

Electrophysiology of Inhibitory Control in the Context of Emotion Processing in Children with Autism Spectrum Disorder

**by
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Ethics Statement

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or

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Abstract

Autism Spectrum Disorder (ASD) is an increasingly common developmental disorder that affects 1 in 59 children. Despite this high prevalence of ASD, knowledge regarding the biological basis of its associated cognitive deficits, including emotion processing and inhibitory control abnormalities, remains scant. In this study, I aimed to identify altered neurophysiological responses underlying inhibitory control difficulties in the context of emotion processing in ASD, together with their associations with various domains of cognitive and social function, and age. This was accomplished by assessing electroencephalographic recordings during an emotional go/nogo task alongside various parent rating scales of behaviour. Event related potential N2 component amplitudes were reduced in children with ASD compared to typically developing (TD) children. Consistent with previous findings, increased age correlated with improved behavioural accuracy and reduced N2 amplitude in the TD group, indicating that as these children develop, their neural systems underlying inhibition become more efficient. However, these associations were not observed in the ASD group. Relations between various behavioural scores and N2 amplitude were also only significant in the TD group, revealing an association between increased N2 amplitudes and improved executive control abilities and decreased autism traits in these children. The newly discovered findings of differences in neural processing between children with ASD and TD children during an emotional inhibitory control task, alongside a lack of correlation between these neural responses, age and various behavioural scores in the ASD group, provide a potential neurophysiological indicator of atypical development of inhibitory control mechanisms in children with ASD.

Keywords: Autism Spectrum Disorder, EEG, ERP, Inhibitory Control, Emotion Processing, Neuropsychology, Cognitive Neuroscience

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List of Acronyms

ACC	Anterior Cingulate Cortex
ADI-R	Autism Diagnostic Interview, Revised
ADOS	Autism Diagnostic Observation Schedule
ANOVA	Analysis of Variance
ASD	Autism Spectrum Disorder
AQ	Autism Quotient
BASC	Behavior Assessment System for Children
BRIEF	Behavior Rating Inventory of Executive Function
DSM	Diagnostic and Statistical Manual
EEG	Electroencephalogram
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
LV	Latent Variable
MEG	Magnetoencephalogram
MSCS	Multidimensional Social Competence Scale
OFG	Orbitofrontal Gyrus
PLS	Partial Least Squares
TD	Typically Developing
WASI	Wechsler Abbreviated Scale of Intelligence

Chapter 1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects 1 in 59 children, which is an increase in prevalence of 130% since 2002 (CDC, 2014). In addition to core deficits in social communication and restricted and repetitive behaviours and/or interests, individuals with ASD commonly present cognitive abnormalities related to inhibitory control and emotion processing (Hill, 2004; Lopez et al., 2005; Aoki et al., 2015). Despite these known abnormalities, the neural underpinnings of these cognitive deficits are not well defined in children with ASD. The electroencephalogram (EEG) is one tool that is particularly helpful for detecting the neurophysiology of specific cognitive functions including inhibitory control and emotion processing due to its ability to measure, with high temporal precision, electrical activity produced in the brain in response to a given task.

The first overall aim of this study was to identify differences in electrophysiological responses underlying inhibitory control and emotion processing in children with ASD compared to TD children. Given the absence of developmental studies addressing the neural correlates of inhibitory control in children with ASD, the second aim of this study was to identify age-related changes in neural and behavioural responses related to inhibition in children with ASD compared to TD children. By assessing these age-related correlations, this study identified potential neurophysiological indicators of atypical development of inhibitory control mechanisms in children with ASD. The third aim of this study was to identify correlations between neural responses underlying inhibition and behavioural measures of intelligence, executive functions, social competence and autistic traits in ASD and TD children in order to provide a more complete understanding of the social and behavioural functioning of these individuals. Ultimately, these neural responses, developmental trajectories and brain-behaviour correlations aim to aid in treatment and diagnostic efforts for children with ASD.

1.1. Autism Spectrum Disorder

1.1.1. Core Neural Abnormalities in ASD

Studies have shown that at birth, individuals with ASD have smaller than average brain sizes; however, as they approach early childhood, they undergo excessive brain growth, resulting in an increased brain volume compared to TD individuals (Courchesne and Pierce, 2005). This early childhood brain enlargement has been observed in the frontal cortex, inferior frontal gyrus, amygdala, fusiform gyrus and the superior temporal sulcus: areas responsible for memory, emotional expression and social cognition and communication (Supekar et al., 2013; Schumann, Barnes, Lord, & Courchesne, 2009). Studies have also shown increased cerebellar volume in individuals with ASD: an area highly connected to motor coordination (Buxbaum and Hof, 2011). Furthermore, many neuroimaging studies show local overconnectivity within certain brain regions, and reduced connectivity across brain regions in individuals with ASD (Barttfeld et al., 2011). This reduced connectivity across brain regions has been identified between the frontal and occipital regions, the insula and the amygdala, the premotor and sensorimotor cortices, the posterior cingulate and the cuneus, Wernicke's area and Broca's area, and the superior frontal gyrus and the caudate nucleus (Barttfeld et al., 2011; von dem Hagen et al., 2013; Maximo et al., 2014).

1.1.2. Behavioural Abnormalities in ASD: Inhibitory Control

Neural abnormalities in ASD underlie a wide range of functional challenges, including core deficits in repetitive behaviours and/or restricted interests (American Psychiatric Association, 2013). These behavioural deficits are often accompanied by impairments in various executive functions including inhibitory control (Hill, 2004; Lopez, Lincoln, Ozonoff, & Lai, 2005; Mosconi et al., 2009; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008). Inhibitory control is defined as the ability to voluntarily inhibit or regulate a prepotent response, and plays an important role in allowing an individual to suppress unwanted thoughts, emotions, or behaviours (Hill, 2004; Lopez, Lincoln, Ozonoff, & Lai, 2005; Mosconi et al., 2009; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008).

Although behavioural scores can be helpful in determining overall executive functioning skills, behavioural studies have drawn inconsistent conclusions regarding

inhibitory control abilities in individuals with ASD (Geurts et al., 2014). For example, several studies found poorer behavioural performance (accuracy and/or reaction time) of individuals with ASD compared to TD individuals on go/nogo tasks, which require inhibition of a prepotent response (Geurts et al., 2004; Christ et al., 2007; Langen et al., 2012; Xiao et al., 2012; Uzefovsky et al., 2016), whereas other studies reveal no significant differences between ASD and TD individuals in respect to behavioural performance on the go/nogo task (Schmitz et al., 2006; Kana et al., 2007; Sinzig et al., 2008; Lee et al., 2009). Due to the inconsistent results obtained from these behavioural studies, understanding the neurophysiological underpinnings of inhibitory control abilities in ASD alongside behaviour has become highly valuable, especially considering the wide range of neural abnormalities that these individuals typically present.

1.1.3. Neural Abnormalities in ASD: Inhibitory Control

The neural basis of inhibitory control involves a distributed functional network, which has been shown to include the inferior frontal cortex, basal ganglia, left hemispheric mesial, medial and parietal cortices, presupplementary motor area, and a frontal-striatal-thalamic loop (Casey et al., 2001; Rubia et al., 2001; Durston et al., 2002; Stevens et al., 2007; De Wit et al., 2012). The anterior cingulate cortex (ACC) has also been consistently correlated with response inhibition (Rushworth et al., 2004; Kana et al., 2007).

In a magnetoencephalography (MEG) study, Vara et al. showed that adolescents with ASD recruited mainly frontal cortex activity during a go/nogo task, whereas TD individuals showed recruitment in parietal and temporal regions as well (2014). This study suggests a restricted inhibitory control network in individuals with ASD compared to TD individuals. Additionally, using functional magnetic resonance imaging (fMRI), Kana et al. showed that during an inhibitory control task, participants with ASD had less brain activation in areas responsible for inhibition, including the ACC, compared to TD individuals (2007). Individuals with ASD also showed reduced synchronization between the inhibition network (ACC, middle cingulate gyrus and insula) and the right middle and inferior frontal and right inferior parietal regions compared to TD participants (Kana et al., 2007). Altogether, this reduced activation and decreased synchronization in individuals with ASD may suggest that these individuals utilize less automatic/specified inhibitory control mechanisms, and instead, more restricted and/or possibly compensatory mechanisms during an inhibition task.

1.1.4. Behavioural Abnormalities in ASD: Emotion Processing

In addition to deficits in inhibitory control, individuals with ASD commonly show impairments in social communication including reduced eye contact, inappropriate responses to emotional displays, and difficulties processing and recognizing faces and emotion (Dawson et al., 2005). Emotion recognition includes the ability to recognize and accurately identify facial expressions related to emotion, as well as express and regulate one's own emotion (Bland et al., 2004).

Behavioural studies assessing recognition abilities of emotional facial expression in ASD have, in general, been inconclusive due to the conflicting findings between studies. Some studies show intact emotion recognition abilities (Ozonoff et al., 1990; Gepner et al., 2001), whereas other studies show emotion recognition impairments in individuals with ASD compared to TD individuals (Celani et al., 1999; Lindner and Rosén, 2006; Rump et al., 2009; Fridenson-Hayo et al., 2016). Trends in the data do, however, seem to show that individuals with ASD are worse at recognizing emotion when face stimuli are presented quickly, and when emotional expression is subtle (Rump et al., 2009). Age has also been shown to have an impact on the differences in emotion processing abilities between ASD and TD individuals, such that children with ASD who are above the age of 12 typically process emotion no differently than TD individuals, however, at 10 years of age, children with ASD are worse than TD individuals at labeling basic prototypic emotional expressions (Capps et al., 1992; Lindner and Rosén, 2006).

1.1.5. Neural Abnormalities in ASD: Emotion Processing

Neurophysiological research has presented compelling evidence towards deficits in face/emotion processing in individuals with ASD compared to TD individuals. A meta-analysis performed by Aoki et al. investigated the neural bases of atypical emotional face processing in ASD using fMRI and found that individuals with ASD show hyperactivation in subcortical structures, including the bilateral thalamus, bilateral caudate, and right precuneus, and hypoactivation in the hypothalamus during emotional face processing compared to TD individuals (2015). Another study revealed that individuals with ASD show reduced fusiform and amygdala activation during emotion processing compared to TD individuals (Corbett et al., 2009). Emotional faces have been shown to elicit increased effective connectivity between multiple brain regions and the fusiform gyrus, which is the

primary causal input into other brain systems that process social and emotional characteristics of face stimuli (Corbett et al., 2009). One study revealed that the coupling between the fusiform face area and other cortical regions, as well as connectivity within this region, are reduced in individuals with ASD, ultimately potentially affecting their emotion regulation abilities (Khan et al., 2013).

1.1.6. Interaction Between Inhibitory Control and Emotion Processing

Provided that the present research aims to assess both inhibitory control and emotion processing deficits in ASD through an emotional inhibitory control task, identifying the potential interaction between these two cognitive processes is also of particular interest. Evidently, inhibitory control is thought to play a role in many cognitive domains, including emotion regulation/recognition (Dennis et al., 2009). One study showed that reduced inhibition of negative and irrelevant stimuli was associated with negative emotion-regulation strategies such as greater rumination, less use of reappraisal, and more use of expressive suppression (Joormann and Gotlib, 2010).

Literature also suggests that emotional processing can have important impactful effects on executive control. For example, studies have shown that emotional stimuli may result in negative performance outcome during an inhibitory control task, particularly on nogo trials (Verbruggen and De Houwer, 2007; de Houwer and Tibboel, 2010; Kalanthroff et al., 2013). These studies largely explain these results through the attention theory, which states that emotional stimuli interrupt ongoing cognitively-controlled tasks, such as the inhibitory control task, ultimately impairing task performance (de Houwer & Tibboel, 2010; Verbruggen & De Houwer, 2007).

One study by Taylor et al. used MEG to identify neural responses to an emotional go/nogo task, specifically comparing the effects of angry and happy emotions on neural responses to the go/nogo task (2018). Behaviourally, this study found that subjects had greater accuracy to nogo trials in the context of angry rather than happy faces (Taylor et al., 2018). Neurologically, the study showed early activation of the orbitofrontal gyrus (OFG), and greater activation in the left OFG, middle temporal gyrus, left precentral gyrus and left anterior pole in the context of angry faces compared to happy faces (Taylor et al., 2018). Additionally, happy faces elicited earlier neural activation at 200ms in the right OFG (Taylor et al., 2018). Given the shorter latency response observed in this emotional

go/nogo task compared to non-emotional go/nogo tasks, this study suggests that an increase in speed of processing is indicative of an increase in salience induced by emotional stimuli (Taylor et al., 2018). Consistent with the greater neural activation to angry stimuli identified in the study by Taylor et al., other studies showed increased neural responses following fearful, sad and angry stimuli compared to neutral face stimuli (Campanella et al., 2002; Schutter et al., 2004).

Employing a task that involves processing and responding to inhibitory control stimuli as well as processing emotional stimuli tests current divergent theories on the potential interactions between these two cognitive processes. This paradigm design can test if emotional stimuli interrupt ongoing cognitively controlled tasks, effectively reducing attentional allocation to the given inhibitory control task, resulting in reduced performance scores. Furthermore, happy and angry faces may have differing effects on inhibition performance, such as greater accuracy in the context of angry rather than happy faces, as shown in the study by Taylor et al. (2018). Alternatively, happy and/or angry faces may increase salience to the inhibitory control task, increasing the processing speed of the inhibitory stimuli. Determining the direction and degree of interaction between emotional and inhibitory stimuli in children with ASD compared to TD children would, therefore, be highly beneficial. Additionally, by separating the timing of emotional face stimuli presentation from inhibitory control stimuli presentation, the differences in both emotional face processing and processing of inhibitory control stimuli can also be assessed separately across groups.

1.2. Electroencephalography (EEG)

In order to accurately identify neural processes underlying inhibitory control together with face/emotion processing abilities in individuals with ASD compared to TD individuals, this study uses electroencephalography. The EEG was used in this study due to its precise temporal resolution allowing for nearly immediate measurements of neural responses to a given task/stimulus, as well as its ease-of-use with children, and in particular, children with ASD.

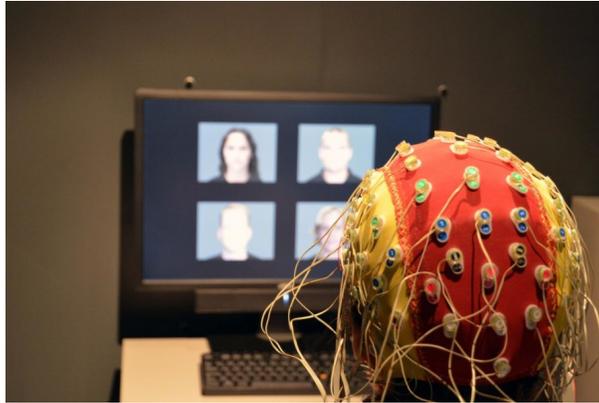


Figure 1: EEG system recording electrical activity in the participant's brain

1.2.1. Event Related Potentials (ERP's)

The high temporal precision of EEG allows us to measure average electrical activity of postsynaptic potentials of a group of synchronously firing neurons produced by a specific timed event on the order of milliseconds. This average electrical activity produced by a given stimulus is referred to as an event related potential (ERP) (Dawson et al., 2005). At the cellular level, ERP's are produced as excitatory or inhibitory neurotransmitters bind to receptors on the membrane of pyramidal cells located in the cerebral cortex, causing ion channels to open or close, in turn, creating a postsynaptic potential as ions flow into or out of the cell (Luck, 2012). A dipole is then formed as this flow of ions occurs at both the apical and basal dendrites, causing negativity at one end of the cell, and positivity at the other (Luck, 2012). When this dipole forms virtually simultaneously in multiple pyramidal cells oriented perpendicular to the cortical surface, electrodes placed on the skull are able to read the summed dipole through the brain, meninges, skull and scalp, as an ERP (Luck, 2012). Since this signal is passed through each of these layers, there is some spatial blurring that occurs due to the spreading out of the voltage signal as it passes through the high resistance of the skull, and low resistance of the overlying scalp, resulting in poor spatial resolution of the EEG signal (Luck, 2012).

An ERP waveform generated after the onset of a given stimulus can be divided into individual 'components' (Figure 2), which are defined by their scalp distribution, voltage (amplitude), polarity (positive or negative going voltage), and time (latency) of maximal response after stimulus onset (Ciesielski et al., 2004). Latencies correspond to neural processing speed such that longer latencies reflect delayed perceptual processes,

and amplitude corresponds to neural resource allocation, or, more specifically, the number of active nearby neurons, the strength and direction of their currents, and their alignment (Bressler and Ding, 2006; Luck, 2012). According to Luck, positivity or negativity of the signal refers to the excitatory or inhibitory nature of the postsynaptic potential, the location of the postsynaptic potential (apical or basal dendrites), the location and orientation of the generator dipole relative to the electrode on the scalp, and the location of the reference electrode (2005).

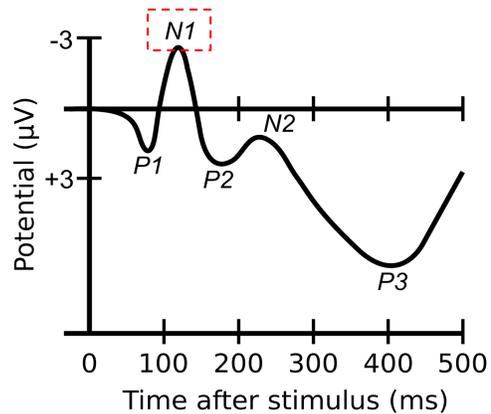


Figure 2: ERP waveform with specific components labeled. The highlighted N1 component depicts a negative going component peaking at approximately 100ms post-stimulus. Figure adapted from commons.wikimedia.org/wiki/File:ComponentsofERP.svg.

ERP components peaking soon after stimulus onset are referred to as exogenous peaks because of their direct relation to stimulus-evoked sensory processing and dependence on the physical properties of the stimulus (Bressler and Ding, 2006). Thus, these components provide important information about the integrity of the cortical and subcortical sensory pathways. Longer latency ERP components are called endogenous components. These peaks represent cortical processing, and are not dependent on external stimulus properties (Bressler and Ding, 2006).

1.2.2. Signal Processing and ERP Analysis

1. Sampling Rate

Sampling rate refers to the number of samples taken per second (Hz) during EEG recording. The sampling rate should be at least twice the highest frequency in the signal otherwise you risk misinterpreting frequency information (i.e. aliasing). If the sampling rate is very high, down sampling is often performed in order to reduce the data file to approximately 250-500 samples per second (Hz) for a typical ERP experiment.

2. Filtering

Filters are used to remove noise obtained from non-neural sources including those from the environment (AC power lines, electronic equipment, and lighting), electronic recording components (thermal, electronic and quantization noise), and physiological sources (changes in skin potential, etc.) (Bressler and Ding, 2006). These non-neural sources can produce noise in the form of very fast voltage changes ($> 15\text{-}100$ Hz), or very slow voltage changes ($< 0.01\text{-}0.1$ Hz). Applying a high pass filter to the raw data allows high frequencies to be passed and suppresses low frequencies from the resulting post-filtered signal. High pass filters are often used to remove a slow signal drift caused by sweat, resulting in a slow change in the electrical potential of the skin. Low pass filters effectively pass low frequencies from the signal, and suppress high frequencies.

3. Epoch

Obtaining ERP components involves marking each event or stimulus onset in the EEG recordings so that these individual events can be averaged together, resulting in a display of repeated brain activity post-stimulus onset (Luck, 2012). Brain activity that is not produced as a result of stimulus presentation will be positive at a given latency on one trial and negative at that same latency on another trial, resulting in a cancellation of this activity when trials are averaged together. Conversely, stimulus locked activity has roughly the same amplitude at a given latency on every trial and will therefore remain in the averaged ERP (Luck, 2012). Each ERP component has a different effect size, and therefore, will require a different number of trials to be in the averaged waveform to produce a reliable and stable peak (Luck, 2012). For example, the P3 peak is a relatively large component (strong effect) and only requires approximately 10-50 trials (Luck, 2012).

4. Artifact rejection

Eye blinks, eye movements, muscle movements, and other physiological artifacts produce voltage potentials that are much larger than the neural event related potentials. Therefore, trials containing these artifacts are typically excluded from the averaged ERP (Luck, 2012). Artifact rejection may be performed via an absolute threshold cutoff, meaning if the voltage of a potential exceeds a certain threshold (typically 100-200 μV), then the trial is rejected.

5. Baseline correction

Baseline correction is used in order to remove any drift (vertical offset) in the signal potentially caused by poor impedances or skin hydration. Mathematically, baseline correction results in a subtraction of the average baseline voltage from each time point in the waveform (Luck, 2012).

6. Mean amplitude and peak latency calculations

As previously mentioned, ERP's are characterized based on their latency and amplitude values. These values are often calculated using peak latency and mean amplitude analyses. Peak latency is calculated as the maximum amplitude contained in a latency window of interest for a given component. The mean amplitude of a component is obtained by measuring the average voltage across a given latency window containing the ERP of interest. This latency window is often defined based on previous literature outlining standard time windows for a given peak of interest, visually inspecting the grand-averaged waveform to identify the window containing maximal component amplitude, and other factors including age. For example, literature consistently shows that children reveal prolonged N2 and P3 latencies compared to adults (Courchesne, 1978; Johnstone et al., 2005; Vuillier et al., 2016).

1.2.3. Statistical Analysis Methods Used in ERP Research

In an EEG experiment involving multiple stimuli conditions, electrode locations, and two or more population groups of interest, a mixed design analysis of variance (ANOVA) (stimuli * electrode * group) is often used. In typical ERP experiments, the dependent variable is the EEG data, such as the mean amplitude or peak latency. The independent variables of interest could include the diagnosis group, the stimulus type, and/or the electrode location. In a situation where two groups are being analyzed, the

diagnosis variable becomes the between subject factor, while the stimulus type and electrode locations become the within subject factors. In an analysis that involves both an independent ANOVA (variation between groups) and a repeated measures ANOVA (RM-ANOVA) (variation within subjects), a mixed design ANOVA is utilized.

A mixed design ANOVA such as this has multiple assumptions that need to be fulfilled (Loiselle, 2006). First, multivariate normality must be met, meaning that individual variables as well as all possible combinations of variables must be normally distributed (Handy, 2005). Second, there must be sphericity for the within-subjects factors, meaning that the variance of the differences between conditions are equal (Loiselle, 2006). Third, there must be independence of scores in different conditions (Vasey and Thayer, 1987). And lastly, there must be homogeneity of variances for the between-subjects factor (Vasey and Thayer, 1987).

1.3. Electrophysiology Reflecting Inhibitory Control and Emotion Processing

1.3.1. Electrophysiology Reflecting Inhibitory Control

The above analyses methods were utilized in the current study to assess ERP's reflecting inhibitory control and emotion processing produced during the presentation of an emotional go/nogo task. The go/nogo task was utilized to assess inhibition because a) it is consistently cited in literature, b) it is easy to accurately perform it, especially for children with ASD, c) one can obtain a large number of trials in a short period of time, allowing for accurate ERP measures and d) it elicits well-defined neural responses upon its presentation (Falkenstein et al., 1999; Bokura et al., 2001). Specifically, EEG studies reveal that during a go/nogo task, two particular ERP components are consistently elicited: a negative component (N2) and a positive component (P3), both directly reflecting mechanisms of inhibition (Falkenstein et al., 1999; Réveillon et al., 2013; Rietdijk et al., 2014).

In initial ERP studies of inhibition, the N2 and P3 were commonly referred to as the "N2/P3 complex", and were often measured as one entity (Okada et al., 1983; Realmuto et al., 1993; Maiste et al., 1995; Azizian et al., 2006). However, more recently,

the N2 and P3 components have been identified as functionally significant. The N2 component appears 200-300ms post-stimulus and corresponds to non-motoric processing stages including detection of novelty, response conflict and error monitoring, whereas the P3 component appears 300-500ms post-stimulus and has been shown to reflect an inhibitory process related to the actual inhibition of the motor response, including selection of responses and confidence of response selection (Donkers and Van Boxtel, 2004; Folstein and Van Petten, 2008; Brydges et al., 2014; Rietdijk et al., 2014; Kompatsiari et al., 2016). In inhibitory and non-inhibitory studies, the P3 is also commonly thought to reflect selective attention (Gray et al., 2004; Polich, 2007). Stimulus factors such as task difficulty, probability of the presented stimulus, and task relevance all also affect the P3 amplitude and latency, such that when stimulus probability decreases and/or task difficulty decreases, P3 amplitude increases (Gray et al., 2004; Polich, 2007). A developmental inefficiency in response inhibition corresponds to an absence or reduction of fronto-central P3-nogo component amplitude (L. M. Jonkman, Lansbergen, & Stauder, 2003), while a deficit in conflict monitoring abilities, also related to inhibitory control, implies abnormalities in the mechanism involving prefrontal/parietal cortex signaling for increased cognitive control, reflected in the N2 component (Botvinick et al., 2001).

The most commonly identified brain regions involved in the functional subsystem that modulates inhibition of the motor response are the prefrontal cortex and the anterior cingulate cortex (ACC) (Bokura et al., 2001; Rubia et al., 2001). Correspondingly, the N2 component observed in both the go (N2-go) and nogo (N2-nogo) trials, and the P3 component observed in nogo trials (P3-nogo) have been localized to frontocentral scalp locations, while the P3 component observed in go trials (P3-go) has been localized to parietal scalp positions (Jonkman et al., 2003; Jonkman, 2006; Jia et al., 2017).

1.3.2. Electrophysiology of Inhibitory Control in ASD

Few studies have investigated EEG/ERP correlates of inhibition in ASD during a go/nogo task, and only two studies have investigated N2/P3 effects during a go/nogo task in these individuals (Høyland et al., 2017; Kim et al., 2018). In the first study, Kim et al. found no significant differences in N2 amplitude on both the go and nogo trials across the ASD and TD groups (2017). They did, however, show significantly smaller go/nogo P3 amplitude differences in the ASD group compared to the TD group, possibly indicating less efficient response priming/selection of nogo trials in the ASD group. The second study

administered a cued-go/nogo task to an older sample of individuals, aged 12-21 years old, and found no significant difference in P3-go/nogo, N2-go/nogo or N2-effect in individuals with ASD compared to TD individuals (Høyland et al., 2017). Although few differences were identified across ASD and TD groups in each of these studies, the study by Kim et al. (2017) tested a small sample size, consisting of 9 individuals with ASD and 17 TD individuals, and investigated a younger age group (kindergarteners with an average age of 5 years), while the study by Høyland et al., (2017) had a larger sample size, however, they investigated participants who were 12-21 years of age. Therefore, electrophysiological inhibitory response differences to a go/nogo task between ASD and TD children during the key developmental period of 6-12 years of age seem to be unknown. Previous studies have shown decreased N2 amplitude with increasing age during this age range in TD children, making developmental studies of these neural processes in ASD of particular interest (Johnstone et al., 2007; Jonkman, 2006).

1.3.3. Electrophysiology Reflecting Face/Emotion Processing

Similar to the electrophysiological responses produced from inhibitory stimuli, it has been consistently shown in literature that face stimuli evoke a distinct pattern of neural activity. Specifically, faces evoke a negative ERP component that peaks at approximately 170ms post-stimulus (N170) in adults (Dawson et al., 2005). Studies have shown that the N170 component latency decreases rapidly with age, and children of approximately 5 years of age elicit an N170 component that peaks at latencies up to 300ms post-stimulus (Taylor et al., 1999, 2001). This component is localized to the posterior temporal lobe and is most commonly greater in the right than left hemisphere (Dawson et al., 2005). The N170 component latency and amplitude are also typically shorter and larger respectively to upright faces and eyes compared to inverted faces and nonface stimuli and are not altered by facial familiarity or recognition of faces (Dawson et al., 2005). The N170 component is instead reflective of early stage processing of faces.

Studies have also shown that the N170 component is modulated by the emotional expression of the face stimuli (Batty and Taylor, 2003; Eger et al., 2003; Japee et al., 2009; Hinojosa et al., 2015). For example, one study showed that positive emotional stimuli evoked earlier N170 components compared to negative emotional stimuli (Batty and Taylor, 2003). However, negative emotions are shown to elicit enhanced ERP activity compared to positive emotions, including enhanced N170 amplitude (Batty and Taylor,

2003; Eger et al., 2003).

1.3.4. Electrophysiology of Face/Emotion Processing in ASD

Electrophysiology studies of children or adults with ASD show slower processing speed for faces depicted by longer N170 latencies, no significant N170 ERP latency differences between faces and nonface stimuli, and impaired right hemisphere specialization for faces, compared to TD individuals (McPartland et al., 2004; Webb et al., 2006; Batty et al., 2011; Hileman et al., 2011). Individuals with ASD are also worse at recognizing faces when this recognition is through eyes versus the mouth, attending to upright faces compared to inverted faces, and recognizing/processing faces as a whole, compared to local facial features, suggesting an emphasis on isolated details rather than global patterns (Dawson et al., 2005). Lastly, ERP studies have shown that individuals with ASD display processing impairments specific to facial expressions of emotion, including reduced and delayed N170 amplitude and latency respectively to emotional facial expressions compared to TD individuals (Dawson et al., 2005; Batty et al., 2011).

1.4. Age-Related Brain Changes and Inhibition

In addition to identifying neurophysiological differences underlying inhibition and emotion processing between ASD and TD children, this study aims to quantify the impact of age on these neurophysiological responses, given that age plays a key role in neural changes throughout development. Specifically, studies have identified important developmental trajectories of structural and functional neural responses relating to inhibition in TD individuals. One study showed significantly reduced ACC modulation (neural generator of the N2 component) for error versus correct trials in TD children compared to TD adults (Velanova et al., 2008). These results suggest improved effectiveness of ACC-related error regulation and conflict monitoring abilities with increasing age (Velanova et al., 2008). Furthermore, EEG studies have shown a reduction in N2 component amplitude alongside improved task performance during an inhibitory control task with increasing age (Johnstone et al., 2005; Jonkman, 2006). These same studies showed conflicting results of P3 component amplitude changes with increasing age; one showing reduced amplitude, and the other showing enhanced amplitude with

increasing age (Johnstone et al., 2005; Jonkman, 2006). Given these differences across age, the N2 component amplitude in particular seems to reveal important developmental information regarding conflict monitoring and response inhibition related processes.

Evidence suggests that individuals with ASD may undergo atypical development of neural networks underlying inhibition. Connectivity studies of TD individuals have shown increased white matter in the prefrontal cortex (an area that contributes to the cognitive process of response inhibition) from childhood to adulthood (Giedd et al., 1999; Paus et al., 2001; Barnea-Goraly et al., 2005; Mesulam, 2009), whereas studies using diffusion tensor imaging (DTI) assessments have shown that individuals with ASD present atypical development of white matter in the prefrontal cortex, the ACC, and the corpus callosum (Barnea-Goraly et al., 2004; Keller et al., 2007; Travers et al., 2012). One study used functional connectivity magnetic resonance imaging (fcMRI) to assess connectivity of the left and right inferior frontal cortex (IFC) with other regions in the frontal, striatal and parietal cortex during a go/nogo task in individuals with ASD aged 8-12 (Lee et al., 2009). They found a negative correlation between age and two right IFC correlation pairs (IFC and bilateral presupplementary motor area and IFC and right caudate) in the ASD group, suggesting atypical development of connectivity between neural regions that underlie inhibitory control in these individuals (Lee et al., 2009).

1.5. Parent Rating Scales of Behaviour

The final aim of this study was to quantify associations of neurophysiological responses (ERP's) to an inhibitory control task in the context of emotion processing, with various parent rating scales of behaviour in both ASD and TD children. The emotional go/nogo task utilized in this study elicits robust ERP responses that are highly linked to inhibition and face/emotion processing. Therefore, it becomes possible to correlate these neural responses with non-neural scores of social and behavioural functioning in children with ASD and TD children in order to obtain a more complete picture of inhibitory control abilities in these individuals. Multiple behavioural measures have shown to be highly useful for identifying these particular executive control and social functions, including the Behavior Rating Inventory of Executive Function (BRIEF), the Behavior Assessment System for Children (BASC-2) and the Multidimensional Social Competence Scale

(MSCS). Identifying the relationship of neural abnormalities with IQ and autistic traits, as measured by the Wechsler Abbreviated Scale of Intelligence (WASI-II) and the Autism Spectrum Quotient (AQ) respectively, also provides important information about traits associated with particular neural deficits.

The WASI-II examination measures the intelligence of examinees aged 6 through 90 years. This test includes both perceptual reasoning abilities (block design and matrix reasoning) and verbal intelligence (vocabulary and similarities). Block design assesses one's ability to analyze and understand abstract visual items by recreating an observed model with blocks. Matrix reasoning involves the participant viewing an unfinished matrix or series then choosing the option that completes the observed matrix/series. The vocabulary subsection involves the participant defining words that are presented visually and/or orally. Lastly, the similarities subsection requires the participant to select from a list of pictures one picture that matches the target picture(s) based on their similar characteristics, as well as identify similarities between words that are spoken to the participant. The WASI-II is often used for research purposes to match experimental groups based on cognitive abilities, with higher scores indicating higher intelligence.

The 50-item AQ parent-report is used to quantify autistic traits including social skills, communication skills, attention to detail, imagination and attention switching/tolerance of change in children 4-11 years old (Auyeung et al., 2008). The AQ is assessed on a scale from 0 to 50, with the response scale being one which assesses the degree to which the parent agrees with the statement about their child, as recorded on a 4-point Likert scale with 0 being definitely agree, 1 being slightly agree, 2 being slightly disagree and 3 being definitely disagree. Higher overall scores signify higher levels of autism traits.

The BRIEF parent-form is used to measure executive function in children aged 5 to 18 years old (Gioia et al., 2000). Executive function is measured by two main categories: behaviour regulation and metacognition. Behaviour regulation is divided into three subgroups, which include i) inhibit (the ability to control impulses/behaviours), ii) shift (the ability to tolerate change or alternate attention), and iii) emotional control (the ability to regulate emotional responses). The metacognition index is divided into five categories, which include i) initiate (the ability to start an activity and develop ideas/problem solving strategies related to the activity), ii) working memory (the ability to retain information during

task completion or when encoding information), iii) plan/organize (the ability to set goals, retrieve main points in presentations, develop steps, etc.), iv) organization of materials (the ability to create order in one's workspace, such as their desk or backpack), and v) monitor (the ability to assess previous work and determine performance level, as well as the ability to reflect on how one's behaviour has affected others) (Gioia et al., 2000). Scores are measured via a 3-point scale that spans from 'never' to 'often', with higher scores indicating greater executive function impairments. This test also includes an inconsistency scale, which measures the degree to which the examinee responded inconsistently to similar questions.

The BASC-2 parent rating scale yields primary clinical, adaptive, and content scores, which are used to determine composite scores of externalizing problems, internalizing problems, behavioural symptoms and adaptive skills in children/adolescents aged 2-21 (Flanagan, 1995). Primary clinical scales include aggression, anxiety, attention problems, atypicality, conduct problems, depression, hyperactivity, somatization and withdrawal. Primary adaptive scales include adaptability, functional communication, leadership and social skills. And finally, content scales include anger control, bullying, developmental social disorders, emotional self-control, executive functioning, negative emotionality, and resiliency. The BASC-2 is measured on a 4-point scale ranging from 'never occurs' to 'almost always occurs'. Higher scores indicate greater impairment on every scale other than the adaptive functioning scales. More specifically, higher scores likely present a range of behavioural challenges including reduced ability to pay attention, speaking or acting inappropriately and difficulties with behavioural and/or emotional regulation.

Lastly, the MSCS is a scale assessing social competence, and is split into seven domains, which include social motivation (level of interest, comfort and enjoyment in interacting with others), social inferencing (ability to interpret social cues and demonstrate 'theory of mind' skills), demonstrating empathetic concern (recognizing the emotions of others and responding empathetically), social knowledge (understanding relationships and social context), verbal conversation skills, (skills necessary for initiating, maintaining and ending reciprocal conversations), nonverbal sending skills (sending non-verbal communication including eye contact, facial expressions, tone of voice, gestures, etc.) and emotion regulation (ability to modulate negative emotion by not acting out when angry or frustrated) (Yager and Iarocci, 2013). The MSCS was designed with the aim of assessing

social behaviours commonly identified among the high functioning ASD population, and sometimes identified in TD individuals presenting milder levels of social impairment (Yager and Iarocci, 2013). Higher scores on the MSCS reflect higher levels of social competence (Yager and Iarocci, 2013).

1.6. Brain-Behaviour Correlations Using Partial Least Squares (PLS) Analysis

One highly effective analysis method used to assess the statistical reliability of associations between neurological responses (e.g. ERP amplitude and/or latency) and another matrix of behaviour variables (e.g. subscales of the WASI-II, AQ, BRIEF, BASC-2 and MSCS) is the behavioural partial least squares (PLS) analysis. In general, behavioural PLS applies one global test and a series of local tests. The global test produces a p-value for each latent variable (LV). These LV's are linear combinations of the original brain and behaviour data. The p-values associated with each LV are based on a series of permutations assessing the effect of the overall correlation between neuroimaging and clinical data. These permutations are obtained through random resampling of scores without replacement. Accordingly, the global PLS test does not require correction for multiple comparisons as it is a single test, making it well suited for complex neuroimaging and/or behavioural data. At the local level, a bootstrapping analysis is performed through random sampling of scores with replacement for both the neural and behaviour domains, producing a score that, when normally distributed, is synonymous with a z-score (Krishnan et al., 2011). In the event of a significant LV, the z-scores for the bootstrap ratio for each individual neural score would indicate which scores contributed to this brain-behaviour association, as well as the strength and direction of this contribution. Standard errors are also calculated via bootstrapping procedure to detect reliability of the correlations between each behavioural score and the corresponding neural scores (Krishnan et al., 2011).

1.7. Knowledge Gap and the Present Study

In summary, the first aim of this study was to test the hypothesis that individuals with ASD show reduced and delayed electrophysiological responses relevant for inhibitory control and emotion processing compared to TD individuals. Specifically, mean amplitudes and latencies of the event related potential components N2, P3, and N170 were examined in order to quantify these responses. The final aims of this experiment were to identify relations among age, parent rating scales of behaviour, task performance, and altered neurophysiological responses related to inhibitory control and emotion processing in individuals with ASD and TD individuals. I predicted that less efficient/implicated brain responses in both the ASD and TD groups would be correlated with younger age, and worse scores of response accuracy, executive function abilities, autistic traits, and intelligence.

To our knowledge, no study has investigated neurophysiological responses of an emotional go/nogo task in individuals with ASD and TD individuals alongside associations of these responses with age, IQ, and behaviour scores of executive functions, social competence, and autistic traits. These investigations are important considering the lack of knowledge and consistency surrounding the relationship between brain and behaviour in the ASD population. The goal of this study is to identify the neural, social and behavioural functioning and developmental trajectories related to inhibition and emotion processing in individuals with ASD in order to ultimately aid in treatment and diagnostic efforts.

Chapter 2. Methods

2.1. Data Collection

2.1.1. Autism Summer Camp

Data were collected from multiple children during four single-day summer camps using methods previously developed by our research group (Moreno et al., 2011, 2015). These camps involved multiple research groups running psychometric, behavioural, and/or neurophysiological examinations to both TD children and children with ASD, allowing for a significant amount of data to be collected from a sizable sample. On each testing day groups of four to six children were tested simultaneously in a large room for a given assessment (see Appendix A), and alternated at one-hour intervals, allowing for approximately 40-minute windows for EEG collection from each group of subjects.

2.1.2. Participants

Participants with ASD had a prior diagnosis of autism as received by a qualified pediatrician, psychologist or psychiatrist associated with the government-funded ASD assessment network or with a qualified private clinic in British Columbia (BC). Over both summer camps 43 TD and 42 participants with ASD were tested, and 30 TD and 25 participants with ASD were retained for analysis of inhibitory control after participant exclusion. Individuals with an IQ less than 70 were excluded from the analysis. Participants with fewer than 30 correct nogo trials, or with a d' score less than 0.5 were also excluded from the analysis (Cohen and Polich, 1997; Luck, 2005; Duncan et al., 2009). The d' score incorporates standard deviation (noise distribution), hit rate (correct go trials), and false alarm rate (incorrect nogo trials) in its formula for calculating overall response accuracy. Finally, significant outliers, based on mean amplitude readings of 1.5 x the interquartile range for the N2 and P3 peaks were also excluded (Leong and Austin, 2006). Due to the inherently low participant count for the sequential N170 component analysis, only extreme outliers, as characterized by mean amplitude readings of 3 x the interquartile range, were removed for the N170 analysis.

For the N2/P3 component analyses, in the TD group, 8 participants were excluded due to low trial numbers, 4 due to outliers and 1 due to a low d' score. In the ASD

group, 11 participants were excluded due to low trial numbers, 3 due to outliers, 2 due to low IQ, and 1 due to a low d-prime score.

Remaining participants were between the ages of 6 and 12, and no significant group differences were identified for age, sex or IQ (Table 1). For the N170 component analysis, 6 participants were removed at electrode P3 in the ASD group, since this site was used as an EOG electrode. In the TD group, 1 participant was removed for qualifying as an extreme outlier.

The following analysis employs a representative sample of the high-functioning ASD population such that participants with ASD with a comorbid ADHD diagnosis are included in the data analysis (Tye et al., 2014). Additionally, in the ASD group, multiple children were diagnosed with other conditions including 2 with learning disabilities, 1 with oppositional defiant disorder, 1 with cerebral palsy, and 1 with developmental coordination disorder. Four of these children in the ASD group were also on various medications including sertraline (1 child), concerta and prozac (1 child), biphentin (1 child), and chlonidine and melatonin (1 child). No child in either group had hearing impairments, and 6 children in the ASD group and 9 children in the TD group wore corrective lenses.

2.1.3. Ethical Considerations

Prior to experimental testing, the principal investigators explained the experimental procedure, the purpose of the study and potential outcomes and risks of the study to the child and their legal guardian(s). The guardian(s) of each participant provided written consent for their child to participate prior to experimental testing. Assent from the child was also obtained prior to, and during, data collection. The estimated risk of a breach of confidentiality in this study is estimated to be extremely low, since data are anonymously coded. No meaningful incidental findings causing significant welfare implications to the individuals can be identified from either the behavioural or EEG data. Although it is possible to identify neuro-electric medical issues using EEG (e.g. epilepsy), the study's investigators were not trained to identify such issues. Furthermore, equipment was properly cleaned and sterilized between participants; therefore, physical harm to the participants was not of concern in this study. The office of research ethics at Simon Fraser University (SFU) approved the ethics for this experiment.

2.1.4. Experimental Design

EEG was recorded during a computerized emotional go/nogo inhibitory response task as depicted in Figure 3. The task presented faces (happy or angry) in the center of the screen followed by the presentation of a shape (circle or a square). Both shapes and faces were randomized. Participants were instructed to press the space bar when they observed a circle on the screen, and to not respond when they observed a square. Squares appeared 20% of the time, and circles appeared 80% of the time. Angry and happy faces each appeared 50% of the time. Participants performed the task in increments of 100 trials; and received 60 second breaks between every 100 trials. A maximum of 500 trials per participant were collected throughout the task. Prior to task presentation, experimenters read from a script containing the task instructions, followed by a brief training period, where participants were able to practice responding to stimuli (10 stimuli during the practice session).

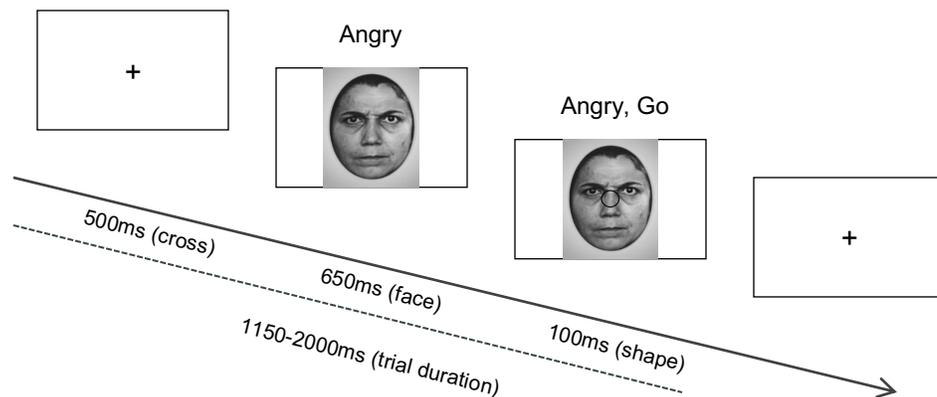


Figure 3: The stimulus display and its time course shown for the go/nogo task displaying the angry, go condition. After the presentation of the fixation cross, an angry or happy face is presented, followed by a circle or a square, to which the participant is either required to respond (circle) or inhibit a response (square).

2.1.5. EEG Acquisition

The EEG data were recorded using 8-channel g.Nautilus EEG systems (manufactured by g.Tec Medical Engineering) at the SFU Behavioural and Cognitive Neuroscience Institute (BCNI). ERPs were recorded from electrodes Fz, Cz, Pz, P3 and P4 (see figure 4 for locations) at a sampling rate of 500 Hz. The electrooculographic (EOG) electrodes were positioned above and beside the left eye as the vertical and horizontal EOG channels respectively. A ground electrode placed on the forehead and a reference electrode placed on the right ear lobe were also used. Electro-gel was used to minimize impedance at each EEG electrode location. Experimenters attempted to achieve EOG and EEG impedance readings of less than 20 kOhms and less than 10 kOhms respectively, however, due to the time restrictions, impedance readings often did not reach this cutoff.

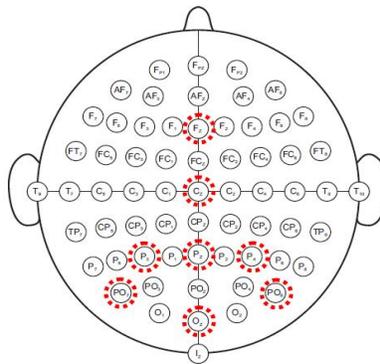


Figure 4: EEG electrode positions (Fz, Cz, Pz, P3, P4) and EOG electrodes (PO7, PO8, Oz).

Prior to behavioural task administration, a resting state EEG measurement was recorded over a period of two minutes. During both the resting state and task recordings, the participant was asked to sit still while focusing on a fixation cross when applicable. Raw EEG data was recorded with the NeuroCatch Platform™ DAS software. Stimuli were presented using the Psychtoolbox plugin in Matlab. All unexpected events during data collection were recorded by examiners including any movements or talking made by the participant, computer malfunctions, etc.

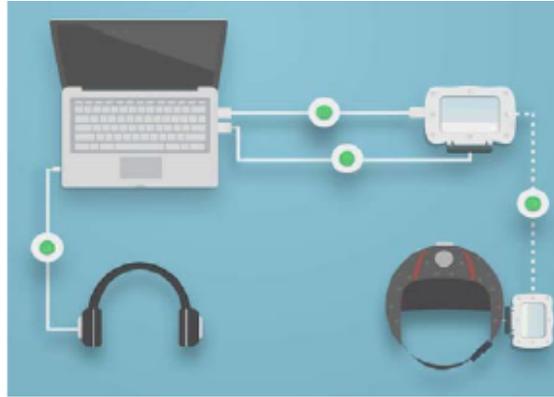


Figure 5: g.Nautilus recording system, including the EEG headset, transmitter, receiving base station, and stimulus computer. Adapted from User Guide to the NeuroCatch Platform™ (Version 1.0), 2017.

2.1.6. Behaviour Score Acquisition

Prior to or during experimental testing at the autism summer camp, parents of the children attending the camp were asked to complete a series of questionnaires including the AQ, BRIEF, BASC-2, and MSCS. During the summer camp, the child completed various other tests, including the WASI-II IQ assessment.

2.2. Data Analysis

Analysis of the anonymized data was performed on password-protected computers at either SFU's BCNI lab, SFU's Digital Health Hub, or SFU's Autism Research Centre. All data analysis was performed using SPSS, Matlab, and the open-source Fieldtrip toolbox. A p-value less than .05 was received as statistically significant in the following analysis.

2.2.1. EEG Analysis

Preprocessing of the EEG data was performed with a 0.5 to 25 Hz, 4th order butterworth bandpass filter (Tanner et al., 2015). Trial epochs of 200ms before the onset of the stimulus to 800ms after the onset of the stimulus were obtained. For analysis of the

N2 and P3 components, these epochs were locked to the onset of the go/nogo stimuli. N170 component analysis epochs were locked to the onset of the face stimuli. Trials with significant eye movements and eye blinks were rejected based on a z-value cutoff of 6 obtained from average amplitude measures retrieved from both EOG electrodes. Trials containing components with peak amplitudes greater or less than $150\mu V$ in EEG channels Fz, Cz, Pz, P3 and/or P4 were also rejected. Stimulus-locked average ERP's were calculated from correctly responded trials, with a 200ms pre-stimulus baseline correction.

The Cz electrode was used to measure mean amplitude and latencies of the N2-go, N2-nogo, and P3-nogo components, while the Pz electrode was used to measure the mean amplitude and latency of the P3-go component (Bokura et al., 2001; Jonkman et al., 2003; Jonkman, 2006; Sokhadze et al., 2009). Finally, the P3 and P4 electrodes were used to measure amplitude and latency of the N170 component. Data obtained from the Fz electrode was not used in any of the analysis, due to broken Fz electrodes on multiple g.Nautilus caps.

Amplitudes of the N2, P3 and N170 components were calculated from the mean amplitude values within latency windows obtained from current literature recommendations and visual inspection of grouped average component latency onset. The peak latency windows of maximal amplitude were 300-400ms for the N2-go/nogo components and 450-600ms for the P3-go/nogo components (Johnstone et al., 2005; Espinet et al., 2012; Vuillier et al., 2016). N170 latency windows of maximal amplitude were calculated at 220-320ms (Taylor et al., 1999; Eimer et al., 2003; Batty and Taylor, 2006). Peak latency values were obtained by selecting the specific time at which the maximal amplitude occurred within the latency window of interest for each component.

The go and nogo N2 and P3 ERP component amplitudes and latencies, as well as the happy and angry N170 component amplitudes and latencies were analyzed at both within-subject and between-subject levels using mixed-model RM-ANOVA's. More specifically, mean go and nogo N2 and P3 component amplitudes and peak latencies were utilized in a RM-ANOVA analysis with Inhibition, being the type of inhibitory stimuli (go, nogo), as the within-subject factor, and Group (TD, ASD) as the between-subject factor. For the N170 analysis, a RM-ANOVA was employed for both N170 amplitudes and latencies with Emotion (angry, happy) and Location (P3, P4) as the within-subject factors and Group (TD, ASD) as the between-subject factor. Post-hoc t-tests were applied for

any significant results obtained in the RM-ANOVA analyses.

2.2.2. Behavioural Analysis

The behavioural task responses (average accuracy and reaction times) of the ASD group and the TD group were calculated and presented as d-prime scores. A RM-ANOVA of go and nogo accuracies was implemented. Differences between angry and happy go and nogo trial accuracy and reaction times were also calculated using a paired-samples t-test, and independent samples t-test for both within-group and between-group analyses respectively.

2.2.3. Correlation Analysis

Correlations between age, significantly different ERP amplitudes and latencies between groups, and behavioural responses, including accuracy and reaction time were investigated for both the ASD and TD groups via Pearson correlations. Correlation between significantly different neural responses across groups and psychometric/behaviour scores from the WASI-II, BRIEF, AQ, BASC-2 and MSCS tests for both the ASD and TD groups were ascertained using a behavioural PLS analysis (McIntosh et al., 1996). This behavioural PLS was based on 10,000 permutations for the global test and 10,000 bootstrap measurements for the local tests.

Chapter 3. Results

3.1. Descriptive Statistics

The inhibitory control analysis was conducted on the EEG and behavioural data of 25 children with ASD and 30 TD children. Group averages of sex, age, IQ and comorbid-ADHD for the inhibitory control analysis (N2/P3) are shown in Table 1. Group averages of sex, age, IQ and comorbid-ADHD for the face processing analysis (N170) are shown in Tables 2 and 3 for electrodes P3 and P4 respectively.

Table 1: The participants retained for analysis consisted of 30 TD individuals and 25 individuals with ASD. From these participants, the table below shows group comparisons of sex, age, IQ and comorbid-ADHD.

Group	N	Sex (number of female participants)	Age	IQ (WASI-II)	Comorbid ADHD
TD	30	9	9.6 (6-12)	107	0
ASD	25	5	10.0 (7-12)	104	6

Table 2: From the participants retained for analysis depicted in Table 1, six participants with ASD were excluded for the N170 analysis at electrode P3. From these participants, the table below shows group comparisons of sex, age, IQ and comorbid-ADHD.

Group	N	Sex (number of female participants)	Age	IQ (WASI-II)	Comorbid ADHD
TD	30	9	9.6 (6-12)	107	0
ASD	19	3	10.1 (7-12)	108	5

Table 3: From the participants retained for analysis depicted in Table 1, one participant with ASD was excluded for the N170 analysis at electrode P4. From these participants, the table below shows group comparisons of sex, age, IQ and comorbid-ADHD.

Group	N	Sex (number of female participants)	Age	IQ (WASI-II)	Comorbid ADHD
TD	30	9	9.6 (6-12)	107	0
ASD	24	5	10.0 (7-12)	105	6

3.2. Behavioural Results

Behavioural results of accuracy and reaction times for both the ASD and TD groups are shown in Table 4 and Figure 6. From the RM-ANOVA, a trend toward a Group main effect ($F(1,53) = 3.662, p = .061, \eta_p^2 = .065$) was observed, however, upon a post-hoc t-test analysis, no significant differences were found between the ASD and TD group on either the go nor the nogo accuracies. An independent samples t-test showed a trend toward group differences of the d-prime score ($t(53) = 1.801, p = .077$), suggesting more accurate responses in the TD group ($d' = 2.13$) compared to the ASD group ($d' = 1.83$). An independent samples t-test of reaction time showed no significant differences across groups. Additionally, no between group or within group differences were found when comparing accuracies and reaction times of both happy and angry go and nogo trials (happy-go, angry-go, happy-nogo, angry-nogo).

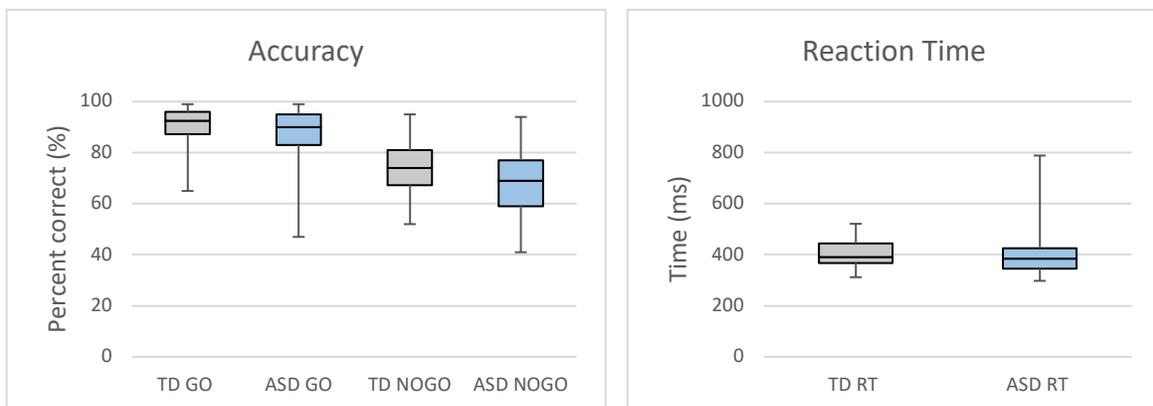


Figure 6: Boxplot diagrams of go and nogo accuracies (left) and reaction times (right) across TD and ASD groups

Table 4: Mean and standard deviation reports of accuracy and response times in TD and ASD groups

Dependent Variable	TD				ASD			
	RT		Accuracy		RT		Accuracy	
	M	SD	M	SD	M	SD	M	SD
Go trials	405.8	52.1	89.5	9.7	405.1	99.2	86.7	11.5
Nogo trials	--	--	74.1	11.9	--	--	69.3	15.9

3.3. EEG Results

Group-averaged ERP waveforms, calculated by the mean of individual subject data, are shown in Figure 7 and Figure 8. A summary of the mean amplitude and peak latency values of the N2, P3 and N170 components are shown in Tables 5-8. A summary of the main effects and interaction effects from the RM-ANOVA's are shown in Tables 9-10.

3.3.1. N2 Amplitude and Latency

Using a RM-ANOVA, a main Inhibition effect for the N2 component amplitude was identified ($F(1,53) = 29.820, p < .001, \eta_p^2 = .360$) at electrode site Cz, indicating a larger N2 amplitude on nogo trials compared to go trials across all subjects. No Inhibition x Group interaction was identified, indicating no significant variance between go/nogo amplitude differences across groups. However, a main Group effect was found ($F(1,53) = 6.939, p < .05, \eta_p^2 = .116$), signifying differences in the go and/or nogo N2 amplitudes across groups. A post-hoc t-test analysis revealed that both the N2-nogo and N2-go peaks were significantly more negative in the TD group compared to the ASD group (*go*: $t(53) = -2.950, p < .01$; *nogo*: $t(53) = -2.041, p < .05$). No significant within group or between group differences were identified for N2 go and nogo latencies.

3.3.2. P3 Amplitude and Latency

Through a RM-ANOVA analysis, a main effect of Inhibition was identified for the P3 component amplitude ($F(1,53) = 12.326, p < .001, \eta_p^2 = .189$), revealing greater P3-nogo amplitudes at electrode site Cz, compared to P3-go amplitudes at electrode site Pz across all subjects. No other significant interactions or main effects were identified for the P3 component amplitude. However, a main Inhibition effect was also identified for P3 component latency ($F(1,53) = 23.144, p < .001, \eta_p^2 = .304$), revealing longer P3-nogo latencies at electrode site Cz, compared to P3-go latencies at electrode site Pz across all subjects. No Inhibition x Group interaction was identified for the go/nogo P3 latencies.

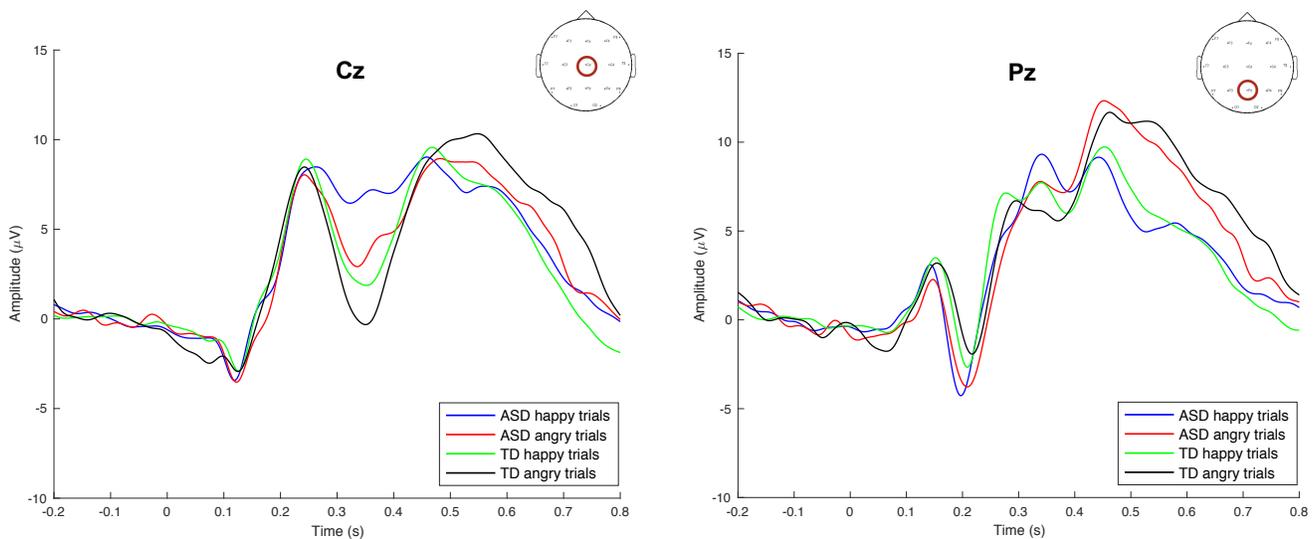


Figure 7: Grand-average go/nogo stimulus-locked waveforms for correct go and nogo trials in TD and ASD groups at electrode site Cz (left) and Pz (right). Mean N2 and P3 component amplitudes were obtained from latency windows of 300-400ms and 450-600ms

3.3.3. N170 Amplitude and Latency

To investigate potential differences between ASD and TD groups for electrophysiological responses relevant to face processing, N170 component amplitudes and latencies were calculated from an average of all trials for each participant. Using an independent samples t-test, results showed no significant amplitude or latency differences between groups, signifying no significant N170 differences between ASD and TD groups.

N170-happy and N170-angry ERP's were also calculated for both the ASD and TD groups at electrode location P3 and P4 (Figure 8). Results from the RM-ANOVA showed no main Emotion effect, suggesting that there were no significant differences in the neural responses to angry compared to happy faces across all subjects. There was also no main Group effect, showing no significant differences between groups on N170 amplitudes and latencies during both angry and happy face processing. However, interestingly, a Location x Emotion x Group effect was identified ($F(1,53) = 6.342$, $p < .05$, $\eta_p^2 = .119$) for N170 amplitude, revealing that the ASD group showed a larger difference between happy and angry trials than the TD group; an effect that was particularly pronounced at the P4 electrode compared to the P3 electrode. No other interaction effects were identified. Since no behavioural differences were identified for angry vs happy effect on inhibitory control response accuracy, and due to low trial numbers, the comparative effect of angry and happy faces on go and nogo neural responses was not analyzed.

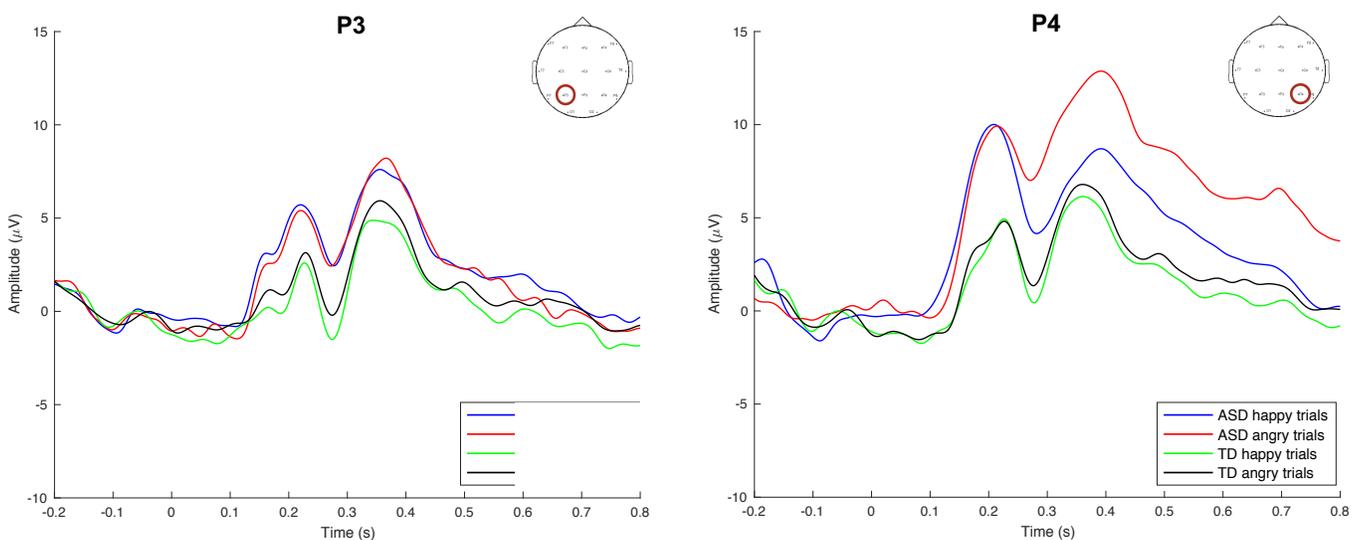


Figure 8: Grand-average face stimulus-locked waveforms for happy and angry trials in TD and ASD groups at electrode site P3 (left) and P4 (right). Mean N170 component amplitudes were obtained from latency windows of 220-320ms at both electrodes.

Table 5: Group mean amplitude at channel Cz for N2-go, N2-nogo and P3-nogo and Pz for P3-go

ERP	TD		ASD	
	Go	Nogo	Go	Nogo
N2	.3878 ± 4.7379	-1.8343 ± 5.1369	4.0048 ± 4.2590	1.0429 ± 5.2857
P3	4.4160 ± 3.3847	6.8079 ± 4.6265	3.5932 ± 2.3757	5.5580 ± 3.9430

Table 6: Group peak latency at channel Cz for N2-go, N2-nogo and P3-nogo and Pz for P3-go

ERP	TD		ASD	
	Go	Nogo	Go	Nogo
N2	.3377 ± .0283	.3361 ± .0315	.3485 ± .0548	.3438 ± .0336
P3	.4734 ± .0398	.5185 ± .0459	.4867 ± .0535	.5204 ± .0548

Table 7: Group mean amplitude of the N170 component at channel P3 and P4

ERP	Channel	TD		ASD	
		Happy	Angry	Happy	Angry
N170	P3	.6357 ±	.9255 ±	2.4959 ±	2.3857 ±
		3.1211	2.6316	5.0189	5.0283
N170	P4	1.3822 ±	1.3696 ±	1.0826 ±	3.4797 ±
		3.9669	4.1339	9.8829	5.8451

Table 8: Group peak latency of the N170 component at channel P3 and P4

ERP	Channel	TD		ASD	
		Happy	Angry	Happy	Angry
N170	P3	.2744 ± .0271	.2695 ± .0284	.2695 ± .0307	.2721 ± .0286
	P4	.2785 ± .0254	.2757 ± .0257	.2708 ± .0347	.2651 ± .0325

Table 9: Main effects and interaction effects from RM-ANOVA analyses of the N2 and P3 ERP components

ERP	Source	Amplitude		Latency	
		F	Sig.	F	Sig.
N2	Inhibition	29.820	.000	.399	.530
	Group	6.939	.011	1.607	.210
	Inhibition * Group	.607	.439	.097	.756
P3	Inhibition	12.326	.001	23.144	.000
	Group	1.715	.196	.557	.459
	Inhibition * Group	.118	.732	.484	.490

Table 10: Main effects and interaction effects from RM-ANOVA analyses of the N170 ERP components

ERP	Source	Amplitude		Latency	
		F	Sig.	F	Sig
N170	Emotion	.416	.522	.134	.716
	Location	.003	.958	3.079	.086
	Group	2.714	.106	.044	.835
	Emotion * Location	.506	.480	.010	.921
	Emotion * Group	.002	.963	.415	.523
	Location * Group	.231	.633	.003	.955
	Emotion * Location * Group	6.342	.015	.308	.581

3.4. Brain-Behaviour Correlation Analyses

3.4.1. Pearson Correlation of Age, D-prime and N2 Amplitude

Given that statistically significant differences between ASD and TD children were identified for N2 component amplitude, this component was utilized in all subsequent correlational analyses. Significant associations between age, d-prime, and N2 ERP amplitude were observed in the TD group as seen in Table 11 and Figure 9, showing that as age increases, N2-go ($r = .532$, $p < .01$) and N2-nogo ($r = .461$, $p < .05$) amplitudes decrease, and d-prime scores increase ($r = .717$, $p < .01$). However, only correlations between age and d-prime ($r = .401$, $p < .05$), and age and N2-go scores ($r = .508$, $p < .05$) were identified in the ASD group.

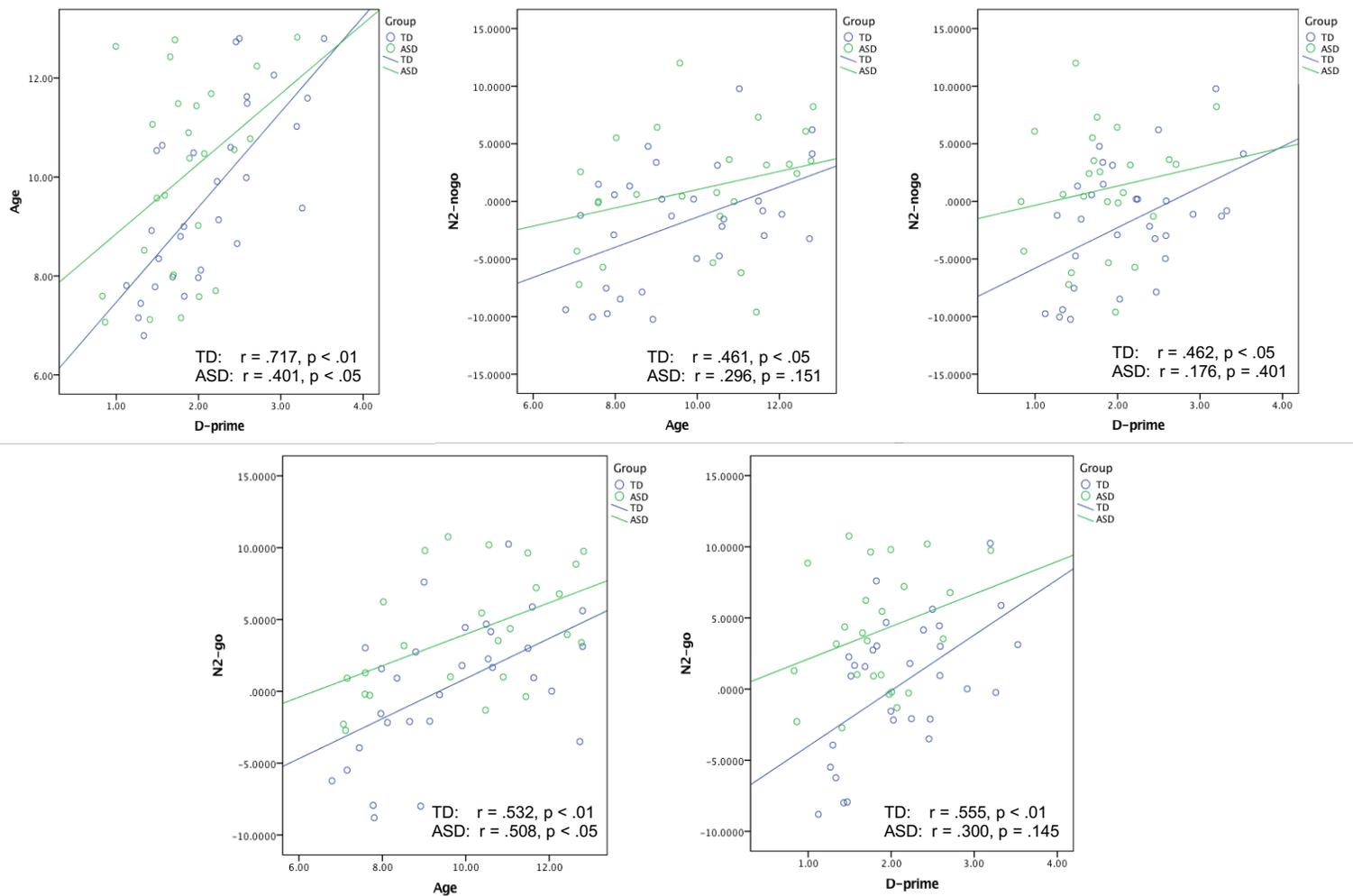


Figure 9: Scatter plot correlations between age, N2-nogo, N2-go and d-prime scores for both the ASD and TD groups

3.4.2. PLS Correlational Analysis of Brain and Behaviour

A behavioural PLS analysis was performed to test for significant associations between the N2 component amplitude and the IQ, BRIEF-2, AQ, BASC-2 and MSCS scores, separately for each group. A significant overall correlation between N2 amplitude and all behavioural scores was identified in the TD group ($p < .05$); however, no significant overall correlation was found in the ASD group. Figure 10 illustrates the correlations between behavioural test subscores and N2 amplitude, alongside their error bars, which reveal an upper and lower error range for the correlation based on a series of

bootstrapping analyses. Given that a high number of error bars in the BRIEF-2 subscores do not cross zero (indicating a reliable brain-behaviour association), the significant correlation between N2 amplitude and behavioural scores in the TD group appears to be driven largely by the BRIEF-2 subscores. The subscores of the AQ also evidently drive this correlation, given their relatively small error bars. Overall, these results from the TD group show that increased N2 component amplitude is associated with improved executive function and fewer autism traits.

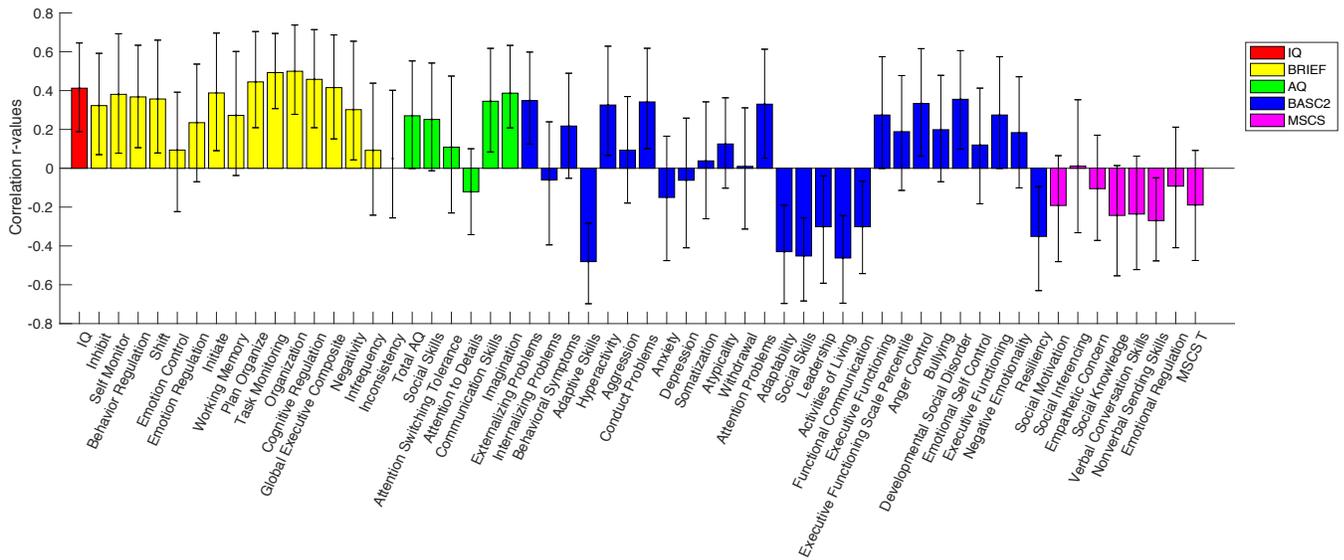


Figure 10: PLS analysis between N2 amplitude and behavioural scores for the TD group. Positive correlation values reflect a positive association with N2 component amplitude. The height of the correlation bars indicates the magnitude of the r-values representing the correlation between behaviour and ERP data, while the direction of the correlation bars indicates the type of association between behaviour and ERP data. A positive bar signifies a positive correlation between behavioural and neural scores (i.e. as the behavioural score increases, N2 voltage also increases). Error bars reveal an upper and lower range for the correlation between behavioural and neural data based on a series of bootstrapping analyses. An error bar that does not include zero indicates a significant correlation between the behavioural variable and N2 amplitude.

Chapter 4. Discussion

Using EEG, we recorded neural responses underlying inhibitory control and emotion processing in children with ASD compared to TD children. Our results show an impaired neural process related to conflict monitoring in children with ASD, evidenced by reduced N2 amplitudes in these individuals compared to TD individuals during an emotional go/nogo task. Furthermore, significant correlations between N2 amplitude, age, d-prime scores, and various behavioural scores were identified in the TD group. These results from the TD population suggest that N2 component amplitude, elicited by a go/nogo inhibitory control task, is an indicator of functional inhibition deficits and is modulated by neural development. Therefore, the absence of these correlations in the ASD group could possibly indicate atypical neurophysiological development related to conflict monitoring in these individuals.

4.1. Behavioural Responses to Go/Nogo Stimuli

Although a trend towards a group main effect for response accuracy was identified via a RM-ANOVA, no statistically significant differences were found between the ASD and TD groups for response accuracy on go or nogo trials using independent samples t-tests. However, a trend towards overall task accuracy differences across groups was also identified in the d-prime analysis, showing slightly better performance in the TD group compared to the ASD group on both go and nogo trials.

Given these results, it stands to reason that children with ASD do not show marked difficulties with performance on tasks requiring inhibition, at least as far as can be seen from the emotional go/nogo task used in the present study. However, Jonkman showed that impulsive behaviour (commonly associated with go/nogo task performance) diminished most significantly after the age of 10 (2006), and if this is also true for children with ASD, the current sample may be too old to accurately identify behavioural differences across groups through task performance analyses. Future studies addressing differences in behavioural effects of an inhibitory control task such as this in a younger age group compared to an older age group, would, therefore, be helpful for clarifying such unknowns. Alternatively, it is possible that individual inhibitory control differences in young children are only distinguishable with objective measures such as EEG.

4.2. Neurophysiological Responses to Go/Nogo Stimuli

The reduced N2-go and N2-nogo component amplitudes in the ASD group indicate that individuals with ASD experience abnormalities with later-stage differentiation of stimuli (i.e. conflict monitoring). The observation of statistically reliable electrophysiological differences related to inhibitory control in the absence of statistically significant behavioural differences may indicate that measurements such as N2 amplitude may be more sensitive markers for inhibitory control deficits in ASD than behavioural measures at this age range (6-12 years). These results are supported by previous findings, showing an absence of behavioural differences paired with significant neurophysiological differences during an inhibitory control task in individuals with ASD compared to TD individuals at age 9-18 (Larson et al., 2012).

Using fMRI, a study by Kana et al. showed that during an inhibitory control task, participants with ASD revealed less brain activation in areas responsible for inhibition, including the ACC (the key generator of the N2 ERP response), compared to TD individuals (2007). The current results of decreased ACC-driven N2 amplitude in the ASD group are consistent with these findings of reduced brain activation in the ACC identified in this fMRI study, and therefore, may also support the theory that decreased brain activation in individuals with ASD is correlated with less automatic inhibitory control mechanisms. Additionally, in the current study, the absence of task performance differences paired with this significant neural response difference between groups may suggest that children with ASD utilize compensatory or less-specified/automatic neural networks to achieve similar behaviour results compared to TD individuals.

The go/nogo task assesses multiple executive functions including inhibition (nogo trial accuracy), and sustained attention (go trial accuracy). These functions are comprised of other processes, such as conflict monitoring and response competition for inhibitory control, which are associated with specific neural regions. Given the multiple functions required to accurately perform the go/nogo task, it is possible that individuals with ASD are less able to effectively integrate functions served by these various neural regions, resulting in a less specified neural network sub serving this performance (compensatory mechanisms).

For both the N2 and P3 component amplitudes, an effect of inhibition was identified

across all participants, showing increased amplitude for nogo trials compared to go trials. Interestingly however, an Inhibition effect for latency was only identified for the P3 component, revealing longer latencies for the nogo condition compared to the go condition across all participants. Taken together, these results may suggest that the increased difficulty of inhibiting a prepotent response compared to continuing a prepotent response requires more effortful processing, evidenced by increased N2 and P3 amplitude to nogo trials, and a slower neural response to nogo trials. The data also show that both ASD and TD children process nogo stimuli at a similar speed, given the absence of a Group x Inhibition effect for N2 and P3 component latency (Magliero et al., 1984).

4.3. Neurophysiological Responses to Face Stimuli

No significant differences in N170 amplitude or latency in response to emotional face stimuli were identified between TD and ASD groups. Additional analysis showed no statistically significant amplitude or latency differences across groups for both the N170-happy and N170-angry stimuli. However, a Location x Emotion x Group effect was identified for N170 amplitude, revealing that at the P4 electrode site, the ASD group showed a larger difference between happy and angry trials compared to the TD group, potentially indicating atypical lateralized response to automatic emotion processing in these individuals.

At a behavioural level, no significant differences of accuracy or reaction time for the happy vs angry go and nogo trials were identified for both the ASD and TD groups. In summary, these results suggest that individuals with ASD a) do not present significant impairments on automatic emotion processing of happy or angry faces at a neural level compared to TD individuals, b) are not affected by the presence of happy vs angry conditions in regard to go/nogo performance accuracy, and c) do not experience go/nogo task performance impairments in the context of either happy or angry face presentation compared to TD individuals.

Given the results in literature suggesting impaired emotion processing abilities in individuals with ASD, it is possible that these findings are reflective of a smaller sample size or inadequate electrode positions. Therefore, larger sample studies and additional

electrodes might be necessary to more accurately reflect neural correlates of emotion processing in children with ASD. Alternatively, differences in neural responses between automatic and deliberate processing of emotional face stimuli may also factor in to the lack of differences observed in the current results. Automatic (employed in the current study) refers to the unintentional processing of stimuli, whereas deliberate refers to processing that involves engaging attention and cognitive control on challenging tasks or intentionally responding to the stimuli. Studies have shown that a lack of attentional processing of emotional expressions, or increasing the difficulty of face discrimination, modulates perceptual processing of faces (Eimer, 2000; Eimer et al., 2003; Sreenivasan et al., 2009). According to these studies, it is possible that deliberate attention devoted to the processing of emotional stimuli would invoke larger N170 amplitudes, and subsequently, show more apparent differences between ASD and TD individuals.

Overall, these results suggest that, at a neural level, children with ASD process automatic emotion stimuli no differently than TD children, and that the presence of angry or happy faces do not impact go/nogo response accuracy significantly differently than the TD group. Therefore, it was assumed that no significant differences in the interaction effect between the presentation of face stimuli and go/nogo neural processing would exist across groups.

4.4. Response Accuracy, ERP Amplitudes, and Age Correlations

Consistent with literature, the TD group showed that increased N2 component amplitude correlates with decreased task performance and younger age (Johnstone et al., 2005b). The correlation between d-prime scores and N2 amplitude in the TD group reveals an effective relationship between efficient/focal neural activation and improved motor response accuracy. These results also support the theory that increasing age results in the development of more efficient cognitive control processes, which require more specified and fewer neural resources. One study showed increased activation of the left superior and middle frontal gyri in younger individuals and enhanced activation in the left inferior frontal gyrus, an area highly correlated with inhibition, in older individuals (Tamm, Menon, & Reiss, 2002). The authors suggest that the more extensive activation

in discrete regions of the prefrontal cortex in younger individuals is due to increased demands and inefficient recruitment of brain regions involved in other important executive functions necessary to perform such a task, including working memory, managing interference, and inhibiting motor responses (Tamm et al., 2002).

Tamm et al., also suggest that the increased focal activation of certain neural regions may coincide with an enhanced ability to strategize and reflect on one's accuracy and precision in order to improve task performance (2002). The current results may, therefore, point towards a compensatory or less focal neural network underlying response inhibition in children with ASD, given their reduced N2 amplitude at a young age. This would imply that these children experience a developmental delay similar to the one observed in the study by Tamm et al. A potentially more diffuse neural network in individuals with ASD through development may reflect a lack or inefficiency of neural resources devoted to effectively organizing, monitoring and strategizing during task performance.

In summary, given that a) no significant relationship was identified between d-prime scores and N2 amplitude in the ASD group, b) a trend towards an across-group difference in task performance was present, and c) decreased N2 amplitude was identified in the ASD group compared to the TD group, it appears that individuals with ASD may be less able to use enhanced or more focal ACC-driven processing to moderately improve their response accuracy compared to TD individuals at a young age. Additionally, given the difference in effective relationship between N2-nogo amplitude and age, and N2-nogo amplitude and d-prime scores in the ASD group compared to the TD group, it is possible that individuals with ASD abnormally develop N2-related processes reflecting top-down regulation of cognitive control and conflict monitoring, potentially indicating the presence of alternative, and less efficient networks responsible for reduced inhibition scores with increasing age. A study assessing the structural neural components of inhibitory control in individuals with ASD would be highly useful for addressing these theories.

4.5. Neurophysiological and Behavioural Correlations

Literature suggests that non-motoric conflict monitoring, and the decision to

withhold a response, reflected in the N2 component, plays an important role in modulating task-driven responses (Bokura et al., 2001; Jonkman et al., 2003; Donkers and Van Boxtel, 2004; Falkenstein, 2006). Therefore, it would stand to reason that the ACC-mediated N2 component would correlate well with other behavioural measures, specifically with those reflecting task-driven responses or executive control, given the role of the ACC in implementing top-down cognitive control. In this study, a correlation between the significantly different neurophysiological response (N2-go/nogo amplitude) between groups, and behavioural data (parent rating scales) was analyzed.

The results showed an overall significant correlation between N2 component amplitude and multiple behavioural scores/subscores in the TD group. Specifically, results showed that as N2 amplitude increases, executive function abilities, as measured by the BRIEF test, improve. This is not surprising, since BRIEF scores are adjusted for age, and therefore, as amplitude increases at a young age (more ideal/specified neural development), their executive function abilities are also enhanced relative to young children with less ideal neural functioning (reduced N2 component amplitude). The results also indicate a reliable positive correlation between AQ and N2 amplitude in the TD group, signifying that as autism traits increase, N2 amplitude decreases, giving further support to the proposal that decreased N2 amplitude is reflective of ASD traits at a young age.

Although correlations between N2 amplitude and the various behavioural scores were not significant in the ASD group, it is possible that with a larger sample size, these effects may become evident. Additionally, despite the neural generator and non-motoric nature of the N2 component, making it relatively optimal for behavioural correlations, it is often difficult to directly compare ERP component amplitudes and/or with various behavioural scores, since the neural generators of these components become more specified during specific tasks such as the go/nogo task, and the scores indicated in the behavioural batteries do not reflect specific brain regions in the same way. Alternatively, it is possible that an abnormal development of the neural processes underlying the N2 component amplitude in children with ASD coincides with a decoupling effect of the N2 amplitude with typical maturational processes such as executive function abilities, explaining the lack of association between N2 amplitude and the various behavior scores assessed in the current study. Despite these theories, the results indicated here are the first to identify associations between neurophysiological responses and the listed behavioural assessment scores in order to aid in a more complete understanding of

inhibitory control in ASD and TD children.

4.6. Limitations

One of the main limitations of the current study is the limited number of electrodes available for analysis. Given that there were only four EEG electrodes, independent component analysis could not be accurately performed. This technique offers a more conservative artifact removal process, as it removes segments of data containing non-neural activity of fixed scalp-amplitude projections, and projects the remaining EEG signal components back into the original time domain (Radüntz et al., 2015). Instead, whole trials were rejected based on threshold values of the EEG and EOG channel data. This method of data cleaning resulted in very few nogo trials (< 30) for some subjects, ultimately leading to rejection of these participants.

Additionally, literature has shown a lateralization effect of inhibitory function (Weisbrod et al., 2000; Bokura et al., 2001) and face processing (Rossion et al., 2003). and with additional electrodes, analysis involving potential lateralization effects during inhibition and face processing could have been employed. Specifically, studies have revealed right orbitofrontal cortex localization for the nogo-N2 component, and left orbitofrontal cortex localization for the nogo-P3 component (Weisbrod et al., 2000; Bokura et al., 2001). Studying these effects could provide important information regarding the specific neurological deficit at hand in individuals with ASD compared to TD controls.

Multiple studies have shown that emotional stimuli have negative effects on performance of an inhibitory control task, suggesting that emotional stimuli interrupt ongoing cognitively-controlled tasks, such as the inhibitory control task, ultimately impairing task performance (Verbruggen and De Houwer, 2007; de Houwer and Tibboel, 2010; Kalanthroff et al., 2013). Therefore, to identify the effect of the presentation of the emotional faces on behavioural task performance, it would be necessary to employ a go/nogo task without the presence of faces. Additionally, if the go/nogo task in the current study was made into a 'secondary' task (depending on the participant's prioritization of the face stimuli), the presence of the faces may have resulted in longer component latencies and reduced amplitudes of the N2 and/or P3 components (Petit, Kornreich, Noël, Verbanck, & Campanella, 2012). Therefore, one further limitation of the study is that our

group did not administer a go/nogo task without the presence of faces behind the shapes. This made it impossible to directly compare the effect of face processing on N2 and P3 component amplitudes and latencies.

The go/nogo task that was used in the current study has a high response accuracy, which was necessary to be able to retrieve a large number of correct trials for ERP analysis, however, this type of task does not test higher cognitive function. Other, more complex inhibition tasks such as the flanker portion of the child Attention Network Task (ANT), where children have to inhibit conflicting flanker information to the target stimuli, have revealed marked inhibition deficits in individuals with ASD, suggesting abnormalities in higher order cognitive function in these individuals. Therefore, it stands to reason that our, more simple, task may not have adequately captured the degree of inhibition deficits in children with ASD (Faja et al., 2016).

Another limitation of the current study is that there were relatively few participants after meeting our exclusion criteria. Ideally, to draw more accurate conclusions regarding developmental neural trajectories, intra- and inter-subject variability and behavioural-neural correlations, we would need to employ a larger sample size.

Chapter 5. Conclusions

Given the high prevalence and reported deficits in executive function, particularly in relation to inhibitory control, and emotion processing, the ultimate aim of this study was to identify differences in neural markers of these deficits in individuals with ASD compared to TD individuals, and compare these neural responses to various behavioural scores including those assessing executive function abilities, autistic traits, social competence and intelligence. The results of the present study reveal similar task performance yet reduced N2 component amplitude in response to an emotional go/nogo task in the ASD group compared to the TD group. It is possible that this reduced neurophysiological output of conflict monitoring is associated with underlying neurological abnormalities including reduced ACC activation and/or other, compensatory networks underlying inhibitory control in children with ASD (Larson et al., 2012). Future source localization studies are required to help identify the source of such cognitive control difficulties in individuals with ASD.

The results also showed that reduced N2 amplitude is correlated with increasing age, improved task performance, improved behavioural scores of executive control, and reduced autistic traits in TD individuals at a young age, revealing important developmental and functional consequences of reduced N2 amplitude. These associations were not identified in the ASD group. Overall, the reduced N2-nogo amplitude in individuals with ASD, paired with a lack of association with task performance, age and various parent rating scales of behavior, may indicate atypical development of neural processes related to inhibitory control in individuals with ASD.

Although experiments using EEG measurements to assess inhibitory control abilities in ASD have previously been performed, no group has assessed neural responses to an emotional go/nogo task alongside behavioural assessments to compare inhibitory control abilities in children with ASD and TD children. By analyzing EEG measurements of inhibitory control, together with age, task performance, and behavioural assessments, we have outlined the relationship between the specific neurological deficit at hand, and particular cognitive and affective difficulties during development. Identifying these neurological responses in the form of ERP component amplitudes produced by a go/nogo task may provide important headway toward effective treatments targeted at these particular neural systems in individuals with ASD at this given age-range.

Furthermore, EEG is, in relative terms, a low-cost method of tracking brain changes, and alongside behavioural tests, could prove to be a highly useful and objective assessment tool for clinicians and therapists to utilize once a supported outline of characteristic neurophysiological responses of inhibition for ASD and TD individuals is determined.

5.1. Future Directions

Given the significant differences in N2 component amplitudes across groups during the go/nogo task employed in this experiment, it would be interesting to administer the same experiment, with a separate conflict-inducing task that also elicits an N2 component, such as flanker, posner-style tasks, or other two-choice tasks (Smith et al., 2010). The flanker task involves the participant responding to stimuli that are flanked by irrelevant stimuli. In response to this task, the N2 is thought to reflect inhibitory processes because of its target-flanker incompatibility effects (Smith et al., 2007). In the posner-style tasks, valid or invalid cues appear prior to the target to which the participant must respond, and the N2 component elicited from these stimuli are larger on invalidly than validly cued trials (Smith et al., 2007). Importantly, both the flanker task and posner-style tasks involve the participant making an overt response to incongruent trials on the flanker task, and invalidly cued trials on the posner task (Smith et al., 2007). Therefore, the N2 in these tasks may reflect conflict of competing responses, as opposed to complete inhibition of the motor response as seen in the go/nogo task. Evidently, employing a go/nogo related task which involves responding to all trials, including stop signals, would allow one to assess the conflict monitoring and categorization abilities of individuals with ASD, without the potential influence/interference of motor inhibition processes. Determining N2 responses to these tasks would also aid in identifying the degree to which the N2 component, reflecting various inhibitory control processes in each task, is a core abnormality in individuals with ASD, or specific to the current sample or given task.

Given the high rate of comorbidity between ASD and ADHD, and the core deficits of response inhibition in ADHD populations, it would be interesting to administer this study on a strictly ASD population, an ASD with comorbid ADHD population, an ADHD population, and a control group. This would provide insight towards the effect of comorbid

ADHD on the response inhibition abilities of individuals with ASD, and would provide meaningful information towards effective treatment efforts.

To verify the current results showing that N2 amplitude decreases with age, further investigation into longitudinal responses to the same go/nogo task should be employed. Alternatively, obtaining a large sample size that is tightly controlled for age, alongside other neuroimaging modalities such as MEG or fMRI would also allow for proper analysis of developmental functional and structural trajectories of neural responses to the go/nogo task.

Measuring the variability of the participant's neural and behavioural responses across different days, time of the day, seasons, etc. could also be helpful for determining the reliability of the current results. Additionally, comparing the observed neural responses to other health measures including genetic, metabolic, oxidative stress-related, immune dysregulation-related, and neurochemical biomarkers could be highly useful for identifying a more 'complete picture' of the biological basis of particular functional abnormalities in ASD (Ragini et al., 2011).

5.2. Significance

EEG is particularly beneficial for identifying neural markers of inhibition due to its precise temporal resolution and high sensitivity and specificity (Cassidy et al., 2012). The current results, which show reduced brain activation of the ASD group to a go/nogo task, differences in neural-behavioural correlations, and differences in affective relationship between neural responses, task performance, and age between the ASD and TD groups, provide robust information regarding the neural and behavioural function and developmental trajectories of children with ASD. Furthermore, acquiring data in an atmosphere such as the one utilized in this experiment, where all data collection is performed in a single room with trained undergraduate/graduate volunteers, provides meaningful translational information. This type of testing simulates school-based or clinical testing that may be performed in a classroom, or by trained clinicians/professionals, and therefore, the current data addresses the quality and meaningfulness of data that would be collected in these particular settings, in order to

ultimately aid in treatment or assessment efforts of individuals with ASD. These types of assessments are made possible by the non-invasive, low-cost, portable and accessible nature of the EEG, which also, again, affords meaningful translational value to the current study.

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Appendix A.

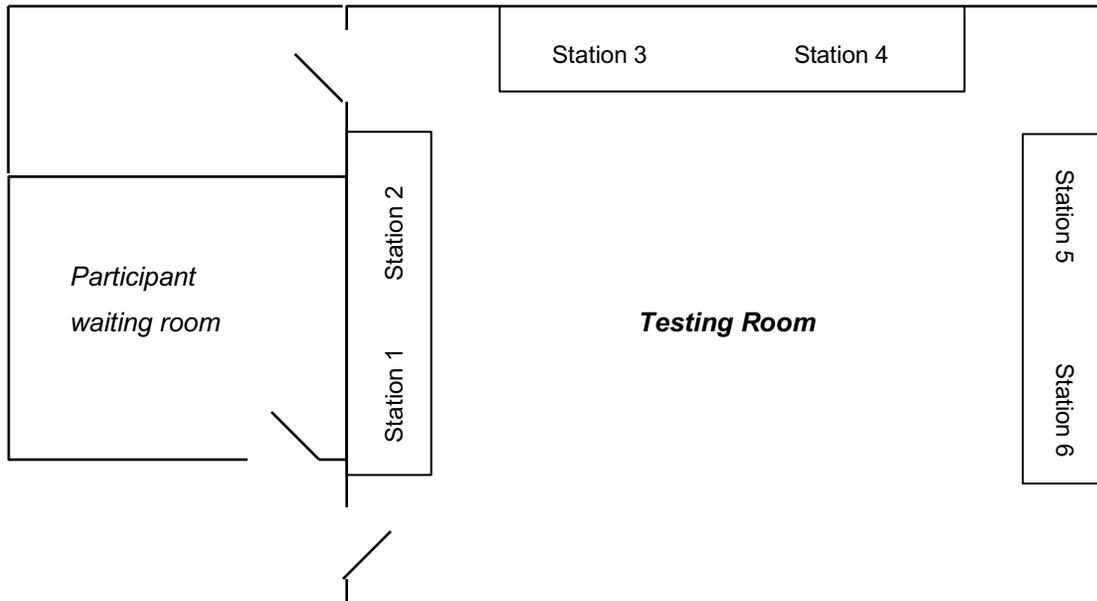


Figure 11: Layout of the autism summer camp testing space in the BCNI lab at SFU Burnaby

Additional summer camp information:

Prior to testing days, 12 graduate or undergraduate volunteers were trained in administering EEG scans using the g.Nautilus EEG systems. Each station at the testing facility was equipped with an EEG system, a stimuli computer (which was used to present the task to the participants), and an EEG acquisition computer. At each station, one volunteer proficient in EEG acquisition was paired with a volunteer experienced in working with children. During testing, the volunteer experienced in EEG acquisition followed an operating procedure for EEG testing specific to the summer camp, while the volunteer experienced in working with children read the task instructions to the participant from a script that was provided to each station. Volunteers were primarily responsible for obtaining assent from the child throughout testing, and taking breaks with the child when necessary. Volunteers were also asked to record all unexpected events during testing such as computer malfunctions, or instances when the participant was off-task.

Table 11: Correlations between age, d-prime, and N2-go amplitude, and N2-nogo amplitude for both ASD and TD groups.

	TD (n = 30)				ASD (n = 25)			
	Age	D-prime	N2-go amplitude	N2-nogo amplitude	Age	D-prime	N2-go amplitude	N2-nogo amplitude
Age								
Pearson Correlation	1	.717**	.532**	.461*	1	.401*	.508**	.296
Significance		.000	.002	.010		.047	.010	.151
D-prime								
Pearson Correlation	.717**	1	.555**	.462*	.401*	1	.300	.176
Significance	.000		.001	.010	.047		.145	.401
N2-go amplitude								
Pearson Correlation	.532**	.555**	1	.794**	.508**	.300	1	.693**
Significance	.002	.001		.000	.010	.145		.000
N2-nogo amplitude								
Pearson Correlation	.461*	.462*	.794**	1	.296	.176	.693**	1
Significance	.010	.010	.000		.151	.401	.000	

** correlation is significant at the 0.01 level (2-tailed)

* correlation is significant at the 0.05 level (2-tailed)