motion biological motion display, they demonstrated increased activation in STS versus a random point-light motion control.

Other studies have gone a long way towards building on these findings to create a coherent theory of STS function in social perception. For instance, Pelphrey et al. (2003) demonstrated that the activation seen in STS for point-light biological motion was activated specifically for biological motion and not just any coordinated, non-random motion. To do so, they showed subjects an array of items (a human, a robot which moved the same way as the human, a
grandfather clock, and assorted mechanical parts), one of which moved in each trial. FMRI analysis demonstrated that STS activation was the same for the human and robot motion conditions, and that both of these conditions showed significantly greater activation than either the mechanical parts or grandfather clock conditions. Based on this finding, Pelphrey argues that STS activation is triggered by biological motion specifically, and that it is not sensitive to the superficial characteristics of the actor performing the movement (i.e., a robot versus a human). Further research has demonstrated that STS not only activates for biological motion, but also shows greater activation for socially-relevant biological motion (such as that of a human) than non socially-relevant biological motion (such as that of a dog; Kaiser et. al., 2011).

Furthermore, the role of STS in socially-relevant biological motion is not limited to gross movement of a figure. Some research has focused on a very specific subset of biological motion: namely, observing mouth movement and shifts in eye gaze in another individual. Early studies demonstrated robust STS activation in response to both eye and mouth movement (Puce et. al., 1998); a finding which was later replicated and fine-tuned, using high-resolution available imaging to demonstrate that perception of eye motion and mouth motion activate different areas of STS (Pelphrey et. al., 2005). This is consistent with single-cell recording studies in macaque monkeys, which have found that while cells in STS in monkeys fire in response to faces and gaze shifts, certain cells show preferential activation for particular orientations of the face and directions of shifted gaze (Perret et al, 1984). Taken together, these findings suggest that the activation seen in STS in response to eye and mouth movement is not simply the effect of those particular movements being a form of biological motion. Rather, this activation seems to be a
result of some form of privileged status given to the eyes and mouth in social interaction – likely
due to the tremendous amount of information that these areas can impart.

These conclusions are generally supported by findings from non-neuroimaging studies as well. While it is relatively difficult to perform spatial localization in electrophysiological studies, some ERP research has examined STS in response to visual stimuli, especially biological motion perception. Puce et. al. (2000) examined two ERP components, N170 and P350, which prior studies had shown to be responsive to face and eye stimuli. They found that N170 over the bilateral temporal scalp was significantly larger in response to mouths opening than to mouths closing, and to eye movement versus a steady gaze, after controlling for activation to movement in general – suggesting that this component is tied to particularly socially-relevant visual stimuli, such as gaze shifts or mouths opening at the beginning of speech. Puce also reports that electrodes over STS and inferior temporal gyrus showed the largest recorded N170 response to faces, both moving and static. Though the technical limitations inherent in ERP studies mean that this data is not enough to make the claim that the results are being driven by STS, Puce et. al. argue that these findings suggest that “(1) bilateral temporal cortex forms part of a system sensitive to biological motion, of which facial movements form an important subset; (2) there may be a specialized system for facial gesture analysis that provides input for neuronal circuitry dealing with social attention and the actions of others” (page 221) - both points that converge with findings from neuroimaging studies of STS. These findings are supported by a pair of papers that trace a face-responsive peak the researchers refer to as N200 to similar areas of the scalp (Allison et. al., 1999; McCarthy et. al., 1999).
These findings seem to point to one conclusion: that STS is fundamentally involved in the perception of social stimuli. In fact, most current research on STS seems to suggest a common underlying process (Redcay, 2008). Based on this research, Redcay argues that this process entails taking in sequences of sensory input, both visual and auditory, and determining if that input is “communicatively significant” (page 128). Ultimately, Redcay argues that if this is in fact the function of STS, STS impairment (and the resulting inability to determine the communicative significance of sensory input) may ultimately play a role in some of the deficits seen in autism.

Redcay is not the only researcher to suggest that autism-spectrum disorders and STS may be linked. In fact, much research has shown that many key STS functions are diminished in subjects with autism. Studies of individuals with ASD have repeatedly shown that STS does not show the same patterns of preferential activation towards socially relevant visual stimuli as it does in typical subjects. In one such study, Pelphrey et. al. (2005), individuals were shown a series of faces while objects appeared near the faces. In one condition, the faces in the images shifted their gaze towards the object after it appeared (as one would expect), while in the other condition the faces shifted their gaze to an empty space when the object appeared (which violates expectations of how someone would normally react in that situation). While both ASD subjects and controls showed STS activation in response to gaze shift, the control subjects showed greater activation for the incongruent trials, while the ASD subjects demonstrated the same level of activation in both trial types. Pelphrey et al argue that this shows that the activation of STS in individuals with autism is not moderated by the social context of incoming visual stimuli (Pelphrey et. al., 2005).
If this is correct, it would signal a major deficit in STS in individuals with ASD, since (as we have discussed) determining socially-relevant from socially-irrelevant information seems to be a major function of STS in typical individuals.

In another, related imaging study, Greene et. al. (2011) gathered imaging data while subjects underwent a cueing task, in which they were shown an arrow or a directed gaze, pointing either left, right, or in a neutral position. After the cue was presented, a target appeared, though not necessarily in the same direction that the cue was pointing, so as to minimize expectation effects. Reaction time until the subjects looked at the target was measured using eyetracking technology. Though no difference between the two groups was found for reaction time, fMRI analysis found that control subjects showed activation in several regions, including STS, in the gaze-cue condition versus the arrow-cue condition, which was not seen in subjects with ASD. In fact, the pattern of activation seen for social cues in individuals with ASD was similar to that seen for non-social cues in control subjects. More recently, Nummenmaa et. al. found that a full diagnosis of autism isn’t even necessary to see this effect. They found that in a group of typically developed subjects, all of whom were tested for autistic traits (as measured through the Autism-Spectrum Quotient, or AQ), that while every subject showed greater activation across several brain regions (including STS) in response to a dynamic gaze shift versus a static gaze, the degree to which STS was activated was inversely correlated with AQ scores. In other words, full autism isn’t necessary to see STS deficits in visual perception; the presence of autistic traits alone is correlated with their presence (Nummenmaa et. al., 2012).

In a similar experiment, Suda et. al. (2011) tested 28 typical individuals who were measured
with a novel form of imaging known as ‘near-infrared spectroscopy’ (NIRS) which allowed the researchers to perform neuroimaging in situations that would be nearly impossible in a classic fMRI – in this case, in a naturalistic social interaction. Suda et. al. found that in their subjects, AQ scores were inversely correlated with STS activation during social interactions, matching Nummenmaa et. al.’s findings. Though it is impossible to determine based on the experimental paradigm whether this activation is driven by visual input, auditory input, or some combination of both, this study ultimately demonstrates that the deficits seen in STS activation in autism are present in naturalistic social interaction, as well.

STS hypoactivation for visual stimuli in people with ASD is not limited to gaze shifting – it is also seen for the biological motion effects seen in neurotypical individuals. Herrington et. al., 2007, examined activation in several regions of visual cortex in response to figures made from dots, manipulated so as to appear to be walking. Participants were asked to report in which direction the figure appeared to be moving. While accuracy of responses did not differ for ASD participants and controls, those with ASD were found to show significantly decreased activation of several cortical regions – including STS – in response to the biological motion condition.

While there is compelling evidence to suggest that strong perceptual deficits in STS can be seen in individuals with autism-spectrum disorders, we still need to tie this in to social cognition and behavior if we hope to use it to test the perceptual theories of autism. For that, we will now turn our attention to another region of the brain: the ventromedial prefrontal cortex.

*Ventromedial Prefrontal Cortex*
The ventromedial prefrontal cortex (or vmPFC) is closely tied to the psychological process known as ‘theory of mind’. Theory of mind refers to the ability to attribute mental states to others – in other words, to recognize that beings other than themselves have a distinct mind. Though the concept of theory of mind is centuries old and has its roots in philosophy, the first psychological research into the phenomenon came in 1978, when Premack and Woodruff attempted to test if theory of mind was present in chimpanzees (Premack & Woodruff, 1978). This finding led to an explosion of psychological research into theory of mind in humans, including Wimmer and Perner’s seminal 1983 study of theory of mind in children.

In this study, children of varying ages performed what the researchers referred to as the “Sally-Anne task”. In it, participants were shown a puppet show in which a puppet hides an item in one location in a scene, and then leaves the scene. A second puppet then enters the scene and moves the item to another location. At this point, the viewer is asked where the first puppet would look for the object that it had hidden if it were to return. Though the obvious answer would be that it would look where it left the item, making such a simple attribution actually requires theory of mind, since the viewer must recognize that the puppet has its own mind and does not know that the item has been moved, even though the viewer knows better. Using this paradigm, Wimmer and Perner demonstrated that none of the participants aged 3-4 were able to guess correctly, while 57% of 4-6 year olds and 86% of 6-9 year olds were able to do so. Based on this, they concluded that humans are not, in fact, born with theory of mind – it is something that develops during childhood (Wimmer & Perner, 1983). Though these findings have proven somewhat controversial (in large part due to the fact that the task used, which is generally
referred to as the ‘false belief task’, may instead measure the presence of deficits unrelated to theory of mind, such as executive control; Bloom & German, 2000), a great deal of research since then has continued to examine theory of mind in more detail – including its roots in the brain.

Over the last decade, a large body of research has begun to trace the roots of theory of mind to several regions of the cortex – including, frequently, vmPFC. While this field has not been researched as thoroughly as social perception in the superior temporal sulcus, there is enough literature available to begin drawing some concrete conclusions. In a study performed by Gallagher et. al. (2000), typically developing subjects read a series of stories and viewed a series of cartoon images in an fMRI. These stories fell in to one of three conditions – theory of mind related, in which the story described a character’s mental state, non-theory of mind related, in which the story contained a description of events with no mental states, and unrelated sentences, in which the story did not contain any narrative and was simply made up of unrelated sentences. After each story, participants were asked a basic question about the events of the story to ensure that they had actually read it. Similarly, the cartoons in the cartoon portion were divided in to three types: theory of mind images, in which understanding the cartoon required attributing mental state to a character, non-theory of mind images, in which understanding the cartoon did not require any such attribution, and jumbled pictures, which were meaningless. Similar patterns of activation were found for both conditions: a broad section of the medial prefrontal cortex displayed greater activation for stimuli that required theory of mind to understand, both in the story and image condition, as compared to those that did not require theory of mind or were
meaningless.

These effects seem to hold for theory of mind in general, regardless of the sensory modality of the incoming information. For instance, one study gathered neuroimaging data on 13 children aged 6-11 years (old enough to have developed theory of mind) who listened to a series of stories read aloud. Each story was divided into three 20-second segments: one describing the physical facts of the story, one describing the characters’ social relationships and appearances, and one describing mental states. Researchers found increased activation of several regions, including vmPFC, for the mental states portion of the stories versus the other two sections (Saxe et. al., 2009).

Findings from non-imaging studies tend to support a vmPFC-based understanding of theory of mind in the brain as well. Though ERP findings are generally unavailable for this region due to technical issues isolating medial signal in the prefrontal cortex, some lesion studies focusing on vmPFC and theory of mind are available in the literature. Stone et. al. (1998) performed basic tests of theory of mind on 10 subjects, 5 of whom had significant damage to the bilateral orbitofrontal cortex (OFC) – a broad region of cortex, which includes the vmPFC – and five of whom had damage to the left dorsolateral pre-frontal cortex (dLPFC), a region of cortex distinct from vmPFC, and five neurologically-intact controls. None of these subjects displayed any deficiencies in the classic false-belief test for theory of mind, but in a second task which required determining faux pas – a task which requires theory of mind, and is generally seen as being more difficult than the false-belief test – control subjects and those with dLPFC damage performed significantly better than subjects with OFC damage. This suggests that, without a functioning
vmPFC, individuals may be able to perform basic theory of mind attributions but are unable to perform more complex tasks (Stone et. al., 1998). This may suggest that regions other than the vmPFC are responsible for more basic attributions related to theory of mind, or that the damage in these individuals was not extensive enough to totally eliminate theory of mind. Regardless, these findings demonstrate that higher-order social cognition is made much more difficult, if not impossible, without a functioning vmPFC. In fact, as Stone points out, the difficulties in social cognition demonstrated by individuals with OFC damage are similar to those seen in another group: individuals with high functioning autism.

The question of what role, if any, theory of mind plays in autism has been debated by psychologists for decades. While a full treatment of this topic would require its own thesis, we will attempt here to at least touch on some of the major ideas and findings in the field. The idea that theory of mind may play a role in autism was first put forth by Baron-Cohen who suggested in a seminal article that deficits in theory of mind could explain the social deficits seen in autism, since it is difficult to function socially without being able to reason about what the other person or people in a social interaction are thinking or feeling. Baron-Cohen also points out that other signifiers of autism, such as a lack of pretend play in children, could also be explained as having their roots in a lack of theory of mind. To test this theory, Baron-Cohen performed the Sally Anne task with typically developing children, children with autism, and children with Down Syndrome. The ASD group showed massive deficiencies on this task relative to the group with Down Syndrome and the typically developing group, despite having a mean age more than seven years higher than the control group (11 years and 11 months for the ASD groups versus 4 years
This finding led to a tremendous amount of research examining whether theory of mind deficits are central to autism, and while this theory has been challenged, more recent research supports the claim that theory of mind plays at least some role in the disorder. That being said, the claim that autism can be traced directly back to theory of mind is likely an oversimplification (Hamilton, 2009). Based on prior research, Hamilton demonstrates that children with ASD do not tend to show any difficulty inferring other people’s intentions or goals. Rather, the difficulty seems to be present in more complicated theory of mind-related tasks. This ties directly back in to Stone et. al.’s findings that non-ASD individuals, after suffering damage to the orbito-frontal cortex, demonstrate no difficulty with simple theory of mind tasks but have great difficulty with more complex ones. This parallel may imply that theory of mind deficits in individuals with ASD are somehow tied to the orbitofrontal cortex (or, based on other research we have examined, the vmPFC more specifically) – a suggestion that many studies of the vmPFC in autism have borne out.

The first study to explore whether or not the deficits in theory of mind in autism are connected to vmPFC was a PET study, in which individuals with Asperger syndrome were asked to read a series of stories that either did or did not require attributing mental state to a character. The researchers found that, compared to a typically developed sample that performed the exact same task in a prior positron-emission tomography study, the subjects showed significantly reduced task-related vmPFC activation, despite showing normal activation in several other regions. Though these results are clouded somewhat by the study’s small sample size (n = 5 ASD
subjects) and the relatively weak spatial resolution of PET, other studies since then have shown similar results. Castelli et. al. (2002) demonstrated that individuals with Asperger syndrome and high-functioning autism, when shown a series of geometric shapes that moved in ways that implied either goal-oriented or intention-based behavior, were not only less able to describe the scenes in which the shapes moved as if they had underlying intentions than members of a control group, but also showed decreased activation of a network of areas, including vmPFC (and, interestingly enough, superior temporal sulcus; Castelli et. al., 2002).

More recently, Watanabe et. al. (2012) performed a study in which individuals with and without autism were shown a series of videos in which actors displayed conflicting vocal and affective information about mental state. The researchers found that the subjects with ASD were both less likely to make attributions for the actors based on the affective information present (an action which, from a theory-of-mind perspective, is much more difficult than making attributions based on vocal information), and showed decreased vmPFC activation when compared to typically developed controls. Finally, research outside of classic neuroimaging methodology supports the conclusion that vmPFC dysfunction plays a role in the deficits in theory of mind seen in autism as well. In a 2011 case study, Enticott et. al. describe a woman with severe autism who had deep repetitive transcranial magnetic stimulation, or rTMS, applied to the bilateral prefrontal cortex in nine sessions over an eleven-day period. While rTMS is best known for being used to temporarily deactivate regions of the brain, it can (at different settings) be used to stimulate the brain as well, as in this case. The researchers found that after a course of rTMS, the patient reported significantly increased social functioning, including more comfort in social
situations and (most tellingly) increased ability to understand and empathize with other people’s feelings – reports that were corroborated by her family. The researchers attributed this effect to an increase in the patient’s overall theory of mind – providing yet another piece of evidence for both the vmPFC’s role in theory of mind, and its status as the possible root of theory of mind deficits in individuals with autism (Enticott et. al., 2011).

Based on the research presented, two facts seem clear. Firstly, theory of mind seems to be related to vmPFC. The region has been consistently found to activate in response to theory of mind related tasks, and clear deficits in such tasks has been shown in individuals with vmPFC damage. Secondly, theory of mind deficits likely play a role in autism-spectrum disorders. Though its unlikely that impaired theory of mind is solely responsible for the social deficits seen in autism, research has fairly clearly shown that autism is strongly correlated with deficits in theory of mind, and that resolving those deficits (such as in the case of Enticott et. al., 2011) can lead to marked improvement in functioning for people with autism. If this is the case, the vmPFC is a clear candidate for examining social cognition (or at least a powerful subset of it) in individuals with autism.

*Justification for the Current Study*

Now that we have discussed a few potentially relevant regions of the brain, we can turn our attention back to views of autism which place social perception front and center. These views provide what could be an extremely powerful framework for understanding social deficits in autism. That being said, while the research supporting these ideas is compelling, it has focused (with a few exceptions) almost exclusively on facial perception, by and large overlooking the
idea that social deficits in autism may be tied to broader issues in social perception as a whole. Additionally there remains no clear and convincing account of what mechanisms drive the connection between social perception and broader patterns of social cognition – or even if this connection exists at all, a possibility considering the dearth of studies on this network in typically developing individuals.

To that effect, the goals of the present study are three-fold: firstly, we wish to demonstrate that broader social perceptual issues in autism play a driving role in the social deficits seen in the disorder; secondly, we wish to demonstrate a neural mechanism by which this effect takes place; and finally, we wish to show that this theorized perceptual/social cognitive circuit is present in typically developing individuals but is absent in individuals with autism. If we are able to effectively demonstrate these three factors, we will begin provide the support and expansion necessary for the perceptual theory of autism to become a robust framework for understanding social deficits in autism.

In order to determine what exactly we wish to examine, we must attempt to trace the neural correlates of both social perception and social cognition. Based on the research presented here, a clear candidate for testing social perception in the brain seems to lie in the superior temporal sulcus. This claim has its roots in the argument that STS plays a significant role the social perceptual deficits seen in autism (including deficits in face perception; Dakin and Frith, 2005). Evidence from research in both ASD and typical subjects supports this argument. Numerous studies demonstrate that the superior temporal sulcus is selectively activated for sensory stimuli that carries social relevance. In general, STS appears to be responsible for parsing sensory input
and determining what is and is not socially relevant, suggesting that STS may be the primary region responsible for social perception (Redcay, 2008). If this is true, it would make sense that abnormal STS function is responsible for social perceptual deficits in autism (as Dakin and Frith claim). Research into STS in individuals with ASD seems to confirm this theory, as STS hypoactivation has been found in response to both socially-relevant auditory and visual stimuli, as well as naturalistic social interactions in general, in individuals with autism-spectrum disorders. All of this, taken together, suggests that the STS is a strong candidate for being the root of social perceptual deficits in autism – and thus, that the STS would be an excellent place to start a broader analysis of the perceptual theory of autism.

Though identifying a suitable region of analysis for social perception is fairly straightforward, identifying such a region for broader social cognition – in other words, what is done with social information once it has been perceived – is significantly more difficult. Several different regions of the brain are known to play a role in social cognition, often in highly divergent ways, and research in this area tends to move forward rapidly, often upending previous findings. In our case (especially considering that our focus is on autism), we plan to examine vmPFC. Though social cognition in general cannot be truly localized to any one specific region of the brain, specific subprocesses of social cognition can, and many have been found to be strongly localized. One of the most vital of these subprocesses is theory of mind. Theory of mind is central to functioning in social situations, and forms a key portion of social cognition in typically developing individuals. Moreover, it has been suggested that deficits in theory of mind in individuals with autism may be the root cause of social deficits in the disorder. Though this theory is not without controversy, it
nonetheless provides a strong foundation from which to make the claim that studying theory of mind is an effective proxy for studying social cognition as a whole in autism. Finally, focusing on theory of mind for our analysis of social cognition has one clear advantage – unlike general social cognition, theory of mind can and has been localized to specific regions of the brain, specifically (as we have demonstrated) the ventromedial pre-frontal cortex. The evidence demonstrating both that vmPFC is implicated in theory of mind in non-ASD individuals, and that vmPFC dysfunction may be involved in theory of mind deficits seen in individuals with autism, makes the region an excellent candidate for testing the social cognition side of perceptual-based theories of autism.

This provides us with the theoretical basis needed to test perceptual views of autism – we want to show that perceptual difficulties, as expressed in the superior temporal sulcus, are implicated in the social cognitive difficulties that have their roots in the ventromedial prefrontal cortex. In order to test this, however, we must be able to show that these two regions of the brain are functionally connected; in other words, that the activation (or hypoactivation) of one can affect on the other. Fortunately, this can be done with a technique known as connectivity analysis. Connectivity analysis, in short, consists of performing specific statistical analyses on fMRI data, along with the experimental stimuli used, to determine patterns of co-activation based on external stimuli between regions that suggest that the involved regions are ‘functionally connected’ - in other words, that the activation of one region due to a specific stimulus is correlated with the activation of a second region (Friston et. al., 1997). While it is not possible to draw causal inferences from functional connectivity analysis, the correlational data that can be
gained from such analysis can still provide a great deal of information about how the brain works. Though measures of functional connectivity can be susceptible to confounds due to multiple regions of the brain activating to the same stimuli for unrelated reasons (Hampson et. al., 2002), this can be controlled for with sufficiently sophisticated analysis across divergent participant groups, and connectivity analysis nonetheless remains an extremely useful tool for researchers hoping to study task performance on a level more complex than simple single-region activations.

Connectivity analysis is especially useful in experiments such as ours, where the goal is to identify how multiple regions work in a network and reason about their behavior (Rogers et. al., 2007). Though connectivity analysis is a fairly recent advance in fMRI research, some researchers have used it to great effect in studies of autism – for example, the Castelli et. al. (2002) article discussed earlier not only found STS hypoactivity when participants with autism viewed figures displaying intention-driven movement, but also reported decreased functional connectivity between STS and visual area V3.

With our theoretical background and methodology addressed, we are left with one final question – how can we best test the role of perception in autism? More traditional fMRI methodology would involve showing images or playing sounds and examining subjects’ neural responses. While this is suitable for most tasks, in our case the closer to naturalistic social interaction we can make our stimuli, the better. The deficits seen in autism are inherently social, and an attempt to test them would be served well by approximating actual social situations as much as possible. Unfortunately, this can be difficult to do in more classic fMRI paradigms, as it
is hard to effectively simulate a true social interaction using only still images or audio. Instead, we propose to test this theory by exposing participants to stimuli that are as close to actual social interaction as possible considering the technical limits of fMRI: watching videos of real social interactions between children.

Unfortunately, using video stimuli in an experiment like this (especially one with participants with autism-spectrum disorders) gives rise to an entirely new set of potential issues. The most significant of these is the question of directed attention. In a classic fMRI paradigm, the distracting influences are few – if an individual is presented with a face, there is nothing else in the visual field to distract them, and if they’re presented an audio recording there is generally no other auditory stimulus present to divert attention. Naturalistic videos, on the other hand, provide a wealth of potential distractions, such as items in the background or potentially attention-grabbing articles of clothing. This can make the kind of analysis we hope to perform nearly impossible – it is difficult to claim that social stimuli has an affect on particular regions of the brain if you’re not certain the participants attended to any social stimuli at all.

These issues are only compounded by the fact that we are working with a research population with autism-spectrum disorders. Caregivers and teachers of individuals with autism often report that children with autism tend not to look directly at another individual with whom they are speaking – instead, they tend to look at the person’s body, or away from them altogether. Such claims have also been verified experimentally. By gathering eyetracking data on individuals observing filmed social interactions, researchers have shown that individuals with autism tend to look at a speaker’s body or the background, rather than at their face (Klin et. al., 2002). Even
when presented faces directly, individuals with autism tend to spend far less time than control subjects looking at areas that contain more social information, such as the eyes, and more time looking at areas that do not carry any such information, such as the mouth (Pelphrey et. al., 2002).

Fortunately, we can use the same eye tracking techniques that these studies use to demonstrate gaze deficits in autism to correct for those same deficits. In other words, we can gather real-time eye tracking data from our participants while simultaneously gathering neuroimaging data, and use that eyetracking data to control for time spent looking at the important sections of our stimuli. This will allow us to use videos of naturalistic social interactions as our stimuli, while also avoiding the introduction of a potentially confounding variable in to our study.

We now have all of the background necessary to test an expanded form of the perceptual theory of autism. We will use connectivity analysis to determine STS and vmPFC co-activation in individuals, both with and without autism, who are observing video recordings of naturalistic social interactions. We will also use eye tracking data used to control for possible deficits in how much attention participants pay to our stimuli. While we will not be able to draw any conclusions regarding causation from this data (since the data that can be gathered from functional connectivity analysis is primarily correlational in nature), simply demonstrating that decreased social perception, as expressed in the superior temporal sulcus, is correlated with deficits in theory of mind will provide strong evidence in favor of perceptually-based theories of autism. With this in mind, our hypotheses are as follows:

**Hypothesis 1:** The superior temporal sulcus and ventromedial prefrontal cortex will show a
significantly greater degree of connectivity in typically developing control subjects who are viewing social interactions, versus viewing people in non-social situations.

**Hypothesis 2**: Superior temporal sulcus and ventromedial prefrontal cortex will show decreased connectivity in subjects with autism-spectrum disorders who are viewing the same social interactions, versus typically developing controls.

**Methods**

**Participants**

A sample of 112 individuals aged 7-18 (84 male, 28 female) was gathered for this experiment. Of this group, n = 57 had an autism-spectrum disorder and n = 55 were typically developing controls. Participants were recruited via word-of-mouth, referrals from family physicians, and Craigslist.

**Procedure**

After obtaining informed consent and performing a brief pre-trial training procedure (and, in some cases, using a mock MRI machine to acclimate participants), participants viewed several video clips while neuroimaging data was collected in a Siemens Verio 3T scanner using a twelve-channel head coil. Functional images were collected using a T2*-weighted gradient echo-planar image sequence providing full head coverage (TR = 2340ms, TE = 25ms, flip angle = 60 degrees, FOV = 225 x 225, 3.5mm isotropic voxels [no gap], 40 axial slices, oblique axial prescription parallel to AC-PC plane). T1-weighted 2D anatomical images with the same slice prescription as the EPI data (TR = 300ms, TE = 2.46ms, flip angle = 60 degrees), and a T1-weighted 3D anatomical MPRAGE volume (TR = 1500ms, TE = 2.54ms, TI = 900ms, flip angle
= 9 degrees, .8 x .8 x .9mm isotropic voxels) were collected during the same session for standard-space image registration. This experiment was presented as one of a series of unrelated experiments while participants were in the scanner. Simultaneous eyetracking data was gathered for each participant with an Avotec RealEye coil-mounted eyetracking camera system. The videos presented to participants fell in to one of two conditions: the joint play condition and the parallel play condition. In the joint play condition videos, two children were recorded playing together with the same toy. In the parallel play condition, two children were recorded playing with separate toys, and did not interact. The videos featured several different children, of varying gender and ethnicity, and several different toys. Each participant viewed 13 joint play videos of 15 seconds each, and 13 parallel play videos of 15 seconds each (with another minute and a half of ‘rest’ blocks consisting of a black screen with a fixation cross distributed throughout, for a total experiment length of eight minutes). After the videos, participants were given a simple, unanticipated test on which toy had been present in the video in order to ensure that they were paying attention to the stimuli.

FMRI data was analyzed using the Functional Magnetic Resonance Imaging of the Brain Software Library (also known as FMRIBSL, or FSL) software package. First, data was registered to MNI space, and data that registered too poorly for manual correction was discarded. FSL was then used to perform statistical analysis (the details of which will be discussed in our next section) on our data and generate center-of-gravity maps for data reporting. Eyetracking data analysis was performed using SMI’s BeGaze software to define areas of interest (or AOIs) on the stimulus videos. These AOIs were used to mark relevant regions on the videos (faces, toys,
potentially salient background objects, and the background itself). Raw timeseries data
(consisting of the position of each participant’s gaze at each 16-millisecond timestep, along with
any AOIs being viewed at that time) was then exported from the software, and custom-written
Python scripts were used to break this data into 2.3-second volumes (to match fMRI volume
duration), with the percentage of each volume spent on faces, toys, and the background reported.

**Results**

*Analysis*

A series of functional connectivity analyses were performed on eyetracking and neuroimaging
data gathered from our participants. Functional connectivity was determined using a statistical
technique known as Psychophysiological Interaction analysis, or PPI. PPI is an applied general
linear model, originally proposed by Friston et. al. (1997), which attempts to determine
significant co-activation of regions of the brain against a particular task. The fundamental
principle underlying PPI is the idea that “[I]f two areas are interacting, the level of activity in
those areas will correlate over time” (O’Reilly et. al., 2012, page 2). Thus, in a PPI analysis, a
representative time series of activation values is extracted from a single ‘seed’ region of the
brain, averaged, and compared to the averages of the entire rest of the brain across each time
point. In order to control for regions that are co-activated regardless of stimuli (such as low-level
visual areas and higher-level perceptual regions, which can be assumed to co-activate in response
to any visual stimulus), activation is compared across two (or more) conditions. If another region
of the brain shows greater co-activation with the selected seed region in one condition, the two
areas are then said to have a functional connection moderated by the task. Multiple regression
over time is used to control for the possibility that two regions happen to be activating in response to the same stimulus at the same time for unrelated reasons – in other words, to show that the two regions are actually connected. That being said, most researchers are quick to point out that PPI analysis can only demonstrate the existence of a connection; it is impossible to draw conclusions regarding directionality (O’Reilly et. al., 2012).

After removing 51 participants with unusable data (participants who either had irretrievably noisy fMRI data, who answered fewer than four out of six questions on the post-test correctly, or who according to eyetracking data spent >20% of the total stimulus presentation time looking away from the screen), we were left with n = 71 participants (n = 32 ASD, n = 39 TDC; mean age 9.52). To test our hypotheses that typically developing individuals would show STS – vMPFC connectivity in the joint play condition but not the parallel play condition, and that children with autism would not show this connectivity in either condition, we performed two PPI analyses, one for each group using right STS as the seed region. We then performed group-level analysis comparing the data between the two groups. In all cases, joint versus parallel play blocks were used as the condition of analysis. As a post-hoc analysis, we performed a non-PPI group-level multiple regression analysis using our eyetracking data on the same 71 participants, using as a regressor the percentage of each 2.3 second long fMRI volume spent looking at faces to determine group-level differences in activation based on gaze target.

PPI Analyses

We had originally intended to report our data by center of gravity, isolating activated regions and their levels of activation. While we did ultimately report centers of gravity for our group-
level PPI and our post-hoc tests, the within-group data from our typically developing controls showed massive, widespread occipital activation, which made getting any meaningful center-of-gravity data nearly impossible (as our initial analysis revealed that more than a quarter of the brain was being counted as a single cluster with an activation z-score over 11), so we used peak analysis for that data instead. All data in this section should be assumed to be describing center of gravity, unless otherwise stated.

**First Hypothesis:** Our PPI analyses support our first hypothesis, that greater STS-vmPFC connectivity would be seen in typically developing controls watching the joint play condition than the parallel play condition. PPI analysis performed on the TDC group found significantly increased right STS-vmPFC connectivity in the joint play condition versus the parallel play condition (peak z = 5.12, p < 0.0001; see Appendix A for full tables of results).

**Second Hypothesis:** Group-level PPI analysis did not support our second hypothesis, that connectivity between STS and vMPFC would be decreased in the joint play condition in children with autism relative to typically developing controls. We found no statistically significant difference for right STS connection with vMPFC between the two groups for joint versus parallel play conditions (p > 0.005). However, analysis revealed statistically significant differences in connectivity across groups between right STS and other (non-vMPFC) frontal areas, most notably areas of the inferior frontal cortex associated with the mirror neuron system. (z = 3.86, p = 0.0001), although no significant difference was found for connection between the left STS and these frontal areas. The mirror neuron system refers to a system of single neurons which fire in response to both performing an action and observing an action being performed, and it will be
discussed in more detail later in this paper. Additionally, a very large group-level difference was found for connectivity between the right amygdala and right and STS across conditions ($z = 4.07, p < 0.0001$).

*Eyetracking Analyses*

We decided to perform a much simpler analysis with our eyetracking data. Rather than using PPI analysis or examining differences based on both eyetracking and joint/parallel play condition, we decided to simply examine group-level activation differences based on eyetracking data, regardless of condition. Correlating neuroimaging and eyetracking data is almost entirely new ground, so we decided that it would be wise to perform a less ambitious analysis with this data, since if we found negative results it would be difficult to determine if these results reflected actual patterns in the data, or were simply the result of vagaries of a new and untested form of analysis. Our current hope is that in demonstrating the use of this technique in relatively simple analyses, we may lay the groundwork for future studies to use more elaborate eyetracking-based neuroimaging techniques.

In our analysis, we examined group-level differences in activation across the entire brain, using the percentage of each fMRI volume (in other words, each 2.3 second timestep) spent looking at faces as a regressor. This would, in effect, show us which regions of the brain showed different patterns of activation between the two groups when participants were looking at faces. Significant group-level differences were found in a few regions, including, most notably the right amygdala ($z = 2.63, p = 0.0043$). Importantly, we did not find group-level differences in activation for either STS or vmPFC ($p > 0.005$).
Discussion

Hypotheses and Recap of Findings

In this study, we set out to test the theory that deficits in social cognition in autism-spectrum disorders are connected to deficits in perception of social situations. To do so, we proposed the existence of a connection between the superior temporal sulcus and ventro-medial prefrontal cortex in typically developing individuals that would be present during the perception of social situations and absent in the perception of non-social situations. We theorized that such a pattern would occur due to social perception (as recorded by STS activity) leading to theory of mind (as recorded by vmPFC activity). The existence of such STS-vmPFC connectivity made up our first hypothesis.

Our second hypothesis built on our first, stating that this theorized connection would not be seen in individuals with ASD. In other words, we believed that individuals with ASD would show the same reduced level of STS-vmPFC connectivity regardless of the social content of the scene being viewed. If both of our hypotheses were correct, we would successfully demonstrate that social perception plays a role in guiding social cognition in typically developing individuals, and that this network is disrupted in individuals with ASD. Such a finding might suggest broader patterns in what drives symptoms of autism in the brain.

Through PPI analysis, we managed to find that vmPFC-STS connectivity, moderated by condition, existed in typically developing individuals, but that this pattern of activation was not significantly different in individuals with ASD. We also found significant differences between our two groups in connectivity by condition between the STS and the inferior frontal cortex (a
key mirror neuron region), and between the STS and amygdala. Post-hoc eyetracking analysis also revealed that there were significant difference between the two groups in level of amygdala and IFC activation in response to eye gaze on faces, regardless of condition.

**Mirror Neuron Effects**

We will begin our discussion by examining our findings concerning the mirror neuron system. Mirror neurons are one of the most intriguing (and least understood) phenomena in modern neuroscience. In the 1990s, a research group based at the University of Parma reported that certain neurons (which they referred to as ‘mirror neurons’) in the macaque monkey cortex fired both when the monkey performed an action, and when it witnessed another monkey performing the same action (Pellegrino et. al. 1992, Rizzolatti et. al. 1996). These experiments have been replicated many times, and the existence of mirror neurons in monkeys has been demonstrated fairly robustly.

While the inherent difficulty of performing single-neuron studies in the human brain has made research in to mirror neurons in humans difficult, several fMRI studies have found that regions of the brain roughly homologous to regions in the monkey brain known to contain mirror neurons, such as the inferior frontal cortex and regions of the right superior parietal lobule, activate in response to both performing an action and watching another person perform the same action (Iacoboni et. al., 1999). Researchers have suggested that the mirror neuron system may be implicated in a wide range of social processes, from understanding another individual’s intentions (Fogassi et. al., 2005) to empathy (Gazzola et. al. 2006, Jabbi et. al. 2007), though these findings have not been without controversy – especially those which claim that mirror
neurons play a role in understanding action intent, which researchers have argued has not ben sufficiently tested in either humans or monkeys (Hickok, 2009).

A recent study in humans with implanted cortical electrodes for seizure control found several specific neurons with mirror properties (Keysers and Gazzola, 2010). Interestingly enough, many of these mirror neurons were located in regions not generally thought of as part of the ‘mirror neuron system’, including the supplementary motor area, amygdala, hippocampus, parahippocampal gyrus, and entorhinal cortex. Keysers and Gazzola argue that this should be taken as evidence that while mirror neurons may cluster in certain areas (the ‘mirror neuron regions’ discussed earlier), they are not limited to such regions, and in fact may be fond throughout the brain.

If mirror neurons do play a role in social cognition relating to understanding and empathizing with the actions of others, it stands to reason that the mirror neuron system may play a role in the social-cognitive deficits seen in autism. Research has shown that a particular EEG-based wave suppression in the mirror neuron system caused when an individual watches another individual move is decreased in participants with autism (Obermann et. al., 2005), and that cortical areas containing mirror neurons are thinner in individuals with autism, with the degree of thinning correlated with the severity of autism symptoms (Hadjikhani et. al., 2006). These findings, however, are extremely controversial (even more so than those concerning mirror neurons and action intent in typically developing individuals), again due to perceived lack of empirical evidence; and the role of mirror neurons in autism is largely still an open question (Dinstein et. al., 2008).
According to our findings, a connection between right STS and inferior frontal cortex (a key mirror neuron region) is seen in individuals without autism while observing joint play, but that connection is decreased in individuals with autism. This finding may suggest that perceptual issues in autism are tied to mirror neuron deficits. More specifically, it suggests that children without autism show less mirror neuron activation than typically developing children when watching a social situation – which we might expect considering the roles that research has suggested mirror neurons play in social cognition. Furthermore (and more interestingly for the theories of perception in autism discussed earlier), these findings suggest that this mirror neuron dysfunction is somehow tied to the right STS – in other words, that issues in perception are linked to mirror neuron deficits in individuals with ASD. This builds on the findings of Villalobos et. al. (2005), who found lessened connectivity between visual cortex (specifically, V1) and IFC in individuals with ASD during a visuomotor task. While these results are promising, further studies in to the connection between mirror neurons and social perception will be necessary to make a strong claim of any connection between the two.

Amygdala Effects

One of the most powerful (and interesting) patterns in our data was also one that was totally distinct from the initial purpose of our study: that of the very strong difference in right STS-amygdala connectivity between our two groups. While the amygdala was not of a priori interest in this experiment, it is generally recognized as belonging to the a network of regions known as the ‘social brain’, along with STS and vmPFC, making it extremely relevant to the current study. The amygdala is a region in the medial temporal lobe of the brain generally thought to play a role
in how humans process memory and emotionally salient stimuli. A large body of research has examined the role that the amygdala plays in social cognition in individuals with autism. This has been researched both on its own – for instance, Ashwin et al. (2007) found that participants with Asperger Syndrome showed decreased amygdala activation in response to images of scared faces – and in a network with other regions of the brain, such as the fusiform face area (Schultz, 2005). Many of these studies are rooted in the theory that due to amygdala dysfunction, individuals with autism do not place the same emotional salience on social stimuli that typically developing individuals do. Various researchers draw differing conclusions from this research. For instance, Schultz (2005) argues that the difficulty individuals with autism have recognizing faces, and the hypoactivation which has been seen in the fusiform face area in such individuals, may occur because amygdala dysfunction in children with autism in response to social stimuli leads them to place less importance on faces during development, which leads to permanent functional changes in the brain. The literature on the role of the amygdala in autism is massive and varied. Many researchers, however, agree that the amygdala is part of the social brain, which is considered key to social functioning in humans. The social brain is generally said to include regions such as the amygdala, the inferior occipital gyrus, the superior temporal gyrus, the orbito-frontal cortex, the anterior cingulate cortex, and – most telling for the current study – the medial prefrontal cortex and superior temporal sulcus (Ashwin et al., 2007).

This idea of the social brain marks an excellent starting point for examining some of the data that we have gathered. As was mentioned in the results section, our PPI analysis found an extremely strong relationship between right STS and the amygdala that differed between
conditions. In other words, the difference between STS-amygdala connectivity between the parallel and joint play conditions in typically developing individuals is much greater than the connectivity difference measured in individuals with an autism-spectrum disorder. This means that some factor in the joint-play condition (most likely the presence of social interaction) caused a change in connectivity between the STS and amygdala in the typically developing participants that did not occur in the parallel play condition, or in either condition for participants with autism. This seems to be a novel finding – while other studies have analyzed the social brain as a whole and found similar results (most notably, Kleinhans et. al., 2008, who found decreased functional connectivity between FFA and STS and FFA and amygdala during face processing in individuals with ASD), we believe that we are the first to show a difference in STS-amygdala connectivity between social and non-social stimuli in typically developing participants versus participants with ASD.

Our Unsupported Hypothesis: Potential Causes and Explanations

Returning to our initial hypotheses, these findings give rise to several significant questions. Firstly, as we have shown, our data appears to support our first hypothesis: that typically developing individuals would show increased STS-vmPFC connectivity in the joint play condition versus the parallel play condition. However, our data clearly did not support our second hypothesis – that we would find reduced STS-vmPFC connectivity in children with autism-spectrum disorders when watching children play together – for either right or left STS. Instead, both groups seem to show a similar pattern of activation differences between the two conditions. While there are several possible explanations for this, most explanations fall in to one
of two categories. The first is that the idea behind our hypothesis – that the connection between the STS and vmPFC is a vital part of social cognition that is not present in children with autism – was simply incorrect. The second is that our underlying idea was correct, but this particular experiment was not able, for whatever reason, to confirm a hypothesis based on it. Several factors suggest that the latter may be the case. Firstly, we may have simply performed too ambitious an analysis: it is possible that children with ASD do show decreased STS-vmPFC connectivity, but that these effects occur regardless of the stimuli being witnessed. If this were true, PPI analysis would not be able to detect this effect, as it can only determine if co-activation is mediated by a particular condition. We might be able to examine if this occurs by comparing data from both the joint and parallel play condition to ata gathered during rest blocks, during which no stimuli are being presented. Unfortunately, our experimental protocol did not contain enough rest periods to be able to effectively make such a comparison. We might need to instead look at zero-order comparisons between children with and without autism-spectrum disorders – looking at activation between groups only within joint or parallel play, rather than at the comparison between the two. Based on a brief literature review, no other researchers appear to have examined this, making it a potentially valuable analysis to perform on this data set in the future. Alternatively, the effects that we are looking for may be very small, and PPI analysis may simply not be powerful enough to detect them. The large number of statistical tests involved in PPI tend to greatly limit the statistical power of the technique (O’Reilly et. al., 2012), making it difficult to detect smaller effect sizes. This interpretation is supported by the fact that preliminary findings from other, as-of-yet unpublished experiments using this same data set have found some
level of difference in STS-vmPFC connectivity across groups, using a technique called Independent Components Analysis, or ICA (John Herrington, in conversation).

While it appears likely that our hypothesis was not supported because of the analysis used, rather than any particular flaw in the underlying theory, it is very possible that the idea underlying it was simply incorrect – that the social-perceptual deficits in autism, which we have shown are likely rooted in the superior temporal sulcus, are not directly linked to the social-cognitive deficits and vmPFC dysfunction that were previously discussed. Instead, a broader social-perceptual-based network theory of social cognition in autism might involve regions other than the vmPFC. We selected the vmPFC for our analysis because of the role that the region appears to play in theory of mind, with the idea that perceptual difficulties stemming from the STS might trigger decreased theory of mind in social situations as represented through vmPFC dysfunction (Gallagher et. al., 2000; Saxe et. al., 2009). That being said, this data suggests that areas not related to theory of mind may provide a more effective element of social cognition from which to approach the question of perception in autism. We have already discussed two such areas (the IFC and amygdala), and future research may suggest other areas worth studying.

Post-Hoc Eyetracking Analysis and the Amygdala

This brings us to a discussion of our eyetracking data. Probably the most important finding in this data is the significant group-level difference in amygdala activation during time spent on faces. This essentially means that looking at faces (regardless of the social nature of the situation) is correlated with amygdala activation in typically developing individuals, but not in individuals with autism-spectrum disorders. Even taken on its own, separated from our PPI
This is a fascinating finding. The data itself essentially replicates previous findings concerning the role of the amygdala in individuals with autism – previous studies have suggested that looking at faces triggers different patterns of amygdala activation in individuals with ASD and typically developing individuals. The key advantage that comes with the use of eyetracking data is the ability to tie these effects to when an individual is looking at another face with a level of certainty not possible in other, more traditional studies. This is especially relevant since, as we have discussed earlier, individuals with ASD tend to have issues looking directly at a single stimulus, especially when faces are involved – showing a picture of a face to an individual with ASD is no guarantee that they will actually look at the face.

While the fact that STS activation is not correlated with time spent on faces seems to contradict the possible STS-amygdala network that we have discussed, such a pattern of findings makes sense considering what our eyetracking data analysis is actually measuring. STS activation, as we have discussed, is generally found in response to perception of social stimuli. Our eyetracking data analysis does not differentiate between the parallel and joint stimuli; time spent on the face is the only factor considered. Since faces are present in both the joint and parallel play conditions, the STS would have no reason to be active in half of the conditions even if the participants are looking at the faces of the children in the video. Even if the participants with autism-spectrum disorders show less STS activation in the joint play condition, the presence of data from both conditions would likely make this effect unnoticeable.

Taken together, findings from our PPI and post-hoc analyses paint an intriguing picture of the connection between STS and the amygdala. According to our PPI analysis, STS and the
amygdala show increased connectivity in typically developing individuals in response to witnessing social situations. It is tempting to argue that this finding supports a perceptually-based theory of autism: that the STS activates in response to the social content of a stimulus, and that this activation then triggers the amygdala. This interpretation is supported by the fact that many (though by no means all) models of perception in the brain place the STS further ‘upstream’ in the processing of sensory information than the amygdala, meaning that social information could be expected to ‘pass through’ the STS before reaching the amygdala. We may, then, want to argue that our initial theory holds correct, but for the amygdala instead of the vmPFC – that STS-driven perception of socially relevant stimuli drives amygdala activation in typically developing individuals, but not in those with ASD.

While this theory’s simplicity and directness make it appealing, our eyetracking results make such an interpretation unlikely to be correct. We have found that looking at faces is correlated with amygdala activation in TDCs regardless of social situation. It is possible that the STS activates the amygdala in response to social stimuli, and that some other factor activates the amygdala in response to non-social stimuli, but it seems unlikely that two separate processes would happen to produce the same pattern of activation in the brain for entirely different reasons.

If the STS is not driving the amygdala, however, we must consider the idea that activation may move in the opposite direction. In other words, it may be the case that the amygdala activates in response to seeing faces regardless of the social valence of the situation. If the situation in question holds any particular social valence, the amygdala then drives activation of the STS. The reduced STS-amygdala connection seen in participants with autism occurs because
the amygdala fails to respond to faces, which then leads to a failure to activate STS. This pattern may explain the preponderance of evidence for STS hypoactivation in response to social stimuli in individuals with autism – such findings reflect the failure of the amygdala to activate properly in situations with social valence. This theorized connection does not contradict the STS-centric perceptually-based theories of autism we have discussed. If anything, it fleshes them out by explaining the mechanisms which drive STS-based perception of social valence. In other words, this network explains what happens before social perception occurs – it is still possible that a lack of such social perception is a major driving force in the symptoms of autism.

If this is the case, one question becomes immediately apparent: why would the amygdala activate the STS, if the STS if the further upstream of the two? Research has shown that output from the amygdala may re-enter several regions of the brain further upstream, including the STS (Vuilleumier and Pourtois, 2007). In this case, our data may reflect information passing through the STS to the amygdala, which then ‘reaches back’ if the stimuli in question have social valence and activates the STS. Alternatively, research has shown that certain classes of emotionally-salient stimuli may bypass some areas of the visual cortex, including the STS, to be processed directly by the amygdala. If this is true, it would explain another possible mechanism by which the amygdala might drive activation of the STS retroactively, after the stimulus initially bypasses the visual cortex. However, these findings are controversial – many researchers have presented strong arguments based on physiological data against the claim that any stimuli can bypass the visual cortex (Pessoa and Adolphs, 2010). Unfortunately, it is impossible to draw any conclusions regarding directionality from our current analyses – any discussion of whether the
effect that we have seen involves the amygdala driving STS activation or vice-versa must be purely speculative until further research is performed.

It should be noted that this theory is speculative, and caution should be used in interpreting these results. While the current analysis suggests that both the STS and the amygdala are at work in the differences in processing of social stimuli seen between individuals with autism-spectrum disorders and typically developing controls, and that the activation of the two are very tightly coupled, none of our analysis is sufficient to determine directionality or causality. It is entirely possible that some third, as-of-yet unconsidered region (perhaps elsewhere in the social brain) is driving the activation seen in both areas, or even that social stimuli simply activate both regions at the same time for entirely separate reasons (though the level of significance seen in our PPI analysis makes this possibility unlikely).

It could also be argued that the pattern of amygdala activation in our post-hoc tests rules out any theory of the amygdala triggering the STS. As we have shown, the amygdala is seen to activate to in response to eye gaze on faces regardless of condition, but shows greater connectivity in the joint than the parallel play condition. If the amygdala is activated in both conditions, why would it activate STS in only one of the two? This can be explained by the coarseness of the results from our post-hoc analysis. Our eyetracking analysis pools the variance of our data, making it difficult to discern particular patterns. This is the same effect that we discussed earlier as likely driving the lack of STS activation seen in our post-hoc test – by measuring activation across conditions, we lose the ability to make claims about how the data relates to any particular condition. This analysis only tells us that the amygdala response to faces
in typically developing controls is greater than the amygdala response to faces in participants with autism; it is entirely possible that amygdala activation in the joint play condition in TDCs is greater than amygdala activation in the parallel play condition. Unfortunately, this cannot be determined conclusively at present from the analyses that we have performed.

Conclusion and Directions for Future Research

This experiment had two closely related hypotheses designed to explore perceptual theories of autism. Namely, by operationalizing social perception and social cognition as being tied to the STS and vmPFC, respectively, we hoped to show that there exists a perceptually-driven network driving theory of mind in typically developing individuals, and that this network is disrupted in people with autism. Our data was sufficient to demonstrate the former, but we were not able to conclusively show the latter. This is likely due to one of two factors: either this network exists in individuals with autism as well, or the tests that we have used were not sensitive enough to detect the difference. Unfortunately we cannot currently distinguish between the two, though other research suggests that our hypothesis is correct and our tests were simply insufficient.

While our second hypothesis itself may not have been confirmed, it is still possible that the underlying theory driving it (that deficits in social perception form an integral part of autism) is correct. While vmPFC was the most obvious region to select in order to isolate social cognition by way of theory of mind, there are many regions of the brain which may both show connectivity with STS in social situations (such as the joint play condition used in this study) and be implicated in the social deficits seen in ASD. We have highlighted one such area (the mirror neuron system), but there are several other regions that could be implicated in such a network.
Additionally, it is possible that attempting to explain the deficits seen in autism by drawing a connection between STS and any single region of the brain is too simplistic a view – it may be necessary to explore the effect of the STS on a variety of interrelated regions at once. Ultimately our findings do not disprove perceptual theories of autism; they merely make it clear that we must expand our search for evidence to prove such theories. Future research in this area should focus on other regions of the ‘social brain’ – both those discussed here, such as the amygdala and mirror neuron regions, and those which we have glossed over, such as the anterior cingulate cortex and inferior occipital gyrus. Additionally, future studies should attempt to examine network effects rather than simple one-to-one connectivity. In fact, the data set used for this experiment could, with different analyses, address these questions as well.

One of the more interesting (albeit unexpected) findings of this study is the major group-level differences found in amygdala activation as a function of condition. As we have discussed, these findings suggest that the amygdala and STS work in a network to process social stimuli in typically developing individuals, and that this network is disrupted due to decreased amygdala activation in individuals with autism. We have argued here that it is likely (though by no means proven) that the effect being seen is in fact the amygdala controlling the activation of the STS. While this does fit well with prior research concerning the social brain, this particular finding is novel. Future research in this area should work to determine the directionality of the effect detected here. In doing so, we will be able to learn much more about how, exactly, this network works – and what larger conclusions about the brain it autism we can draw from its existence.

Methodologically speaking, one of the most important contributions made in this paper is our
novel attempt to use eyetracking data as a regressor in the analysis of neuroscience data. We have found that this approach allows researchers to answer questions which are very difficult to explore with other, more traditional methodologies, provides a way to control for some of the most frustrating issues present in fMRI research, and allows for fuller, more nuanced interpretations of the data generated by more traditional neuroimaging analysis techniques – but the use of eyetracking in this experiment was largely preliminary. Even with this data set alone, there are several other analyses we could have performed – for instance, we could have included joint or parallel play condition as another regressor to determine if activation to faces differs across conditions. We also could have performed PPI analysis, with some cutoff for the eyetracking percentages working to differentiate our conditions. Even so, we have managed to show that it is not only possible to get usable data from an analysis combining eyetracking and neuroimaging, but that this data can be used both to support or disprove hypothesis on its own, and to inform and fine-tune the results of other, more traditional analyses – such as the PPI used in this study. We believe that in doing so, we have demonstrated that the use of eyetracking data as a regressor for neuroscientific analysis is both viable and useful, and effectively laid the groundwork for future, more complex research in this area.
Works Cited


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Appendix A: Data Tables

PPI TDC-Only Results (STS as Seed Region)
Regions listed here are those for which TDCs were tested for increased STS-region connectivity in the joint play condition than in the parallel play condition; p < .005 indicates that such a difference was found

<table>
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<tr>
<th>Right STS</th>
<th>Region</th>
<th>Peak</th>
<th>Intensity</th>
<th>P Value</th>
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<tbody>
<tr>
<td>vmPFC</td>
<td>46, 81, 26</td>
<td>5.12</td>
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<td>Amygdala</td>
<td>33, 62, 25</td>
<td>8.74</td>
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<tr>
<td>Inferior Frontal Cortex</td>
<td>18, 79, 38</td>
<td>7.42</td>
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<td>&lt; 0.0001</td>
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</table>

PPI Group-Level Results (STS as Seed Region)
Regions here are those which were tested for a significant difference in single-group PPI results; p < .005 indicates that such a difference was found
### Right STS

<table>
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<th>Region</th>
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<th>P Value</th>
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<tr>
<td>vmPFC</td>
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<td>N/A</td>
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<td>Amygdala</td>
<td>34.9, 59.6, 28.3</td>
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<td>Inferior Frontal Cortex</td>
<td>23.3, 76.8, 38.9</td>
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**Post-Hoc Eyetracking Analysis Results**

Regions listed here are those which were tested for correlation between activation within the region and time spent on faces during eyetracking data; p < .005 indicates significant correlation

### Right

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<th>Intensity</th>
<th>P Value</th>
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