Brain Activation In Children With and Without Autism

During a Tapping Task

by

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ABSTRACT

Autism Spectrum Disorder (ASD) is currently the fastest growing developmental disorder in the United States, affecting 1 in 68 children. Common deficits seen in children with ASD include social and speech impairments, as well as repetitive, stereotyped behaviors. Children with ASD have other deficits that are not explicitly stated in the diagnostic criteria. Studies have shown children with ASD display abnormalities in visual and auditory processing. These abnormalities can hinder their performance on tasks requiring the processing of certain stimuli. Motor deficits are also prevalent in children with ASD. The prefrontal cortex (PFC) is an area of the brain involved with motor planning, decision-making, and top-down processing. Studies have shown abnormal activation levels of the PFC and irregular connectivity to other areas of the brain in people with ASD. This study was conducted to test the motor performance of children with ASD, in comparison to typically developing (TD) children, in response to auditory and visual stimuli, as well as measure the hemodynamic changes in the PFC during the motor performance. This study included 10 total participants, split into 3 groups: an ASD group (N=3), a TD group (N=3), and an adults group (N=4). Participants were required to perform a tapping task, in which they were instructed to respond, and attempt to match a stimulus by tapping a sensor. The stimulus was either a visual stimulus in the form of a blinking light, or an auditory stimulus in the form of a low-level tone. The stimulus was presented at 4 different frequencies: 60bpm, 85bpm, 120bpm, and 150bpm. Under each frequency, participants had 3 trials, for a total of 12 trials under each condition, respectively. A MOART Reaction and Movement Time Panel was used to record the tapping task, while a Functional Near Infrared Spectroscopy (fNIRS) device measured oxygenation levels of the PFC during the task. We compared the relative inter-tap intervals between groups for each stimulus condition and frequency. A three-way repeated ANOVA found a significant interaction ($p=0.18$) between stimulus type and group, as well as a significant interaction ($p=0.20$). These findings support previous findings of visual and auditory processing deficits in children with ASD, as well as motor deficits. Future studies could further explore the effect frequencies of stimuli have on children with ASD, and why they may show greater or worse performance levels in regards to these different frequencies.

Chapter 1

INTRODUCTION

1.1 Overview

Autism Spectrum Disorder (ASD), as defined by the National Institute of Neurological Disorders and Stroke (NINDS), is "a range of complex neurodevelopment disorders, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior" [1]. ASD is the fastest growing developmental disorder in the United States, as indicated by Autism Speaks, affecting 1 in 68 children, of which boys are five times more likely to be diagnosed; in addition, families that have a child with ASD spend on average an additional $60,000 each year [2]. In May of 2013, the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which provides an improved way of diagnosing individuals with ASD [3]. DSM-5 focuses on two major areas for diagnosis of ASD: deficits in social communication, and the presence of restricted, repetitive behaviors, both of which are seen early in development [4]. According to DSM-5, a minimum of 5 symptoms must be seen in children, including all three symptoms of social communication deficits, and two of four possible symptoms related to restricted, repetitive behaviors, in order to be diagnosed with ASD [5]. Two of the potential symptoms for restricted, repetitive behavior are hyper- or hypo-reactivity to sensory stimuli, and stereotyped or repetitive motor movements [5]. The prevalence of sensory system abnormalities in ASD has been supported through multiple studies.

Stereotyped or repetitive motor movements, however, do not specify the nature of motor deficits associated with ASD, which remain uncertain. Motor deficits in individuals with ASD affect their daily activities and ability to participate in group activities in order to have proper social interaction. Impairments in visual and auditory information processing may lead to these abnormalities in motor performance. Therefore, the purpose of this research is to examine the motor performance of children with ASD in response to different stimuli, as well as hemodynamic changes in the prefrontal cortex during the motor performance.

1.2 Visual Processing Abnormalities

Visual processing occurs in the occipital and parietal lobes of the brain via two primary routes, the ventral pathway responsible for detecting objects, and the dorsal pathway responsible for recognizing the location of the object in space [6]. These two pathways communicate with each other via connections to the frontal cortex, which may be critical in visual processing [6]. People with ASD often show abnormalities in visual processing that can be either hypo- or hyper-responsiveness to stimuli [7], which may be explained by increased brain activity in certain areas, and decreased activity in others. A study by DeRamus et al. shows that, during an object location task, children with ASD, when compared to the typically developing (TD) children, had greater activation in the parietal lobe and less connectivity of the temporal area with the parietal and occipital areas [6]. In a different study conducted by Ring et al., brain activation levels were measured between a normal group and a group with ASD, as they completed a visual processing task. The results showed that subjects with ASD, in respect to the normal group, had a greater level of activation in the right occipital

cortex, and less activation in the prefrontal cortex [8]. A review by Dakin and Frith states there are

> "Three classes of perceptual phenomena that have repeatedly been associated with ASD: superior processing of fine detail (local structure), either inferior processing of overall/global structure or an ability to ignore disruptive global/contextual information, and impaired motion perception" [9].

Dakin and Frith also explain two hypotheses that have surfaced from these findings in order to explain the phenomena: the weak central coherence hypothesis (WCC), and the enhanced perceptual function hypothesis (EPF). The WCC is based of the normal tendency for people process global information, or the overall meaning, at the expense of smaller details, whereas people with ASD tend to focus on local information, causing failure to extract the "big picture". This proposes an explanation about why people with ASD can show either inferiority or superiority depending if the task requires global or local processing, respectively. The EPF suggests that people with ASD have facilitated, enhanced processing of stimulus elements caused by an overdevelopment of low-level perceptual operations. Unlike the WCC, the EPF does not assume people with ASD fail in processing global information, but rather that the progression from local visual processing to global visual processing is compromised, leading to a greater retention to local structures [9].

1.3 Auditory Processing Abnormalities

Auditory stimuli are transmitted via a series of specialized nuclei through fiber tracts until it reaches the auditory cortex where the information is then processed [10]. The auditory cortex is made up of the primary area located in the superior temporal gyrus, the secondary regions located in the supramarginal gyrus, superior temporal

gyrus, insula gyrus and angular gyrus, and the associative regions located in the parietal gyrus and inferior frontal gyrus [10]. The primary area is mainly active in the processing of simple stimuli, while the secondary and associate regions are activated to process more complex stimuli [10]. Similar to visual processing, people with ASD, when compared to TD groups, have either lower or greater levels of activation in certain areas of the brain associated with auditory processing [10]. A study conducted by Hesling et al. measured brain activity amongst people with and without ASD as they listened to a connect speech stimulus. The results showed people with ASD, in relation to the TD group, showed lower levels of activation in the left middle temporal gyrus and the left medial prefrontal cortex [11]. Wang et al. measured neural activation during a task that required participants to listen to a short situation and determine if it was ironic or not. It was found that, with respect to the TD group, the ASD group showed greater activity in the temporal regions and the right inferior frontal gyrus [12]. Abnormalities with brain connectivity may explain the presence of auditory processing symptoms in people with ASD. Diffusion tensor imaging (DFI), an imaging technology that can determine neuronal connectivity by measuring water diffusion along what matter fiber tracts, has shown that children with ASD show lower white matter connectivity in several regions of the brain, including regions crucial for the exchange of auditory information within hemispheres [13]. The Neural Complexity Hypothesis (NCH) is a theory designed to explain auditory processing in ASD. The theory states that, in tasks involving simple auditory stimuli, people with ASD display superior performance, whereas in tasks involving more complex auditory stimuli, people with ASD display inferior performance [14].

1.4 Prefrontal Cortex

The prefrontal cortex (PFC), located just behind the forehead, is thought to have a significant role in cognitive control, and is responsible for regulating behavior as well as regulating thoughts during short-term and long-term decision-making. The PFC plays a crucial role in top-down processing, in which internal states or intentions guide behaviors [15]. It is also important in situations when the "mappings between sensory inputs, thoughts, and actions either are weakly established relative to other existing ones or are rapidly changing" [15]. The PFC is divided into different areas; with each area having connects to different cortices of the brain. The lateral PFC, especially the dorsolateral and ventrolateral areas, receives information from the visual, auditory, and somatosensory cortices [15]. It has also been found that the dorsolateral PFC has connections to several premotor areas in the brain [16]. This may explain how the PFC has control over behavior. Studies that involve some level of auditory or visual processing have shown abnormal brain activity in children with ASD. Choi et al. used an auditory discrimination task in a study in which children were required to listen to auditory stimuli presented at different frequencies. Results from the study showed that children with ASD, when compared to the TD children, had reduced brain activity, especially in the right dorsolateral PFC [17].

1.5 Motor Deficits

Behavioral studies have shown that children with ASD display a wide range of motor deficits [18]. Green et al. conducted a study to investigate motor impairments in children with ASD using Movement Assessment Battery for Children (MABC) [19]. In the group of children with ASD, 79% were determined to have definite motor impairments, 10% of which had borderline problems [19]. Another study, conducted by

Leonard et al., motor skills were tested between infants at risk for ASD, and infants not at risk; 17 of the at risk participants displayed difficulty in developing fine motor skills, and were later diagnosed with ASD [18]. While it still remains unclear, studies have been conducted to determine if these motor impairments are strictly associated with ASD, or a broad range of developmental disorders. Dewey, Cantell, and Crawford tested and compared motor skills amongst 5 groups of children with different disorders: ASD, Developmental Coordination Disorder (DCD), ASD with Attention Deficit Hyperactivy Disorder (ADHD), ADHD without ASD, and TD [20]. It was found that children with ASD had significantly lower scores than all other groups in a test of basic motor skills [20]. One idea for the presence of motor deficits in children with ASD relates to abnormal neural connections. Mostofsky, Burgess, and Gidley Larson tested motor skills of children with ASD and ADHD while using anatomic magnetic resonance imaging [21]. The results showed a significant difference between motor skills and left motor cortex white matter levels [21]. This study supports the idea that motor deficits could be caused by abnormal neural connections.

ASD is the fastest growing developmental disorder in the United States. While the public view tends to focus mainly on the social irregularities, people with ASD tend to have problems in other aspects as well. Visual processing and auditory processing abnormalities are common amongst people with ASD. Studies that involve some level of auditory or visual processing have shown that people with ASD, when compared to TD individuals, have abnormal levels of brain activation in certain areas, and tend to have lower levels of connectivity between areas of the brain. People diagnosed with ASD tend to have difficulties, to a certain degree, in motor development. The PFC is involved in motor function, and abnormal levels of

activation in people with ASD could explain a reason for these motor deficits. There are three specific aims in this study.

1.5.1 Specific Aim 1: Will children with ASD show different behavioral performance on the tapping task compared to children without ASD?

Hypothesis: Children with ASD will have larger deviations in relative inter-tap intervals (RITI) during all four frequency conditions in a tapping task as compared to TD children

1.5.2 Specific Aim 2: Will children with ASD respond differently between the auditory and visual stimuli?

Hypothesis: Children with ASD will have smaller deviations in the auditory than in the visual conditions in the tapping tasks.

1.5.3 Specific Aim 3: Will children with ASD show a difference in the hemodynamics of the PFC compared to children with ASD?

Hypothesis: Children with ASD will have less prefrontal cortex activity indicated by lower values of oxygenated hemoglobin as compared to children without ASD during tapping tasks.

Chapter 2

Methods

2.1 Participants

A total of 10 male individuals participated in this study. A group of three children made up the ASD group. To be qualified for the ASD group, the children had to meet criteria under the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as well as had a previous diagnosis by a professional. Children in the ASD group had to follow directions as well as understand the researcher. Three age- and gender-matched children made up the TD group. Exclusions of participants included previous head injury, open forehead wound, history of seizure disorder, or an allergy to rubbing alcohol. The average age of the two groups was 13.7 ± 2.7 years. The third group consisted of four adults who were healthy and had no family history of mental disease. The average age of the adult group was 25.9 ± 5.09 years. Participants were excluded if they had a previous head injury, open forehead wound, history of seizure disorder, or an allergy to rubbing alcohol. All procedures were approved by the University of Delaware Institutional Review Board prior to participant recruitment and data collection.

2.2 Instrumentation

This study used two devices to collect data: the MOART Reaction and Movement Time Panel (MOART), and the Functional Near Infrared Spectroscopy device (fNIRS). The MOART panel has multiple touch sensitive keys that can be

used for different tests, as well as lights and a built in speaker to present stimuli. In this test, the MOART panel was used to measure the reaction time of participants in response to different stimuli. The fNIRS device is a sensor pad that has four light sources and 10 light detectors, which sense light in a total of 16 channels. It detects hemodynamic changes stimulated by brain activity based on the optical properties of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb). The sensor pad is placed over ones forehead and emits infrared light into the prefrontal cortex at two different wavelengths, 730nm and 850nm. Oxy-Hb and deoxy-Hb absorb different amounts of photons in different infrared wavelengths [22], which allows one to determine the concentration of oxy-Hb and deoxy-Hb in the PFC. Infrared light is emitted into the forehead, where the photons are either absorbed or scattered. The scattered photons follow an arch-shaped path back to the scalp, and are then collected by the light detectors on the sensor pad. The fNIRS sensor pad was used to measure levels of oxy-Hb and deoxy-Hb in the prefrontal cortex while participants performed the tapping task.

2.3 Procedure

Participants were invited to the Human Performance Lab at the University of Delaware. Upon arrival, they were briefed on the study and tasks they would be performing, and signed the inform consent if they were over 18, or had a legal guardian sign if the participants were under the age of 18. Participants were instructed to sit in a chair positioned so the MOART panel was in front of them at a comfortable level. Alcohol swabs were used to clean the fNIRS sensor pad and the forehead of participants, where the sensor pad was then placed securely for the duration of the task. A resting level of oxy-Hb and deoxy-Hb was collected for each participant at the

beginning of testing. The tapping task consisted of two different tests in which the participant was presented with either a visual stimulus in the form of a light on the MOART panel, or an auditory stimulus in the form of a low-tone beep emitted from the MOART panel. Each test consisted of four conditions in which the stimuli were presented at 4 different frequencies: 60 beats per minute (bpm), 85 bpm, 120 bpm, and 150 bpm. The order of conditions was randomly assigned. Participants were given three trials for each condition, for a total of 12 trials under each test. Each trial lasted 25 seconds. Participants were instructed to respond to the presented stimulus by tapping a sensor located in the middle of the MOART panel. The stimulus remained constant for each trial, however the conditions were selected at random. Participants were given a practice test for each stimulus prior to starting the test.

2.4 Data Processing

The MOART panel data shows the time (ms) at which the stimulus was presented, and the time (ms) at which a tap was recorded. From this data, the Inter-tap Interval (ITI) and the Relative Inter-tap Interval (RITI) were calculated. To normalize the data, the first five seconds of each trial was removed from the data. The ITI is the time it took between consecutive taps, and was calculated by finding the difference between the participant's taps (tap 2 – tap 1, tap 3 – tap 2, etc.). Each condition has an optimal ITI where two consecutive taps are made exactly as the stimulus is presented. Those values are 1000ms, 705ms, 500ms, and 400ms for 60bpm, 85bpm, 120bpm, and 150bpm, respectively. The RITI was calculated by dividing the ITI of each trial by the optimal ITI of each respective condition. A RITI of 100% indicates the ITI matched the optimal ITI. A RITI greater than 100% or less than 100% indicates a RITI longer or shorter than the optimal ITI, respectively. The data collected from the fNIRS

sensor pad displays the micromolar (μm) amount of oxy-Hb and deoxy-Hb absorbed in the PFC during each tapping task and at rest. The concentration of oxy-Hb (μm) and deoxy-Hb (μm) were calculated for the resting period, the tapping task with the auditory stimulus, and the tapping task with the visual stimulus for each participant, respectively. Changes in oxy-Hb and deoxy-Hb concentration levels from resting to visual and auditory tapping conditions were calculated, respectively, for further analysis.

Chapter 3

Results

3.1 Tapping Data

The performance on the tapping task of each group is reported in Table 3.1. Normalized RITI percentages for each frequency with the auditory and visual stimulus are reported in Figure 3.1 and Figure 3.2, respectively. A three-way repeated measures ANOVA was used to examine the main effect of type of stimulus, frequency of tapping, and group, and the interaction between the three factors on the tapping task. The results found a significant interaction between type of stimulus and group, *F(2, 7) = 7.546, p = 0.18, partial eta squared = .683,* as reported in Figure 3.3. A main effect of frequency was also found, *F(3, 5) = 8.712, p = 0.20, partial eta squared = .839.*

Table 3.1: Performance during tapping task of each group.

	Frequency (bpm)	ASD	TDC	Adults
Auditory	60	97.02% ± 2.21%	101.80% ± 3.67%	99.94% ± 0.17%
	85	85.60% ± 21.90%	97.19% ± 2.25%	99.18% ± 0.43%
	120	91.30% ± 5.48%	100.31% ± 0.63%	100.03% ± 0.19%
	150	93.11% ± 10.81%	101.49% ± 2.47%	100.06% ± 0.12%
Visual	60	60.12% ± 31.96%	103.79% ± 7.72%	99.99% ± 0.12%
	85	76.02% ± 18.82%	112.69% ± 24.52%	100.02% ± 2.35%
	120	87.58% ± 16.44%	94.76% ± 0.85%	100.53% ± 3.64%

150	97.55% ± 23.28%	95.47% ± 3.28%	105.41% ± 16.19%

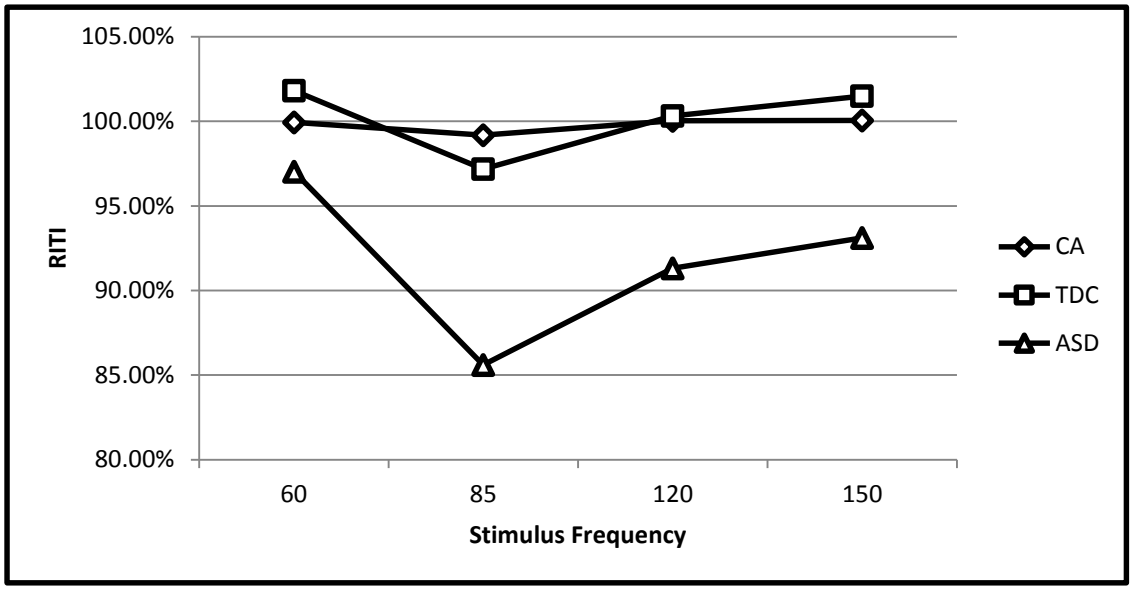

Figure 3.1: Performance of each group in response to an auditory stimulus

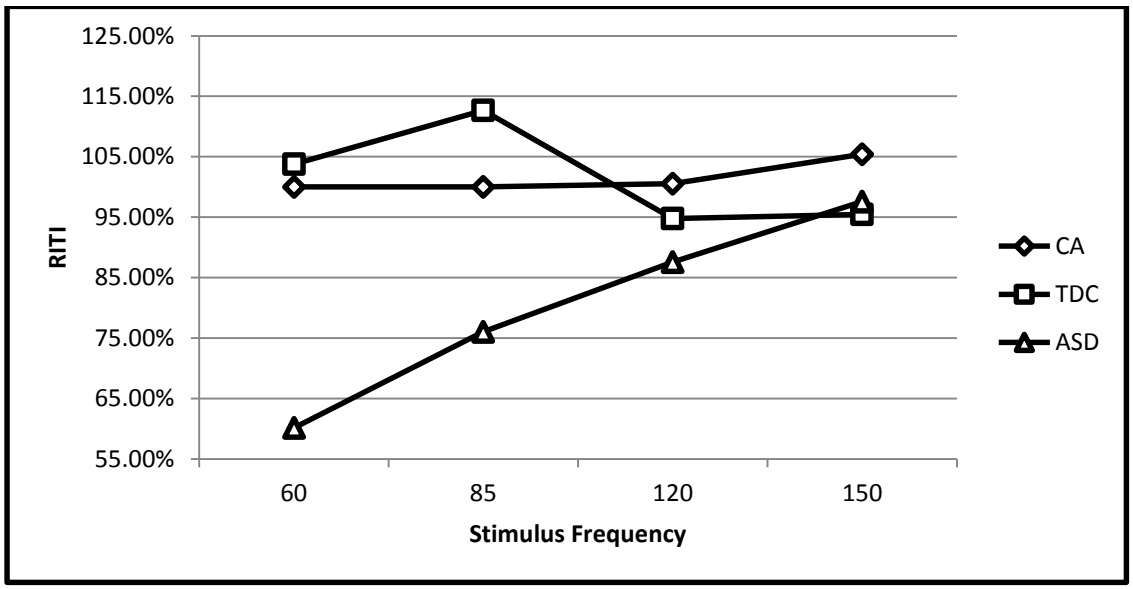

Figure 3.2: Performance of each group in response to a visual stimulus.

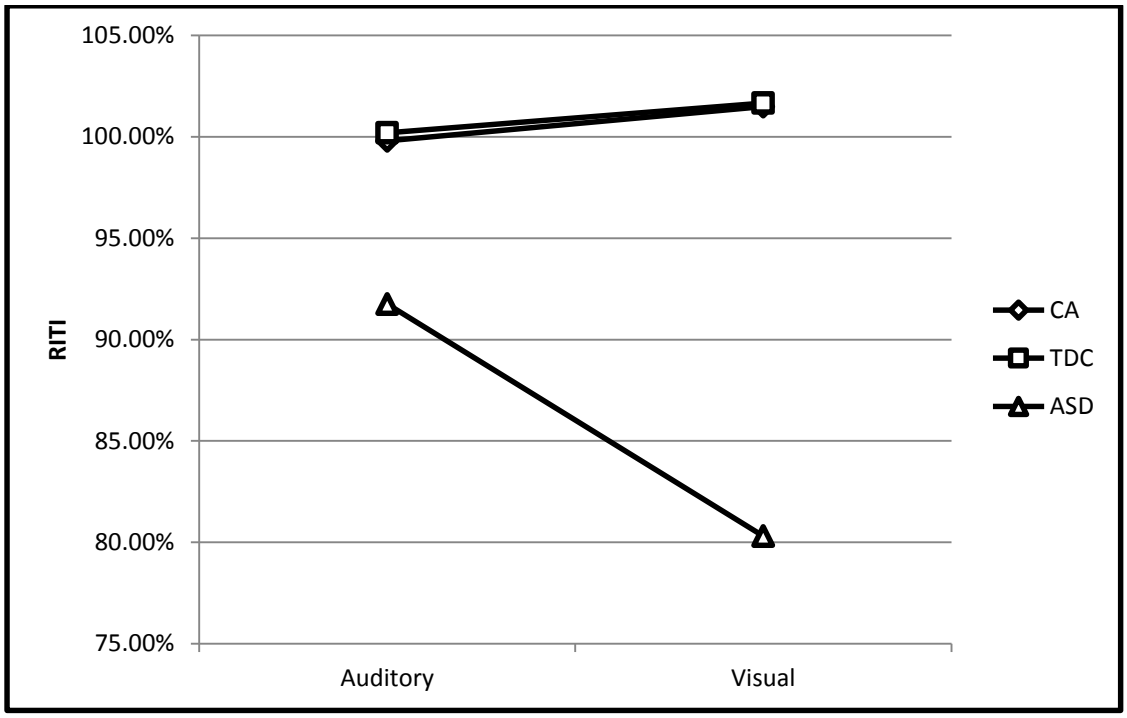

Figure 3.3: Performance of each group in response to visual and auditory stimuli.

3.2 fNIRS Data

The gains in oxy-Hb and deoxy-Hb concentration from rest to tapping conditions of each group are reported in Table 3.2. Two-way repeated measures ANOVA was used to examine the effect of type of stimulus and group, and their interaction on the concentration of oxy-Hb and deoxy-Hb. A significant effect of type of stimulus on changes of deoxy-Hb concentration was found, *F(1, 7) = 20.302, p = .003, partial eta squared = .744.* Concentration of deoxy-Hb decreased when participants engaged in tapping activity. The amount of the decrease in deoxy-Hb was significantly smaller during auditory trials, than decreased during visual trials. A significant interaction between type of stimulus and group was also found, *F(2, 7) = 6.122, p = .029, partial eta squared = .636.* No significant effect of all the factors and

interaction between factors on changes of concentration of oxy-Hb was found. There was no correlation between oxygenation and tapping performance.

Table 3.2: Gains in oxy-Hb and deoxy-Hb from rest to tapping conditions of each group.

		ASD	TDC	Adults
Oxy-Hb (μm)	Visual	1.956 ± 2.773	-2.632 ± 3.183	0.413 ± 0.684
	Auditory	1.650 ± 2.407	-4.826 ± 2.934	1.380 ± 0.959
Deoxy-Hb (μm)	Visual	0.005 ± 1.262	-4.664 ± 1.744	-1.564 ± 0.408
	Auditory	1.814 ± 1.504	-4.703 ± 1.742	-0.183 ± 0.629

Chapter 4

Discussion

This study was conducted to test the motor performance of children with ASD, with comparison to children without ASD, in response to different stimuli, as well as hemodynamic changes in the PFC during motor performance. The TD children had adult-like motor performance during the tapping task under both the auditory and visual stimuli, in which no RITI fell below 94% of the OITI. Children in the ASD group, however, performed significantly worse during both. These results can be explained by deficits in visual and auditory processing in children with ASD. During tasks that require visual processing, it has been found that children with ASD, when compared to TD children, have greater activation levels in the occipital cortex [8]and less connectivity to other areas of the brain [6]. In tasks requiring auditory processing, children with ASD, in comparison to TD children, show both greater levels of activation in the temporal region [12]and lower levels of activation in the temporal region [11]. In comparison to the TD group, the ASD group displayed shorter ITI for each stimuli and frequency, except when the tapping task included a visual stimulus presented at a frequency of 150bpm, in which the ASD group had an ITI closer to the optimal ITI than did the TD group, as seen in Figure 3.2. Children in the ASD group had an ITI that was similar to the TD group during the tapping task with an auditory stimulus presented at a frequency of 60bpm, as seen in Figure 3.1. Since the performance data was normalized, it may explain why the ASD appeared to preform better than the TD group during the 150bpm tapping task. In Figure 3.2, the ASD

group had poor performance for the other 3 frequencies, with 60bpm being the worst. As the frequency increased, better performance was seen, however this could be from the children not attempting to match the stimulus, but rather tapping on their own regardless of the stimuli. While their RITI may have been closer to the optimal ITI, it does not necessarily support better performance, but rather they continued to tap at their own pace as the optimal ITI became faster.

When comparing between auditory and visual conditions in the ASD group, there was significantly better performance for the children during the auditory condition. It has been studied and reported that children with ASD have deficits in both visual and auditory processing. The NCH may help explain why the ASD group performed better with the auditory stimulus than with the visual stimulus. This hypothesis states that children with ASD tend to perform better in auditory processing tasks with a simple auditory stimuli, and as the stimuli becomes more complex, their performance becomes worse [14]. The auditory stimulus was a simple low-level tone, therefore did not require much processing, which may have allowed the ASD to show a greater perform level than in response to the visual stimulus.

There was no significance found in the hemodynamics of the PFC between groups. There were limitations in the number of participants in the study, which may explain why no trend or significant data was found. The study required participants to perform a motor task, which may also explain no significant difference. Brain activity was only measured in the PFC, so we were not able to measure activity levels induced by the task in the motor cortex. While the PFC operates in motor planning, this was a simple task, which may not have required top-down processing, and therefore did not cause noticeable changes in oxygenation of the PFF. A different approach to

processing the fNIRS data may have shown differences in the PFC oxygenation levels. Different parts of the PFC have neural connections to different areas of the brain, and will show more or less activation depending on the task. Comparing oxygenation levels of a select few channels, especially those covering the parts of the PFC involved in auditory and visual processing, may have shown differences between the groups, rather than looking at the averages across all 16 channels.

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