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An Examination of Interhemispheric Transfer and Asymmetry in Autism: Behavioral and Neuroimaging Evidence for Underconnectivity

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by

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Abstract

Though diagnosis of idiopathic autism spectrum disorders (ASD) is primarily based on observations of abnormal social communication and behavior, a neurological basis of this prevalent disorder is widely agreed upon. The underconnectivity hypothesis is one theory that characterizes this physiological abnormality by proposing a failure of integration at both the neural and cognitive levels, a generalization also applied to other cognitive disorders. Here we used an index known as interhemispheric transfer (IHT) to assess connectivity in ASD. Impairments in IHT impede communication between the hemispheres and can potentially lead to a myriad of cognitive and behavioral abnormalities. The goal of the present study was to assess the impact of IHT deficits both in this population and in NT populations to achieve a better understanding of how these deficits can give rise to the symptoms of this disorder, making it distinct from, but still connected to, other disorders of underconnectivity. We also assessed the impact of IHT deficits on cognitive development by examining patterns of asymmetry for hemisphere dominant tasks using both behavioral tasks and neuroimaging techniques. Our results specifically implicate IHT deficits and consequential reduction of functional asymmetry in the behavioral profile of ASD. Collectively, this research supports underconnectivity in this population and provides insight to how deficits in IHT can cause the symptoms specifically associated with this diagnosis. These findings have potential contributions for the standard protocols by improving diagnostic and intervention methods to serve the ASD population more effectively.

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Chapter 1: General Introduction

1.1 Introduction

Complex cognition, coordinated motor activity, and a cohesive experience of the sensory world depend on the integrity of the connections between brain regions. Research has supported reductions in long-range connections in ASD, which could result in the inability to dynamically coordinate activity during complex cognitive tasks (Courchesne, 2004; Frith, 2003; Just, Cherkassky, Keller, &Minshew, 2004). This suggests that the social, communicative, and behavioral abnormalities observed in these individuals may be attributed to ineffective communication between relevant brain regions. However, which networks are affected and how this one general theory can coexist in other diagnostic populations remain unclear. Each aspect of this research aims to test how underconnectivity specifically impacts ASD to provide a better understanding of what underlies the fundamental characteristics that make it a unique disorder.

1.2. Underconnectivity theory

The underconnectivity hypothesis suggests a failure of integration at both the neural and cognitive levels, arising from underfunctioning integrative circuitry (Just, Cherkassky, Keller, Kana, &Minshew, 2007). Higher-order cognition requires recruitment of multiple cortical regions to facilitate the skills necessary for socialization, communication, and a range of adaptive behaviors (Coben& Myers, 2008). Consequently, any disruptions to the connections between cortical regions have the potential to impact these domains that are characteristically abnormal in

ASD. Additionally, coordinated motor activity and a cohesive experience of the sensory world depend on the integrity of long-range connections and will also be jeopardized as a result of diminished connections. Sensory and motor abnormalities are often identified early in life of individuals with ASD, making them potentially useful for early screening (Baranek, 2002). Abnormalities include both oversensitivity and under-sensitivity to sensory input, possibly contributing to the stereotypic and repetitive behaviors that have become some of the hallmark traits in autism (Baranek, Foster, &Berkson, 1997). Motor impairments include a wide range of both fine and gross movements, including eye-hand coordination, speed, imitation, gait, posture, and balance (Dawson & Watling, 2000). Collectively, impairments in cognition, behavior, and sensory and motor processing, as observed in ASD, are potential indications of general underconnectivity.

Functional connectivity is one way to assess the integrity of communication between brain regions based on their correlation of activations levels. ASD groups have demonstrated abnormalities in long-range connectivity in imaging studies (Anderson et al., 2011; Ebisch et al., 2011; Just et al., 2004; Kana, Libero, Hu, Deshpande, &Colborn, 2014), suggesting a general deficit in interregional communication. Functional imaging studies employing cognitive tasks, such as reading and language comprehension (Just et al., 2004), socialization (von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2012), and memory (Luna et al., 2002) have provided support for underconnectivity in ASD in these domains. However, each of these reports only accounts for specific characteristics of the disorder.

Therefore, an investigation of how underconnectivity impacts brain development in ASD to consequently cause multiple abnormalities in cognition and behavior is needed to account for the variation and severity of symptoms observed in this population.

1.3 Support for corpus callosum involvement

Connectivity between the left and right hemispheres of the brain, known as interhemispheric connectivity, has previously been used as an index of long-range connectivity (Hardan, Minshew, &Keshavan, 2000). The corpus callosum is the large bundle of axons that connects the hemispheres and serves as a primary source of connectivity between homologous cortical regions (Hellige, 1993), but there are different theories regarding how the corpus callosum functions. The predominant theory is that it serves an excitatory function by integrating information from each hemisphere, but it has also been proposed to serve an inhibitory function such that each hemisphere can inhibit the other to enable one of them to dominate (Bloom &Hynd, 2005). Research has suggested that the corpus callosum is a complex structure with distinct components that enable it to adapt its function based on processing demands (Hellige, 1993). Thus, although it is primarily excitatory, inhibition can occur, depending on what benefits the task. This dynamic function enables a wide range of cognitive, sensory, and motor tasks.

The corpus callosum is topographically organized, such that fibers connecting cortical areas from each hemisphere are adjacent (Witelson, 1989). The most anterior portion connects prefrontal cortices as well as anterior inferior parietal regions; middle portions connect pre-motor, motor, parietal, and superior temporal cortices; and posterior portions connect inferior temporal and occipital cortices (Bloom &Hynd, 2005). This topographic organization suggests that different regions of the corpus callosum act as designated pathways for domain-specific information, depending on the cortices they connect. As such, cognitive and behavioral abnormalities that are attributed to corpus callosum deficits may depend entirely which specific subregions are impacted.

In addition to reduced functional connectivity, neuroimaging studies have investigated the structure of the corpus callosum in ASD and reported various deficits in its size (Anderson et al., 2011; Vidal et al., 2006, Just et al., 2007, Frazier &Hardan, 2009). Research has shown reductions in both the total volume and subregions (Frazier &Hardan 2009; Coben& Myers, 2008). Additionally, reduced density of white matter has been identified in each general subregion of the structure (Chung, Dalton, Alexander, & Davidson, 2004). Diffusion tensor imaging (DTI) studies have supported smaller volumes, high mean diffusivity, low anisotropy, and increased radial diffusivity in ASD groups (Alexander et al., 2007). However, although these imaging studies all suggest some type of corpus callosum deficit, sample sizes tend to be small and several methods still need to be employed to acquire consistent accounts of how interhemispheric connectivity is impacted by structural differences.

In developing methods to investigate interhemispheric connectivity deficits in ASD, populations defined by corpus callosum abnormalities should be considered as prototypes. These include callosotomy, which is a surgical procedure that severs the corpus callosum to treat epilepsy, and agenesis of the corpus callosum (AgCC), which is a congenital disorder marked by partial or complete absence of the corpus callosum axons. Both of these patient groups reliably exhibit abnormal behavioral patterns that can be attributed to impaired communication between the two hemispheres. In addition, they exhibit distinct differences from NTs when tested in formal experimental paradigms. Thus, one way to assess disconnectivity in ASD is to investigate similarities between this population and these patient groups in the contexts of their behavioral characteristics and how they perform compared to NTs in these experiments.

Callosotomy does not always have a profound impact on the patient's overall personality, but reports of abnormal verbal output suggest that some aspects of discourse are affected (Devinsky&Laff, 2003). Attention span may decrease, causing task completion to be more challenging (Dimond, 1979). In some cases, patients display dramatically altered emotional behaviors in particular situations that would typically provoke strong negative reactions (Hoppe &Bogen, 1977). They may appear unaffected by emotionally traumatic events that would cause anger, hatred, jealousy, embarrassment, or shame for others. Emotional processing is also a signature deficit of ASD, especially regarding emotion identification in others, displaying socially appropriate behavior, and having empathy (Downs & Smith, 2004). Cases of abrupt social and emotional changes in callosotomy patients that resemble those of ASD suggest that disconnection of the hemispheres could impact emotion in both of these conditions.

Children with AgCC also exhibit social behaviors that fit into the diagnostic criteria for ASD (Badaruddin et al., 2007). Both conditions show problems initiating and maintaining conversation, developing relationships with peers, and understanding the reciprocity of social etiquette. Individuals with AgCC have general problems with complex problem solving, which could be related to the problems individuals with ASD have with executive functioning (Corbett, Constantine, Hendren, Rocke, &Ozonoff, 2009). Similar patterns of aberrant emotional and social processing appear across AgCC and ASD. For example, the Thematic Apperception Test (TAT) evaluates processing of social information, attitudes, observational capacity, and emotional response. Participants tell stories about what cards portray about people in a variety of settings and situations. Linguistic inquiry and word count showed that individuals with AgCC used less words pertaining to emotion, cognitive processes, and social processes (Turk, Brown, Symington, & Paul, 2010). Based on their narratives of the TAT pictures, they showed deficiencies in imagining and inferring the mental, emotional, and social functioning of others. They also show a decreased appreciation of the subtleties of social interactions and deficits in comprehension of jokes and stories (Brown, Paul, Symington, & Dietrich, 2005). On cartoon and narrative joke tests, adults with AgCC performed significantly worse than controls on the narrative joke test. This lack of humor comprehension is consistent with previously discovered problems in individuals with ASD, who demonstrate impaired understanding and appreciation of humor (Lyons & Fitzgerald, 2004). Compromised attention shifting is also characteristic of AgCC, supported by visuospatial tasks that require the shifting of attention between visual fields (Reuter-Lorenz &Fendrich, 1990). When AgCC participants were cued to attend to one of two potential target locations in either visual field, they demonstrated significantly greater difficulty shifting attention to invalidly cued target stimuli occurring in the opposite visual field (Hines, Paul, & Brown, 2002). This suggests that an intact corpus callosum is necessary for reorienting attention between visual fields, and deficits in this structure will impact visual attention. Attention problems are also consistently found in ASD. Specifically, some individuals with autism cannot accurately or rapidly shift their attention to different sensory modalities (Courchesne et al., 1994). The inability to shift attention efficiently can lead to further difficulties, including coordinating and distributing attentional resources. Because we know that AgCC is a congenital disorder classified by a diminished corpus callosum, we can compare its behavioral characteristics with ASD to better understand how impaired interhemispheric connectivity could impact ASD during the developmental years in which it is usually diagnosed.

Behavioral paradigms can assess the integrity of communication between the hemispheres, known as IHT. These are designed to reveal measurable effects of hemispheric disconnectivity, such that both callosotomy and AgCC populations exhibit distinct patterns of results. Specifically, they execute motor responses faster to bilateral stimuli compared to slower responses for unilateral stimuli- a phenomenon that is commonly referred to as redundancy gain and reflects greater response time cost for unilateral stimuli (Roser&Corballis, 2002). In contrast, neurotypical (NT) controls only show a very small or absent unilateral cost. Using the same paradigm, another informative measure of IHT can be obtained, known as the crossed-uncrossed difference (CUD). The CUD represents the response time difference for unilateral crossed and uncrossed stimuli. Crossed stimuli appear in the visual field contralateral to the hand that is being used for response, and therefore rely more on IHT to activate the response hand. Uncrossed stimuli appear in the visual field ipsilateral to the response hand, and therefore provide direct input to the hemisphere that needs to activate the response hand. Patient populations exhibit prolonged CUDs compared to NT groups (Roser&Corballis, 2002), reflecting IHT deficits. The prolonged unilateral response times and CUD in patient groups are classified as performance detriments because they reflect less efficient processing of information. However, IHT deficits can facilitate superior performance on different experimental tasks. For example, when isolation between the hemispheres prevents general processing overload, IHT deficits help performance by keeping two sets of conflicting information confined within their respective hemispheres. A perceptual load paradigm tests this by presenting two patterns of stimuli individually to each visual field (Holtzman&Gazzaniga, 1985). If the patterns are the same, and therefore redundant, NTs only have to process one overall pattern. However, if they are different, they must process two patterns, and they must be able to distinguish them from each other. This is considered an increase in the perceptual load, and performance deficits occur in NTs when they are asked to recognize one of the patterns. In contrast, patient populations with impaired IHT do not struggle, presumably because the patterns from each visual field are being processed separately and simultaneously, as each is isolated within the contralateral hemisphere.

Understanding how the diminished integrity of the corpus callosum, and therefore IHT, can affect everyday behavior and cognition, as well as performance in experimental paradigms, can help clarify the importance of IHT in basic tasks. A thorough exploration of how IHT is impacted in ASD should take into consideration how individuals in this group may be similar to these patient groups, both in everyday behavior and in experimental tasks. By identifying these similarities, more meaningful inferences can be made about how the core deficits in ASD arise from underconnectivity.

1.4 Impact on asymmetry

While IHT is an assessment of how well the hemispheres share information, the degree of asymmetrical activation for hemisphere dominant tasks may reflect the hemispheres' abilities to suppress one another to allow one to dominate. Since ASD is a developmental disorder present early in life, IHT deficits could impact the pattern of asymmetry that is typically established during brain development (Bloom &Hynd, 2005). Less asymmetry, represented by more bilateral activation for relevant tasks, may be a confirmation, as well as an indication, of one of the consequences of these deficits. Thus, tasks that are either left or right hemisphere dominant in NT's should be examined and compared between ASD and NT groups.

Facial processing is a prime task for investigation, as it is typically lateralized in the brain, and individuals with ASD are known to have deficits in this domain (Teunisse& de Gelder, 2001). For survival and social functions, NT's automatically discriminate, recognize, and identify faces. They can infer contextual information from facial expression, but studies in ASD have shown that abnormalities in this domain emerge early in development (Dawson et al., 2002). These deficits appear in a range of behavioral studies from gender discrimination, recognition (Behrmannet al., 2006), emotion identification (Humphreys, Minshew, Leonard, &Behrmann, 2007), and memory for faces (Hauck, Fein, Maltby, Waterhouse, & Feinstein, 1998). Functional imaging has supported normal early visual processing in ASD (Hadjikhani et al., 2004a), suggesting that their facial processing deficits must arise from problems with higher level cognitive functioning, rather than the visual pathway.

Although facial processing deficits are not explicitly listed in the diagnostic criteria for ASD, any problems in this domain inherently affect social interaction. Research investigating the visual scanpaths in faces has shown that individuals with ASD spend significantly less time on core facial features, such as the eyes and mouth, than NTs, and significantly more time on non-feature areas (Pelphrey et al., 2002). This may contribute to the deficits they show in recognizing and understanding the emotional states of others, as the shape of the eyes and mouth are key in distinguishing emotions. Additionally, emotional processing is requisite for such typical instincts as empathy and theory of mind, the ability to attribute mental states to others, both of which are abnormal in ASD (Baron-Cohen, Tager-Flusberg, & Cohen, 1994; Schulte-Rüther et al., 2011). Specific findings on recognition of basic emotion in ASD are mixed, some suggesting difficulties (Humphreys et al., 2007) and some that do not (Adolphs, Sears, &Piven, 2001). If emotion recognition differences exist between individuals with ASD and NT's, whether deficits occur for some or all emotions remains unclear. For example, different studies have reported deficits in disgust and fear (Humphreys et al., 2007) but not other emotions, while others have specifically reported deficits in recognizing surprise (Baron-Cohen, Spitz, & Cross, 1993). These behavioral findings of facial processing deficits and the imaging studies attempting to localize the deficits need to be considered together in a context that attributes the physiological abnormalities to the characteristics affected.

Facial processing is often regarded as a right hemisphere-lateralized task, such that certain regions in the right hemisphere become more active than homotopic regions in the left hemisphere (Rossion et al. 2003). However, research suggests that this right hemisphere dominance for faces may be specific to the particular stimuli and tasks. For example, NTs show stronger right hemisphere lateralization for familiar faces compared to novel faces (Gainotti, 2013). Additionally, right hemisphere dominance is associated with processing faces holistically, but left hemisphere dominance when faces are processed by their features (Rossion et al., 2000). Regardless of whether left or right hemisphere dominance occurs for a facial processing task, these patterns suggest that asymmetrical activation is typical when viewing and processing faces.

The fusiform face area (FFA), a region in the fusiform gyrus identified as being specialized for faces and more active in the right hemisphere, has been investigated in ASD to determine whether this specific structure can be implicated in facial processing deficits. Results have been mixed, with research showing that individuals with ASD have weaker activation in the FFA when viewing faces (Grelotti et al., 2005), but other research showing normal overall fusiform gyrus activation (Hadjikhani et al, 2004b) and normal right FFA asymmetry for faces (Pierce, Haist, Sedaghat, &Courchesne, 2004). Underconnectivity between the right FFA and left amygdala has been identified in ASD (Kleinhans et al., 2008), suggesting that the FFA itself cannot explain abnormal facial processing in ASD. This could explain the variance in previous studies that focus solely on this structure if connections within the broader network that includes, but is not limited to, the FFA are impaired.

Studies have shown thinning of the corpus callosum in subdivisions connecting regions that may include the FFA (Hughes, 2007), which could attribute facial processing deficits to differences in asymmetry or IHT. In addition to the FFA, research suggests that the occipital face area (OFA), in the inferior occipital cortex, also shows right lateralized activation in NTs during face processing (Rossion, Schiltz, &Crommelinck, 2003). Although the OFA has not yet been specifically investigated in ASD, the splenium of the corpus callosum, which connects the left and right occipital lobes, is thinner (Vidal et al., 2006). Connectivity abnormalities between facial processing regions and other structures during facial identification de-emphasize the role of a specific structure and attribute facial processing deficits in ASD to more complex networking in the brain (Kleinhans et al., 2008) .

It is not clear if processing deficits in ASD also occur with different types of faces. For example, research has shown that children with ASD interact more with robots than people in the clinical setting (Scassellati, Admondi, &Mataric, 2012). They also show increased directed speech to robots compared to adults (Kim et al., 2013). One possibility is that individuals with ASD process robot faces like objects, rather than relatively equal to human faces. Research has suggested that their object processing is typical compared to NTs, or even superior (Ozonoff et al., 2008; Swettenham et al., 1998). For example, the N290, an event related potential (ERP) component that has shown face sensitivity, has faster responses to faces than objects in NTs, but faster responses to objects than faces in individuals with ASD (Webb, Dawson, Bernier, &Panagiotides, 2006). Additionally, research has shown that individuals with ASD do not show ERP differences between familiar versus unfamiliar faces, but they show ERP differences between familiar versus unfamiliar objects, whereas NT children showed differentiation for both sets of stimuli (Dawson et al., 2002). NTs tend to process different types of faces similarly, such as cartoon faces (Kanwisher&Yovel, 2006), and thus we assume that they would treat human and robot faces relatively equally. However, individuals with ASD may treat these differently, by processing robots as though they are objects. Comparing lateralization patterns during facial processing for human versus robot faces in both groups may help explain this difference. Asymmetrical processing for non-human stimuli may have developed in ASD in regions where IHT is intact. If there is support for different degrees of asymmetry for each of these types of faces in ASD, this suggests that these individuals are treating them as different stimuli. This information can help explain the success of robot use over humans in the clinical setting (Diehl, Schmitt, Villano, & Crowell, 2012).

Investigating asymmetry patterns can provide further insight to how IHT deficits impact this population. If asymmetry for faces occurs in individuals with ASD the same way it does for NTs, we can exploit this by investigating accuracy and response time differences for tasks that require IHT from the dominant to the non-dominant hemisphere. For example, if there is a dominant hemisphere for facial processing, information about stimuli initially projected to the non-dominant hemisphere needs to be shared by way of IHT. In this case, any deficit in IHT may cause discrepancies in both the timing and accuracy of processing faces projected to the visual field ipsilateral to the dominant hemisphere. If IHT deficits occur in ASD, these individuals should perform significantly worse at facial processing tasks when stimuli are presented in the ipsilateral visual field, relative to the contralateral visual field, whereas NT's should perform about the same regardless of visual field presentation, due to intact IHT.

In this research, we are testing the alternative hypothesis that hemisphere dominant tasks are instead less lateralized in developmental disorders involving IHT deficits. The theory that supports this asserts that the development of hemispheric asymmetry is dependent upon an intact corpus callosum (Hellige, 1993). In typical development, the structure's inhibitory properties enable each side to become specialized for different tasks (Cook, 1984; Kinsbourne, 1975). This maximizes efficiency by allowing one hemisphere to inhibit the other so it can be dominant for a certain function, preventing redundant processing in each hemisphere (Hellige, 1993). An IHT deficit present early on could have impacted inhibitory connections and prevented these asymmetries from developing. In this case, both hemispheres may process tasks, which would typically be hemisphere dominant, relatively equally. As such, performance on these tasks may suffer; neither hemisphere is optimally processing information, and there is reduced collaboration of the information from each hemisphere. Because anatomical studies have shown thinning of the corpus callosum in subregions that connect face areas (Hughes, 2007), this could explain some of the cognitive deficiencies observed in ASD in domains that are typically lateralized. Specifically, more bilateral activation may occur, rather than the typical right hemisphere asymmetry for holistic processing and viewing novel faces, as well as for the reversed patterns of left hemisphere asymmetry for feature based facial processing. Since the asymmetry observed in NTs is facilitating optimal performance, regardless of whether the specific task and facial stimuli elicit left or right hemisphere lateralization, decreased asymmetry in ASD can potentially cause deficits in multiple aspects of facial processing.

Language skills, such as reading, are also known for eliciting asymmetrical activation, particularly in the left hemisphere. Research in individuals with AgCC supports reduced asymmetry for language, suggesting that this may have arisen from the inefficient transfer of information between hemispheres from birth (Riecker et al., 2007). In accordance with this finding, language lateralization has been found to correlate with corpus callosum size (Josse, Seghier, Kherif, & Price, 2008). This effect was even observed in an NT population- individuals with larger corpus callosum sizes had greater left asymmetry for language. This suggests that, regardless of whether a diagnosis is present or not, the integrity of IHT can ultimately impact asymmetry for lateralized cognitive functions, such as language.

If asymmetry for language is impacted, IHT deficits in any congenital and developmental disorder should also affect asymmetry for facial processing. Support for this comes from data suggesting that hemispheric specialization for words and faces do not develop independently. Word processing shows hemispheric lateralization earlier in development than facial processing, and asymmetry for faces is correlated with reading comprehension (Dundas, Plaut, &Behrmann, 2013). This suggests that the mechanisms that drive lateralization for language may also drive lateralization for faces. As such, if certain syndromes lead to abnormal asymmetry for language, they should also be accompanied by abnormal asymmetry for faces.

Studies have used different methods for assessing asymmetry in ASD. Early ERP data has shown less left hemisphere lateralization for speech stimuli in an ASD group (Dawson, Finley, Phillips, &Galpert, 1986). The evaluation of hand dominance is a standard clinical method for inferring cerebral laterality, such that individuals with stronger right hand dominance have more typical laterality (Bryson, 1990). Under this premise, individuals with ASD may have abnormal patterns of laterality, based on observation of decreased proportion of right hand dominance, and an even greater decrease for individuals with ASD who have disordered early language development (Escalante-Mead, Minshew, & Sweeney, 2003). Imaging data further supports this by showing differential patterns of asymmetry in ASD during a category and letter fluency task compared to NTs, who showed leftward asymmetry (Kleinhans, Müller, Cohen, &Courchesne, 2008). These abnormalities appear to be present in different age groups; at-risk toddlers between 12-48 months have not shown the left temporal specialization for language that NTs in the same age range do, and this difference becomes more severe over time, being the most severe in 3- and 4-year olds (Eyler, Pierce, &Courchesne, 2012). However, research on the connection between reduced asymmetry and IHT deficits has not thoroughly been investigated in facial processing. Thus, one aspect we examine here is whether ASD is a disorder of IHT that is coupled with reduced lateralization for facial processing tasks.

1.5 Common symptomology in disorders of underconnectivity

Finding support for IHT deficits in ASD still leaves unacknowledged the question of how the underconnectivity theory has been applied to other distinct populations. Impaired IHT has also been implicated in dyslexia (Fine, Semrud-Clikeman, Keith, Stapleton, &Hynd, 2007), attention deficit hyperactivity disorder (ADHD) (Moore, Brown, Markee, &Theberge, 1995), and specific language impairment (SLI) (Klimkeit, Sheppard, Lee, & Bradshaw, 2004). Like ASD, each of these disorders is also marked by common cognitive and behavioral impairments among their portraits of symptoms. In particular, a language task like reading, which requires coordination between cortical regions in both hemispheres, is consistently impacted in each of these disorders (August &Garfinkel, 1990; Bishop &Snowling, 2004; Frith&Snowling, 1983). Because each of these disorders is diagnosed behaviorally, a better approach for understanding them may be to investigate underconnectivity based on its relationship to symptomology, rather than to each individual diagnosis.

Different assessments of IHT have suggested that each of these disorders may be linked to ASD based on the common basis of underconnectivity. Dyslexia is a disability that specifically impairs a person’s ability to read, despite relatively intact intelligence and sensory abilities. In addition to studies that have supported these structural abnormalities in ASD (Chung et al., 2004; Vidal et al. 2006), studies have also found anatomical differences in the corpus callosum in dyslexia, suggesting a positive correlation between reading skill and total area of the structure (Fine et al., 2007). Behavioral performance on the Bimanual Coordination

Task, which requires both hemispheres to provide constant feedback to each other, was worse for dyslexic subjects, and they had more difficulty producing angles that required both hands working together (Moore et al., 1995). These results are comparable to those found when individuals with AgCC were tested on a similar task (Mueller, Marion, Paul, & Brown, 2009). In a lexical decision task, participants with dyslexia benefited from lateralized presentation of words to either visual field, while normal readers only benefited from right visual field presentation (Shaul, 2012). This may be due to a lack of efficient and coordinated IHT. Like in ASD, the corpus callosum in ADHD has been found to be significantly thinner in the anterior and posterior callosal sections (Luders et al., 2009). Behavioral evidence supports this finding by showing that bimanual coordination is also compromised for people with ADHD: they perform significantly worse than controls at tasks that require symmetrical hand movements (Klimkeit et al., 2004). SLI is a broad term for linguistic disorders that occur in the absence of neurological damage, hearing deficits, mental retardation, or environmental deprivation (Bishop, 1992). In this disorder, the corpus callosum has been examined, and a significantly smaller splenium was found, compared to the rest of the body, affecting IHT in the temporal cortex (Herbert et al., 2005). Behavioral studies measuring motor coordination in subjects with SLI support callosal involvement. Participants with SLI performed significantly worse responding with their hands to crossed stimuli than uncrossed stimuli, compared to control subjects, who performed well on both types of tasks (Fabbro, Libera, &Tavano, 2002). Anatomical and behavioral indices of IHT complement each other to support interhemispheric connectivity deficits in all of these disorders, but this evidence requires an examination of how a common physiological basis can give rise to discriminating sets of symptoms.

Brain networks for reading are developed through learning efforts over childhood and adolescence, but they also require properly functioning physiology. Despite training efforts, deficits in the coordination of relevant brain regions can lead to reading impairments. Disruptions to interhemispheric connectivity can lead to problems with complex cognitive tasks, including reading. For example, a callosotomy patient struggled with sustained reading after surgery (Gazzaniga, Bogen, & Sperry, 1965). He also had problems reading words in the left visual field, and often omitted shorter words. Additionally, two children with callosal agenesis both exhibited reading impairments similar to phonological dyslexia (Temple et al., 1990). The integrity of the posterior third of the corpus callosum is important for IHT between regions involved in reading tasks, such as the visual word form area (VWFA); this is potentially complementary to the posterior regions involved in facial processing, such as the FFA and OFA (Dundas et al., 2013). Thus, the impact that posterior IHT deficits have on language skills could be impacted both by deficits in online, interhemispheric integration and, additionally, reduced asymmetry, as previously suggested in the context of facial processing impairments.

ASD is characteristically marked by impaired language skills, and this population often exhibits specific problems with reading comprehension, despite relatively intact phonological processing (Frith & Snowling, 1983; Nation, Clarke, Wright, & Williams, 2006). This suggests a deficit with semantically connecting words and phrases into a cohesive, relevant story. Similar deficits are also observed in other disorders. Individuals with dyslexia often show significant impairments in reading comprehension, writing, spelling, and rapid naming of digits, compared to individuals without dyslexia (Warmington, Stothard, & Snowling, 2013). Typical reading development is often reflected by activation across frontal and temporal regions, but disruptions in this activity may vary in dyslexia depending on the task, language, type, and severity (Shaywitz et al., 2002). Although ADHD is characterized by a short attention span and trouble concentrating, greater than a chance proportion of people who have this diagnosis also have a coexisting reading disability (August & Garfinkel, 1990). These individuals often show reading impairments with control and phonological functions (Willcutt et al., 2001), as well as rapid naming (Tannock, Martinussen, & Frijters, 2000). SLI includes problems with both language comprehension and production that can consequently impact reading abilities. Specifically, this disorder has been associated with orthographic spelling errors, word omission, and grammatical morphology omission (Mackie, Dockrell, & Lindsay, 2013), as well as problems with reading comprehension (Tallal, Allard, Miller, & Curtiss, 1997), suggesting that this disorder is not limited to deficits in understanding and producing spoken language, but also with problems decoding and producing print. While each of these disorders presents a variety of characteristics that make them distinct from ASD, they share in common some form of impairment in this particular language domain.

Although these disorders are fundamentally different, anatomical, functional, and behavioral support for IHT deficits has been reported in each of them. They also have some overlapping symptomology, particularly in reading impairments. Directly investigating the relationship between IHT and common symptomology can help explain how one theory can be applied to so many cases and provide insight to how IHT deficits specifically impact ASD.

1.6 Is ASD a distinct disorder of interhemisphericunderconnectivity?

Deficits in long-range connections can cause cognitive and behavioral abnormalities, like those characteristic of ASD. Specifically, impaired IHT can impact the quality of information integration and consequently alter the development of efficient, lateralized brain networks. These should lead to observable cognitive and behavioral abnormalities in domains that reflect the extent and location of these deficits in IHT.

By examining the consequences of impaired IHT with behavioral and neuroimaging measures, we aim to provide perspective on how ASD may be considered a distinct disconnection syndrome. Achieving a better understanding of how IHT deficits impact ASD and other populations can help educators and clinicians utilize more accurate screening methods based on IHT performance and not solely on observable behavior. This will help promote intervention approaches that stimulate integration to more effectively improve symptoms in ASD and other populations.

1.7 Study aims

This dissertation describes a series of experiments designed to enhance the current support for the theory of underconnectivity by assessing the impact of IHT deficits in ASD. The two main variables we assessed were IHT and asymmetry. We measured IHT in ASD and in relation to relevant symptomology, and we also assessed how patterns of asymmetry may be impacted by IHT deficits in this population. The subsequent chapters each describe specific experiments that we conducted to answer these questions. First, can we demonstrate IHT deficits in ASD through behavioral paradigms? We hypothesized that they would perform comparably to populations with known corpus callosum impairments on tasks of unilateral cost and increased perceptual load. Second, do individuals with ASD exhibit less asymmetry through behavioral performance on facial processing tasks? We hypothesized that comparing the accuracy of judgments between left- and right-lateralized facial stimuli would show asymmetry differences between an ASD and NT group. Third, are asymmetry differences for facial processing observed in neuroimaging measures? We wanted to compare between groups the differences between cerebral oxygenation changes in both hemispheres during a facial recognition task as an objective method for testing our behavioral measures. Finally, can we relate IHT deficits to specific cognitive impairments rather than specific diagnoses? We tested whether performance in reading, a language skill impacted in several of these disorders of connectivity, could predict performance on an IHT task. If IHT helps facilitate reading, results should give us a better understanding of how ASD can share the same underlying theory as other disorders, based on commonly affected skills. Each of these experiments was aimed at determining the impact of IHT deficits in ASD to better understand the mechanisms that make it similar to other populations, while meriting recognition as a unique disorder.

Chapter 2: Interhemispheric Transfer in ASD

2.1 Introduction

The behavioral effects of underconnectivity between cortical regions have been studied extensively in callosotomy patients and, to a lesser degree, patients with AgCC. In these groups, atypical patterns of behavior on various types of lateralized cognitive tasks are attributable to the loss or reduction of fibers within the corpus callosum (Bloom & Hynd, 2005). Studies of the corpus callosum in ASD have reported size reduction (Vidal et al., 2006; Just et al., 2007; Frazier & Hardan, 2009), decreased white matter concentration (Chung et al., 2004), and high mean diffusivity, low anisotropy, and increased radial diffusivity (Alexander et al., 2007). These reports all support differences in the corpus callosum, but performance on the lateralized behavioral tasks established in patient populations can also be tested in ASD to complement the anatomical evidence.

Compared to individuals with ASD, patient populations defined by diminished interhemispheric connectivity demonstrate similar behavioral abnormalities (Badaruddin et al., 2007; Devinsky & Laff, 2003). In behavioral paradigms, patient groups show enhanced CUD and unilateral response time cost (Roser & Corballis, 2003). Callosotomy patients also show resistance to increased perceptual load when conflicting stimuli are presented simultaneously to each visual field (Holtzman & Gazzaniga, 1985). These populations have demonstrated distinct patterns of results in these tasks, but these patterns need to be compared to those of an ASD group to show that the anatomical evidence for corpus callosum abnormalities translates in behavioral tasks.

As the efficiency of IHT has not been studied behaviorally in the specific case of ASD, this first experiment implements two different behavioral measures to assess IHT in ASD. Experiment 1 tested unilateral cost and CUD with a stimulus-response task. We predicted significantly enhanced CUD and unilateral cost due to delayed information transfer across hemispheres. Experiment 2 tested the effects of increased perceptual loads on both response accuracy and response time in ASD participants. We predicted that performance of the ASD participants, similar to callosotomy patients, would not be as impaired as NT participants with increased perceptual load. Both experiments utilized paradigms already known to elicit distinct results in these patient populations in order to obtain indices of interhemispheric connectivity in ASD.

2.2 Experiment 1: Unilateral cost

Experiment 1 required manual responses upon presentation of bilateral and unilateral colored squares. We assessed the CUDs and unilateral costs in a group of boys with ASD and a group of NT boys. Less efficient callosal transfer should be reflected by prolonged CUDs and enhanced unilateral cost. Thus, we predicted that response time differences for crossed and uncrossed stimuli would differ significantly for the ASD group, with longer times for crossed stimuli, while these response times would be comparable for the NT group. We also expected that the ASD group would have larger discrepancies between response times for bilateral and unilateral stimuli compared to the NT group, such that their responses for bilateral stimuli would be faster.

2.2.1 Methods

2.2.1.1 Participants

Participants in this study were 12 boys with a diagnosis of ASD and 13 typically developing boys. All participants were between the ages of 6-17, and all testing and consent procedures were approved by the internal review board at the University of Nevada, Reno. Participants were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (The Psychological Corporation, 1999) to determine full-scale, verbal, and performance IQ, and the Edinburgh Inventory (Oldfield, 1971) to determine a laterality quotient (LQ) for handedness. Each of the participants with ASD had been previously diagnosed by a licensed clinical psychologist or medical doctor not associated with this research, and they each had prior assessment using the Autism Diagnostic Observation Schedule (ADOS). For this research, the symptom severity of each individual in the ASD group was assessed using the Gilliam Autism Rating Scale 2 (GARS-2) (Gilliam, 2006). Parents and guardians filled out information for both the Edinburgh Inventory and the GARS-2. They indicated the boys' hand preferences for 10 different everyday activities and provided current ratings of how often they observed specific behaviors in their child in the categories of stereotyped behaviors, communication, and social interaction.

There were no significant differences between groups in these measures, except for the full-scale IQ measure. However, verbal and performance IQ, the components that determine full-scale IQ, were not significantly different between the groups. No participant had a history of a medical disorder known to cause characteristics associated with ASD. NT participants had no current or past diagnosis of ASD or other psychiatric or neurological disorder. Parents and guardians signed written consent forms, and all participants provided verbal and nonverbal assent prior to and throughout the testing.

2.2.1.2 Procedure

Participants sat 57 cm away from a 13.5 inch LCD laptop monitor. Stimuli were presented on the monitor, and participants made all responses on the keyboard. The order in which participants did the experiments, as well as the order in which they used their response hands, were counterbalanced.

Participants were instructed to make a manual key press in response to visual stimuli. A center fixation point remained in the center of the screen throughout the duration of each block of trials. Stimuli were small red- or green-filled squares that subtended a visual angle of .64°. They were presented on a black background and flashed to symmetric positions on the right visual field, left visual field, or both sides, 9.55° from center fixation. Participants were instructed to press the spacebar key as soon as they saw the stimuli.

The experiment consisted of two blocks of 40 trials. Participants alternated response hands in between blocks. Stimuli were either unilateral (presented to the left or right side of fixation) or bilateral (presented simultaneously to both the left and right sides of fixation). There were eight possible display types: four unilateral displays (Green Left, Green Right, Red Left, Red Right) and four bilateral displays (Green + Red, Red + Green, Green + Green, Red + Red). Each block of 40 trials consisted of 8 randomly generated presentations of each display type. Participants could practice up to 10 trials, if needed, prior to beginning the experiment.

Participants initiated the beginning of the experiment by pressing the spacebar key with the hand they were using for that block of trials. The fixation point then appeared and remained on the monitor until the end of the block. Stimuli appeared after a randomly generated time between 500 and 5000 ms and remained on the screen until participants responded by pressing the spacebar, or until 5000 ms elapsed. Response times were recorded from stimulus onset to key press. If the participant did not make a response after 5000 ms, the session timed out and moved to the next trial in the block.

2.2.2 Analysis

Mean response times (ms) were calculated for each participant. Trials for which the response times reached 5000 ms were treated as unattended trials, and were not included in the data analysis. Initially, a marginal means model was constructed to assess the impact of diagnosis (ASD and NT groups), condition type (bilateral or unilateral), and response hand (left or right). Within the bilateral conditions, color (single color presented twice or two different colors presented) was a nested factor, and within the unilateral conditions, cross type (stimulus crossed or uncrossed from the response hand) was a nested factor. All data from the individual participants were treated as repeated measures and compound symmetry was assumed. Variables that were not significant were removed from the model, and the final model included diagnosis and condition. The participants' variables of age, IQ, and LQ were later included as covariates to assess their impact, if any, on the overall findings.

2.2.3 Results

Overall, ASD participants had longer average response times (M = 1025.88, SE = 145.98) than NT participants (M = 510.69, SE = 140.25; $F(1, 23) = 6.48$, p = .018) and, as expected, response times to the crossed trials (M = 812.06, SE = 120.99) were longer than those for the uncrossed trials across both participant groups (M = 703.89, SE = 105.49; $F(1, 23) = 12.01$, p = .002). Relative to the NT participants, ASD participants showed longer response time costs on the crossed trials compared to the uncrossed trials (CUD; $F(1, 23) = 6.40$, p = .019) (Figure 1). Thus, as predicted, ASD participants showed longer CUDs (M = 252.35) relative to the NT participants (M = 33.45), suggesting a deficit in IHT during a simple response time task. Finally, the severity of symptomology, as assessed by the GARS-2 did not predict the magnitude of the CUD for the ASD participants ($r(10) = .186$, p = .563).

To assess the level of unilateral cost, diagnosis, condition type (bilateral versus unilateral), bilateral color, unilateral color and response hand were all considered as predictors of response time in a marginal means model of the individual trials. Response hand, bilateral color, and unilateral color were not significant as main effects or in combination with any of the other variables. These three factors were removed from the model, leaving the factors of diagnosis and condition.

There were significant main effects of both diagnosis ($F(1, 23) = 7.48$, $p = .012$) and condition (bilateral versus unilateral; $F(1, 1973.1) = 17.13$, $p < .001$), as well as an interaction between diagnosis and condition ($F(1, 1973.1) = 7.84$, $p = .005$). The ASD group had faster reaction times for bilateral stimuli than unilateral stimuli compared to the NT group, whose reaction times did not differ as greatly across conditions (Figure 2).

As expected, older subjects responded more slowly to both bilateral ($r(23) = -.517$, $p = .008$) and unilateral ($r(23) = -.516$, $p = .008$) stimuli, however the unilateral cost (unilateral minus bilateral) was only modestly influenced by age ($r(23) = .374$, $p = .066$). When age was added as covariate to the overall model, the pattern of results did not change. Additionally, our assessment of laterality did not correlate with unilateral cost ($r(23) = -.295$, $p = .152$) and also did not alter the pattern of results in the overall model. Using performance IQ as a covariate in the model did not alter the pattern of results and there was no relationship between performance IQ and the unilateral cost ($r(23) = .086$, p = .682). When verbal IQ was added as a covariate, the two main effects remained significant, but the interaction between diagnosis and condition was not significant ($F(1,1894.17) = 1.347$, $p = .246$). This is despite only a moderate, nonsignificant correlation between the verbal IQ values and the average difference in response times between bilateral and unilateral conditions for each individual participant (*r*(22) = .385, *p* = .063). Finally, the severity of symptomology, as assessed by the GARS-2, did not predict the magnitude of the unilateral cost for the ASD participants (*r*(10) = -.288, *p* = .364).

2.2.4 Discussion

This simple stimulus-response task provided a means for assessing the efficiency of IHT. We acquired measures of the CUDs and unilateral costs in both groups to identify similarities in patterns with those observed in patient groups with known IHT deficits. The CUD for the ASD group was longer than that for the NT group, resembling the results observed in patient populations. This matches our prediction that initiating action of the response hand takes longer when the opposite hemisphere is not directly activated by the stimulus and must rely on IHT.

Response times also differed between groups depending on whether the stimuli were presented bilaterally or unilaterally. The ASD group had faster response times for bilateral stimuli than unilateral stimuli, while the NT group did not exhibit significant response time differences between these conditions. These results show a greater unilateral costs for the ASD group than for the NT group. Bilateral presentations presumably increase the overall response signals from activation of both hemispheres and therefore do not require callosal transfer to initiate response. This would contribute to the notable benefit the ASD group showed in performance for bilateral conditions, as it does for patient populations.

The results from adding covariates showed that only verbal IQ, but not performance IQ, affected the interaction between diagnosis and condition for the unilateral cost values. The diagnostic profile for ASD suggests that deficits on the language portions of IQ tests are part of the disorder and consequently not easily matched with NT groups (Lincoln, Courchesne, Kilman, Elmasian, & Allen, 1988). Therefore, we felt that it was only critical that performance IQ did not change the results, as it is a measure of abilities that are generally not impaired in ASD (Allen & Courchesne, 2003). Additionally, there was no correlation between IQ and response time difference for bilateral and unilateral conditions for each participant. Thus, we cannot assume that IQ was driving the results, and, taken into consideration with the CUD results, this experiment provides initial behavioral support for IHT deficits in ASD.

2.3 Experiment 2: Perceptual load

The second experiment was based on a previous study comparing a single callosotomy patient with two NT participants (Holtzman & Gazzaniga, 1985) and compared the effects of two levels of perceptual load on processing performance in the ASD and NT groups. Participants had to remember patterns presented to both visual fields. Pattern presentations could either be the same on both the left and right side (redundant) or different (mixed). When different patterns of stimuli are presented to each visual field, they may compete for common processing mechanisms. In NT individuals, since interhemispheric connectivity is intact, performance on the mixed trials is reduced to chance levels, as conflicting information from each hemisphere must be processed. In the callosotomy patient, since the hemispheres largely function independently, whether the patterns were redundant or mixed did not impact processing. We predicted that the performance of the NT participants would match the previous report with strong performance in the redundant conditions, but severely impaired performance on the mixed conditions, reflecting the cost of doubling the overall perceptual load. Because interhemispheric communication may be diminished in the ASD group, we also predicted that they would show a smaller performance cost on the mixed conditions, relative to their performance on the redundant conditions.

2.3.1 Methods

2.3.1.1 Participants

All of the participants were the same as in Experiment 1 and had provided scores for the WASI, GARS- 2, and Edinburgh Handedness Inventory. One participant from the original ASD group was not willing to complete the study and was withdrawn. This experiment therefore had 11 boys in the ASD group, and 13 boys in the NT group.

2.3.1.2 Procedure

Participants sat 57 cm away from the same 13.5 inch LCD laptop from Experiment 1. For all trials, participants fixated on a black center point, presented on a white background. In both the left and right visual fields, there was a 3x3 grid of squares that remained on the screen throughout the duration of the experiment. Trials began with both grids displaying target sequences- red filled squares that blinked successively in four different cells. Each red square was displayed in its cell for a duration of 150 ms, with a 500 msinterstimulus interval (ISI) separating each display. Upon completion of the target sequences, a fixed 1500 ms ISI elapsed, and then a unilateral probe sequence in only the left or right grid followed. This probe sequence either followed the same pattern as the target sequence in that visual field, or the second or third square blinked in a different cell (Figure 3). The program then prompted the participant to indicate with a key press if the probe sequence matched the target sequence.

This experiment consisted of three factors, yielding eight possible stimulus conditions. The first factor was target type: mixed or redundant. The second factor was the visual field that the probe sequence appeared on. This could be to the left or right of fixation, preventing participants from attending to one visual field over the other. The third factor was whether the probe sequence matched the target sequence or not. Each block consisted of an equal number of redundant and mixed conditions, an equal number of trials in which the probe sequence was on the left or right visual field, and an equal number of trials in which the probe sequence matched or did not match its corresponding target sequence. Presentation of the trial types was randomized within blocks. All participants completed two blocks of 40 trials, one with each hand, for a total of 80 trials. The order of the two blocks was counterbalanced across participants.

2.3.2 Analysis

Both accuracy and response times were assessed for each participant's performance with each hand and for each condition. All response times equal to, or exceeding, 15000 ms were assumed to be unattended trials and were excluded from data analysis. Accuracy was determined using the average number of trials each participant provided correct responses for in each condition. A 2x2 ANOVA of these accuracy rates was used to assess both diagnosis and the mixed and redundant trial types. The simple main effects of trial type were evaluated for each diagnosis. Because of the task difficulty, a binomial test was run for each of the four conditions to assess whether accuracy was above chance.

Only response times from correct trials were included in our assessment of response time differences. To evaluate performance, a 2x2 marginal means model was constructed with diagnosis (ASD and NT groups) and condition type (mixed or redundant) as independent variables with response times as the dependent variables. The final model was rerun with age, IQ, and LQ as covariates to assess their impact on the pattern of results.

2.3.3 Results

Overall accuracy did not differ between the ASD and NT groups ($F(1,22) = 1.247$, $p = .276$), however participants showed greater accuracy for the redundant trials relative to the mixed trials ($F(1,22) = 15.45$, $p = .001$). ASD and NT participants differed in their pattern accuracy to the mixed and redundant trials ($F(1,22)=10.509$, $p = .004$). As predicted, following presentation of bilateral patterned stimuli that were the same (redundant), NT participants were able to accurately indicate whether a subsequent lateralized pattern matched the pattern previously presented to that half of the screen ($p < .001$). In contrast, the accuracy of NT participants was no different from chance when the initial bilateral stimuli were mixed ($p < .963$) which demonstrates a clear cost to the increased perceptual load ($F(1,22) = 28.06$, $p < .001$) for the control group. In comparison, ASD participants showed a very different pattern of results. Relative to NTs their accuracy in the redundant trials was decreased, but still above chance ($p < .001$). For the mixed trials, ASD participants showed little cost in accuracy when the perceptual load was increased ($F(1,22) = .219$, $p = .645$). The correct number of trials for the ASD group ($M = 24.91$, $SD = 4.23$) and the NT group ($M = 18.38$, $SD = 4.05$) in the mixed condition was significantly different ($F(1,22)=16.316$, $p = .001$). As a group, the ASD participants had higher accuracy with mixed condition trials than NT participants. However, in the redundant condition, the ASD group ($M = 26.09$, $SD = 5.54$) did not perform significantly different than the NT group ($M = 29.08$, $SD = 7.43$, $F(1, 22) = 1.159$, $p = .293$) (Figure 4a). When age, verbal IQ, performance IQ and LQ were added as covariates, the pattern of these results did not change. Finally, the GARS-2 scores did not predict the difference in accuracy between the mixed and redundant trials for the ASD subjects ($r(9) = -.151$, $p = .658$) performance on the mixed trials.

When only the correct trials were considered, ASD participants showed overall longer response times relative to the NT participants ($F(1, 22.12) = 7.149$, $p = .014$). There was no difference in the average response times to the redundant and mixed trial types ($F(1, 1151.12) = .001$, $p = .980$), but the interaction between diagnosis and condition type was significant for response time ($F(1, 1151.12) = 4.59$, $p = .032$) (Figure 4b).

2.3.4 Discussion

Presentation of different, rather than identical, patterns of stimuli to the left and right visual fields imposes an increased perceptual load on the visual processing system, as more information must be encoded. The NT group performed better when these patterns were redundant, but responded at chance levels when the patterns differed. Performance decline for the mixed conditions in NT subjects can likely be attributed to the increased processing load caused by contrasting information presented to each visual field. In contrast, ASD participants responded above chance for both the redundant and mixed condition and showed little cost when the perceptual load was increased. When each hemisphere functions like an independent processor, as in callosotomy, processing occurs with little interference or regard for information in the opposite hemisphere (Ivry, Franz, Kingstone, & Johnson, 1998). This shows that they were not responding at random and that their accuracy indicates competence at distinctly processing information from both visual fields.

The challenging nature of this task makes the ASD group's performance on mixed conditions even more remarkable, resembling that of a callosotomy patient (Holtzman & Gazzaniga, 1985). If their performance was also superior in redundant conditions, we could not rule out a general advantage for processing spatial information. However, they did not perform better than NT's in these conditions, attributing their performance to greater resistance to the increased perceptual load, which may be a function of greater isolation between the hemispheres.

2.4 Chapter 1 discussion

Using behavioral measures that have been employed in other populations of hemispheric disconnection, Experiments 1 and 2 support the theory of interhemisphericunderconnectivity in ASD. The larger CUD values, greater unilateral cost, and resilience to increased perceptual load observed in this group were remarkably similar to those patterns reported in callosotomy and AgCC populations. These findings provide initial behavioral evidence for long-range connectivity, but their relationship to the cognitive and behavioral symptoms that characterize the disorder remains to be determined.

Hemispheric disconnection is detrimental in paradigms that require hemisphere integration, but beneficial when integration creates processing overload. Experiment 1 demonstrated the former by revealing a performance detriment for the ASD group when responses required IHT, such as with crossed and unilateral stimuli, a pattern comparable to that found in individuals with AgCC and callosotomy (Roser & Corballis, 2003). Similarly, results from Experiment 2 demonstrated the latter by showing that the ASD group was not compromised for tasks that require hemisphere isolation and typically cause interference problems (Treisman & Davies, 1973). Both of these experiments provide behavioral support for the more general theory that ASD is a disorder of underconnectivity. Although we specifically assessed integration between hemispheres, deficits in this crucial pathway can signify problems with functional connectivity (Just et al., 2007), which can impact integration between several distant cortical regions.

Although this group of experiments was inspired by studies of developmental and acquired disconnectivity in other disorders, alternative explanations are possible. For example, the Load Theory of Attention and Cognitive Control assumes that full perceptual capacity must be used at all times so, when a perceptual task is not exhaustive, extraneous information is also processed (Lavie, 2005). As individuals with ASD have shown better performance with reduced response times in visual search tasks (O'Riordan, 2004), they may have a general perceptual advantage that could explain their superior performance in the mixed conditions in Experiment 2. If this is the case, the Load Theory of Attention and Cognitive Control would suggest that the task was less loading for the ASD group, which resulted in additional capacity to process two differing patterns. However, reduced response time for visual search tasks could also be explained by increased hemisphere isolation. If each hemisphere is processing stimuli from each visual field independently, search time should be reduced by up to half of what is typical, if there are about the same amount of stimuli in each visual field. Additionally, if the ASD group had increased capacity for attending to spatial patterns, they should have performed better than the control group in the redundant conditions as well. For future studies, a better test of whether this increased perceptual load can be attributed to interhemispheric isolation would be to compare performance in the ASD participants for stimuli oriented horizontally and vertically.

Differences in general motor abilities between groups may have been another factor that affected performance during these experimental tasks that required manual responses. Motor impairments in ASD, including both fine and gross motor dysfunction, are frequently reported in the literature (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010). Movement planning and execution have been implicated as underlying deficits that greatly contribute to the behaviors associated with this disorder (Leary & Hill, 1996). Children with ASD executed more movements to do the same reach and drop tasks as their NT counterparts (Forti et al., 2011), suggesting deficits in the planning stages of motor tasks. This may have caused the participants with ASD to be less efficient with their responses and perhaps be more fidgety and distracted overall, impacting their performance on both tasks. Additionally, individuals with ASD require longer preparation times when executing responses with their upper limbs (Rinehart, Bradshaw, Brereton, & Tonge, 2001), which may have caused prolonged response times in both Experiments 1 and 2. Despite the possibility that movement planning and execution are impaired in ASD, we compared response times for different conditions within individuals, which takes into account absolute differences between groups. Thus, overall prolonged response times in one group should not affect the interpretation of the data.

There are several practical limitations in the present study. Although one experimenter monitored central fixation for every participant throughout each block of trials, we did not use an eye tracker because the study required mobility, and active monitoring proved to be the most efficient method for keeping participants on task and fixated appropriately throughout the entirety of the experiment. Additionally, the WASI required verbal responses for a complete assessment. Hearing and speaking can be impaired in individuals with ASD, even if language comprehension is otherwise intact, making this a potentially invalid measure of IQ for some lower language functioning individuals. However, all participants in the present research were verbal communicators, and only one chose not to complete the IQ test.

This study offers the first direct behavioral support for the proposed theory that ASD arises from underconnectivity between brain regions, affecting both the neural and cognitive levels. The designs of these experiments specifically assessed integration across the midline and showed that the ASD group did not experience the same performance benefits or detriments from interhemispheric transfer efficiency as the NT group. Comparing ASD to populations affected by underconnectivity reveals important similarities and distinctions that can be used to determine the physiological basis of a disorder that is not as well understood. In addition to impacting simultaneous recruitment of multiple brain regions, IHT deficits may have profound effects on the development of certain brain processing functions, such as hemisphere specialization. Further exploring the impact of IHT deficits on brain function is needed for a more comprehensive understanding of all the ways underconnectivity can cause the cognitive and behavioral abnormalities associated with ASD.

2.5 Figures

Figure 1: (a) Average response times (ms) for crossed and uncrossed unilateral conditions in each group. The ASD group had prolonged response times for crossed trials while the neurotypical group performed similarly in both conditions. (b) The CUD's for each group (average uncrossed time subtracted from average crossed time) show that the ASD group had larger CUD's than the neurotypical group. All error bars represent standard error of the mean.

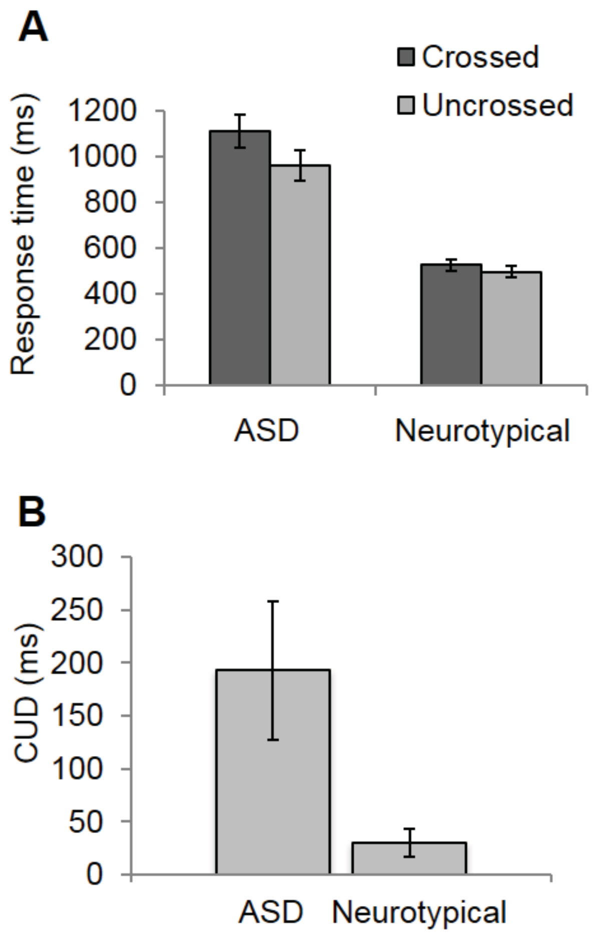
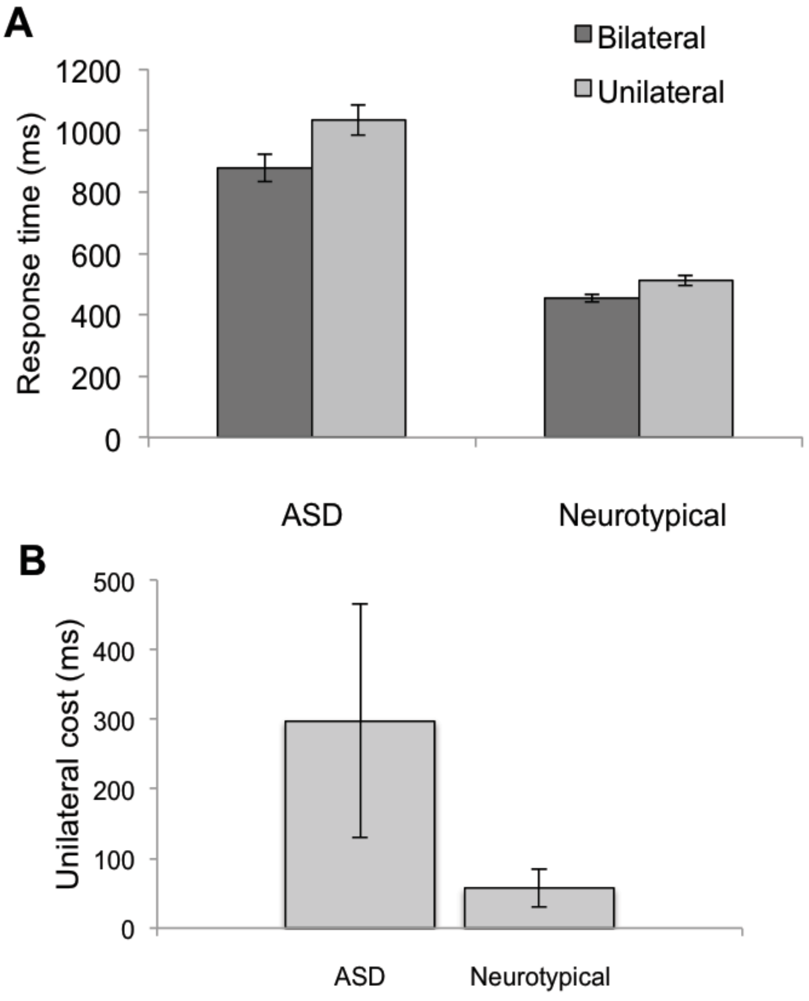


Figure 2: (a) Average response times (ms) for bilateral and unilateral conditions in the ASD and neurotypical groups. Both groups had faster response times for bilateral trials, but only the ASD group gained a significant advantage for these trial types. (b) Unilateral cost for each group (average response time in bilateral conditions subtracted from average response time in unilateral conditions) show that the ASD group had a larger unilateral cost than the neurotypical group. All error bars represent standard error of the mean.



<u>Figure 3:</u> Experiment 2 stimuli. (a) Possible mixed target stimuli. Arrows represent the path the red squares blink along. (b) Possible match probe stimuli in the left visual field. (c) The sequence of frames in a redundant/no match trial. The target and probe frame were displayed a total of 2.6 seconds, separated by an ISI of 1.5 seconds.

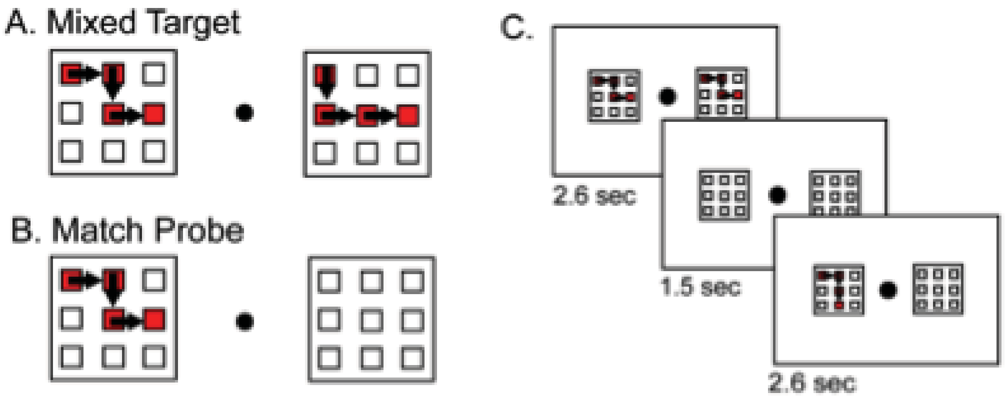
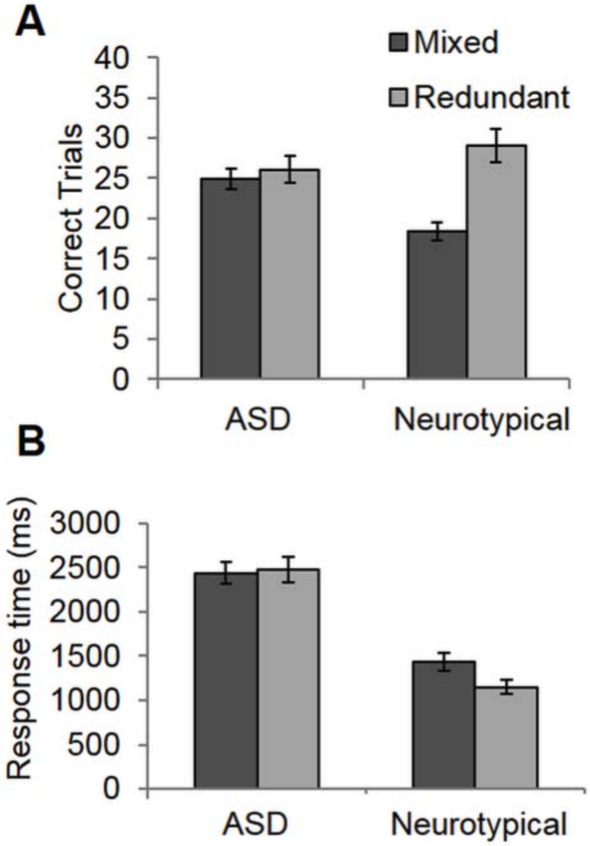


Figure 4: (a) Average accuracy for the ASD group compared to the neurotypical group in the mixed and redundant conditions. The ASD group performed significantly better than the neurotypical group in the mixed condition, but slightly worse in the redundant condition, although this difference was not significant. (b) Average response times (ms) for mixed and redundant conditions in the ASD and neurotypical groups. Only response times for correct trials were included. Response times were similar in both conditions for the ASD group, but the neurotypical group had significantly prolonged response times for the mixed trials. All error bars represent standard error of the mean.



Chapter 3: Assessing Performance for Lateralized Facial Processing Tasks

3.1 Introduction

Facial processing impairments, such as with emotion recognition, have consistently been reported in ASD, potentially impacting social skills (Dawson et al., 2002). Studies have shown thinning of the corpus callosum in subdivisions that include regions connecting the FFA to its homologous areas (Hughes, 2007), which could attribute facial processing deficits to abnormal IHT and patterns of asymmetry in these regions. A thinner splenium has also been identified (Vidal et al., 2006), impacting connections between regions in the left and right occipital lobes, such as the OFA. The subregions of the corpus callosum that are compromised may directly relate to which deficits arise, based on what regions of the cortex are impacted by these IHT deficits.

In the presence of IHT deficits, processing for lateralized stimuli should be more difficult than more centrally presented stimuli during central fixation. Even when a facial stimulus is laterally presented, if it is close to the center of the visual field, viewers rely on perceptual information use for processing (Hsiao & Liu, 2012). This means that they have preferences for fixating on more informative features or specific locations within the stimulus (Gosselin & Schyns, 2001; Bindemann, Scheepers, & Burton, 2009). For example, research has shown that that the left eye is the earliest diagnostic feature that people use in face processing (Vinette et al., 2004) and that people prefer to look at the left side of faces (Hsiao & Cottrell, 2008). However, when the lateralized stimulus is presented 8° horizontal to center, or further, the influence from hemispheric asymmetry emerges in place of perceptual information use. Thus, at this lateralized distance from center, typical asymmetrical brain networks and IHT are recruited for processing facial stimuli. Building on the assumption that facial processing is lateralized in NT's, we can look for specific patterns of performance differences between ASD and NT groups. IHT deficits present from birth could impact asymmetry such that lateralization during facial processing is not as compelling in ASD. Both hemispheres may share processing more equally, but weakly; thus, performance for left visual field presentation of faces should not be significantly different than right visual field presentation. The stimulated hemisphere is only weakly activated to begin with, and inefficient IHT causes the quality of this signal to degrade even more by the time it reaches the opposite hemisphere for additional processing. Facial processing for lateralized stimuli should be worse than that of NT's, regardless of the visual field presentation.

By investigating facial processing in conjunction with lateralized presentation, a characteristic deficit in ASD can be assessed in the context of laterality. This experiment was designed to use behavioral measures to compare processing for laterally presented faces between groups. We used lateralized presentation of faces that expressed one of seven different emotions and compared accuracy of recognition for those emotions in a group of boys with ASD and a group of NT boys. Half the presentations were lateralized but adjacent to the visual midline, and the other half were presented further lateralized. Our first prediction was that the ASD group would perform comparably to the NT group in the close conditions, as these presentations elicit perceptual processing. Our second prediction was that the groups would differ in performance for the far conditions, as these elicit hemispheric asymmetry; we hypothesized that the ASD group would perform worse than the NT group in these conditions, as they recruit both IHT and hemispheric asymmetry. Finally, we predicted that there would be overall performance differences between groups for which emotions were more correctly identified. These findings can help identify IHT deficits as well as asymmetry differences in the ASD group and, in conjunction with the task, provide insight to how these differences could impact facial processing for emotions.

3.2 Methods

3.2.1 Participants

Participants in this study included 5 boys with a diagnosis of ASD and 6 typically developing boys. All participants were between the ages of 7-18 at testing. Participants in the ASD group had previously been tested and diagnosed with the ADOS by a licensed clinical psychologist or doctor qualified to administer this assessment, prior to this research. Everyone was assessed with the WASI to obtain a Full-2 IQ (The Psychological Corporation, 1999), the Edinburgh Inventory (Oldfield, 1971) to determine an LQ, and the GARS-2 (Gilliam, 2006) for current ratings of abnormal behavior for the ASD group only. Parents and guardians filled out information for the Edinburgh Inventory and the GARS-2. They indicated the boys' hand dominance for 10 different everyday activities to obtain an LQ for each participant. The current severity of symptoms was determined using the GARS-2.

Parents and guardians provided current ratings of how often they observed their children exhibit certain characteristics in the following categories: stereotyped behaviors, communication, and social interaction. The groups did not significantly differ on age or LQ. There was a significant difference in IQ between groups, but further analysis showed that groups did not differ on either the vocabulary or the matrix reasoning subcomponents that made up the IQ score. No participant had a known history of a medical disorder known to cause characteristics associated with ASD. NT participants had no current or past diagnosis of ASD or other psychiatric or neurological disorder. Parents and guardians signed written consent forms, and all participants provided informed assent prior to, and throughout, testing.

3.2.2 Procedure

Participants sat 57 cm away from a 20 in monitor. Stimuli were presented on the monitor, and participants made verbal responses. Prior to beginning the task, participants did a preliminary exercise to ensure they knew the different response options and had enough practice to achieve relative competency for the experiment. Throughout the entire preliminary and experimental sessions, video and sound were recorded for eye tracking and to log verbal responses.

In the preliminary exercise, participants were instructed to maintain fixation at a central cross. Each block consisted of trials in which one grayscale face appeared for 250 ms, followed by 6 cartoon images displaying the following emotions: anger, disgust, fear, happiness, sadness, and surprise. Participants were instructed to choose from these emotions which one they believed the graycale face was conveying and indicate their answer verbally. If they thought the expression was neutral, they should say “none” or “neutral”. After completing 3 blocks, or until participants reached a score of at least 80%, they were able to move on to the experimental task.

The instructions were the same for the experimental task, except the location of face presentation on the monitor changed, and there was no cartoon prompt. The experiment was composed of 4 spatial locations for face presentation (far right, far left, close right, close left), 7 emotional expressions, 6 identities (3 male, 3 female), and 8 presentations of each (Figure 1). The order of these trial types was randomized for each participant. The experiment was divided evenly into 4 sections between which participants were offered a break.

3.3 Analysis

Accuracy was assessed for each participant in each combination of conditions. This was determined using the average number of trials each participant provided correct responses for in each condition. These accuracy rates were initially run in a 2x2x2x7 repeated measures ANOVA with a between-subjects factor of diagnosis (ASD and NT) and within-subjects factors of lateral distance (far and near), visual field (left and right), and emotion type (angry, disgusted, happy, sad, scared, surprised, and neutral). Because there were no main effects or interactions with visual field, the model was rerun as a 2x2x7 repeated measures ANOVA without this variable. This final model was rerun with age, IQ, and LQ as covariates to assess their impact, if any, on the pattern of results.

3.4 Results

The NT group performed better overall at correctly identifying the emotions in the displays (F (1, 9) = 26.493, p = .001). Participants performed better in the near conditions compared to the far conditions (F(1, 9) = 12.315, p = .007), and emotion identification performance differed across emotions (F(1, 9) = 5.737, p < .001), with the highest correct identification for the happy conditions.

The interaction between diagnosis and lateral distance was significant (F(1, 9) = 8.234, p = .018), such that the ASD group performed worse in the far conditions compared to the NT group (Figure 2). The interaction between diagnosis and emotion approached significance (F (1, 9) = 2.21, p = .056); the largest discrepancy between groups was for the disgust and neutral conditions, with the ASD group performing worse than the NT group for both (Figure 3). The three-way interaction between diagnosis, distance, and emotion was not significant (F(1, 9) = .028, p = .872). The results from adding age, IQ, and LQ as covariates did not change the patterns of results.

3.5 Discussion

This experiment was designed to investigate how individuals with ASD perform on tasks that recruit hemispheric asymmetry processing methods, compared to NT individuals. Research has shown that when lateralized facial stimuli are presented close to central fixation, there is greater influence from perceptual information, but when they are farther away, left or right, from center, there is greater influence from hemispheric asymmetry (Hsiao & Liu, 2012). As such, we predicted that atypical asymmetry for faces in the ASD group would result in a more dramatic performance decrement for far conditions compared to near conditions. Our results support this hypothesis and provide initial behavioral support for atypical asymmetry for facial processing in ASD.

The overall worse performance for the ASD group supports the existing literature that these individuals have impairments with facial processing and emotion recognition in particular (Baron-Cohen et al., 1993; Humphreys et al., 2007). However, the more specific patterns of results offer some insight as to why these problems occur. Based on what has been shown in the NT population (Hsiao & Liu, 2012), we assume that individuals in the ASD group performed better when stimuli were lateralized closer to center because presentation was within the foveal region and therefore projected bilaterally. Thus, they could use perceptual information from the half of the face on which their eyes were fixated to infer the emotional expression.

The most interesting result is that the ASD group showed significantly worse performance for the stimuli lateralized far from center than for the stimuli close to center, compared to the NTs. In these far conditions, the stimulus is presented outside the foveal region, where hemispheric asymmetry effects are more reliable (Hsiao & Liu, 2012). The stimulus is lateralized far enough to the left or right visual field that the contralateral hemisphere is initially stimulated, rather than both hemispheres. For individuals with typical asymmetry for faces, either the dominant hemisphere will directly receive the input, or it will receive the input via intact IHT.

However, if there is more bilateral and weaker activation for faces in ASD, performance will be poor, regardless of which hemisphere is contralateral to the stimulus. Additionally, IHT deficits will cause the information to become further degraded when it is shared with the other hemisphere. Individuals with ASD have shown a normal ratio between central and peripheral visual field representation compared to NT's (Hadjikhani et al., 2004a), which suggests that their performance decrement for the far lateralized condition was influenced by hemispheric asymmetry deficits, rather than impaired peripheral vision.

In NT individuals, the task should be easier when the right hemisphere receives the information, but we did not find any visual field advantage in this study. Hemisphere dominance in NTs is a matter of degree, and it is difficult for a behavioral task to be sensitive enough to capture these asymmetries, which are typically not drastic (Reuter-Lorenz & Miller, 1998). Therefore, although hemispheric lateralization occurs for the far conditions, measuring the accuracy of their performance may not have been sensitive enough to detect a right hemisphere advantage. Because of the effects previously discovered using only accuracy analysis in a similar paradigm (Hsiao & Liu, 2012), as well as the fact that response times are indiscriminately longer for every emotion in ASD (Humphreys et al., 2007), we did not perform analyses on response times. Additionally, because we required verbal responses, we did not have a simple, objective way to acquire response times. Perhaps if we had investigated response times as well, we would have noticed a right hemisphere advantage, expressed by faster response times to faces presented to the far left visual field. Additionally, research has suggested that positive and negative emotions elicit different patterns of lateralization (Ahern & Schwartz, 1979). We incorporated several emotional states that are not easily categorized into positive and negative, which could have diminished clear visual field effects. The nature of the task also could have influenced visual field effects by enabling participants to adopt a method for basing their decisions on facial features that are telling of emotional expression, like the shape of the mouth or eyes. These NT participants may have had more right visual field and left hemisphere asymmetry compared to NT participants who used holistic processing. Future studies should use a similar paradigm that requires facial recognition, rather than emotion recognition. This would encourage more holistic processing, and thus eliminate the variability in processing methods. It would also confine the response options to "yes" and "no", which can be indicated with a key press. This would provide response times, which could potentially make the paradigm more sensitive to visual field effects.

Our results also suggest that the ASD group had overall problems recognizing neutral and disgusted expressions compared to the NT group. While these results did not reach significance, this supports research that has identified deficits in ASD for recognition of disgust (Humphreys et al., 2007). Their poor performance for neutral faces means that they ascribed emotions to these faces, which supports problems with discriminating between emotion and no emotion. This is consistent with reports of impaired discrimination for neutral and fearful faces in children with

ASD, compared to NT children, as expressed by early ERP components (Dawson, Webb, Carver, Panagiotides, & McPartland, 2004). Problems discriminating neutral from emotional faces support abnormalities in both general face processing and emotional recognition.

Overall, this data offers preliminary support that individuals with ASD have facial processing deficits that are exacerbated by lateralized presentation. This supports the theory of impaired IHT deficits in this population and also suggests that they may have atypical asymmetry for faces. The following experiment further investigates this latter theory by comparing asymmetry in an ASD group and an NT group during facial processing tasks to assess the impact of IHT deficits on functional development in the brain.

3.7 Figures

Figure 1: Examples of stimuli used. Faces represent one of seven different emotions: angry, afraid, disgusted, happy, sadness, surprise, or neutral.

Figure 2: Accuracy performance for both groups in the near-lateralized and far-lateralized conditions. The ASD group showed significantly greater performance decrement for the far conditions than the near, compared to the NT group. All error bars represent standard error of the mean.

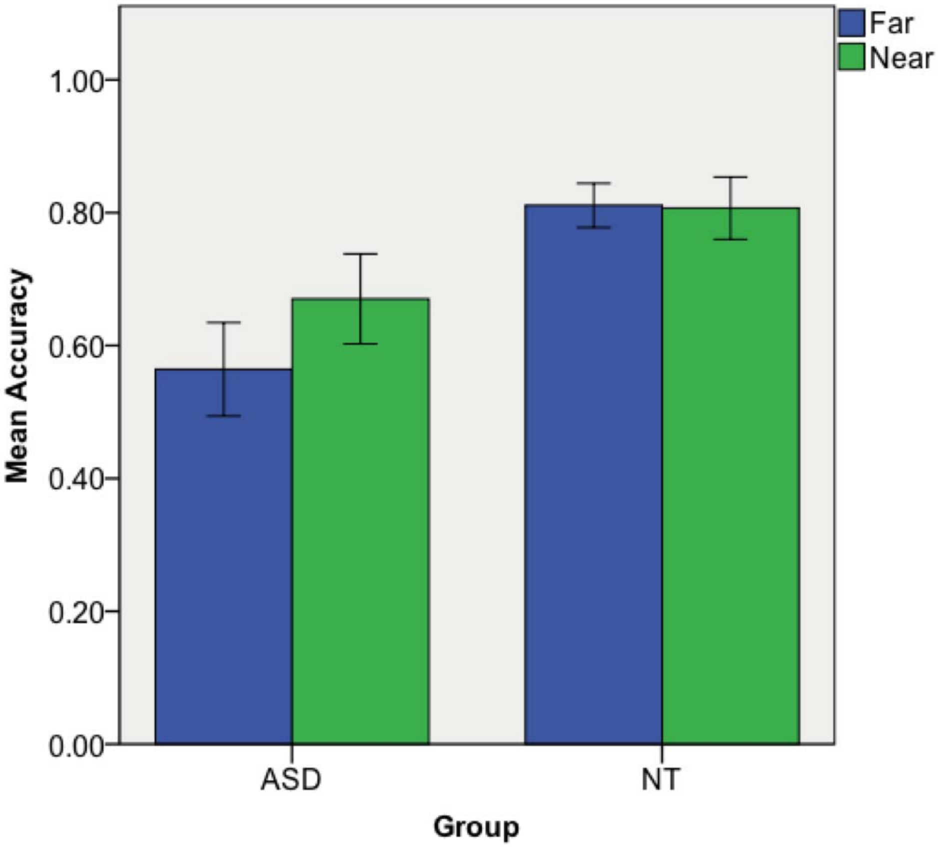
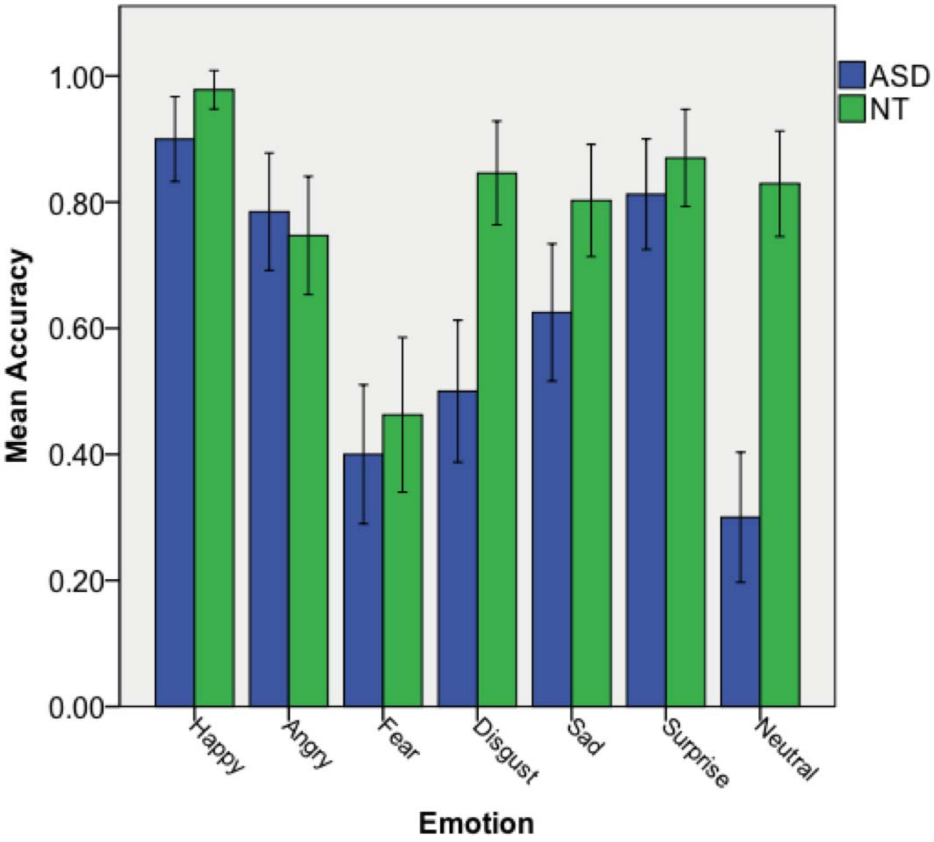


Figure 3: Accuracy performance for each emotion in both the ASD and NT groups. The ASD group had the greatest recognition impairments for disgust and neutral expressions, compared to the NT group. All error bars represent standard error of the mean.



Chapter 4: Assessing Asymmetry for Hemisphere-dominant Tasks with fNIRS

4.1 Introduction

Distinct cognitive and behavioral deficits observed in ASD may be attributed to altered patterns of hemispheric asymmetry (Lo et al., 2010). Less asymmetry, represented by more bilateral activation for these tasks, could indicate inefficient cognitive functioning that would lead to observable deficits in language and facial processing. Atypical patterns of asymmetry have been identified in ASD, but most of these studies have only investigated asymmetry for language processing (Escalante-Mead, Minshew, & Sweeney, 2003). Furthermore, these results are mixed. Reduced asymmetry (Anderson et al., 2010; Kleinhans et al., 2008), reversed patterns of asymmetry (Flagg, Cardy, Roberts, & Roberts, 2005), and typical asymmetry (Knaus, Tager-Flusberg, Mock, Dauterive, & Foundas, 2012) have all been observed in these studies.

Facial processing deficits in ASD affect recognition (Joseph & Tanaka, 2003), emotion identification (Humphreys et al., 2007), and cause abnormal patterns of cortical activation to human faces (Kleinhans et al., 2008). However, there has been recent support for improved social interaction when presented with robots (Robins, Dautenhahn, Boekhorst, & Billard, 2005; Scassellati et al., 2012), which raises the question of whether these deficits are specific to human faces. These few studies do not include how an NT group would compare with the same stimuli, creating the need for investigation that compares human and robot processing in both groups. It is possible that individuals with ASD process robot faces as objects, for which they generally have typical processing (Wallace, Coleman, & Bailey, 2008). NTs, on the other hand, tend to process different types of faces similarly, including schematic and cartoon faces (Kanwisher & Yovel, 2006). Therefore, it is likely that their brains show similar activation for human and robot faces because they automatically interpret them as being in the same general category.

4.1.1 Functional near-infrared spectroscopy as a tool

This research employed a functional neuroimaging technique to examine asymmetry in ASD. Functional near-infrared spectroscopy (fNIRS) is practical for special populations because it offers a non-invasive method for measuring hemoglobin oxygenation in selective regions of the cortex. It provides indices of neural activity, while allowing participants to sit openly in a chair without being confined within a scanner or exposed to a magnetic field and loud noises, like functional magnetic resonance imaging (fMRI).

FNIRS measures the absorption of near-infrared light by the oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) in the cerebral cortex (Chance et al., 1993; Edwards et al., 1993), based on differential absorption spectra. Light emitters send light through the scalp, skull, cerebrospinal fluid, and cortex, about 1-3 cm. Detectors pick up the signals that come back, reflecting HbO and HbR. Each path from the light emitters to the detectors creates a banana shape. Two wavelengths must be used: 830 nm, more sensitive to HbO, and 690 nm, more sensitive to HbR, so that changes in the relative concentrations can be calculated. Increases in the difference between HbO and HbR signify increases in oxygen demand and are thus interpreted as increases in brain activation in the area being measured. During a cognitive task, hemodynamic changes take 6 to 8 seconds (Bunce, Izzetoglu, Izzetoglu, Onaral, & Pourrezaei, 2006), and these signals are measured at a sampling rate of 50 Hz.

FNIRS has been used in ASD to assess interhemispheric connectivity during the resting state (Zhu, Fan, Guo, Huang, & He, 2004) and in prefrontal areas (Narita et al., 2012), but using this technique in this population is still in its infancy. Comparing blood flow changes in both hemispheres with fNIRS can provide a way to compare lateralization of activation between ASD and NT groups. For example, administering language or facial tasks while measuring activation from the corresponding processing regions and their homologous regions in the other hemisphere should provide an approximation of an individual's degree of lateralization for the task.

In this experiment, we used fNIRS to compare the degree of asymmetry in an ASD and an NT group for tasks that required processing of both human and robot faces. Because ASD subjects show deficits in basic facial processing tasks, our first objective was to test the hypothesis that the ASD group would show reduced lateralization for human face stimuli relative to the NT group. Second, because individuals with ASD show improved interactions with robot faces, we wished to see whether these stimuli would show increased lateralization in the ASD group. Comparing patterns of activation for the robot faces in both groups could provide supporting evidence for the successful use of robots in a clinical setting and encourage more effective methods of stimulating interaction. Overall, this study was designed to provide information about the domains in which asymmetry is impacted in ASD and novel insight to what drives some of the distinct behavioral idiosyncrasies observed in this population.

4.2 Methods

4.2.1 Participants

Participants in this study included 8 males with a diagnosis of ASD and 12 NT males. All participants were between the ages of 7 and 36. Participants, or parents of participants under 18 years of age, signed written consent forms, and all participants provided verbal and nonverbal assent prior to and throughout the testing. Individuals in the ASD group had previously been diagnosed with ASD by a licensed clinical psychologist or doctor, not associated with this research. All participants in the ASD group had also previously been assessed with the Autism Diagnostic Observation Schedule (ADOS) by a clinical psychologist or speech pathologist qualified to administer this assessment. Boys in the NT group had no previous diagnosis of ASD or a history of a medical disorder known to cause characteristics associated with ASD.

All participants were assessed using the WASI to obtain a Full-2 IQ (The Psychological Corporation, 1999), the Edinburgh Handedness Inventory (Oldfield, 1971) to determine LQ, and the GARS-2 (Gilliam, 2006) for the ASD group only. Participants or their parents, if they were under 18 years of age, filled out information for the Edinburgh Handedness Inventory. They indicated the boys' hand dominance for 10 different everyday activities so that we could obtain an LQ for each participant. For the GARS-2, parents or caregivers provided current ratings of how often they observed the individual exhibit certain characteristics in the following categories: stereotyped behaviors, communication, and social interaction. The groups did not significantly differ on age or LQ. There was a significant difference in IQ between groups, but further analysis showed that, of the vocabulary and matrix reasoning subcomponents that made up the IQ score, only vocabulary significantly differed between groups. Although groups are generally matched on IQ to control for general cognitive abilities, the diagnostic profile for ASD suggests that matching groups for performance on language tests may not be appropriate (Lincoln, Courchesne, Kilman, Elmasian, & Allen, 1988). Therefore, we felt that it was only critical that the groups did not significantly differ on the matrix reasoning task, a measure of abilities that are generally not impaired in ASD (Allen & Courchesne, 2003).

4.2.2 Facial stimuli

During the experiment, each participant was seated 57 cm away from the experimental laptop, and all stimuli were presented using E-prime software (Psychology Software Tools, Inc.). To keep participants engaged in the stimuli, they were asked to do a 1-back task, in which they were instructed to press a key when the current stimulus repeated from the one prior and another key if it was different. This task requires quick and constant decision-making and was therefore meant to keep participants actively involved with the stimuli, rather than passively looking at the screen. Face stimuli in the human condition included pictures of 5 males and 5 females, without glasses or jewelry, showing neutral expressions (Figure 1a). Face stimuli in the robot condition included pictures taken of 10 robots used in the clinical setting that all had distinguishable heads and facial feature landmarks (Figure 1b). All stimuli were grayscale, subtending approximately 8° visual angle horizontally and 10° vertically, similar to the size of a real face viewed from about 100 cm away (Hsiao & Cottrell, 2008). There were 10 blocks of human faces and 10 blocks of robot faces. Each block consisted of 15 stimuli presented successively. Each stimulus remained on the monitor for 1000 ms, with set 500 ms ISIs that were not dependent on key responses. After the last stimulus of each block, there was an 8 second rest period. The order in which the blocks were presented was randomized. The entire experimental session lasted about 12 minutes. Prior to beginning fNIRS recording, each participant ran through the behavioral task once for practice.

4.2.3 FNIRS set up

Oxygenation changes were measured with a continuous wave fNIRS system (TechEn CW6 fNIRS System, Milford, MA), measuring two wavelengths (690 nm and 830 nm) that were sampled at 50 Hz (20 ms). Each participant's head was measured using the international 10-20 system as a reference for probe placement (Jasper, 1958). Specifically, channels in the left hemisphere were placed such that one emitter-detector pair was directly over T5, with six other channels placed around it, and channels in the right hemisphere were placed symmetrically, with one directly over T6, for a total of 14 channels. This placement was chosen because T5 and T6 are bilateral temporal areas where asymmetry for faces has previously been detected with fNIRS (Ichikawa et al., 2004). In each hemisphere, optical channels were set at 2.6 cm in distance in a 2x3 lattice attached to a custom-made headband to ensure that the configuration was constant within each hemisphere for all participants (Figure 2). Prior to beginning the experiment, the channels were screened for clear respiratory patterns at both wavelengths. If the signal was not clear enough to see the respiratory pattern and cardiac pulsation, we adjusted the set up on the participant's head. Any channels that remained noisy were noted for later exclusion from data analysis.

4.3 Analysis

Concentration changes of oxygenation from raw signals were obtained using the modified Beer-Lambert approach (Chance et al., 1998) and analyzed with the HomER2 software package (Huppert, Diamond, Franceschini, & Boas, 2009). Raw fNIRS data were pre-processed with a low pass filter of 0.5 Hz to eliminate respiratory noise. As HbO has previously been shown to correlate best with blood flow compared to HbR and total hemoglobin values (Hoshi, Kobayashi, & Tamura 2001), we focused on HbO signals for analysis.

To compare relative HbO values across channels and participants, we normalized the raw scores into z-scores, which can be averaged regardless of the unit (Schroeter et al., 2003; Shimada & Hiraki, 2006). We based these scores on the baseline rest period starting from 5 seconds prior to the task period. Thus, each z-score represents the change of the hemodynamic response during the presentation of the faces from baseline. Z-scores were calculated as follows: $(x_{task} - m_{baseline})/s$ (Ichikawa et al., 2014). x_{task} represents the raw data at each second during the task period, $m_{baseline}$ represents the mean of the raw data during the last 5 seconds of the baseline period, and s represents the standard deviation of the raw data during baseline.

For each hemisphere, we calculated the average HbO levels across channels at each second with these normalized scores (Zhang, Sun, Sun, Luo, & Gong, 2014), excluding channels that did not meet our predetermined criteria for an acceptable signal, as well as corresponding channels in the opposite hemisphere. To account for the rise of the hemodynamic response from resting levels (Ichikawa et al., 2010; Nakato et al., 2011), we then took the peak HbO level from those averages in the 3 to 10 second time frame after the facial stimuli onset.

To test our first hypothesis that the ASD group would show less asymmetry than the NT group for human faces, we conducted a 2x2 repeated-measures ANOVA for the human faces condition, with a between-subjects factor of diagnosis (ASD and NT) and a within-subjects factor of hemisphere (left and right). To test our second question of whether the ASD group would show more comparable asymmetry to the NT group, we conducted a 2x2 repeated-measures ANOVA for the robot faces condition, also with a between-subjects factor of diagnosis and a within-subjects factor of hemisphere. The participants' variables of age, IQ, and LQ were later included as covariates to assess their impact, if any, on the overall findings.

4.4 Results

The analysis for our investigation of the human faces condition showed that there were no overall differences in lateralization ($F(1, 18) = 3.085$, $p = .096$) or diagnosis ($F(1, 18) = 1.476$, $p = .24$). However, the ASD group showed less lateralization than the NT group, such that the NT group showed more right hemisphere lateralization ($F(1, 18) = 6.12$, $p = .012$) (Figure 3).

The analysis for our investigation of the robot faces condition showed that there were no overall differences in lateralization ($F(1, 18) = 1.241$, $p = .28$) or diagnosis ($F(1, 18) = .444$, $p = .514$). Additionally, there was no interaction between diagnosis and lateralization for robot faces ($F(1, 18) = .298$, $p = .592$) (Figure 4).

All of these results were upheld after adding age, IQ, and LQ as covariates. Finally, the GARS-2 scores for all ASD participants excluding one, who did not have a caretaker to provide scoring, did not predict left or right hemisphere activation for the ASD group in either the human faces condition (left: $r(5) = .685$, $p = .089$; right: $r(5) = .346$, $p = .447$) or the robot faces condition (left: $r(5) = .116$, $p = .805$; right: $r(5) = .552$, $p = .229$).

4.5 Discussion

This experiment was designed to test two hypotheses regarding facial processing and asymmetry. First, we wanted to assess whether individuals with ASD elicit less lateralized activation than NTs during facial processing tasks for typical human faces. Second, we wanted to determine whether lateralization patterns did not differ between groups for viewing robot faces. As predicted, the NT group showed right hemisphere lateralization for the human faces, but the ASD group did not. Interestingly, however, the ASD group showed similar lateralization patterns to the NT group for robot faces. Taken together, these novel findings have implications for attributing characteristic behaviors in ASD to atypical functional asymmetry.

Previous reports of atypical asymmetry for language related tasks in ASD are limited and inconsistent. Here, we explored this variable in the context of facial processing to complement these studies and enhance the current understanding of abnormal asymmetry in this population. The reduced asymmetry for human faces exhibited by the ASD group corresponds with reports of the isthmus corpus callosum subsection abnormalities in ASD (Chung et al., 2004; Vidal et al., 2006), as deficits in this subsection could have inhibited development of asymmetry in temporal face processing regions. Additionally, this finding complements the existing reports of reduced asymmetry for word processing observed in ASD. Because these processes arise in symmetrical regions of the temporal cortex (Dundas et al., 2013), disruption to posterior asymmetry development might likely affect both face and word processing.

The second main finding was that the ASD group did not have reduced asymmetry for the robot faces, as compared to the NT group. The data suggest that these differences may be attributable to how the ASD group is categorizing these stimuli. While NTs generalize across all categories of faces, it seems that individuals with ASD treat human and non-human faces differently, potentially recruiting different regions of the cortex. This provides insight to the existing behavioral data that suggest individuals with ASD interact better with robots than humans (Scassellati et al., 2012). Additionally, it suggests that, while NTs may generalize all faces, individuals with ASD categorize them distinctly.

Because we only assessed asymmetry for human and robot faces, it is difficult to reach the conclusion that the ASD participants were treating the robot faces like objects. A future study should incorporate an additional assessment of asymmetry in both groups for object stimuli that are complex enough to also be processed holistically or by their features, such as houses. This would help provide more insight as to the reason why individuals with ASD process robot faces differently than human faces.

The results from this experiment support our hypothesis that facial processing deficits emerge in ASD, in part, because of reduced asymmetry, which is likely a developmental consequence of abnormal IHT. The more typical patterns observed in the ASD group asymmetry for robots help explain and support clinical reports that children with ASD exhibit improved interaction to robots, but this introduces a more complex and targeted approach to understanding abnormal asymmetry patterns in this population. If interhemispheric connections are not collectively impaired, it is possible that what makes ASD a distinct disorder of underconnectivity is its combination of behaviors that arise from localized, and not global, IHT deficits. The final experiment in this dissertation explores this idea by shifting the focus of IHT to its relationship with a specific cognitive skill that is impacted in ASD, rather than on an entire diagnosis.

4.6 Figures

Figure 1: Examples of stimuli. (a) The human face conditions consisted of neutral expression faces with no accessories. (b) The robot face conditions consisted of robots with distinct head shapes and key facial feature landmarks.

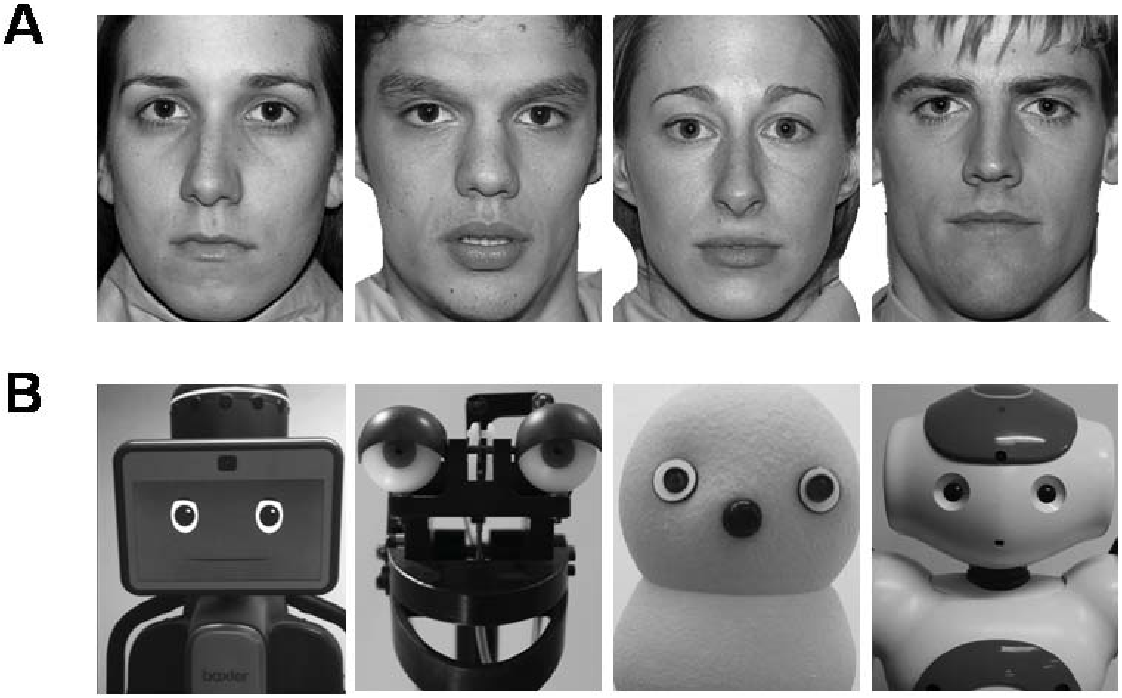


Figure 2: Example fNIRS set up. The participant has the headband adjusted on his head so that the emitters and detectors are symmetrical on each side. He is seated 57 cm away from the experimental laptop.

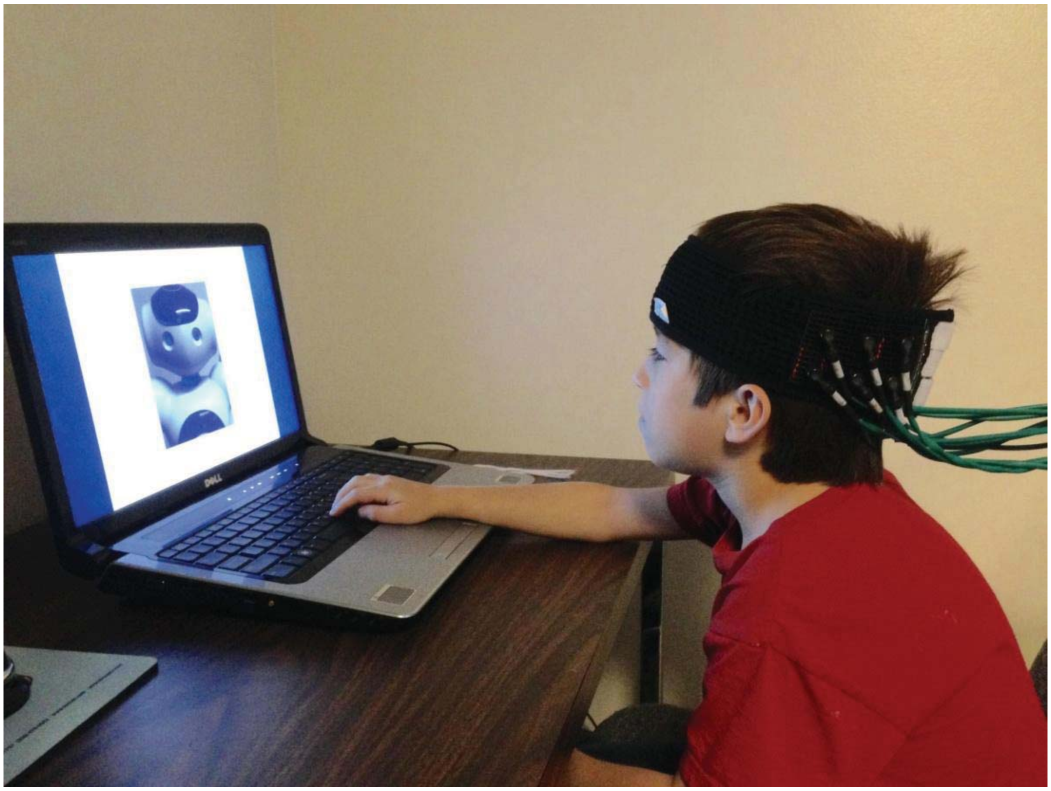


Figure 3: Lateralization for the human faces in both groups. The NT group showed more right hemisphere lateralization than the ASD group. Error bars represent standard error of the mean.

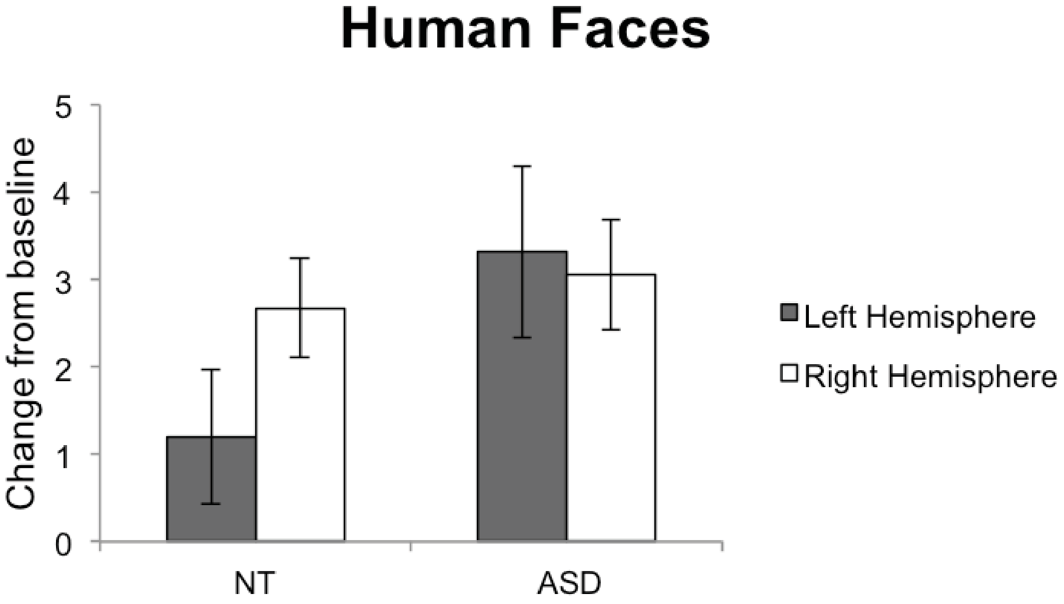
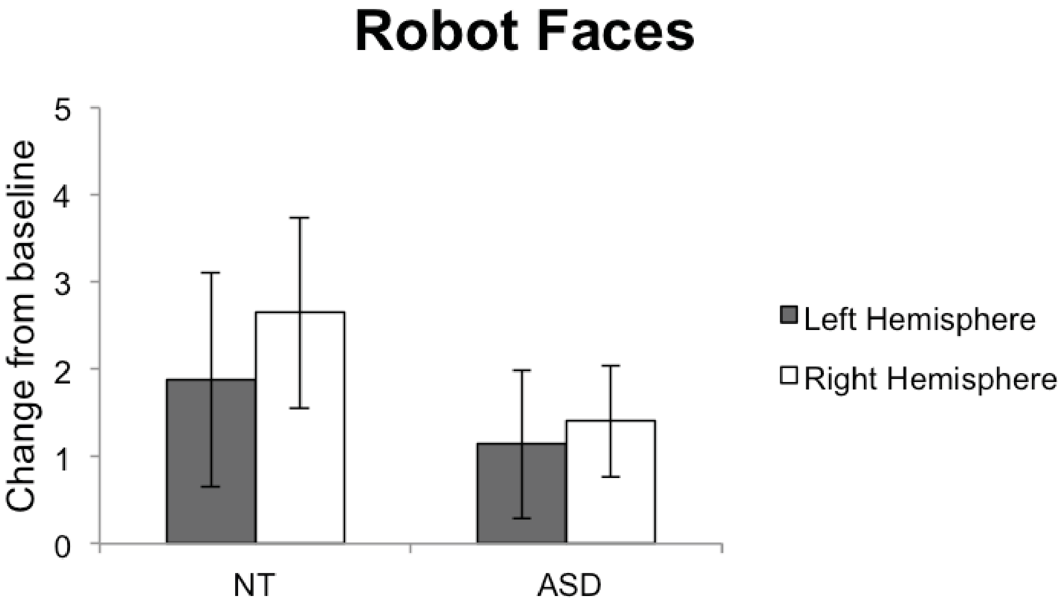


Figure 4: Lateralization for the robot faces condition in both groups. Error bars represent standard error of the mean.



Chapter 5: The relationship between IHT and specific cognitive impairments

5.1 Introduction

The investigations of impaired IHT in ASD do not account for the ubiquity with which it has been proposed in other disorders, such as dyslexia, ADHD, and SLI (Fine et al., 2007; Moore et al., 1995; Klimkeit et al., 2004). As each of these disorders is also marked by impairments in complex cognition and behavior, one way to better understand the impact of IHT deficits is to identify a relationship with a common impairment, rather than on the diagnoses individually. Language, and reading in particular, is known to be a lateralized task that also happens to be consistently impacted in each of these disorders. Thus, if we demonstrate a relationship between reading ability and measures of IHT, we can gain a better understanding of how IHT deficits can impact multiple disorders.

Although the left hemisphere is often associated with language functions like reading, the right hemisphere and interactions between both hemispheres are involved in this process (St George et al., 1999). As such, some studies have investigated the integrity of the corpus callosum in reading disabled and illiterate individuals (Castro-Caldas et al., 1999). Findings suggest that this structure is compromised, supporting the role of IHT in reading, as this task must ultimately recruit both hemispheres. Additionally, abnormal asymmetry for language, which may arise from IHT deficits, can exacerbate problems with this task. When reading in AgCC was specifically tested, problems with phonological processing were found, supporting the importance of IHT for this skill (Temple et al., 1990). While these disorders present a wide range of reading difficulties, research points to a potential underlying link between ASD, AgCC, and other developmental disorders in which this skill is compromised.

ASD is fundamentally different from the disorders discussed here, but, in addition to the underconnectivity theory, impairments in the domain of language are common among them. This experiment disregards diagnoses and instead focuses on identifying a relationship between a commonly impacted skill and measures of IHT. We employed a perceptual load task building on the principles assumed and supported by previous research (Holtzman & Gazzaniga, 1985; Jung & Hutsler, under review). We assessed performance for both reading and IHT in NT individuals to determine whether there was a relationship between these variables. If so, individuals who perform better on the reading measures should have increased IHT, as assessed by performance discrepancy between different and identical stimuli, compared to individuals who perform worse on the reading measures. By looking at a range of reading skills, such as speed, accuracy, comprehension, and production, we aimed to identify some specific aspects of language that may be more predictive of IHT. This information will help determine whether there is a relationship between reading and connectivity, as well as how that relationship may be involved in, and connect, ASD with other distinct cognitive disorders.

5.2 Methods

5.2.1 Participants

Seventy-one adults (40 females) participated in this experiment. Participants were college students between the ages of 18-59 and were recruited through the University of Nevada, Reno's online subject pool for the Department of Psychology and through the Disability Resource Center. Prior to testing, informed consent was obtained from all individual participants included in the study. All participants indicated their hand preferences for 10 different everyday activities on the Edinburgh Handedness Inventory to obtain their LQ. The Full-2 method of the WASI was used to obtain an IQ score (The Psychological Corporation, 1999).

5.2.2 Reading assessment

The York Adult Assessment Battery-Revised (YAA-R) is a battery of tests used to assess reading performance in adults in higher education on several measures. This tool was appropriate for the demographic because it was designed to test reading skills in higher education adult students, a population for which few reading assessments specifically target (Prevett, Bell, & Ralph, 2013). For this research, participants were tested on areas of reading comprehension, accuracy and rate; writing comprehension, accuracy, and rate; and rapid naming (RAN) for digits.

5.2.3 Procedure

Stimuli were presented on a 13.5" laptop monitor, and responses were made on the keyboard. The laptop's camera was used to capture video of participants' eye movements and the display on the monitor throughout the experiment. Participants were seated 57 cm away from the computer monitor, with one hand placed on the keyboard. They fixated on a black central point presented on a white screen, throughout the experiment. In one block, a 3x3 grid of squares remained on the left and right sides of fixation. On each target trial, both grids displayed 4 cells successively flashing red. Each red flash sustained for 150 ms, with 500 ms ISIs in between. This sequence was followed by a 1.5 sec pause and then a probe trial. The probe sequences were presented unilaterally, to either the left or right grid. The sequence either matched the target sequence originally presented on that side or differed by placement of the second or third cell. Participants were then prompted to decide of the probe sequence matched the target sequence and respond by pressing the "Y" key if they thought it was a match, or the "N" key if they thought it was different.

The block consisted of two conditions. In the redundant condition, the target sequences matched each other. Conversely, in mixed conditions, they differed. Redundant conditions are expected to impose less of a perceptual load, as accuracy depends on encoding only a single sequence. A block consisted of an even number of redundant and mixed conditions, an equal number of trials in which the sequence was presented on each side, and an equal number of trials in which the probe sequence matched or did not match its corresponding target sequence, yielding eight combinations of stimulus types. Each of these trial types were randomized within blocks. Participants completed one block of 32 trials (4 trials of each of the 8 possible conditions) for each hand.

The task for the second block was conducted identically, but instead of the grids being placed to the left and right of fixation, they were placed vertically: one grid directly above the fixation point and one directly below. These vertical trials served as a control condition to help eliminate the possibility that enhanced performance on mixed trials was due to increased attentional capacity, rather than reduced interhemispheric communication. The order in which the horizontal and vertical trial type was presented was counterbalanced across participants.

5.3 Results

Assuming adequate comprehension of and focus on the task, participants should perform optimally for redundant trials (Holtzman & Gazzaniga, 1985). Thus, we excluded participants who performed below 60% on redundant trials from analysis. After these participants were removed, total sample size was 53 adults (25 female, 28 male) between 18-58 years old, and their ages and their scores for IQ, laterality, and the literacy components were averaged (Table 1). Individual trials in which participants shifted their eyes from central fixation during the initial frame of target stimulus presentation, as confirmed by video recording, were excluded from analysis.

Overall performance on the perceptual load task was assessed using a two-factor (stimulus orientation and trial type) repeated-measures ANOVA. Because the eleven reading and IQ variables were often significantly correlated with each other, a principal component analysis with orthogonal varimax rotation was undertaken to simplify the number of predictive variables and create independent predictive components. The final number of components was determined by both parallel analysis of the eigenvalues and a visual examination of Scree plot. Individual participant scores for each resulting component were calculated using the Anderson-Rubin method (SPSS, Inc.). These calculated scores were then used to predict the behavioral performance on the perceptual load task.

5.3.1 Overall perceptual load results

Performance for mixed and redundant trials was initially compared for all included participants. A two-way ANOVA was used with orientation (horizontal and vertical) and trial type (mixed and redundant) as independent variables (Figure 1a). Orientation did not make a significant difference for performance ($F(1, 52) = 2.257$, $p = .139$), and there was no interaction between orientation and trial type ($F(1, 52) = .083$, $p = .774$). Trial type impacted the amount of errors participants made, with significantly worse performance for mixed conditions compared to redundant conditions ($F(1, 52) = 454.94$, $p < .001$). Mean response times, in milliseconds (ms) were calculated for each participant. Only correctly answered trials were included in a two-way ANOVA for response time, also with orientation and trial type as independent variables. Participants were significantly slower for mixed trials relative to redundant trials ($F(1, 52) = 29.116$, $p < .001$) (Figure 1b). As with accuracy, there were no main effects of orientation on response time ($F(1, 52) = 2.261$, $p = .139$) and no interaction between orientation and trial type ($F(1, 52) = .09$, $p = .766$).

5.3.2 Factor analysis results

We wished to determine if the reading and IQ variables predicted the participant’s performance on the perceptual load task and if the orientation of the stimuli (vertical along the midline or horizontal with each stimulus lateralized to a visual field) made a difference. Because the eleven reading and IQ variables were often significantly correlated with each other a principle components analysis with orthogonal varimax rotation was undertaken to both simplify the number of predictive variables and create independent predictive factors. Parallel analysis of the eigenvalues indicated that a three-component model was most appropriate which agreed with a visual examination of a Scree plot. Loading scores greater than .30 are shown in Table 2 for three components and together these components accounted for 72.39% of the variance for the entire set of variables. The first component had high positive loadings for reading comprehension (.669) and the IQ measures (.803 to .952), and a moderate loading for written content (.461). This *Comprehension/Intelligence* component accounted for 27.63% of the total variance and indicates that higher intelligence values are strongly associated with reading comprehension abilities and the ability to reproduce previously read content when writing. The second component had high loadings for reading accuracy (.887), reading rate (.870), the rate of spelling errors (-.621) and the speed of digit naming (.651). This *Speed/Accuracy* component accounted for 23.95% of the total variance and indicates that faster reading speed and faster digit naming are associated with improved reading accuracy and, interestingly, fewer spelling errors while writing. The third component had high loadings for the written content produced (.651), the number of words written (.931), and the total amount of time taken (.871). This *Writing Ability* component accounted for 20.81% of the variance and indicates that the participants who wrote more produced a greater amount of content and, of course, took longer to complete the task. When age was included in the factor analysis, it did not load highly on any of the three factors described and reduced the cumulative predictive value of the three-factor model. When a fourth factor was considered, age loaded highly, but none of the other variables had their highest loading on that factor. It was therefore not included in the calculation of the factor scores and was used on its own in the subsequent linear regressions.

5.3.3 Linear regression results

These three reading components were used to predict both error rates and response times in the perceptual load task. Differences in the number of errors made on Redundant and Mixed trial types (Accuracy Costs) were calculated for each participant for both the vertical and horizontal trials. Differences in the response times to Redundant and Mixed trials were also calculated for the vertical and horizontal trials (Speed Costs). All possible models were considered (SPSS Inc.) to determine the best predictors of both errors and response times. The Speed/Accuracy component was a significant predictor of the difference in response times to redundant and mixed trials, but only in the horizontal configuration ($F(1,51) = 6.81$, $p = .012$). Speed/Accuracy did not predict response time differences in the vertical orientation, and neither the Comprehension/Intelligence component nor the Writing Ability component contributed in a meaningful way to either the vertical or horizontal trials. This confirms our general prediction that participants with better reading performance demonstrate greater costs on the perceptual load task for mixed trials, but only for Speed/Accuracy abilities. In contrast, the difference in accuracy between mixed and redundant trials was not predicted by the Speed/Accuracy component or the other components (Table 3). Age was not a significant predictor of performance on the perceptual load task and, when considered alongside the three reading factors, did not change the pattern of results.

5.4 Discussion

The underlying objective of this final experiment was to begin to better understand the relationship between ASD and other cognitive disorders in which IHT deficits have been supported. We did this by focusing on the relationship between IHT and a skill that is commonly impaired, rather than on specific diagnoses. We assessed IHT in an NT group by examining their performance for a behavioral task in which effective integration between hemispheres should have distinct detrimental effects. This was considered in relation to different language-related tests to determine which aspects of reading can be used as predictors of interhemispheric connectivity. Performance related to reading rate, reading accuracy, and spelling was significantly predictive of the IHT measure; individuals who performed worse on this subset of reading measures had decreased discrepancy of response time differences between mixed and redundant trials.

Examining overall performance for mixed and redundant conditions reaffirmed that, in general, simultaneously processing different, and therefore more, information is more difficult than processing redundant information. In the vertical orientations, mixed conditions impose more information than redundant conditions. Horizontal conditions, however, involve transfer of information between hemispheres, introducing an additional component that interferes with processing, especially affecting performance for mixed conditions. Results show that participants showed a greater performance decrement for mixed conditions in the vertical, compared to horizontal, orientations. In horizontal conditions, each stimulus is initially projected to different hemispheres, as they are presented to different visual fields. However, in vertical conditions, each hemisphere immediately gets information about each stimulus, as both top and bottom stimuli are centrally presented. This confirms that the behavioral task adequately imposed increased load in the mixed trials. Thus, initial isolation of information in horizontal conditions may help with processing of mixed conditions by alleviating some of the detrimental effects of interference. Since the expected overall results were confirmed, we can assume that individuals who have impaired interhemispheric connectivity will exhibit performance on mixed trials that does not significantly differ from performance on redundant trial in horizontal conditions (Holtzman & Gazzaniga, 1985).

After including the performance variables, those related to speed and accuracy were significant for predicting our measure of IHT. This component consisted of reading accuracy, reading rate, rapid naming, and spelling performance. Individuals who performed worse on the measures included in this component showed less difference for the mixed trials compared to redundant trials, as expressed by response time. This is comparable to the pattern of performance observed in split-brain patients and suggests some degree of interhemispheric underconnectivity in these individuals, relative to those who performed higher in this reading subset. Furthermore, this component was only predictive for the horizontal conditions and not the vertical conditions. If the component could predict performance for both, we would not be able to rule out the possibility that it is instead predictive of processing capacity, rather than interhemispheric connectivity and integration. The finding that the Speed/Accuracy component was predictive for the horizontal condition and not the vertical condition is valid confirmation that IHT differences contribute to specific types of reading performance.

As a disorder diagnosed by behavior, discriminating ASD from other disorders diagnosed by similar behaviors is challenging. None of the participants in this research had a current diagnosis, allowing us to focus on a family of impairments that overlap in ASD (Nation et al., 2006) and other disorders, such as dyslexia (Shaywitz & Shaywitz, 2005), ADHD (Rasmussen & Gillberg, 2000), and SLI (Mackie et al., 2012). This experiment employed a unique method for exploring one theory behind different disorders. We sought to identify a direct relationship between IHT and a specific skill impacted in each of these diagnoses. Results indicate that IHT can be predicted, to a certain degree, based on specific language measures including reading accuracy, rate, and spelling. Although this is a limited subset of skills, this compelling finding offers preliminary support for emphasizing the need to understand how certain IHT deficits lead to certain symptoms, rather than to certain diagnoses. By confirming this relationship in a population without any clinical diagnoses, we provided a foundation for further pursuit of how distinct disorders of higher order cognition can share the same underlying theory of underconnectivity.

5.6 Tables

Table 1: Descriptive statistics for all measures (N = 53).

	Mean	SD	Range
Age (years)	23.4	8.59	18-58
IQ	98.36	12.34	73-130
LQ	62.89	32.76	70-100
YAA-R reading comprehension			
Comprehension (maximum = 15)	8.49	2.38	3-12
Accuracy (maximum = 492)	480.7	9.05	40-492
Reading rate (words/minute)	151.62	23.13	73.07-195.5
YAA-R written précis			
Content (maximum = 20)	8.43	2.62	3-15
Time (seconds)	325.98	137.37	115-814
Rate (words/minute)	22.03	4.93	8.78-35.7
Spelling error rate	180.72	236.31	0-1445.78
YAA-R rapid naming			
Digits (words/second)	3.01	0.73	1.5-4.58
YAA-R writing speed			
Handwriting speed (words/minute)	28.35	4.47	19.5-41.5

Table 2: Factor loadings from IQ and reading variables.

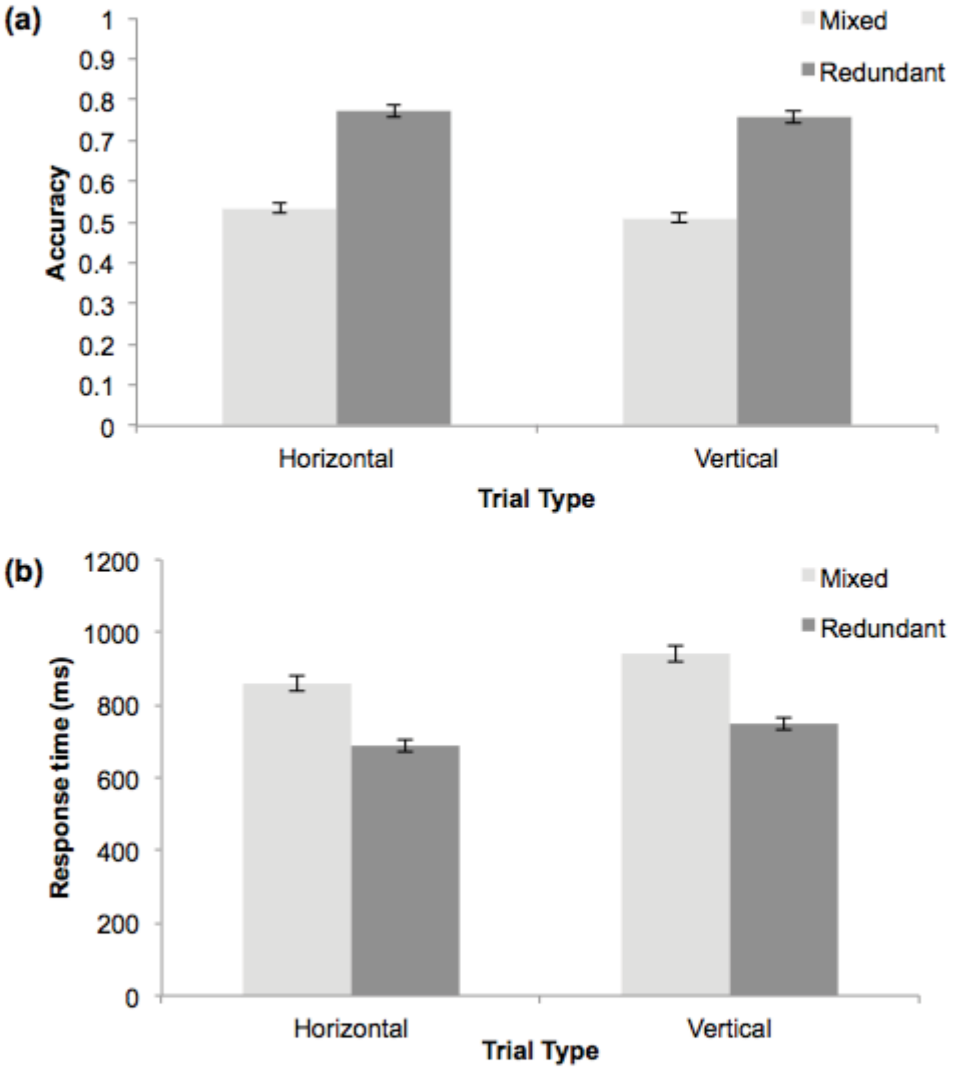
	Loadings		
	Factor 1: Comprehension/ Intelligence	Factor 2: Speed/ Accuracy	Factor3: Writing Ability
IQ			
Full-2	.952		
Vocabulary	.803		
Matrix reasoning	.851		
YAA-R reading comprehension			
Comprehension	.669		
Accuracy		.887	
Reading rate		.870	
YAA-R written précis			
Content	.461		.651
Time			.871
Words written			.931
Spelling error rate		-.621	
YAA-R rapid naming			
Digits		.651	
Percentage of total variance	27.631	23.954	20.806

Table 3: Regression analysis for Speed/Accuracy component as predictor of response time differences in the horizontal condition.

Predictor	**B**	**SEB**	**ß**	**t**	***p***
Component 2: Speed/Accuracy	-101.588	38.940	-.343	-2.609	.012

5.6 Figures

Figure 1: Overall perceptual load performance. Error bars represent standard error of the mean. (a) Average accuracy for mixed and redundant trials for the horizontal and vertical conditions. Performance was significantly worse for mixed trials, regardless of orientation. (b) Average response times (ms) for correct trials for mixed and redundant trials for the horizontal and vertical conditions. Response times were significantly prolonged for mixed trials in both conditions.



Chapter 6: General Discussion

ASD is currently diagnosed based on observable behaviors, despite the general consensus that it has a physiological basis. Although there are numerous reports of underconnectivity in ASD, a theory of generally impaired cortical integration does not fully explain the variation of symptoms and severity in this spectrum disorder. Additionally, it is unclear how it can simultaneously be proposed and supported in other behaviorally diagnosed disorders. The goal of this research was to identify how IHT deficits contribute to the characteristics associated with ASD to identify more accurate ways to mark the disorder, based on its cause, to promote optimal efficiency with diagnosis and treatment. Quantifiable methods of assessing IHT, such as with neuroimaging, can be implemented as part of diagnosis before a child begins exhibiting noticeable impairments in cognition and behavior, potentially allowing for earlier intervention.

The present research explored these key issues through a multifaceted assessment of IHT. In our initial studies, we compared performance between an ASD and an NT group in two behavioral paradigms that have previously revealed distinct results in patient populations with impaired IHT. We found support for IHT deficits in ASD by demonstrating that this group performed comparably to populations with callosotomy and AgCC. We subsequently built upon these findings to assess the impact of IHT deficits on brain development. By measuring asymmetry in ASD, we tested the theory that IHT deficits inhibit typical development of cerebral lateralization (Bloom & Hynd, 2005). In combination with our initial findings, these results depict a consistent account of how IHT deficits and the consequent impact on development of lateralized networks support ASD as a disorder of underconnectivity. An important caveat to consider in all research demonstrating underconnectivity in a specific population is that it does not account for how this theory has been proposed in other distinct populations. To work towards an integrative exploration of this issue, we demonstrated that, in an NT population, there is a direct relationship between performance on IHT tasks and language tasks that are impacted in ASD and other disorders. Individuals who performed worse in regards to reading speed and accuracy showed less performance decrements for increased perceptual load, suggesting greater isolation between hemispheres. Taken together, the present findings provide support for the profound involvement of IHT deficits on cognitive functioning and how they lead to a set of symptoms that determine the diagnosis.

Problems with IHT can, at least in part, be attributed to alterations to the structure of the corpus callosum. Although studies have shown differences in each subregion of the corpus callosum, these are not necessarily the same in each person. Different subregions could be impacted to different degrees in any given individual with ASD. The subregions that are affected should determine which cortical areas will be affected by IHT deficits. This is important to note, as not every task involving IHT will be impacted across the population. Consequently, more typical patterns of asymmetry may develop for some domains that recruit regions that are not affected by IHT deficits. We have supported this by showing a juxtaposition of reduced asymmetry in ASD for human faces, but comparable asymmetry to NTs for robot faces. This suggests that individuals with ASD categorize these stimuli differently and consequently recruit different regions of the brain where IHT and, thus, asymmetry are not equally impacted. This variation in altered regions of the corpus callosum, IHT, and asymmetry may be directly correlated with the variation of symptoms within this disorder.

General alterations to IHT in underconnectivity syndromes have several underexplored implications. One definitive advantage to better understanding ASD as a disorder of interhemispheric underconnectivity is that this information can potentially be utilized to improve the efficacy of diagnostic evaluations. The portion of the Diagnostic and Statistical Manual of Mental Disorders (DSM) that describes the guidelines and criteria for diagnosing ASD has been significantly updated in the last few years (Mandy, Charman, & Skuse, 2012). This suggests that, as the current understanding of the disorder evolves with research developments, new information can be applied to promote more accurate diagnoses. With increasing support for IHT deficits in this population, behavioral tasks and neuroimaging data, such as those presented in this research, can be used to complement the existing, relatively subjective, criteria provided in the DSM-5. For example, part of the battery of assessments included in making a diagnosis could incorporate perceptual load tasks to test hemispheres isolation and neuroimaging methods to test for asymmetry. Additionally, methods utilizing these principles can potentially be used for early screening. Children often do not receive their diagnoses until they are 3-4 years old (Siegel, Pliner, Eschler, & Elliot, 1988), and, consequently, they begin intervention after the optimal time window in which brain networks are the most plastic (Fenske, Zalenski, Krantz, & McClannahan, 1985; Simmeonson, Olley, & Rosenthal, 1987). One advantage of fNIRS is that it can easily be used with infants (Bunce et al., 2006), so it can help identify asymmetry abnormalities at an early age. This will provide early warning for parents so they can have their child formally tested sooner. Although these methods for testing IHT deficits should not be determining factors for diagnosis on their own, they will add more objective parameters to identify ASD at an earlier age and help increase the reliability of diagnosis between clinicians.

After a diagnosis of ASD has been made, the intervention methods implemented must challenge a disorder that involves a physical alteration in the brain. It is unknown whether these materials should be constructed in a manner that exploits the deficiencies and strengths associated with interhemispheric isolation or if they should help promote integration. For example, one method is to take advantage of hemisphere isolation by sending different input to each hemisphere to maximize information acquisition. In NT's, IHT causes interference when conflicting information is presented to each hemisphere (Holtzman & Gazzaniga, 1985). However, this can potentially benefit individuals with impaired IHT in controlled educational settings specifically designed to exploit hemisphere isolation. Presenting different information to each hemisphere (i.e. via visual or auditory mediums) can maximize efficiency for learning so that both hemisphereare simultaneously processing. This takes advantage of IHT by assuming that decreased sharing of information between hemispheres will allow them to be active at the same time, while processing twice the amount of information.

Although exploiting IHT deficits may offer some benefits for a limited range of intervention methods, promoting integration may have better long-term and more generalizable outcomes. Research has demonstrated remarkable callosal plasticity in children with AgCC and patients who received callosotomy in early childhood, compared to patients who received callosotomy in adolescence or later (Lassonde, Sauerwein, Chicoine, & Geoffroy, 1991). Therefore, interhemispheric pathways can potentially be established through intervention methods that promote integration early in life. Art therapy has been considered one method for coordinating activity across brain regions (Silver, 2001). Bilateral art is a specific form of art therapy that requires patients to use both hands to draw in order to simultaneously activate both sides of the brain and help with integration and balancing (McNamee, 2005). Promoting integration can also occur through generalizing a more commonly practiced form of intervention. The picture exchange communication system (PECS) is a more conventional method that improves communication skills by using pictures (Frost & Bondy, 1994). It implements a bottom-up approach by beginning with pictures of objects that the individual would like to request and then builds up to forming complete sentences. PECS has had large success in improving communication (Flippin, Reszka, & Watson, 2010), but generalizing this method to contexts outside of therapy, including school and home, can improve integration by allowing mastery of constituent parts before progression to more complex concepts. For example, understanding the of social interaction may be acquired through breaking down the cause and effect scenarios that typically occur from positively or negatively viewed actions towards others. Following mastery of cause and effect, individuals can build towards understanding more complex and subtle social cues. By operating on the underlying principles of PECS for promoting integration early in brain development, infinitely more domains can be improved.

The results from the current research provide ample support for further investigating ASD under the premise that it is a disorder of hemispheric disconnectivity. Future studies can build on these findings by identifying more precise locations of IHT deficits in ASD, which should correspond to the subregions of the corpus callosum that have structural deficits. By localizing these deficits, the bases of specific symptomology observed within this population can be better qualified. Furthermore, behavioral profiles can potentially be predicted, based on which regions of the cortex are most vulnerable to the localized IHT deficits. This principle can also be applied in other populations to provide more insight to how different diagnoses can all be attributed to hemispheric disconnectivity, but have distinct behavioral profiles. One way to do this is to assess IHT for qualitatively different stimuli within individuals. For example, performance for a match-mismatch auditory task, where a target is presented to one ear and either a match or mismatch to the target is subsequently presented to each ear, can be compared to a match-mismatch tactile task, where a target is presented to one hand and either a match or mismatch to the target is subsequently presented to each hand (Passarotti, Banich, Sood, & Wang, 2002). Because IHT is required when the target matches the stimulus in the crossed ear or hand, IHT deficits can be identified in these populations based on prolonged response times for these crossed conditions. Moreover, auditory and tactile stimuli recruit different regions of the brain and, thus, rely on different corresponding regions in the corpus callosum- the isthmus and anterior midbody, respectively- for IHT. These differences can then be compared within an entire group of individuals within a population to identify where IHT is impacted. Similarly, by testing asymmetry during functional imaging, neuroimaging techniques can infer general locations of IHT deficits based on the cognitive task and, thus, which areas of the brain are being recruited the most. Ultimately, knowing where the IHT deficits occur and, consequently, which cognitive and behavioral domains will be impacted the most, better informs diagnostic and intervention processes.

The importance of identifying the physiological basis of ASD becomes increasingly apparent as the prevalence of this disorder continues to grow. As this research presents, IHT deficits may be key to obtaining a more specific understanding of how ASD is a disorder of underconnectivity. In addition to the immediate detriments they cause during information processing, we have also shown how they can impact the development of brain function, perpetuating the characteristic problems that already emerge due to less efficient information transfer. With this information, future research can build on these results to improve methods for earlier diagnosis that include more objective assessments to not rely solely behavioral observations. These contributions can also pave the way for developing more concrete intervention approaches that will serve both ASD and other populations more effectively.

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