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Theta Wave Coherence in Pre-Semantic Processing: An EEG study of Autism Spectrum Disorder

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Honors College of Arts & Sciences Undergraduate Thesis

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Abstract

Language deficits are a pertinent and characteristic feature of Autism Spectrum Disorder (ASD), particularly in higher-level functions like semantic processing. Compared to the typically developing (TD) population, people with ASD have shown significant differences in neural semantic processing activity after the presentation of a stimulus. However, lower-level functions like word decoding are typically intact, suggesting a disconnect between these two processing levels in the brain. Theta coherence has been linked to the presence of such lower-level, pre-semantic activity in the TD population. The present study used electroencephalography (EEG) to measure the presence of theta coherence and examine the pre-semantic neural connectivity of participants with ASD to determine whether early disruptions might contribute to semantic misunderstandings. Gaining a better understanding of neural communication during pre-semantic processing would further the current understanding of language impairments in ASD and could also lead to more targeted and effective therapies.

Introduction

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that manifests itself through numerous persistent behavioral and neurological deficits. According to the DSM-5, the diagnostic criteria for ASD are the presence of enduring social communication deficits and two or more restricted and repetitive behaviors, but it is often characterized by many added deficits as well (APA, 2013). Such deficits include impaired theory of mind, difficulties with language production and comprehension, inflexibility in learning, and a host of social deficits and difficulties (Simonoff et al., 2008; Ben-Sasson et al., 2009; Seltzer et al., 2003).

Due to ASD being a spectrum disorder, each case is highly specialized and unique, and consists of an individualized set of symptoms with varying severities. Current therapy involves intense behavioral interventions that can begin as soon as a diagnosis is made and can help with symptom mediation, but there are no disorder-modifying treatments to date. Despite this lack of treatment, the disorder is growing in prevalence. Both the frequency of diagnosis and prevalence have steadily increased between 2000 and the most recent CDC survey in 2016, in which the prevalence was 18.5 per 1,000 children, meaning that approximately 1 in every 54 children would receive an ASD diagnosis (CDC, 2018). The variation in symptoms between cases of ASD makes the disorder extremely difficult to study, but its prevalence highlights the importance of continuing research in the field. In studying the symptomatology of ASD, language impairment and semantic misunderstandings are especially interesting symptoms to consider, as their impacts are widespread and highly variable.

The neurological basis of such impairments and misunderstandings has been challenging to investigate. It is known that ASD has varying physiological effects on a number of areas throughout the brain (Courchesne et al., 2011; Schipul et al., 2011; Ha et al., 2015; Mohammen-Rezazadeh et al., 2016). Due to a lack of understanding of the physiological and neurological changes that occur, ASD continues to be diagnosed using behavioral measures (Baird et al., 2003). In addition to the known atypical behaviors used to diagnose ASD, a number of cognitive deficits have also been observed in these individuals. Word decoding, which is the ability to identify a word and its correct pronunciation, independent from its meaning, is one component of cognition that can be measured to test for deficits (Swank & Catts, 1994). When looking at the ability to decode words and understand their meanings both in isolation and in different contexts, participants with ASD have shown intact word decoding abilities, but deficits in holistic language comprehension (Frith & Snowling, 1983; Whitehouse & Harris, 1984; Huemer & Mann, 2009; Norbury & Nation, 2010). These findings suggest that lower-order processing is functional in ASD, and that dysregulation in higher-order processing could be contributing to the well-established comprehension deficits.

Semantic Processing

Semantic processing, a higher-order cognitive process, refers to the ability to receive a stimulus, whether spoken or written word, picture, or sound, and apply meaning to it based on previously stored knowledge (Kelley et al., 2006; Yang et al., 2015). For linguistic stimuli, deficits in semantic processing are common among individuals with ASD and could contribute to the previously mentioned comprehension deficits when linking decoded words together (Tager-Flusberg et al., 1991; Kamio et al., 2006; Coderre et al., 2017). Even people considered to be in the "optimal outcome" stage of ASD, meaning they were diagnosed at a very young age but due to early intervention or developmental changes, no longer meet diagnostic criteria, retain slight difficulties with their semantic and pragmatic language (Kelley et al., 2006). This deficit in language development might also contribute to impairments outside of the language realm, such as the inability to notice social cues and understand contextual information, as they share similar cognitive processing loops.

For this project and proposal, semantic processing refers specifically to semantic integration, which is the ability to integrate a stimuli with previous and contextual knowledge to extract meaning. One way to measure semantic processing is by mapping event-related potentials (ERPs), which are derived from the scalp-recorded electroencephalogram (EEG). ERPs are time locked increases in brain activity that indicate cognitive functioning and activity after the presentation of a stimulus.

The N400 ERP

The N400 ERP is specifically thought to reflect semantic processing, and is named as such because the peak occurs 400ms after the presentation of a stimulus (Kutas and Hillyard 1980; Lau et al. 2008; Kulakova et al., 2016). In the TD population, an N400 effect is elicited when a subject recognizes a disruption in semantics, which typically occurs when subjects compare congruent and incongruent words, or related and unrelated words (Holcomb et al., 2003; Lau et al., 2008; Kudas & Federmeier, 2011). Despite it being an established ERP component, there is ample discussion surrounding the exact onset and end time of this effect. Some researchers argue that the N400 effect begins immediately following early lexical access processes, such as the N170 effect, which represents the identification of letter strings and occurs 170ms after the presentation of a stimulus (Serena & Rayner, 2003). Other researchers argue that the N400 has an onset of strictly 400ms after stimulus presentation, while still others argue that the N400 effect encompasses even higher-order processes such as syntactic processing (Brouwer & Crocker, 2017).

Despite the varying opinions on the neural processes represented by the N400 effect, one idea has remained constant: the order of ERP latencies mirrors a hierarchy of complexity in the neural processes they portray. It is agreed upon that earlier neural activity represents the presence of lower-level neural processing compared to later activity peaks, due to the need for basic language coding processes, such as lexical access, to occur before information can be synthesized into a more complex understanding. Regardless of the precise neural functions that the N400 effect encompasses, the present study is investigating the integrity of this earlier, lower-level processing, relative to any later, higher-level processing.

<u>The N400 in Language & ASD</u>

Previous work has shown that individuals with ASD have reduced or absent N400 effects in response to language, suggesting difficulties with semantic processing (Tager-Flusberg, 1991; Verbaten et al., 1991; Valdizán et al., 2003; Pijnacker et al., 2010; Coderre et al., 2017). Few studies, however, have examined the potential dysregulation of earlier, lower-level language coding.

When Tager-Flusberg (1991) measured word recall in groups of ASD and TD children, she found that the ASD subjects had comparable performance to TD participants when recalling lists of unrelated words, but that the ASD group performed significantly worse than the TD group when recalling lists of related words. These findings could suggest that higher-order, integrational-level language processing systems might be impaired in children with ASD, and that such dysfunction could prevent them from accessing stored semantic information (Tager-Flusberg, 1991). When looking at the electrophysiological component of these findings, Verbaten et al. (1991) noted that the N400 effect in children with ASD did not increase in amplitude as it should in response to a stimulus unexpectedly changing its location. This was noted after the ASD group showed no significant differences in their N400 activity in response to a novel stimulus, suggesting that the simple coding of an object was fully functional in that group (Verbaten et al., 1991). Another study looking at the N400 effect following pairs of either congruent or non-congruent auditory stimuli found that although the amplitude of the N400 did not differ in the ASD children compared to the control group, the ASD subjects showed an increase in N400 latency compared to the controls (Valdizán et al., 2003).

Pijnacker et al. (2010) found contradictory results to those of Verbaten et. al (1991) and Valdizán et al. (2003) when measuring context sensitivity and context-specific reasoning between ASD and control groups. They tested two conditions: one was looking at either semantically congruent or incongruent sentences, while the other was processing congruent or incongruent reasoning problems (Pijnacket et al., 2010). The ASD participants in their study showed no N400 effect across either condition, whereas the control group showed N400 effects in both cases (Pijnacker et al., 2010). The control group also showed a later positive peak during the sentence context, and sustained negative activity during the reasoning context, while the ASD participants showed only a late positive peak under both conditions (Pijnacker et al., 2010). This peak was larger in response to semantically anomalous sentences than to congruent ones, but no sustained negativity was present (Pijnacker et al., 2010). Other work has linked the lack of N400 and later positivity in ASD, suggesting that the lack of an initial effect could represent a lack of early semantic processing, requiring them to double back and reinterpret the stimulus later on (Groen et al., 2008; Nijhof et al., 2018). This return to interpretation could account for the later positivity (Pijnacker et al., 2010). These differences at the higher-order semantic integration level could very likely have their roots in dysfunction in the earlier, lower-order processing loops, whether they be structural or functional, which the present study proposes to be compromised in ASD. Other work has suggested that the lack of initial N400 effect could represent a lack of initial semantic processing, requiring

<u>The Underconnectivity Hypothesis</u>

Another possible contribution to semantic processing difficulties in ASD is underconnectivity between brain areas responsible for language and semantic processing. Previous studies using functional magnetic resonance imaging (fMRI) to examine functional connectivity, measured as a degree of synchronized and correlated activity over time, have shown that connectivity is significantly lower across the brain in the ASD group compared to the TD group, and particularly in left-hemisphere fronto-parietal connections (Just et al., 2004).

The frontal lobe houses Broca's area, crucial for speech production, and the temporo-parietal lobe houses Wernicke's area, crucial for language comprehension (Homan et al., 1987). The arcuate fasciculus is a white matter tract that runs between these two language processing centers, which has been shown to play a crucial role in language production, processing, and comprehension (Yeatman et al., 2011; Wan et al., 2012; Roberts et al., 2014; Moseley et al., 2016; Lebel & Beaulieu et al., 2009; Lopez-Barroso et al., 2013; Catani et al., 2008; Joseph et al., 2014). This known language tract underlying these fronto-parietal connections makes them of particular interest to this study.

In 2008, Just et al. ran another functional magnetic resonance imaging (fMRI) study on participants with ASD and those with typical development (TD). They found that ASD participants showed higher levels of activity in Wernicke's area compared to the TD group, but lower levels of activity in Broca's area (Just et al., 2008). Just et al. (2008), along with many others, thus interpreted that people with ASD might have separate neural mechanisms for semantic processing than the TD population, and that this difference accounts for the difficulties they experience when integrating semantic stimuli into a complex and comprehensive understanding (Tager-Flusberg, 1991; Verbaten et al., 1991; Valdizán et al., 2003; Kamio et al., 2007; Lau et al., 2008; Pijnacker et al., 2010). These findings suggest that underconnectivity between these brain areas, which have also been shown to have disrupted structural connectivity linked to language deficits, could also be contributing to semantic misunderstandings (Just et al., 2004; Eluvathingal et al., 2007; Wan et al., 2012; Moseley et al., 2016).

Theta Coherence

One down-side to fMRI estimates of connectivity is the poor temporal resolution of this technique. As mentioned, individuals with ASD show intact low-level word decoding abilities, but impairments in higher-level semantic processing. This suggests that there may be a disconnect between these two processes that should occur prior to the onset of semantic processing, i.e. before the N400 ERP component. A tool that has sufficient temporal resolution to capture rapid changes in the temporal dynamics of a neural response is coherence, which are obtained through EEG. Coherence represents the connectivity and functional relatedness of different brain areas through the comparison of electrical activity at different electrodes on the EEG net. They are hypothesized to represent the communication through either long- or short-range networks throughout the brain, as they reflect the synchronization of oscillations at specific frequency bands (Fries, 2005). Coherence specifically describes the extent to which two signals, within the same frequency band, share a consistent phase relationship, meaning that the waves are similarly offset from an initial starting point (Thatcher et al., 2004; Roach & Mathalon, 2008; Seigel et al., 2012; Bastos & Schoffelen, 2016).

Coherence allows us to infer that similar neural oscillation patterns are the result of two areas of the brain functioning together to process a stimulus or complete a neural task. Although the exact neural underpinnings of this coherence have yet to be uncovered, this synchronous synaptic activity is thought to reflect the functional relatedness of brain areas. Oscillations specifically falling within the theta band (3-7.5 Hz) have been linked to semantic processing in word integration, sentence comprehension, and semantic priming tasks (Mellem et al., 2013; Halgren et al., 2015; Meyer et al., 2015). In this project, we examine theta coherence in several connections across the scalp, divided into three distances, relative to each other: short, medium, and long (Coben et al., 2008). Not all of these pairs are directly associated with white matter tracts in the brain, but the longer-distance left hemisphere pairs are thought to reflect the path of the arcuate fasciculus (Coben et al., 2008).

Research Question

In the present study, theta coherence in a range of electrode connections across the brain, with fronto-parietal connections being of particular interest, will be examined to identify whether there are differences in neural connectivity during pre-semantic stages of language processing. Any theta coherence between the two areas after the presentation of a stimulus will be representative of active cross-cortical connections that could play a role in semantic integration. It is hypothesized that the ASD group will show lower coherence levels than the TD group, especially across longer-distance, left hemisphere connections, during the early stages of (pre)semantic processing.

Background Information

Previous Work

The data used in this project is taken from a follow-up study of Coderre et al. (2017). In that prior study, Coderre et al. used a semantic priming task to compare the N400 effect in response to both lexico-semantic processing (the processing of written words) and visuo-semantic processing (the processing of pictures) in adults with ASD versus TD. Participants were presented with four blocks of pictures and four blocks of words, each containing 50 pairs of stimuli. Twenty-five of those pairs were related and 25 were unrelated. The participants were asked to press a button after each pair to indicate whether the stimuli were related. In contrast to previous studies, Coderre et al. did not find significant differences in the N400 effect in response to linguistic stimuli between ASD and TD subjects. They suggested that the lack of significant differences may have been the result of an explicit semantic judgement task, proposing that an implicit task, which does not direct the attention of the subjects to the relatedness of the stimuli, may elicit larger differences. A follow-up study was run to test for implicit processing (O'Rourke & Coderre, under review) in which only participants' automatic semantic processing response was recorded, and this project will use the EEG data collected during the implicit task to examine theta coherence differences between groups during both lexico-semantic and visuo-semantic processing.

Project Significance

Although many studies have examined the N400 effect in ASD subjects, none have examined the early coherence prior to the involvement of semantic processing (Tager-Flusberg, 1991; Verbaten et al., 1991; Valdizán et al., 2003; Kamio et al., 2007; Lau et al., 2008; Pijnacker et al., 2010; Coderre et al., 2017). This project will examine neural connectivity using EEG coherence measures, because the excellent temporal resolution of EEG creates a unique opportunity to study widespread neural connectivity on a fine-grained time scale, unlike other methods such as magnetic resonance imaging (MRI) or fMRI.

The semantic difficulties that are common in ASD are thought to originate from deficits in higher-order processing; however significant differences in pre-semantic activity could suggest that lower-order, structural differences are disrupting communication before higher-order processes can even be initiated. The large majority of current ASD interventions involve behavior therapies that attempt to teach patients alternative higher-order processing routes. Although these interventions can be helpful, attempting to compensate for deficient upper processing loops assumes that the lower-order circuits are functional. Finding evidence that these circuits might be dysregulated could shift the focus of research and interventions and allow for more effective care.

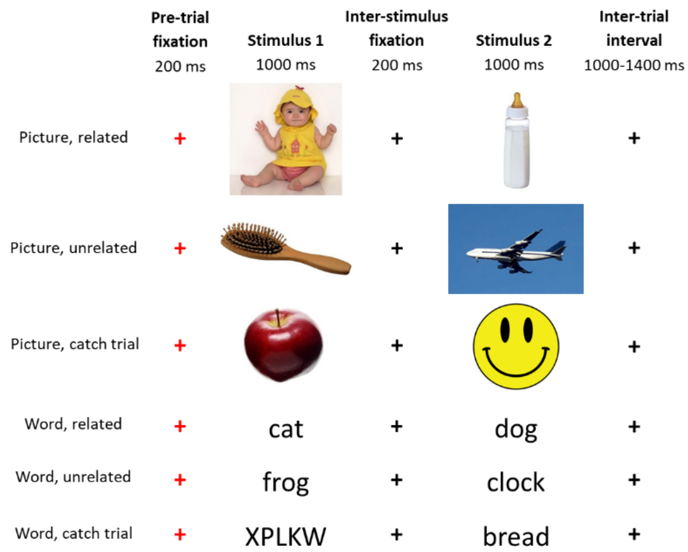
Methodology

Testing Procedure

The data were collected as a part of Dr. Emily Coderre's ASD and language lab, in which 22 adult ASD and 22 adult TD participants were screened and tested using an electroencephalogram (EEG). Screening tests involved administering the Peabody Picture Vocabulary Test (PPVT), the Kaufman Brief Intelligence Test (KBIT), and the Wide Range Achievement Test (WRAT) to assess baseline levels of vocabulary and language abilities, and the Digit Span Test to measure working memory. All ASD participants underwent an Autism Diagnosis Observation Schedule (ADOS) assessment to confirm the presence of ASD. Once placed in the EEG net, all subjects completed the previously explained implicit semantic priming task, where they were shown four blocks of pairs of either related or unrelated pictures, and four blocks of pairs of either related or unrelated words. They were also asked to monitor for a target stimulus ("catch trials") to ensure that they remained focused (25 related pairs, 25 unrelated pairs, and 16 catch trials per block). Each stimuli type (related pictures, unrelated pictures, related words, unrelated words) contained 100 trials, with 64 additional catch trials in each modality (Figure 1). Participants completed all four blocks of one modality, and then all four blocks of the other. The stimuli were counterbalanced to either complete the picture or word pairs first.

Stimuli were presented using E-Prime. On each trial, a red fixation cross was presented for 400 ms, followed by the first word or picture for 1000 ms; an inter-stimulus blank screen for 300 ms; and the second word or picture for 1000 ms. After the second stimulus a blank screen was presented for 400 ms, followed by a black fixation cross presented at an inter-trial interval ranging from 1000-1400 ms (mean 1200 ms). Only the response to the first stimulus was examined for this study. Concurrent EEG data was recorded at 500 Hz using a 128-channel Geodesic Sensor net and NetStation.

Figure 1: Example Stimuli from Implicit Semantic Priming Task (taken from O'Rourke & Coderre, Under Review)



IRB Approval

This study is in accordance with all International Review Board (IRB) standards and protocol, has been approved by the IRB, and has the protocol number 18-0072.

Data Preprocessing

Data were preprocessed using EEGlab version 14.1.1 and Matlab 2018a. The data were filtered using a 0.1-50 Hz bandpass filter and re-referenced using an average reference transform. The cleaned continuous data were then divided into epochs time-locked to the onset of the first stimulus. Segments extended from 100 ms before to 2300 ms after the first stimulus (in order to capture the response to the second stimulus, presented at 1300 ms). Independent component analysis (ICA) was then used to identify and remove eye movement artifacts. The mean of each trial was removed before beginning ICA decomposition (Groppe, Makeig, & Kutas, 2009) and the data were reduced to 32 components. After ICA decomposition, eye movements, blinks, muscle artifacts, and other noise components were visually identified and manually removed from the data. EEG coherence analysis was performed using the *newcrossf* function in EEGlab. Spectral decomposition was performed using a Morlet wavelet of 2 cycles with an expanding factor of 0.5 and a Hanning taper. Coherence was calculated for 12 interhemispheric electrode pairs across the scalp (Figure 3) at electrodes taken from the 10-20 distribution (F3, F4, C3, C4, P3, P4, O1, O2) at approximately every 0.1 Hz and every 8ms. There were 6 short distance pairs (F3-C3, C3-P3, P3-O1, F4-C4, C4-P4, P4-O2), 4 medium distance pairs (F3-P3, C3-O1, F4-P4, C4-O2), and 2 long distance pairs (F3-O1 and F4-O2). These were not associated with specific white matter tracts but instead represented various lengths of cortical. Although the specific cutoffs of the theta frequency band vary among studies, here we defined this band as 3.5-7.5 Hz, in accordance with other researchers (Gavrilov et al., 1995; Yordanova & Kolev, 1998; Von Stein & Sarnthein, 2000; Vyazovskiy & Tobler, 2005; Coben et al., 2008; Mellem et al., 2013; Halgren et al., 2015; Meyer et al., 2015).

Statistical Analysis

Group differences in theta coherence between the ASD and TD participants were statistically analyzed by running repeated-measures ANOVAs in 100ms from 0-800ms after the presentation of the first stimulus. This allows the full time course of semantic processing and its underlying neural connectivity to be examined. The upper limit of 800ms was chosen because this was the longest time latency analyzed in the manuscript reporting the ERP data for this study (O'Rourke & Coderre, under review). The levels of the ANOVAs, which were run separately for each modality (pictures vs. words), were: group (TD/ASD), distance (between electrodes, and whether it was short/medium/long), and laterality (of the electrodes, and whether they were on the left/right) (See Figure 3). Scores from the Peabody Picture Vocabulary Test (PPVT, assessing receptive vocabulary), verbal and non-verbal Kaufman Brief Intelligence Tests (KBIT, assessing verbal and non-verbal IQ), and DigitSpan tests (assessing working memory) were included as covariates in all analyses to account for any language and intelligence differences between groups. Due to the observation of differing trends between the picture and word modalities, findings for each will be separated into distinct sections.

<u>Results</u>

Words

When running an ANOVA to compare all intrahemispheric pairs between both groups for the word modality, there was a significant group by distance interaction from 300-400ms ($F(2, 76) = 3.47$, $p<0.05$; Table 1). This interaction was broken down further using independent-samples *t*-tests to compare group coherence across each interhemispheric pair, at 300-400ms (Table 2). The hemisphere of each pair was also noted.

Four electrode pairs showed a significant difference in mean coherence levels between groups in this time window. For the short-distance pairs C3-P3 in the left hemisphere and C4-P4 in the right, the TD group showed more coherence than the ASD group (C3-P3: TD mean=0.02, ASD mean=-0.02, $t(76.75) = 2.48$, $p<0.05$; C4-P4: TD mean=0.03, ASD mean=-0.02, $t(78) = 2.34$, $p<0.05$). The F3-P3 pair, a medium-distance connection in the left hemisphere, also showed TD having more coherence than ASD (TD mean=0.004, ASD mean=-0.03, $t(77.81) = 2.05$, $p<0.05$). In the long-distance connection between F4-O2 in the right hemisphere, ASD showed more coherence than TD (TD mean=-0.01, ASD mean=0.03, $t(72.10) = -2.24$, $p<0.05$).

When graphing the coherence levels of both groups across all time points, the F3-P3 pair showed clear peaks in the TD group around 200ms (Figure 2). For the F4-O2 connection, clear peaks could be seen in both groups around 200ms (Figure 2).

Table 1: ANOVA F-Values - All intrahemispheric pairs, all groups, word modality

Time Window (ms)	100-200	200-300	300-400	400-500	500-600	600-700	700-800
KBIT verbal	3.18	1.11	0.00	0.05	0.00	0.14	0.79
KBIT non-verbal	0.25	1.33	0.90	0.63	1.00	1.31	1.47
PPVT	**9.99 ** **	3.43	0.01	0.01	0.01	0.02	0.24
DigitSpan_forward	0.30	0.51	0.61	0.97	2.10	1.05	0.07
Group	0.41	0.53	0.02	0.04	0.11	0.27	0.01
Hemisphere	0.02	0.35	0.53	0.00	0.93	0.00	0.52
Group:Hemisphere	0.01	0.03	0.49	0.85	1.31	2.56	1.63
Distance	**16.71 *** **	**13.64*** **	1.86	0.39	0.98	1.48	0.77
Group:Distance	0.04	1.14	**3.47***	0.76	0.13	0.22	1.02
Hemisphere:Distance	1.18	0.54	0.15	1.00	0.60	0.39	0.54
Group:Hemisphere: Distance	0.98	0.36	0.27	0.28	0.16	0.01	0.29

Significance codes: p<0.05 = "." ; p<0.01 = "*"; p<0.001 = "**"; p< 0 = "***"

Table 2: t-Test values - All interhemispheric pairs, between groups, word modality, from 300-400ms

Pair	Length	Hemisphere	T-value	Degrees of Freedom	P-Value	TD Coh Mean	ASD Coh Mean	Direction
F3-C3	Short	Left	-0.25	77.99	0.80	-0.01	-0.01	TD<ASD
P3-O1	Short	Left	0.81	74.15	0.42	0.01	-0.001	TD>ASD
C3-P3	**Short**	**Left**	**2.48**	**76.75**	**0.02.**	**0.02**	**-0.02**	**TD>ASD**
F4-C4	Short	Right	0.24	78.00	0.81	-0.03	-0.03	TD>ASD
P4-O2	Short	Right	-0.27	77.01	0.79	0.00	0.01	TD<ASD
C4-P4	**Short**	**Right**	**2.34**	**78**	**0.02.**	**0.03**	**-0.02**	**TD>ASD**
F3-P3	**Medium**	**Left**	**2.05**	**77.81**	**0.04.**	**0.004**	**-0.03**	**TD>ASD**
C3-O1	Medium	Left	-1.00	76.89	0.32	0.01	0.03	TD<ASD
F4-P4	Medium	Right	0.50	77.87	0.62	0.02	0.01	TD>ASD
C4-O2	Medium	Right	-1.00	75.88	0.32	-0.02	-0.00	TD<ASD
F3-O1	Long	Left	-1.19	69.31	0.24	0.01	0.03	TD<ASD
F4-O2	**Long**	**Right**	**-2.24**	**72.10**	**0.03.**	**-0.01**	**0.03**	**TD<ASD**

Significance codes: 0.05 “.” 0.01 “*” 0.001 “**” 0 “***”

Figure 2: TD vs. ASD Theta Coherence, Word Modality, Time Locked to First Stimulus, at Pairs of Interest

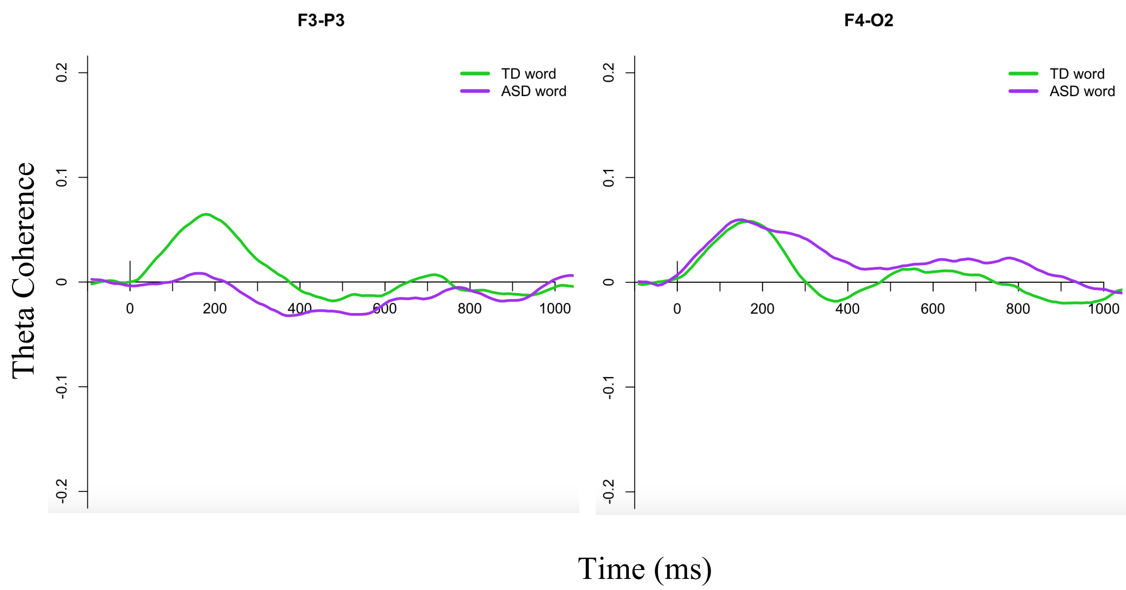


Figure 2 shows TD vs. ASD Theta Coherence levels for the word modality, across all time points. For the F3-P3 pair, clear peaks can be seen in the TD group around 200ms. For the F4-O2 pair, a clear initial peak can be seen at 200ms for both groups.

<u>Pictures</u>

All interhemispheric pairs across both groups for the picture modality were compared using ANOVAs. There was a three-way significant interaction between group, hemisphere, and distance from 700-800ms ($F(2, 76) = 3.71$, $p<0.05$) (Table 3).

This group by distance interaction was then broken down by running *t*-tests comparing group coherence levels at all interhemispheric pairs during the 700-800ms time window. The hemisphere of each pair was also noted.

The short-distance, left hemisphere pairs of F3-C3 and C3-P3 showed significant differences in mean coherence between groups. In the F3-C3 connection, the TD group had greater coherence levels than ASD (TD mean=0.02, ASD mean=-0.02, *t*(75.55) = 2.42, *p*<0.05) (Table 4). In the C3-P3 connection, the opposite direction was significant: the ASD group showed more coherence than TD (TD mean=-0.02, ASD mean=0.02, *t*(72.56)=-3.02, *p*<0.05) (Table 4). When graphing theta coherence levels for each pair across all time points, the C3-P3 pair showed slight peaks in both groups around 700ms (Figure 3). The significant pairs and the direction of their interactions in both modalities can be seen in Figure 4.

Table 3: ANOVA F-Values - All intrahemispheric pairs, all groups, picture modality

Time Window (ms)	100-200	200-300	300-400	400-500	500-600	600-700	700-800
KBIT verbal	2.83	1.41	0.74	0.11	0.10	0.33	0.19
KBIT non-verbal	0.01	0.02	0.91	0.05	0.18	0.47	0.62
PPVT	0.29	0.93	0.06	0.11	0.41	1.27	0.82
DigitSpan_forward	1.98	1.17	0.22	0.03	0.06	0.83	0.38
Group	0.31	1.41	0.46	0.00	0.02	0.25	0.29
Hemisphere	0.02	0.98	2.84	3.78	0.08	0.90	0.17
Group:Hemisphere	0.17	0.01	0.10	0.00	0.94	0.79	0.91
Distance	**12.81*****	**11.128*****	**9.54*****	**9.41*****	1.67	0.18	0.07
Group:Distance	0.21	0.40	0.42	0.61	0.60	0.10	0.03
Hemisphere:Distance	0.08	0.08	0.23	0.47	0.40	0.84	0.86
Group:Hemisphere: Distance	0.19	0.40	1.16	0.92	0.44	1.35	**3.71***

Significance codes: 0.05 “.” 0.01 “*” 0.001 “**” 0 “***”

Table 4: t-Test values - All interhemispheric pairs, between groups, picture modality, from 700-800ms

Pair	Length	Hemisphere	T-value	Degrees of Freedom	P-Value	TDCoh Mean	ASDCoh Mean	Direction
F3-C3	**Short**	**Left**	**2.42**	**75.55**	**0.02.**	**0.02**	**-0.02**	**TD>ASD**
P3-O1	Short	Left	0.44	77.98	0.66	-0.01	-0.01	TD>ASD
C3-P3	**Short**	**Left**	**-3.02**	**72.56**	**0.00.**	**-0.02**	**0.02**	**TD<ASD**
F4-C4	Short	Right	1.60	76.60	0.11	-0.01	-0.01	TD>ASD
P4-O2	Short	Right	0.05	77.06	0.96	-0.00	-0.00	TD>ASD
C4-P4	Short	Right	-0.98	72.55	0.33	-0.01	0.00	TD<ASD
F3-P3	Medium	Left	-1.35	77.02	0.18	-0.01	0.01	TD<ASD
C3-O1	Medium	Left	0.36	72.96	0.72	-0.00	-0.00	TD<ASD
F4-\P4	Medium	Right	0.79	77.30	0.43	-0.01	-0.02	TD>ASD
C4-O2	Medium	Right	1.40	76.16	0.17	0.02	-0.01	TD>ASD
F3-O1	Long	Left	1.46	65.80	0.15	-0.01	-0.01	TD>ASD
F4-O2	Long	Right	-0.88	78.00	0.38	-0.00	-0.01	TD>ASD

Significance codes: 0.05 "." 0.01 "*" 0.001 "**" 0 "***"

Figure 3: TD vs. ASD Theta Coherence, Time Locked to First Stimulus, Picture Modality, at Pairs of Interest

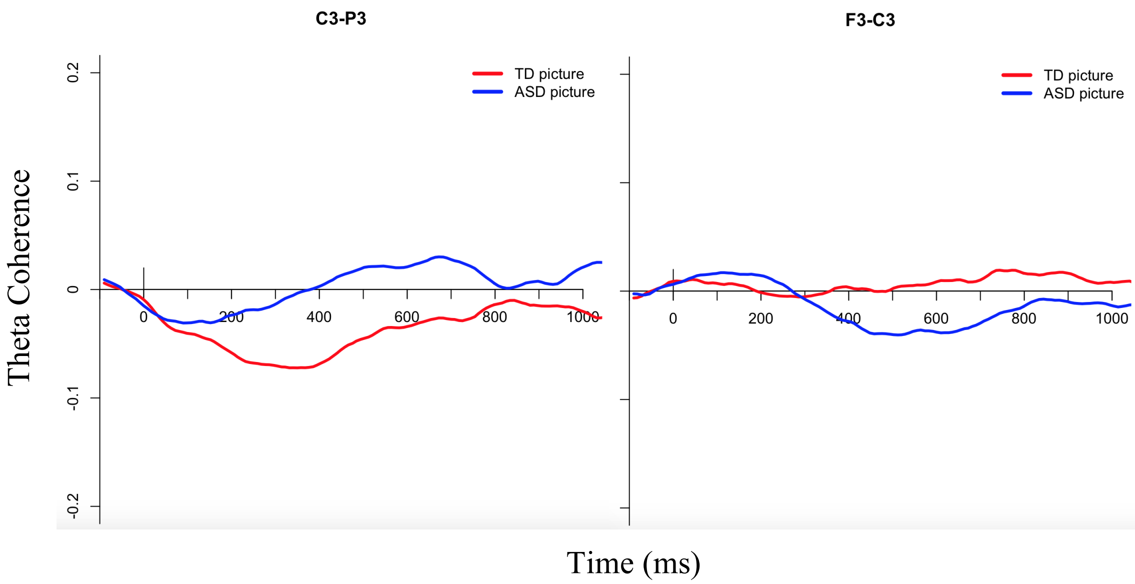


Figure 3 shows TD vs. ASD theta coherence levels for the picture modality, across all time points. For the C3-P3 pair, both groups show a slight peak in coherence between 400-800ms. For the F3-C3 pair, there are few clear peaks, but both groups show a slight upward trend from 600-800ms.

Figure 4: HydroCel GSN 128-channel EEG net with Labeled Electrode Pairs and significant direction effects

a. Words, 300-400ms b. Pictures, 700-800ms

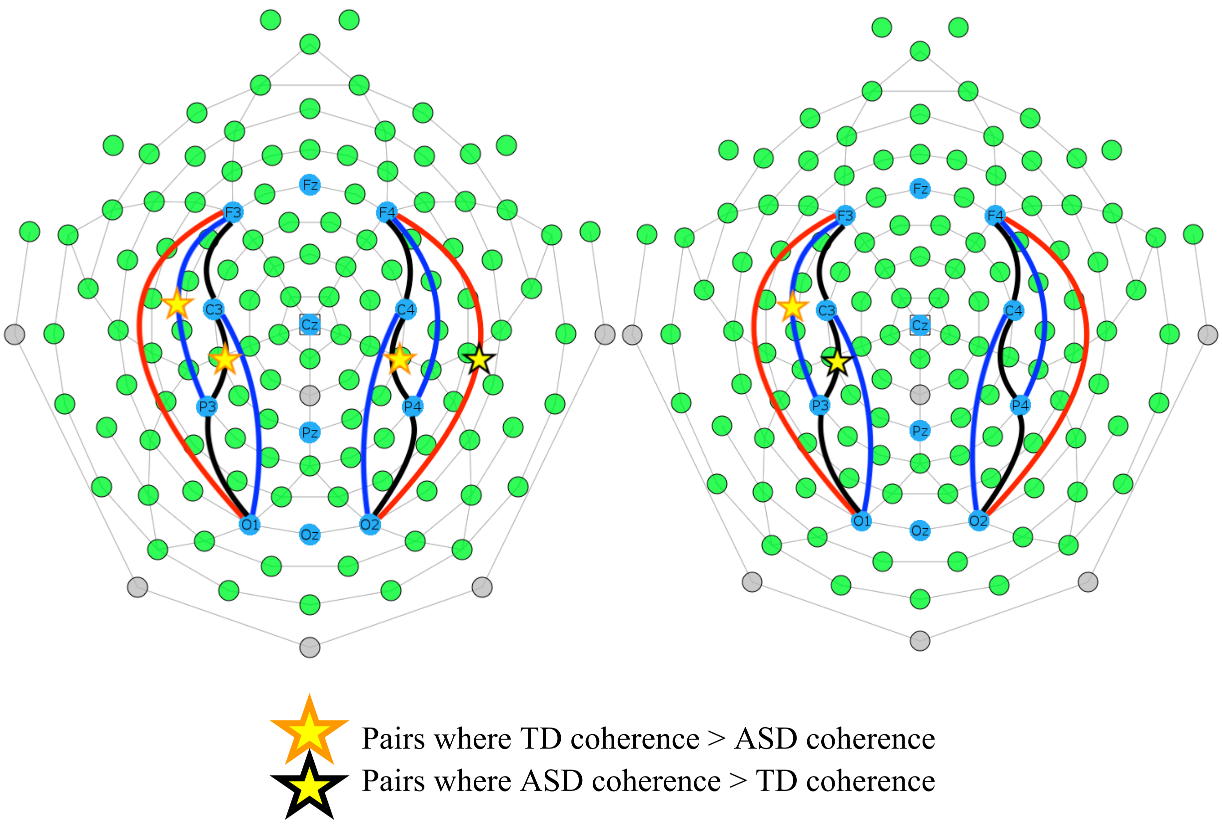


Figure 4 shows the 128-channel EEG net used in this study. The electrode pairs of interest are highlighted according to the distance of the connection: short distance pairs are in black, medium distance pairs in blue, and long distance pairs in red. Figure 4a shows the significant connections for the word modality, which were all between 300-400ms. The connections where the TD group showed greater coherence than the ASD group are highlighted with a yellow and orange star. The connections where the ASD group showed greater coherence than the TD group are highlighted with a yellow and black star. Figure 4b uses the same labeling system to highlight significant pairs for the picture modality, all of which were found within the 700-800ms time window.

Discussion

This study aimed to compare theta coherence activity across 12 electrode pairs in response to implicit semantic priming tasks, in ASD and TD participant groups. Fronto-parietal connections were of particular interest due to the white matter language tracts found to connect those brain areas, such as the arcuate fasciculus. Significant differences between ASD and TD theta coherence would indicate discrepancies in ASD semantic processing compared to the TD group, which could contribute to the semantic processing deficits known to be present in ASD (Tager-Flusberg, 1991; Verbaten et al., 1991; Valdizán et al., 2003; Pijnacker et al., 2010; Coderre et al., 2017). Early differences in theta coherence were of particular interest.

There were no significant group differences in theta coherence prior to the 300-400ms time window. This finding does not support the hypothesis, which stated that earlier, pre-semantic processing would be disrupted in subjects with ASD. However, the noted effects were still early relative to the N400 effect for words (O'Rourke & Coderre, Under Review). According to the ERP data, the N400 effect was observed from 300-600ms for words and from 300-800ms for pictures (O'Rourke & Coderre, Under Review). In our coherence data, the TD group showed a clear peak in coherence from 0-400ms in both the F3-P3 and the F4-O2 pairs in words, whereas the ASD group did not (Figure 2). These findings show activity prior to 400ms that is not sustained throughout the full N400 effect. This supports the idea that early, pre-semantic activity is present in the TD group but disrupted in the ASD group. This effect is most clearly shown at the F3-P3 pair, where the ASD group showed no significant increase in activity but the TD group did (Figure 2).

The F3-P3 pair is particularly significant because it is a medium-distance frontal-parietal connection in the left hemisphere that follows a similar path to that of many white matter tracts, such as the arcuate fasciculus, known to play a role in language. These tracts are integral in semantic processing in the TD population and have previously been found to be dysregulated in many subjects with ASD (Bashat et al., 2007; Fletcher et al., 2010; Moseley et al., 2016; Roberts et al., 2014; Wan et al., 2012). The TD group showing significantly higher coherence levels than the ASD group at this pair shows that connections across these areas are dysregulated in ASD. This could be due to a lack of structural integrity, a lack of functional connectedness, or a difference in semantic circuitry, but regardless of the underlying source the difference in coherence activity is clear.

The pair opposite to F3-P3 is F4-P4. In the word modality, there was no significant difference in coherence levels between the TD and ASD groups in this right hemisphere F4-P4 connection (Table 2). The long-distance right hemisphere connection between F4-O2 was the only other significant pair in the word modality, but here the ASD group showed more coherence than the TD (Table 2, Figure 4). ASD having less coherence than TD in the left hemisphere but more than TD in the right hemisphere suggests that the right hemisphere might increase its activity levels in an attempt to compensate for left hemisphere deficits (Kleinhans et al., 2008; Knaus et al., 2008; Knaus et al., 2010; Joseph et al., 2014). Language tends to be left hemisphere lateralized in the TD population (Frost et al., 1999; Knecht et al., 2000; Glasser & Rising, 2008; Knaus et al., 2010). This increase in right hemisphere activity during semantic tasks in ASD subjects also suggests that language is processed more bilaterally in ASD than in TD. There may be various compensatory mechanisms, especially in the right hemisphere, to correct for any left hemisphere differences.

For the word modality, significant differences in coherence levels were seen early on, between 300-400ms (Table 1). Underlying differences in connectivity and functional networks were therefore present very early on and would affect more fundamental processing. For pictures, significant effects were not present until much later, between 700-800ms (Table 3). This suggests that up until then, all processing was relatively similar between both groups and that there were no significant differences in ASD. This interpretation is in line with other studies that have found intact semantic processing for visual stimuli in individuals with ASD (Coderre et al., 2017; Kamio & Toichi, 2000; McCleery et al, 2010). Visual processing might be preserved longer than linguistic processing in ASD because visual coding and processing relies more on lower order neural coding loops (Johannes et al., 1995; Bullier et al., 2001; Correa et al., 2006). These lowest level processing loops would not be specialized for language - they would be the same loops subjects with ASD would use to constantly process their visual world and therefore would not necessarily be affected if language were impaired. Language, however, is processed using learned, higher-order processing loops and involves more immediate processing of stimuli.

Future studies are needed to further investigate the neurological and structural basis of these differences in theta coherence activity. An emphasis on high definition, structural imaging techniques would be beneficial to understanding the underlying integrity of the white matter connections under examination. Increasing the use of correction factors to account for multiple comparisons could help improve the power of the statistics, as well as an increased number of participants. This information would also help researchers gain a better understanding of the development of these differences, so that effective interventions could be developed. These findings are useful in understanding the different processing loops that these various populations might rely on, as it is clear they process semantic stimuli differently, but there is still much to be discovered about how the brain functions with ASD.

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