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Entropy as a Method for Identifying Treatment Resistant Autism Spectrum Disorder

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Entropy as a Method for Identifying Treatment Resistant Autism Spectrum Disorder

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Abstract

Background: Individuals diagnosed with Autism Spectrum Disorder (ASD) experience lifelong challenges which can impact peer relationships, adaptive functioning, and independent living. Verbal intelligence has proven to be the strongest indicator of outcomes and responsiveness to behavioral intervention, but this property only stabilizes in children between 6 and 8 years of age. Behavioral treatment is the primary intervention for individuals diagnosed with ASD, but it is most effective when delivered as an early intervention strategy for toddlers and very young children. A biomarker which could distinguish treatment resistant subgroups of ASD from would allow for the development and implementation of alternative treatments in an attempt to improve long term outcomes.

Methods: Our study used data from 49 participants made available through the National Database for Autism Research (NDAR). The sample group contained children between 4 and 11 years of age diagnosed with ASD and typically developing peers. Our study used EEG and behavioral measures to explore whether sample entropy analysis of EEG, as developed by Bosl et al. (2011), could distinguish between individuals with ASD and low verbal IQ from their average verbal and typically developing peers.

Results: The analysis we performed found that higher levels of sample entropy were correlated with lower ASD symptoms and better adaptive functioning. ANOVA analysis also suggested that sample entropy could distinguish ASD and typically developing children. Sample entropy was not correlated with verbal IQ and could not distinguish the ASD low verbal IQ group from both ASD with average verbal IQ and typically developing groups.

Conclusion: Researchers interested in identifying biomarkers for treatment resistant ASD should look beyond sample entropy for reliable measures. Sample entropy does appear to play a role in autistic symptomatology, and greater research into its role as a possible indicator of underlying neurological abnormalities should be explored. Researchers may also find value in including sample entropy in longitudinal studies to see how this measure changes with behavioral improvements as a result of behavioral treatment.

Introduction

The Most Pressing Need

Individuals diagnosed with Autism Spectrum Disorder (ASD) experience a range of challenges later in life as a result of their neurodevelopmental condition. These challenges range from limited peer interaction, high rates of joblessness, and difficulties managing the demands of independent living. Estimates of individuals with ASD facing significant challenges in these domains can be as high as 58% (Howlin, Goode, Hutton, & Rutter, 2004). The fundamental problem facing clinicians and researchers working with ASD is how to improve outcomes for this group.

While investigation into the biology of ASD are ongoing, there is no well-defined etiology and no reliable pharmacological interventions that target the core symptoms of ASD. Behavioral interventions emphasizing early detection and treatment of ASD have proved effective, however, outcomes remain poor for many who do not respond as well to these interventions as their peers (Eikeseth, 2009). The problem with this situation is that children who do not response positively to behavioral intervention have wasted an important developmental window wherein treatment is deemed most effective. This has led researchers to investigate early markers that might indicate how a child might respond to behavioral intervention.

The most reliable predictor of outcomes in ASD is verbal intelligence. The influence of this factor has been demonstrated in numerous studies (Anderson, Liang, & Lord, 2014; Lord, Bishop, & Anderson, 2015; Kim, Bal, & Lord, 2018), and verbal ability has also been shown to be an important factor correlated with responsiveness to behavioral intervention (Fossum, Williams, Garon, Bryson, & Smith, 2018).Instruments such as the Mullen Scales of Early Learning are used to measure intelligence in very young children with ASD, however, behavioral

measures of intelligence at this age are unreliable, with correlation between IQ at age one and fifteen being as low as r=.15 (Gottfried, Gottfried, & Guerin, 2009). Intelligence is generally believed to stabilize between the ages of 6 and 8, casting doubt upon the reliability of IQ measures for children as method of detecting responsiveness to intervention, or predicting later outcomes.

Biological measures that can be reliably implemented, can predict responsiveness to intervention, and are correlated with outcomes later in life would be an invaluable contribution to this field. These measures could allow for the early detection of treatment resistant ASD, allowing for novel interventions to be administered during the crucial developmental window associated with better outcomes. Our study investigates whether an early biomarker of ASD may be sensitive to low verbal IQ, a feature associated with poor outcomes in children diagnosed with ASD.

Literature review

Autism Defined.

In 2012 ASD in the United States had a prevalence rate among 8-year-old children of 1 in 68. Prevalence among boys is higher, with 1 in 42 boys receiving the diagnosis compared to 1 in 189 in girls (Christensen, Baio, & Braun, 2016; Center for Disease Control, 2014). ASD is defined behaviorally in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and can presently only be diagnosed through behavioral observation. The disorder is categorized by deficits in social communication and the presence of restrictive and repetitive behaviors. Social communication and social interaction deficits can affect the performance of nonverbal communication, reciprocal engagement, and the development of interpersonal relationships. Restrictive and repetitive behaviors can include stereotyped motor movements,

inflexible adherence to routines, restricted interests, and sensitivity to sensory stimuli (American Psychiatric Association, 2013).

Although ASD is diagnosed through behavioral observation, it is assumed to be rooted in the biology of individuals with the condition. Advances in research investigating the etiology of ASD have led to the proposal that ASD be conceptualized as a neurodevelopmental disorder, highlighting its biological foundations (Insel, 2014). The systems implicated in ASD are varied, ranging from from immunology (Masi et al, 2015) to gastrointestinal problems (Vissoker, Latzer & Gal, 2015). The most common and heavily researched domains, however, are genetics and neuroscience (Insel, 2014). Research into the genetic underpinnings of ASD has discovered several genetic abnormalities responsible for clusters of individuals with the condition, and neuroscience research has discovered possible neural systems and processes which may be responsible for the symptoms of ASD.

Genetics.

The genomic underpinning of ASD is evidenced by the strong correlation of ASD between siblings, specifically between monozygotic twins (Tick et al.,2016). Despite positive indications for the genetic causes of ASD, specific genomic disturbances can only account for approximately 5% of cases. Three specific genetic disorders present with the behavioral symptoms typical of ASD, namely, Rett Syndrome, 22q11.2 Deletion Syndrome (22q11DS) and Klinefelter Syndrome. All three of these disorders are excluded from the ASD category precisely because they are understood as discrete genetic conditions (Miyake et al., 2011; Manning et al., 2004; Biswas & Furniss, 2016; van Rijn, 2015).

These genetic conditions present with behavioral profiles consistent with ASD and shed light on the problem of heterogeneity in the field. ASD is a broad phenotype that has made

classification using behavioral diagnostic rubrics difficult (Tsai & Ghaziuddin 2013; Young & Rodi 2013). Genetic research into the etiology of ASD aims to deal with this heterogeneity by identifying discrete genetic conditions responsible for distinct symptom clusters. Research has shown that isolation of 22q11DS and Klinefelter Syndrome within a broader group of individuals diagnosed with ASD significantly decreases phenotypic heterogeneity of the sample (Bruining et al., 2010). This raises the hope that ASD may be understood as a collection of rare genetic disorders, each responsible for a cluster of symptoms within the autism spectrum.

Unfortunately, specific genetic explanations for ASD remain elusive aside from the cases discussed above. The ability of genetics to explain phenotypic heterogeneity appears to have its limits. Chaste et al. (2014) collected a sample of individuals with ASD to explore the relationship between genetics and phenotypic heterogeneity. The researchers in this study divided the sample into clusters based upon behavior profiles to create homogenous subgroups. Then, they compared the genetic makeup between groups to see if genetic heterogeneity had likewise been reduced, but it had not. While the possibility of distinct subgroups within ASD remain, with strict adherents of this position using the term “autisms” (Cantio, et al., 2016), genetics alone cannot currently define this heterogeneous condition.

While the genetic disorders discussed above identify gene abnormalities as the ultimate, or distal, cause of ASD symptomatology, they implicate neural functioning as the proximate cause of ASD behavior profiles. Rett Syndrome, for example, results from a mutation in the MeCP2 gene which in turn influences the expression of genes essential for brain development (Miyake et al., 2011). 22q11DS also results in structural and connective abnormalities in the brain, as well as abnormalities in neurotransmitters such as COMT (Biswas & Furniss 2016).

The impact these genetic disorders have on neural development suggest that the brain may be an additional candidate system for research into the etiology of ASD.

Neuroscience.

The majority of ASD cases are idiopathic, where no clear genetic or environmental cause for the disorder has been identified. In these cases, the role of neural systems is paramount, because it provides insight into the mechanisms which underpin aberrant behavior, regardless of the ultimate underlying cause. Research in the neuroscience of ASD can be generally divided by the technology used to investigate the neural system. The most common neuroimaging techniques are computed tomography (CT), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG). Abnormalities in both structure and function of neural systems are investigated by these technologies, with CT and MRI used to detect structural abnormalities, and fMRI and EEG used to detect abnormalities in functioning.

Research has discovered abnormalities in several brain regions and networks that are implicated in ASD. CT scans have contributed to our understanding of neurobiological underpinnings of ASD (Eigsti & Schuh, 2008), and MRI research has been used to inform changes in diagnostic criteria of ASD (Pina-Camacho et al., 2013). Structural abnormalities have been detected in nearly every region of the brain for individuals with ASD, and these varied results are presumed to be the byproduct of the heterogeneity of the condition itself (Sivapalan & Aitchison, 2014). Differences are usually determined by greater volume in white or grey matter, and a larger volume of neural matter is general found in individuals with ASD. The wide range of brain regions implicated in ASD has led researchers to look beyond the structure of the brain and turn their focus to the networks which connect these regions (Sivapalan & Aitchison, 2014).

Connectivity between brain regions is often established using fMRI measurements, and this has become a leading method for investigating neural system in ASD. Due to its spatial resolution of 2-3 millimeters and the ability to monitor neural processing by detecting changes in blood flow associated with neural activation, it is a well-suited method for examining neural connectivity. fMRI studies have discovered abnormal functioning in the ventral visual cortex, prefrontal cortex, anterior cingulate in individuals with ASD (Ewbank et al., 2015; Solomon et al., 2015). An emerging field of inquiry has also implicated the cerebellum and its functional connectivity to other neural structures (Crippa et al., 2016). While fMRI explores connectivity between brain regions by measuring blood flow, EEG can measure connectivity at a finer timescale and record the most salient phenomenon in neural networks, namely, the action potential and resulting electrical activity.

An early indication that ASD may involve abnormalities in the brain's electrical patterns was suggested by the high comorbidity between ASD and Epilepsy (Kanner, 2000). These two conditions are diagnostically distinct, but researchers have explored the clinical significance of individuals presenting with both conditions, finding that the presence of Epilepsy in conjunction with ASD is associated with more severe symptomatology and poorer treatment outcomes (Viscidi et al., 2013; Schubarata et al., 2015; El Achkar and Spence, 2015). Additional research has shown that epileptiform patterns of electrical activity are present in ASD, even in the absence of Epilepsy (Spence & Schneider, 2009; Boutros et al. 2015). Bosl, Loddenkemper & Nelson (forthcoming) found that specific methods of nonlinear analysis can be used to distinguish ASD, Epilepsy, and healthy controls, but that the ASD population represented a midpoint between Epilepsy and control groups, suggesting that ASD and Epilepsy may share a common pathology, with ASD being a moderate form of the later. In addition to the similarities between ASD and

epilepsy, more traditional EEG measurements have found abnormalities in a variety of areas including gamma oscillations, theta and beta power spectra and interhemispheric connectivity (Maxwell et al., 2015; Bink et al., 2015; Machado et al., 2015; Lazarev et al., 2015;).

Developmental Trajectories.

Research into the genetics and neuroscience of ASD continues investigating the mechanisms of action and discrete causes of this disorder, but the condition is still diagnosed behaviorally. Behavioral conceptions of ASD have evolved over the past few years, in part reflecting the discoveries from genetics and neuroscience regarding the etiology of the disorder. From a behavioral perspective, the continuity of ASD as a singular disorder has been challenged in the research literature (Georgiades et al. 2013; Tek, Mesite, Fein, & Naigles 2013; Sullivan, Daly, & O'Donovan 2012; Jeste & Geschwind 2014; Happé, Ronald, & Plomin, 2006). The broad phenotype of ASD has made it difficult to classify using behavioral diagnostic rubrics (Tsai and Ghaziuddin 2013; Young and Rodi 2013). The recent transition from the DSM-IV-TR to the DSM-5 involved significant changes to the categorization of ASD, and were in part motivated by the heterogeneity of the disorder. While the DSM-IV provided separate diagnostic criteria for Autistic Disorder, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified, the DSM-5 realigns these categories into one umbrella diagnosis – ASD.

The unification of this diagnostic criteria has been met with some resistance from researchers who support the discrete categories of the DSM-IV-TR, arguing they identify clinically useful subgroups (Tsai & Ghaziuddin 2013). A survey of the literature does reveal some distinct phenotypes between the DSM-IV-TR categories (Tsai & Ghaziuddin 2013), but advocates of the DSM-5 criteria cite broad overlap of symptoms and the absence of evidence for distinct biological etiologies to justify the spectrum model (Young & Rodi 2013). Those who

favor the DSM-5 changes do not endorse a homogeneous view of ASD, but instead argue that discrete categories without biological justification are invalid (Young & Rodi 2013). In this case, no categories are better than false categories. Broad support exists on both sides of the debate that ASD is a heterogeneous disorder, the disagreement is simply around what role biological considerations should play in diagnosis (Tsai & Ghaziuddin 2013; Young & Rodi 2013).

While the DSM-5 has taken an important step in abandoning discrete categories not supported by biological research, more work needs to be done to identify clinically useful subgroups of the autism spectrum. The most promising behavioral research with this goal proposes developmental trajectories, which account for individual change over time, as a potential method for dividing ASD into meaningful subgroups (Venker et al., 2014). Foss-Feig et al. (2016) make the most explicit endorsement for this transition and argue that a model which clusters symptoms along positive, negative and cognitive features would help capture development over time. More traditional models of lifespan development have also been suggested as suitable for the purpose of generating developmental trajectories for ASD (Franklin et al., 2015). In both cases authors are advocating for perspectives in which ASD is flexible, not only in terms of symptom severity, but also in terms of change over time.

Developmental trajectories based on behavioral data have the advantage of incorporating clinical concerns into what would otherwise a science of taxonomy. By collecting and examining longitudinal behavioral data, researchers can explore which factors in early development are associated with better or worse outcomes, as well as responsiveness to intervention. Statistical methods such as group-based trajectory modeling have been employed to identify subgroups of the autism spectrum based on changes in symptomatology over time (Fountain, Winter, & Bearman, 2012). This research, however, does not address the critical issue of identifying

individuals with ASD who experience poor outcomes and do not respond favorably to treatment. Serious engagement with the research around treatment of ASD highlights these concerns and has informed important research on developmental trajectories in ASD.

Current State of Clinical Treatment.

Pharmacological.

Medical intervention for individuals with ASD involves the use of prescription medication. Two of the most commonly prescribed medications for ASD are risperidone and aripiprazole. Both are atypical antipsychotic medications that are used to treat irritability in children with ASD and have been shown to be effective in this treatment (Aman et al., 2015; Maloney, Mick, & Frazier, 2014). A comparison of the studies supporting the use of these medications found similar effectiveness between aripiprazole and risperidone, with each possessing similar secondary effects such as weight gain, sedation and extra pyramidal syndrome (Cohen et al., 2013). New medications, such as arbaclofen, are currently being researched as alternative treatments for aggression in individuals with ASD that may avoid unwanted secondary effects (Erickson et al., 2014).

Oxytocin is being researched as a possible medication for the treatment of core symptoms of ASD, as opposed to treating aggressive behavior like atypical antipsychotics. While there is some evidence that risperidone can improve the social functioning in children with ASD, this is likely a result of the primary effect of this drug decreasing aggressive behaviors (Aman et al., 2015). Oxytocin was initially considered as a possible treatment for ASD due to the role it played in modulating similar symptoms in animal models (Stohn et al., 2018; Štefánik, Olexová, & Kršková, 2015). While Oxytocin appears to have fewer secondary effects compared to

atypical antipsychotics, the current research does not demonstrate meaningful effectiveness for the core symptoms of ASD (Cai, Feng, & Yap, 2018; Keech, Crowe, & Hocking, 2018)

While atypical antipsychotic medications are effective in treating aggressive symptoms and irritability in individuals diagnosed with ASD, they occur with serious secondary effects, and are not effective at treating the core symptoms of ASD. Oxytocin has been proposed as a possible treatment for the core symptoms of ASD, but research has yet to demonstrate this effectiveness. There are also no known cures for the ASD (Bölte, 2014). In the absence of effective pharmacological interventions, behavioral treatment has become the primary method for improving outcomes of individuals with ASD.

Applied Behavioral Analysis.

The first treatment to consider when looking at interventions for ASD is Applied Behavioral Analysis (ABA). This treatment is considered the first-line therapy for ASD and is the most empirically validated treatment program for ASD (Magiati, Tay, & Howlin, 2012; Munshi et al., 2011). ABA therapy was developed through the 1970's and 80's by Dr. Lovaas and was originally described as the "Lovaas Method" (Dillenburger & Keenan, 2009; Lovaas, 1987). This treatment method evolved out of B.F. Skinner's work on behaviorism and proceeds by controlling the client's environment in order to elicit desired behavior. This treatment follows the stimulus-response model of human behavior and shapes patient's behaviors by imposing a system of reward and punishment for desired and undesired behaviors (Bondy, Esch, & Sundberg, 2010).

ABA treatment is developed according to an individual needs assessment. The behavioral needs assessment is traditionally done by administering a behavioral instrument such as the Verbal Behavior Milestones Assessment and Placement Plan (VB-MAPP) which indicates

the level of functional behavior of patients (Sundberg, 2008). This assessment provides a template from which therapists develop the initial behavior plan, which targets specific behaviors for increase or decrease, and outlines the intervention protocols for each behavioral goal. Specific behavior goals can range – from a child remaining seated for a period of time, to answering WH questions (who, what, where and when) effectively, to decreasing self-injurious behavior. The protocols for achieving each goal can vary, but the most common is Discrete Trial Training (DTT), which consists of presenting a patient with a specific task and rewarding appropriate behavior (Magiati, Tay & Howlin, 2012). Rewards are labeled "reinforcers" since ideally, they reinforce preferred behaviors. As ABA therapy progresses, goals are revised depending on the progress of an individual patient. Behavioral data is taken over a series of sessions and informs a behavioral therapist's judgment regarding the need to adjust goals or treatment protocols.

Reliance on DTT has waned in recent years as new methods of ABA have been developed. Pivotal Response Treatment (PRT) and Early Start Denver Model (ESDM) are two methods of behavioral treatment which rely on identifying goals for children and using behavioral reinforcement techniques to achieve those goals. PRT is distinguished from DTT because goals are areas of development, such as motivation and social initiation, as opposed to discrete behaviors (Duifhuis et al., 2017). Research has demonstrated the effectiveness of PRT in improving functioning for children with ASD in the domains of socialization, communication, and daily living skills (Ventola et al., 2014; Ventola et al., 2016; Duifhuis et al., 2017). As with all forms of ABA, however, responsiveness to PRT is not consistent across all participants and researchers are looking for markers that might identify those who are less responsive to intervention (Fossum, Williams, Garon, Bryson, & Smith, 2018). Research into this modality has

incorporated neural measurements which may help identify treatment resistant subrgoups of ASD (Ventola et al., 2015).

ESDM involves more parent participation than other ABA methods and allows therapists to work on developing interpersonal relationships with their clients (Ryberg, 2015). The effectiveness of this approach has provided practitioners with another viable method for treating ASD (Dawson et al., 2010). Most noteworthy about the ESDM approach, however, is that is demonstrated the importance of timing and intensity of behavioral intervention. Behavioral treatment of children with ASD is most effective when it is intensive, at least 20 hours of intervention a week, and delivered as early as possible, even for children as young as 12 months of age (Rogers et al., 2012). Benefits of early and intense intervention have been replicated with other ABA techniques and is not restricted to ESDM (Elder, Kreider, Brasher, & Ansell, 2017). The importance of early intervention has impacted clinical approaches to diagnosis, since better outcomes are associated with earlier treatment, clinicians have started to provide effective methods for early diagnosis (Vietze & Lax, 2018). The Autism Diagnostic and Observation Schedule was revised in 2012 to include a new toddler module, which allows for the earlier detection of ASD, even among children as young as twelve months of age.

Treatment Outcomes and Effectiveness.

Quality of life for individuals diagnosed with ASD is significantly lower than their typically developing counterparts (van Heijst & Geurts, 2015), and the majority of children receiving the diagnosis will likely require lifelong care (Billstedt, Gillberg & Gillberg, 2005). In one of the largest samplings to explore the question of outcomes for individuals with ASD, researchers found that 58% of participants had ‘Poor’ or ‘Very Poor’ outcomes in terms of employment, independent living, friendships, and language ability (Howlin, Goode, Hutton, &

Rutter, 2004). Poor outcomes were most strongly correlated with low verbal IQ (<70) even though participants with verbal IQ's below 50 were excluded from this study. These outcomes appear to be the result of variable responses to treatment, rather than a necessary outcome of the disorder.

Although intense, early intervention ABA is the most empirically validated treatment for ASD (Peters-Scheffer et al., 2011) portions of the population continue to respond less favorably than others (Eikeseth, 2009). This variable responsiveness has led researchers to look for patient factors that may predict outcomes of behavioral intervention. While researchers continue to examine behavioral profiles to answer this question, two factors have achieved consensus in terms of their impact on treatment responsiveness, namely, verbal IQ and early intervention (Peters-Scheffer et al., 2011). Access to early and intensive behavioral intervention has been shown to be a necessary condition for positive outcomes in individuals with ASD, and these findings have influenced social policy to increase provision of these services to families. The impact of verbal IQ on treatment outcomes has been more problematic, particularly because this feature is difficult to measure in young children receiving early and intensive behavioral intervention.

Developmental trajectories which incorporate clinical considerations have also highlighted the importance of verbal IQ when identifying outcomes in adults with ASD. The first study of this kind used longitudinal data to show that outcomes at age 19 of children diagnosed with ASD was strongly predicted by verbal IQ at age 2 or 3. In particular, individuals with verbal IQs below 70 were found to have poor outcomes in 85% of cases (Anderson, Liang, & Lord, 2014). Additional research using similar methods has replicated these findings, showing that grouping individuals with ASD into low and average IQ groups, based upon a verbal IQ

benchmark of 70, strongly predicts outcomes in later life (Lord, Bishop, & Anderson, 2015). These findings were also replicated in a study with a dividing point of verbal IQ at 85 (Kim, Bal, & Lord, 2018). These crucial findings provide a starting point for researchers interested in identifying early biomarkers that could detect treatment resistant subgroups of ASD.

Purpose of this Study

The purpose of our study is to investigate a potential biomarker that could distinguish individuals with autism and low verbal IQ from their average verbal IQ, and typically developing, counterparts. The analysis we propose attempts to distinguish these groups within a sample of children age four to eleven-years-old, when IQ is considered more stable and measures of verbal IQ are more reliable. The utility of this biomarker, however, would ultimately be found in its application to distinguish these groups in toddlerhood, when treatments are first introduced and there is a need for early identification of treatment resistant subgroups. For this reason, we have chosen a biomarker which has demonstrated its effectiveness at identifying ASD among toddlers.

Bosl et al. (2011) demonstrated that sample entropy analysis of resting state EEG signals could effectively distinguish a group of children at high risk for autism, due to a sibling diagnosis, and healthy controls. Participants in the study were between 6 and 24 months old, with the most significant findings for children between 9 and 12 months of age. Sample entropy measurements have the potential to aid in early diagnosis of ASD as indicated by Bosl et al. (2011). However, the most pressing clinical need for this population is the early detection of individuals who do not respond as well to behavioral intervention and have worse outcomes in adolescence and adulthood. The purpose of our study is to examine whether sample entropy is able to identify this group in a sample of children between the ages of four and eleven.

Research Questions

The analysis presented in our study proceeds in two parts. The initial analysis sheds light on the sample by examining the cognitive profiles of participants, and the relationship between demographic factors, such as sex and age, with scores on behavioral measures. The second phase of the analysis introduces sample entropy, and this is where our research questions are posed. Our first research question – is sample entropy correlated with measures of ASD symptoms, IQ, and adaptive functioning? – is addressed in a correlational analysis between sample entropy measurements and scores on the ADOS-2, DAS-II, and Vineland-II. Our second research question – can sample entropy distinguish Typ, ASDAvg, and ASDLow groups? – is addressed through an ANOVA analysis of sample entropy measurements between these groups. Additional considerations addressed by our research are covered in the "Discussion" section of this paper, however, the above are our two primary research questions.

Relevance of this Study

The relevance of this study comes from the introduction of biological measures to improve our understanding of ASD. Research into the biological underpinnings of ASD is part of a broader movement to define disorders through physiological measurements, embodied most concretely in the RDoC project (Insel, et al., 2010). Our research builds on previous research by Bosl, et al., (2011), which has demonstrated that sample entropy is effective at distinguishing children at high risk of ASD from typically developing counterparts. It could be argued that the relevance of our study is derived from the extension of this method is an attempt to broaden our understanding of ASD from a biological perspective.

More importantly, however, this study uses biological measures to address a pressing clinical need in the field of ASD research. The goal of this study is to use the method of sample

entropy analysis identified in Bosl, et al. (2011) to distinguish low verbal individuals with ASD from their high verbal, and typically developing, counterparts. If this method has the ability to distinguish these groups, then it is possible that clinicians could identify treatment resistant ASD in infancy. This would allow clinicians and researchers to develop and test alternative treatments with the goal of improving outcomes for those with the highest need on the autism spectrum. If our study shows promise, then sample entropy would be a worthwhile measure to incorporate into longitudinal studies on ASD, to improve our understanding of biological measures in the context of change over time.

Defining Entropy

Entropy has different definitions depending on the discipline in which it used, most notably thermodynamics and information theory. The use of entropy, or sample entropy, in our study is more closely aligned with the definition of the term used in information theory. Here, entropy was first defined by Claude Shannon in a paper titled *A Mathematical Theory of Communication* (1948). Entropy in information theory is defined as a measure of uncertainty determined by the probability of possible outcomes. Under this definition, the outcome of a dice roll has greater entropy than the flip of a coin, since the dice roll resolves uncertainty related to six possible outcomes and the coin flip resolves uncertainty related to two possible outcomes.

One of the earliest applications of entropy in describing a sequence of events occurred in Claude Shannon's living room with his wife, Betty. They observed together that, when provided the first few words of a sentence in English, subsequent words became easier and easier to guess. That is to say, the uncertainty of guessing possible words early in a sentence in English is greater than the uncertainty of guessing words later in that same sentence (Horgan, 2016). Information theory has transformed the observations made in the Shannon's living room into a science which

characterizes the nature of information in communication systems such as English, as well as those found in the natural world.

Costa, Goldberger, and Peng (2005) applied information theory and the concept of entropy to biological signals, looking specifically at cardiac rhythms. These researchers found that the complexity of biological signals generated by the heart were an indicator of advanced age, atrial fibrillation, and congestive heart failure. Complexity in this study was measured by multiscale entropy, which analyzed time series data generated by cardiac rhythms and examined how frequently pairs of data points were replicated in the remaining sequence. Signals which were highly ordered and regular, where pairs of data points were replicated frequently constituted a signal with less complexity and lower entropy. These patterns were more commonly associated with pathological heart conditions. In contrast, signals that were less regular were associated with healthier heart conditions. Considered from the perspective of entropy, the more regular cardiac rhythms can be said to contain less uncertainty because data later in the sequence can be more accurately predicted based upon data early in the sequence. Signals with more complexity have higher entropy because there is greater uncertainty about the position of data later in the sequence, based upon knowledge of data early in the sequence.

Bosl et al. (2011) applied the method developed by Costa, Goldberger, and Peng (2005) to EEG signals in order to distinguish a group of children at high risk of ASD from typically developing peers. This method is the basis of our study. Other researchers have used measures of entropy in neuroscience, most notably identifying entropy within fMRI data as a possible indicator of intelligence (Saxe, Calderone, & Morales, 2018). The use of sample entropy to identify a subgroup of ASD with low verbal ability, as proposed in our study, is part of an expanding use of entropy within the neuroscience research community.

Methods

Research Design

The data for our study was retrieved from the National Database for Autism Research (NDAR), which is an NIMH Data Archive. This data archive serves as a repository for de-identified, research participant data made available to the wider research community. Researchers can access participant data based upon search parameters, which return appropriate collections of client data. This is a useful mechanism for researchers interested in meta-analytic studies because it does not impede cross-study comparisons. For our purposes, however, it was necessary to find a single study with the relevant participant data, because a small sample was more suited to the pilot study we were pursuing.

A preliminary review of research in NDAR generated five candidate studies which had collected data appropriate for our research. The data required for our study was, EEG measurements, IQ tests (either WAIS or DAS), ADOS scores, and Vineland scores. Five studies had performed research which included this data. Ultimately, we selected the Autism Biomarkers Consortium for Clinical Trials (NDAR #2288) as our data source because it had the appropriate number of participants (51), the subject records were largely complete (forty-nine of the fifty-one participants had EEG, IQ, ADOS, and Vineland data), and EEG data was the appropriate length (resting state measurements were about one minute long). There were also multiple resting state EEG measurements in case of bad electrodes or eye movement artifacts. This study collected three resting state measurements taken on two visits, for a total of six possible data points. EEG data files were also in Matlab format, which was conducive to our proposed analysis.

The Autism Biomarkers Consortium for Clinical Trials is an investigation led by James McPartland at Yale University and its principle aim is to collect EEG, eye tracking(ET),

intelligence, and social impairment data to identify biomarkers which may help stratify the currently heterogeneous category known as ASD into subgroups. Assessments in this study were conducted at three timepoints, including baseline, 6 weeks and 24 weeks. The ADOS-2, DAS-II and Vineland-II were only administered at baseline, but EEG, ET and social impairment measures were administered at all time points. Participant data was made available through NDAR with the help of the Data Acquisition and Analysis Core. The rationale and methodology of the study is outlined in McPartland (2017).

Participants

This Autism Biomarkers Consortium for Clinical Trials recruited typically developing children and children diagnosed with ASD between 4 and 11 years of age. Participants were recruited at five sites throughout the Unites States – Boston Children's Hospital, Duke University, UCLA, University of Washington, and Yale Child Study Center. While enrollment in this study is ongoing, at the time of our analysis there were fifty-one participants with data available through NDAR. Participant demographics and cognitive profiles are considered in more detail at the beginning of the "Results" section.

Procedures

For our research, data from NDAR study #2288 was accessed, downloaded, and cleaned using Matlab code. The data tables provided by NDAR contained numerous redundancies and omissions when initially accessed. Redundancies were eliminated and omissions were standardized in the cleaning of this data. Relevant scores from the ADOS-2, DAS-II, and Vineland-II were organized by participant for our analysis. Participant groups were divided by diagnostic categories and verified using ADOS-2 comparison scores. Participant groups were

further refined by identifying a “Low Verbal” subgroup of children diagnosed with ASD who had verbal IQ scores below 85.

The Autism Biomarkers Consortium for Clinical Trials collected EEG data using a Clinical Geodesic EEG System 400 with 128 electrodes. A map of electrode locations for this system is included in Appendix A. For our analysis of sample entropy, fewer electrode sites were required and we selected the most commonly used 19 sites, including C3, C4, O1, O2, Cz (Ref in Appendix A), F3, F4, F7, F8, Fz, Fp1, Fp2, P3, P4, P7, P8, Pz, T7, T8. The 1000 Hz sampling rate of the Clinical Geodesic EEG System 400 allowed for an analysis of sample entropy at six frequencies, High Gamma, Gamma, Beta, Alpha, Theta, Delta.

Sample entropy was calculated within these frequencies at each of the nineteen scalp locations recorded for participants, resulting in one hundred and fourteen sample entropy measurements per participant. This method of identifying sample entropy was first identified by Costa, Goldberg, and Peng (2014), and can be applied to any physiological data represented as a time series, traditionally EEG and EKG data. This method for determining sample entropy has been adapted and modified by subsequent researchers, most notably in the study distinguishing typically developing infants from those at high risk of ASD. The sample entropy measurements for our study follows the method developed in this study. (Bosl, et al., 2011)

Measures

The behavioral measures selected for our study are the ADOS-2, DAS-II, and Vineland-II. The ADOS-2 comparison score was used to confirm ASD diagnosis and distinguish the control group and children diagnosed with ASD. The DAS-II was used to identify children with verbal IQ scores lower than 85. Additional scores provided by the ADOS-2 and DAS-II were included in our initial analysis to present a complete picture of the sample. The Vineland-II was

also included to present adaptive behavior profiles of participants, and ensure that the expected correlations between ASD severity, IQ scores, and adaptive functioning were intact for this sample. Below is a summary of the three measures used.

ADOS-2.

The ADOS-2 is an assessment instrument used for the diagnosis of ASD. It consists of standard activities for clients which allow the assessor to observe behaviors relevant to ASD diagnosis (Lord, et al., 2012). Many of the activities used in the ADOS are planned social activities designed specifically to create a context where the communicative and social impairments of ASD become apparent. The assessment may be administered to anyone over 12 months of age and there are five modules for clinicians to select between. Each module contains a list of activities designed for different ages and verbal ability. The toddler module can be administered to children between 12 and 30 months of age. It consists of simple social interaction that does not require verbal ability, such as passing a ball back and forth with the assessor and presents the child with cause-and-effect toys which often elicit restricted and repetitive behavior. Modules 1-4 present activities appropriate for older children and adults. Module 4 consists largely of conversation where the assessor asks the client to discuss topics such as friendship, emotional attunement, and social difficulties, among others. Tactile activities, such as a spinning disk, are also presented to explore potential repetitive and restrictive behavior.

Each module of the ADOS-2 is scored in a similar fashion. The assessor takes careful observational notes during the assessment and provides the client with a score between 0-3 in a number of domains. Zeros are given for typical behavior, and threes for behavior consistent with ASD. For example, in Module 4 domain A10, Emphatic or Emotional Gestures a 0 is given when a client exhibits “a range of appropriate emphatic and/or emotional gestures that are well

integrated with speech," and a 3 is given when there is "no or very limited emphatic or emotional gestures." (Lord, et al., 2012) The algorithm for diagnosis selects those domains which distinguished typically developing children from children with ASD in the validation sample. A sum of scores in these domains is converted to a comparison score between 1 and 10. The modules are aligned so that a comparison score of 4 in any module is considered consistent with a diagnosis of ASD.

The ADOS-2 can be administered by clinical psychologists and physicians with prior education, training, or experience with the instrument. (Lord, et al., 2012) The Autism Biomarkers Consortium for Clinical Trials administered the ADOS-2 for every client and the scores are considered valid for our purposes. Participants in our study were distinguished into typically developing and ASD groups by clinical diagnosis, and each participant was verified as having an ADOS-2 comparison score of 4 or greater.

Validity and reliability for the ADOS-2 built upon previous studies of the original ADOS since many of the items and administration remained the same. The ADOS-2 extended validation sample contained 1,415 individuals and 2,195 assessments. While the toddler module was introduced in the ADOS-2, our study only relied on administration of modules 1, 2, and 3. Interrater reliability of items within the validation sample had an exact reliability of 91.5%, 89%, and 88.2% for modules 1, 2, and 3 respectively. Test-retest reliability was .87, .83, and .87 for module 1, 2, and 3 over the course of 10 months, with much of this change attributed to the effects of behavioral intervention. Item validity and their correlation with ASD diagnosis remained largely consistent between the ADOS and ADOS-2, however, new diagnostic algorithms were developed to increase sensitivity of the instrument to the verbal ability of children. For example, module 1 contains two algorithms for children based on their ability to

produce five or more words during the assessment. Children able to produce more words receive higher Comparison scores based on fewer symptoms, because children with lower language abilities naturally produce more autistic-like symptoms to facilitate their social communication. Additional items that do not factor into diagnostic scores, such as “Anxiety” and “Overactivity”, are included in the assessment, because they can influence behavior observation during the assessment.

DAS-II.

The DAS-II is composed of cognitive batteries that measure verbal ability, nonverbal reasoning, and spatial ability. The Early Years battery can be administered to children between the ages of two and a half and six years eleven months. The School-Age battery can be administered to children between seven and eighteen years of age. The division of batteries allows for flexibility in administration so that older children with lower ability may be administered the Early Years battery, while younger children with greater ability may be given the School Age battery (Elliott, 2007).

The DAS-II General Conceptual Ability (GCA) score is derived from the three cluster scores – verbal, nonverbal, and spatial ability – and is a measure of psychometric *g*, often referred to as intelligence or IQ. The author of the DAS-II, however, finds the labels “intelligence” and “IQ” problematic, and stresses the value of cluster scores over the GCA. Each cluster is a homogeneous assessment of a particular component of *g*, with verbal ability measuring crystallized intelligence, nonverbal reasoning measuring fluid reasoning, and spatial ability measuring visual processing and visual-spatial ability. (Elliott, 2007) Therefore, interpretation of cluster scores, and their differences, provides a more nuanced picture of a child’s cognitive profile when compared to the single GCA score. While the Autism Biomarkers

Consortium for Clinical Trials uses the DAS-II as a measure of intelligence, and the term "IQ" is commonly used in the literature we reviewed, our individual analysis is more in line with the method of interpretation advocated by the author of the DAS-II, since we rely on the Verbal Ability score rather than the GCA to differentiate participant groups.

Like the ADOS-2, the DAS-II is the second iteration of an established psychometric assessment and builds upon its predecessor to establish reliability and validity. Intercorrelations between subtests of the DAS-II support the conclusion that distinct, but related abilities, are measured by the instrument. Factor analysis of DAS-II scores indicated that the number of cognitive abilities measured by this instrument increased with age, consistent with findings in the original DAS sample. This development supported the division of the DAS-II into the Early Years and School Age subtest. External validity of the DAS-II was established through a comparison with other measures, most notably the Wechsler Intelligence Scale for Children, Fourth Edition, with correlations between GCA-Full scale IQ, Verbal Ability-VCI, and SNC-PRI being .84, .73, and .77 respectively.

Vineland-II.

The Vineland-II is a measure of adaptive functioning commonly used to assess an individual's ability to manage the practical requirements of daily life. It measures functioning in the domains of Communication, Daily Living Skills, and Socialization. The Communication domain assesses receptive, expressive and written language skills, Daily Living Skills assesses personal, domestic, and community skills, and Socialization measures interpersonal relationship, play and leisure, and coping skills. (Sparrow, Cicchetti, & Balla, 2005) The domain scores are combined to provide an Adaptive Behavior Composite score, which estimates overall adaptive

functioning. Additional domains assessing motor skills and maladaptive behaviors can also be administered.

The Vineland-II is frequently used as a measure of adaptive functioning for children with ASD. Adaptive functioning is a particularly useful area for assessment because it identifies barriers individuals may encounter as they work towards independent living. Along with diagnostic instruments such as the ADOS-2, and IQ measurements such as the DAS-II, the Vineland-II is administered to individuals with ASD to provide a more complete picture of their behavioral profile. When new instruments are developed for assessing individuals with ASD, the Vineland-II is often included to demonstrate correlations between established measures and the proposed instrument (Craig et al., 2017).

The Autism Bioarkers Consortium for Clinical Trials provided results of the Vineland-II assessment for all participants in the NDAR database. The adaptive profiles of participants included the three domains scores as well as the Adaptive Behavior Composite. Our study included Vineland-II scores to generate a more complete picture of participants behavioral profile.

Data Analysis Plan

The data collected for our study was processed according to the Matlab code presented in Appendix A. The first step in the research process was to import the data from NDAR, clean the data, standardize values, organize data across measures by participant, and separate participants into typically developing (Typ), ASD with average verbal ability (ASDAvg), and ASD with low verbal ability (ASDLow) groups. While the more common point of division between average and low verbal ability is a verbal IQ of 70, two standard deviations below the norm (Lord, Bishop, & Anderson, 2015; Anderson, Liang, & Lord, 2014), our sample contained only two participants in

the lower category using this metric. To remedy this problem, we used a dividing score of verbal IQ 85, one standard deviation below the norm, which raised our participant number in this group to eight. This method of grouping has also been used in studies which identified low functioning subgroups of ASD (Kim, Bal, & Lord, 2018).

The second step involved an analysis to determine the cognitive profiles and demographic features of the sample, looking specifically at the effects of sex and age on the sample. The third step was a correlational analysis examining the relationship between behavioral measure scores, including the ADOS-2, DAS-II, and Vineland-II. The fourth step included participant's sample entropy measurements and examined the correlation between sample entropy and scores on behavioral measures. The fifth and final step was an ANOVA analysis which attempted to distinguish Typ, ASDAvg, and ASDLow groups using only sample entropy measurements.

Results

Initial Analysis

The psychological scores of subjects in this study indicate a wide range of abilities in adaptive functioning, levels of intelligence and presence of autistic symptomatology. Table 1 presents a summary of the scores for scales and subscales on the ADOS-2, DAS-II and Vineland-II. These scores depict the wide variety of cognitive profiles present in the current sample. Verbal intelligence, for instance, ranges from the very high at 148 to very low at 30. The ADOS-2 Comparison scores range from 0, suggesting no autistic symptomatology to 10, the highest possible score on this measure. The Vineland-II Communication subdomain scores span from the Low range at 42 to the High range at 130. These scores indicate that a variety of cognitive abilities occur within this sample and suggest that, although the sample size is limited, it has

captured the diverse cognitive presentations in the wider population of typically developing children and children diagnosed with ASD.

Table 1

Summary of Subject Age Distribution and Assessment Scores

Row	Min	Max	Mean	Standard_Deviation
Age	49	138	87.81632653	26.5021017
ADOS_SA	0	17	5.897959184	5.792397668
ADOS_RRB	0	8	1.734693878	2.233975438
ADOS_Total	0	23	7.632653061	7.460154929
ADOS_Comparison	1	10	4.265306122	3.480753691
IQ_Verbal	30	148	104.4081633	21.03560312
IQ_Nonverbal	55	133	105.6041667	14.99040769
IQ_Spatial	46	136	101	16.23890783
IQ_GCA	42	133	104.9787234	18.2178715
IQ_SNC	42	124	104.1041667	15.28069229
Vineland_Comm	42	130	95.44897959	21.93746911
Vineland_DLS	45	121	90.08163265	17.22018769
Vineland_Soc	57	118	90.28571429	18.41760933

Within the sample we found that there are strong correlations between domains of intelligence, adaptive functioning and autistic symptomatology. Correlations between subscales of individual measures are to be expected and reflect the internal consistency of well-developed psychological testing instruments. The correlations between measures, however, indicate that abilities were consistent across domains. For example, in our sample, strengths in intelligence were correlated with higher levels of adaptive functioning and lower levels of autistic symptomatology, while higher levels of autistic symptomatology were correlated with lower adaptive functioning and IQ scores. A full correlational analysis between subscales of the psychological measures are provided below in Table 2. For each correlation coefficient listed there is a related p-value below .05, with blank cells having nonsignificant correlations.

Table 2

Summary of Correlations Between Assessment Scores

Row	ADOS_SA	ADOS_RRB	ADOS_Total	ADOS_Comparison	IQ_Verbal	IQ_Nonverbal	IQ_Spatial	IQ_GCA	IQ_SNC	Vineland_Comm	Vineland_DLS	Vineland_Soc	Age
ADOS_SA	1	0.661178383	0.974437395	0.947874968	-0.584590959	-0.435728125	-0.645030726	-0.65976221	-0.633231218	-0.779006986	-0.676632428	-0.778709749	0.339156792
ADOS_RRB	0	1	0.812822739	0.764778326	-0.519521817	-0.305920964	-0.413714719	-0.494210928	-0.424126821	-0.616043193	-0.527982869	-0.629533255	
ADOS_Total	0	0	1	0.964988639	-0.612029457	-0.431621484	-0.627125547	-0.662906004	-0.620383304	-0.788478528	-0.683474393	-0.793141216	0.308711525
ADOS_Comparison	0	0	0	1	-0.534940322	-0.356765322	-0.547858056	-0.583065693	-0.527965942	-0.764982798	-0.637472448	-0.779526234	0.380405887
IQ_Verbal	0	0	0	0	1	0.612382413	0.667240465	0.920715132	0.753693428	0.644506746	0.572792993	0.536673003	
IQ_Nonverbal	0	0	0	0	0	1	0.454779814	0.779777763	0.836013695	0.399791667	0.354620133	0.345235535	
IQ_Spatial	0	0	0	0	0	0	1	0.829612335	0.867553906	0.700990542	0.733379266	0.601395476	
IQ_GCA	0	0	0	0	0	0	0	1	0.944927347	0.696429523	0.65339078	0.590381706	
IQ_SNC	0	0	0	0	0	0	0	0	1	0.653530352	0.648792962	0.559577108	
Vineland_Comm	0	0	0	0	0	0	0	0	0	1	0.859226181	0.860934278	
Vineland_DLS	0	0	0	0	0	0	0	0	0	0	1	0.864776295	
Vineland_Soc	0	0	0	0	0	0	0	0	0	0	0	1	
Age	0	0	0	0	0	0	0	0	0	0	0	0	1

The strongest correlations occur between subscales of the same measure, as we might expect. There are some interesting correlations between measure subscales, most notably the ADOS-2 subscales and Vineland-II subscales. Total ADOS-2 scores are correlated with the Vineland-II Communication and Socialization scores at -.78 and -.79 respectively. DAS-II subscale correlations are more modest, with the Verbal, Nonverbal, Spatial and GCA correlated with ADOS Total scores at -.61, -.43, -.62 and -.66 respectively. These correlations are intuitive since the adaptive functioning scales of communication and socialization measure behavior more closely aligned with the core features of ASD, in contrast to intelligence measures.

An additional noteworthy feature of Table 2 is the age column and its correlational coefficients. This column was included because, unlike Sex which is binary, age is a continuous measurement which can be easily compared to a range of scores provided by psychological measurements. In Table 2, age has a correlation of .33, .30 and .38 with the Social Affect, Total and Comparison scores of the ADOS-2, respectively. These correlations are important because they explain the significant difference in age we find between our sample subgroups, described below. The significant relationship between age and autistic symptoms in our sample presents a possible confound in our final analysis, and is important to keep in mind.

When we divide our sample into three groups, Typ, ASDAvg, and ASDLow we find significant differences in group performance across measures. Tables 3, 4 and 5 provide t-test comparisons between Typ-ASDAvg, Typ-ASDLow and ASDAvg-ASDLow respectively. We consider each comparison in turn.

Table 3

Summary of T-Tests Between Typically Developing Children, and Children with ASD and Average Verbal IQ

Row	T_test	p_value	Typ Mean	Typ Stand_Dev	ASDAvg Mean	ASDAvg Stand_Dev
Age	1	0.009492594	79.84615385	23.93272623	101.3125	26.16287127
ADOS_SA	1	2.69482E-14	1.153846154	1.222859197	10.625	3.913651322
ADOS_RRB	1	6.75654E-07	0.192307692	0.491465626	3	2.366431913
ADOS_Total	1	4.92593E-17	1.346153846	1.354763675	13.625	4.145278439
ADOS_Comparison	1	1.97056E-21	1.192307692	0.401918476	7.6875	1.701714821
IQ_Verbal	1	0.004574464	115.2307692	13.79364402	102.125	13.61800279
IQ_Nonverbal	0	0.360184567				
IQ_Spatial	1	0.005838726	108.7692308	10.69320417	97.9375	13.21851605
IQ_GCA	1	0.002452185	114.0769231	9.337764516	103.8	10.53700961
IQ_SNC	1	0.008059528	111.0384615	8.032338485	102.875	10.89877669
Vineland_Comm	1	1.55032E-08	111.2692308	14.27041048	80.9375	12.1735711
Vineland_DLS	1	9.59943E-05	100.3461538	13.95691171	82.75	10.5229907
Vineland_Soc	1	9.51556E-09	103.5769231	12.1759536	76.125	11.64402565
Sex	0	0.119002227				

Table 3 reviews the results of t-tests comparing psychological scores of the Typ group compared with the ASDAvg group. The pervasive differences across virtually every domain is striking. While differences in ADOS scores are predictable, what is interesting about this comparison is that the ASDAvg group has, in some ways, controlled for intelligence by removing those subjects with low verbal IQ. Nevertheless, we find that there remain significant differences in all domains of intelligence apart from nonverbal IQ. This may be due to the elevated IQ scores of the Typ group as we see in their mean GCA of 114. This is nearly a full standard deviation higher than we would expect of a normal sample of typically developing children. On the one hand, this presents challenges related to the generalizability of our study and on the other hand it increases differentiation in performance between groups based on the metric we hope to quantify through EEG sample entropy. These considerations will be explored more fully in the discussion section of this paper.

Table 4

Summary of T-Tests Between Typically Developing Children, and Children with ASD and Low Verbal IQ

Row	T_test	p_value	Typ Mean	Typ Stand_Dev	ASDLow Mean	ASDLow Stand_Dev
Age	0	0.526767				
ADOS_SA	1	3.87467E-15	1.153846154	1.222859197	12.71428571	3.545621042
ADOS_RRB	1	4.73035E-17	0.192307692	0.491465626	4.571428571	0.975900073
ADOS_Total	1	6.51288E-17	1.346153846	1.354763675	17.28571429	4.34796066
ADOS_Comparison	1	8.28383E-21	1.192307692	0.401918476	7.857142857	1.345185418
IQ_Verbal	1	3.41376E-08	115.2307692	13.79364402	69.42857143	18.29259543
IQ_Nonverbal	1	0.000136451	110	11.65160933	84	18.86796226
IQ_Spatial	1	7.06561E-07	108.7692308	10.69320417	75.5	16.08415369
IQ_GCA	1	2.76346E-10	114.0769231	9.337764516	68.5	16.58613879
IQ_SNC	1	1.62968E-07	111.0384615	8.032338485	77.33333333	20.02664891
Vineland_Comm	1	1.44043E-07	111.2692308	14.27041048	69.85714286	14.85966096
Vineland_DLS	1	6.05433E-06	100.3461538	13.95691171	68.71428571	12.29788987
Vineland_Soc	1	1.39492E-06	103.5769231	12.1759536	73.28571429	10.93487213
Sex	0	0.698519558				

The results displayed in Table 4 are largely consistent with those displayed in Table 3. As we would expect, the differences between Typ and ASDLow are more significant than those between Typ and ASDAvg, which now includes nonverbal IQ. What is interesting to note about these two groups is the absence of any significant difference based upon age. As opposed to the Typ-ASDAvg comparison which did yield a significant difference based on age, the Typ-ASDLow groups are not significantly different by age. This further analysis suggests that the correlation between ADOS scores and age observed in Table 2 may be explained by the disproportionately high age of the the ASDAvg group. As with the unusual IQ scores among the Typ group discussed above, the differences in age within our sample poses some challenges with the full analysis, which we discuss more fully below.

Table 5

Summary of T-Tests Between Children with ASD and Average Verbal IQ, and Children with ASD and Low Verbal IQ

Row	T_test	p_value	ASDAvg Mean	ASDAvg Stand_Dev	ASDLow Mean	ASDLow Stand_Dev
Age	0	0.234278766				
ADOS_SA	0	0.239943281				
ADOS_RRB	0	0.108224763				
ADOS_Total	0	0.068351606				
ADOS_Comparison	0	0.81815885				
IQ_Verbal	1	0.000101497	102.125	13.61800279	69.42857143	18.29259543
IQ_Nonverbal	1	0.00286087	106.5625	11.74716278	84	18.86796226
IQ_Spatial	1	0.003186254	97.9375	13.21851605	75.5	16.08415369
IQ_GCA	1	1.14746E-05	103.8	10.53700961	68.5	16.58613879
IQ_SNC	1	0.000937043	102.875	10.89877669	77.33333333	20.02664891
Vineland_Comm	0	0.073886234				
Vineland_DLS	1	0.010714545	82.75	10.5229907	68.71428571	12.29788987
Vineland_Soc	0	0.589875197				
Sex	0	0.113958894				

Table 5 presents a comparison of psychological scores between the ASDAvg and ASDLow groupings. These t-tests are consistent with the broader analysis and demonstrate no significant differences within ADOS scores, although the ADOS-2 total scores approach significance. The ADOS Comparison scores, which can be used to determine ASD severity, are not significantly different. The ASDAvg and ASDLow groups are significantly different on every IQ scale, which is to be expected given that the ASDLow group was selected precisely for their lower verbal intelligence. There are some differences in adaptive behavior between these groups, particularly in the daily living skills domain. The communication domain is approaching significance, while the socialization domain is not significantly different. This is also consistent with our expectations, since the groups are separated by verbal IQ but not social deficits common to ASD.

While the sample appears to have some unusual features related to the high IQ of the Typ group and age across groups, the tables above demonstrate that there are no significant

differences related to sex within the sample. Table 6 below provides a full analysis comparing psychological scores between males and females on every measure. While differences in IQ and age remain to be addressed as we continue our analysis, differences based on sex do not appear to be a factor in this sample.

Table 6

Summary of Sex Differences by Age and Assessment Scores

Row	T_test	p_value
Age	0	0.827296779
Sex	1	0
ADOS_SA	0	0.182528699
ADOS_RRB	0	0.646728537
ADOS_Total	0	0.24165425
ADOS_Comparison	0	0.216283066
Diagnosis	0	0.32956458
ADI_A	0	0.595916102
ADI_C	0	0.580348519
ADI_D	0	0.107494795
IQ_Verbal	0	0.268538444
IQ_Nonverbal	0	0.496495635
IQ_Spatial	0	0.589462648
IQ_GCA	0	0.246893575
IQ_SNC	0	0.466080784
Low_Verbal	0	0.376655932
Vineland_Comm	0	0.067189902
Vineland_DLS	0	0.165954578
Vineland_Soc	0	0.156217139
Final_Cats	0	0.807642463

Given the differences in age identified above, it is worthwhile to explore more deeply the relationship between age and psychological scores within this sample. Tables 7, 8 and 9 below present t-tests comparing three age groups within the sample, the youngest, middle and oldest thirds of subjects. Table 7 indicates that there is no significant difference between the youngest and middle third on any psychological measure collected in this sample. Table 8 indicates a significant difference between the youngest and oldest group on the ADOS Comparison score,

and table 9 indicates the same difference between the middle and oldest group. The differences on the ADOS Comparison scores arise due to the significantly higher older group average, 6.125, while the younger and middle group are 3.176 and 3.562 respectively. These differences help explain the correlations between age and ADOS scores seen in table 2. Tables 7, 8, and 9 also demonstrate that no significant differences are present between age groups in other domains assessed.

Table 7

Comparison Between the Youngest and Middle Third of the Sample by Age, Sex, and Assessment Scores

Row	T_test	p_value	Young_Mean	Young_SD	Med_Mean	Med_SD
Age	1	7.5E-10	59.58823529	7.38290952	86.125	9.97246208
Sex	0	0.109393				
ADOS_SA	0	0.724838				
ADOS_RRB	0	0.496628				
ADOS_Total	0	0.939044				
ADOS_Comparison	0	0.721563				
IQ_Verbal	0	0.847627				
IQ_Nonverbal	0	0.909224				
IQ_Spatial	0	0.730877				
IQ_GCA	0	0.5941				
IQ_SNC	0	0.850829				
Vineland_Comm	0	0.478065				
Vineland_DLS	0	0.440804				
Vineland_Soc	0	0.785106				

Table 8

Comparison Between the Youngest and Oldest Third of the Sample by Age, Sex, and Assessment Scores

Row	T_test	p_value	Young_Mean	Young_SD	Old_Mean	Old_SD
Age	1	1.43E-18	59.58823529	7.38290952	119.5	10.6332811
Sex	0	0.618854				
ADOS_SA	0	0.053486				
ADOS_RRB	0	0.28587				
ADOS_Total	0	0.066258				
ADOS_Comparison	1	0.016018	3.176470588	2.94183816	6.125	3.6855574
IQ_Verbal	0	0.529656				
IQ_Nonverbal	0	0.687872				
IQ_Spatial	0	0.301457				
IQ_GCA	0	0.539968				
IQ_SNC	0	0.425117				
Vineland_Comm	0	0.405948				
Vineland_DLS	0	0.759921				
Vineland_Soc	0	0.532245				

Table 9

Comparison Between the Middle and Oldest Third of the Sample by Age, Sex, and Assessment Scores

Row	T_test	p_value	Med_Mean	Med_SD	Old_Mean	Old_SD
Age	1	3.41E-10	86.125	9.97246208	119.5	10.6332811
Sex	0	0.278873				
ADOS_SA	0	0.102874				
ADOS_RRB	0	0.094053				
ADOS_Total	0	0.073055				
ADOS_Comparison	1	0.044891	3.5625	3.22425702	6.125	3.6855574
IQ_Verbal	0	0.566819				
IQ_Nonverbal	0	0.75813				
IQ_Spatial	0	0.108865				
IQ_GCA	0	0.122058				
IQ_SNC	0	0.20558				
Vineland_Comm	0	0.137058				
Vineland_DLS	0	0.238494				
Vineland_Soc	0	0.381701				

This initial analysis summarizes the psychological scores within our sample and compares these scores to demographic features of participants, namely age and sex. When looking at psychological scores within the sample, they are strongly correlated with one another. That means that higher performance in one domain is correlated with higher performance in other domains, while lower performance is one domain is correlated in lower performance in others. Age is not significantly correlated with any psychological score apart from ADOS-2 comparison scores, and there are no significant differences based on sex. When we compare Typ, ASDAvg and ASDLow groups we find that, consistent with the correlational analysis, there are many significant differences across domains between groups. As a result of the groups being separated in part based on ADOS-2 comparison scores, age is significantly different between the Typ and ASDAvg group. The perturbation of age within the sample appears to stem from the unusually high ADOS-2 comparison scores among older participants. The second stage of our analysis involves comparing psychological scores and subject groups with sample entropy measurements.

Sample Entropy Analysis

The sample entropy analysis proceeds in two parts. First, we explore the correlation between subjects' psychological scores and sample entropy measurements. This analysis includes subtests of the ADOS-2, DAS-II and Vineland-II measurements, as well as age. Sample entropy is measured at 114 points for every participant, composed of six wavelength bands for each of 19 scalp locations. The second, and final phase of the analysis, proceeds by comparing the sample entropy between Typ, ASDAvg and ASDLow using ANOVA at each of the 114 measurement points.

Of the 114 sample entropy calculations available to provide a significant correlation with age or psychological scores, 25 measurements generated positive results. These are displayed below in Table 10, which has been divided in two for ease of reference. Fifteen of 19 scalp locations bore positive correlations with psychological scores, which are reported in the first row of Table 10. Wavelength bands are reported in the second row and suggest that specific bands are much more important for our analysis compared to others. The totals come to High Gamma (0), Gamma (1), Beta (1), Alpha (12), Theta (5), Delta (6). This suggests that sample entropy within the Alpha, Theta and Delta bands are most strongly correlated with the abilities, or symptoms, measured in the ADOS-2, DAS-II and Vineland-II.

The correlations presented in Table 10 are remarkably consistent in terms of direction of correlation across measures. Every significant correlation with ADOS-2 measures are negative, suggesting that higher levels of sample entropy are related to lower ADOS-2 scores and less symptomatology on this measure. Correlations with IQ and adaptive functioning are all positive, indicating that higher levels of sample entropy are related to higher performance in these domains. These results seem to suggest that higher levels of sample entropy in the locations and frequency bands identified below are indicative of better functioning across psychological domains and may help distinguish typical developing children and children diagnosed with ASD.

Notably absent from the correlations presented in Table 10 are any positive relationships between sample entropy and verbal IQ, the measurement used to distinguish the ASDAvg and ASDLow groups. This may help explain the lack of differences detected between the ASDAvg and ASDLow discussed in Tables 11 – 16 below. Also important to note is the relative infrequency of correlations between age and sample entropy. Correlations with age are found in only 3 measurements, and in two of these age is the only attribute correlated within that

measurement. While age appeared to be an important factor in our initial analysis, demonstrated by its correlation with ADOS sores, it does not appear to be a significant factor in the sample entropy portion of our analysis.

Table 10.1

Summary of Correlations Between Entropy and Assessment Scores

Row	C3_4	C4_4	F3_6	F4_6	F7_4	F7_6	F8_6	Fz_4	Fp1_4	Fp1_5	Fp2_4	Fp2_6
Frequency Scale	Alpha	Alpha	Delta	Delta	Alpha	Delta	Delta	Alpha	Alpha	Theta	Alpha	Delta
Age	-0.293805573											0.353759846
ADOS_SA					-0.384789229	-0.293874332				-0.282332101	-0.338235322	
ADOS_RRB					-0.315325566		-0.313480494					
ADOS_Total		-0.281710832			-0.393193148	-0.310930561		-0.281713274			-0.287863962	
ADOS_Comparison		-0.299826013			-0.375098686	-0.292085328		-0.32125593	-0.305878252	-0.354203646	-0.320622389	
IQ_Verbal												
IQ_Nonverbal												
IQ_Spatial										0.406690464		
IQ_GCA												
IQ_SNC												
Vineland_Comm			0.300035292	0.364403366		0.282001807		0.299420835				
Vineland_DLS											0.297647331	
Vineland_Soc			0.297902926	0.285309293	0.307060005			0.317175071		0.295369341		

Tale 10.2

Summary of Correlations Between Entropy and Assessment Scores

Row	P3_4	P3_5	P3_6	P4_2	P4_4	P4_5	Pz_3	Pz_4	Pz_5	T7_4	T7_5	P7_4	P8_4
Frequency Scale	Alpha	Theta	Delta	Gamma	Alpha	Theta	Beta	Alpha	Theta	Alpha	Theta	Alpha	Alpha
Age												-0.298849466	
ADOS_SA	-0.292377421				-0.290391313	-0.359160601		-0.314235224	-0.320895105	-0.302475922		-0.407844333	-0.36660881
ADOS_RRB					-0.289692668			-0.341572741					
ADOS_Total					-0.312222506	-0.345983792		-0.346271695				-0.354166529	-0.296820316
ADOS_Comparison					-0.350539837	-0.372218768		-0.308978085	-0.342987742			-0.398097401	-0.357284088
IQ_Verbal													
IQ_Nonverbal													
IQ_Spatial		0.303592445									0.320040613	0.307958542	0.321646005
IQ_GCA											0.296163955		
IQ_SNC													
Vineland_Comm			0.29969164	0.300701486				0.318490201				0.32121917	0.33302196
Vineland_DLS				0.299461493			0.295081067					0.341155895	0.353219201
Vineland_Soc								0.351154922				0.40897845	0.340980719

The ANOVA analysis proceeded in two steps. The first step involved comparing three groups – Typ, ASDAvg, ASDLow at each of the 114 sample entropy measures to see if there are

any differences between groups. This analysis identified 10 sample entropy measurements with group differences. The second step involved comparing Typ, ASDAvg, ASDLow groups at each of the ten measurements to identify significant differences. Of the 10 groups originally identified, 6 had at least two groups that were significantly different.

Table 11

Entropy Comparison between Typically Developing Children, Children with ASD and Average Verbal Ability, and Children with ASD and Low Verbal Ability at the Fp1 Theta Measurement.

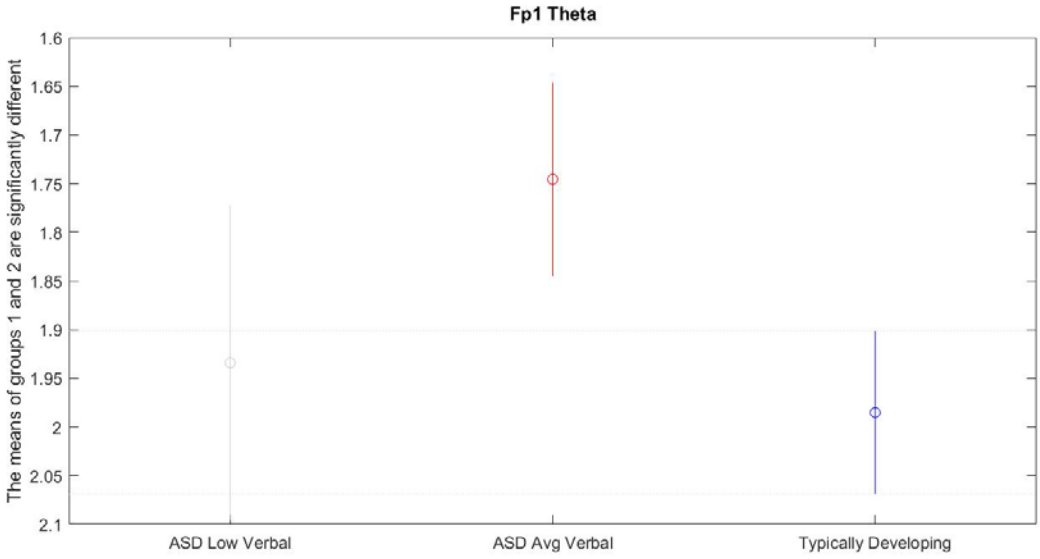


Table 12

Entropy Comparison between Typically Developing Children, Children with ASD and Average Verbal Ability, and Children with ASD and Low Verbal Ability at the Fp2 Alpha Measurement.

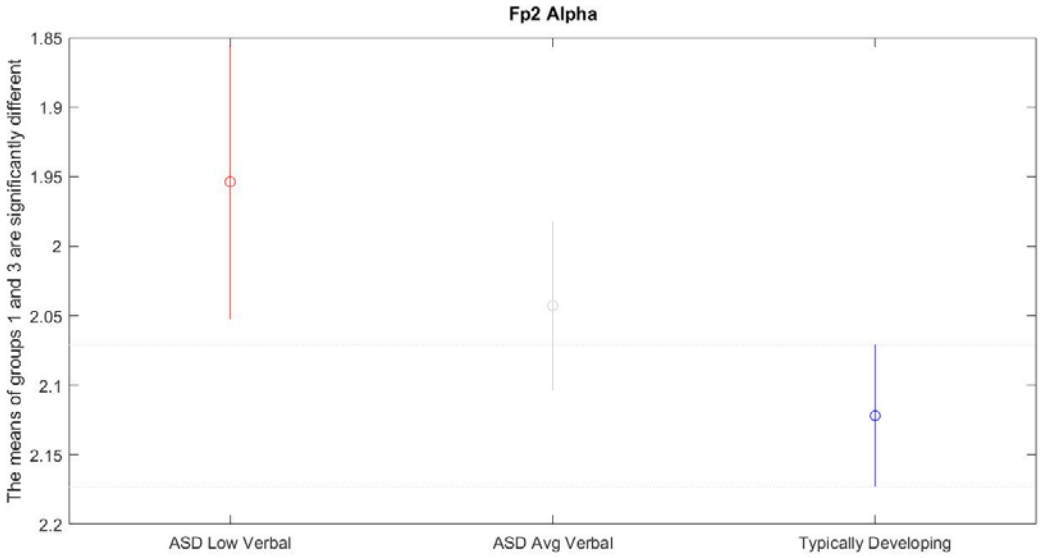


Table 13

Entropy Comparison between Typically Developing Children, Children with ASD and Average Verbal Ability, and Children with ASD and Low Verbal Ability at the O2 Theta Measurement.

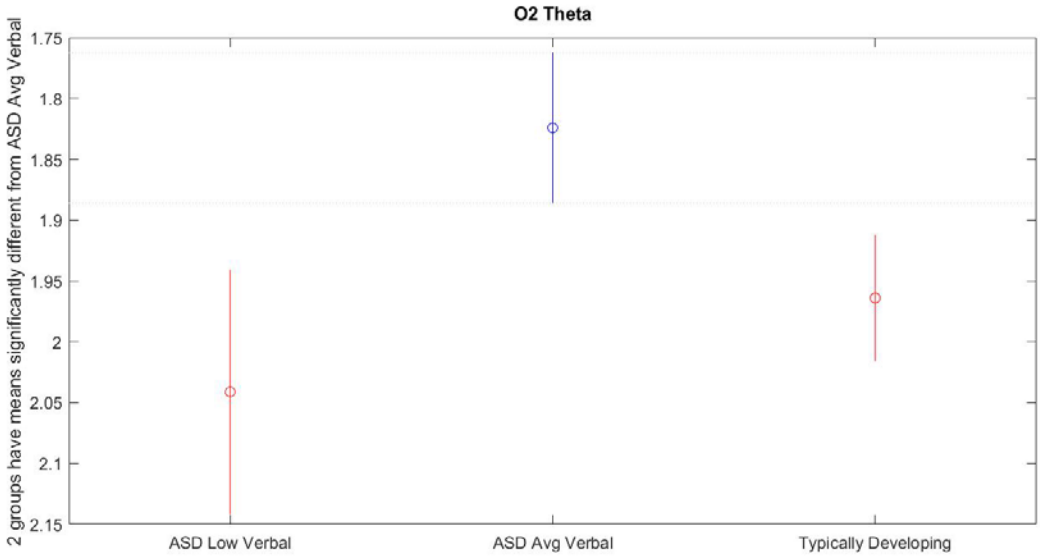


Table 14

Entropy Comparison between Typically Developing Children, Children with ASD and Average Verbal Ability, and Children with ASD and Low Verbal Ability at the P4 Alpha Measurement.

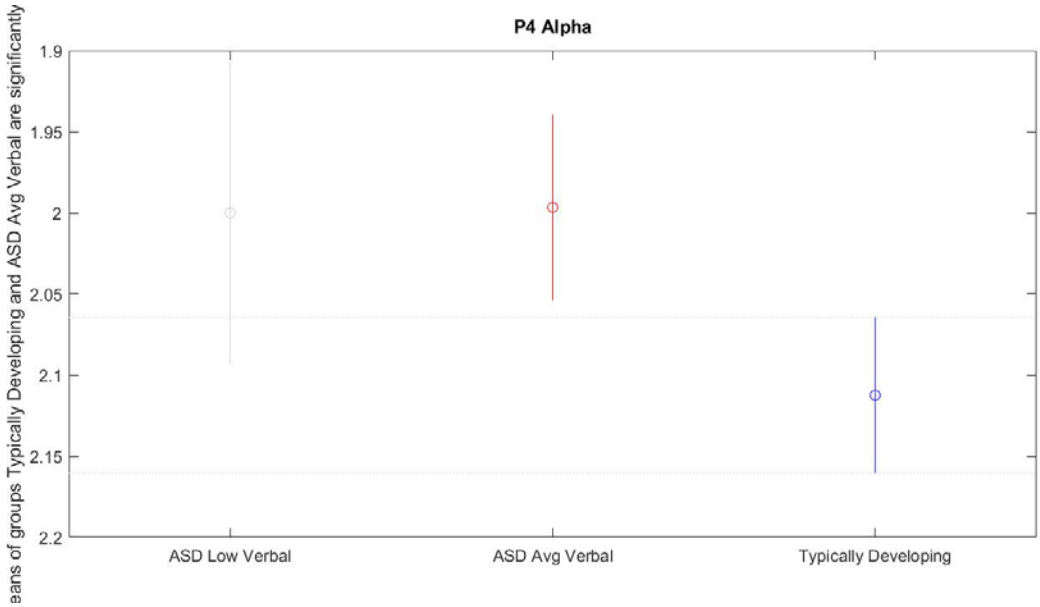


Table 15

Entropy Comparison between Typically Developing Children, Children with ASD and Average Verbal Ability, and Children with ASD and Low Verbal Ability at the P4 Theta Measurement.

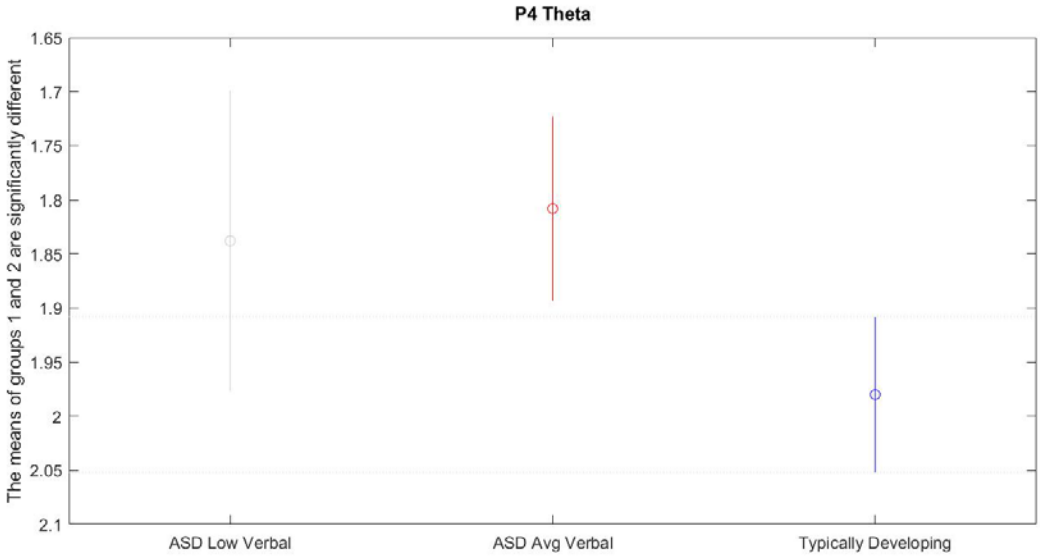
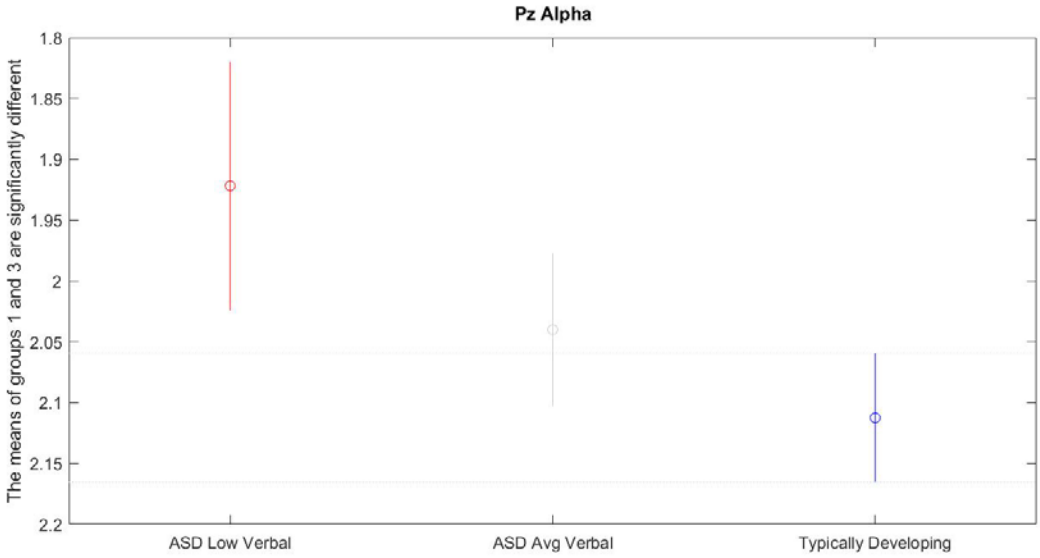


Table16

Entropy Comparison between Typically Developing Children, Children with ASD and Average Verbal Ability, and Children with ASD and Low Verbal Ability at the Pz Alpha Measurement.



These results are interpreted with greater detail in the discussion section, however, it is important to note a few important features. The first is that all groups belong to either the Alpha or Theta band. This reinforces the conception that group differences are strongest within these EEG frequency bands. Scalp locations are also consistent, with positive results primarily from the prefrontal cortex and parietal lobes. The group differences displayed in Table 13 are interesting for two reasons. First, the difference originates in the occipital lobe and there were no correlations between psychological scores and sample entropy in the occipital lobe, as displayed in Table 10. Second, Table 13 shows ASDAvg with lower sample entropy than both Typ and ASDLow groups. This is inconsistent with all other ANOVA measures, and the correlations in Table 10, which suggest that higher sample entropy is associated with typical development. The prefrontal cortex and parietal lobe also play a more central role in the cognitive processes which

tend to distinguish typically developing children and those diagnosed with ASD. Future studies will be needed to confirm the significance of the results presented in Table 13.

Discussion

The sample used in this study appears representative of the broader population of children with ASD in terms of sex and cognitive ability. Sex was not correlated with ASD symptoms, adaptive functioning, or IQ, however, older children in the study appeared to have been diagnosed with ASD at a higher rate than younger children in the sample. This irregularity provides some challenges in interpreting our results and establishing the relationship between sample entropy and ASD symptomatology.

Sample entropy was correlated with behavioral measures at 25 of the 114 possible locations, with the majority occurring in Alpha, Theta, and Delta frequency bands. The ANOVA analysis differentiated groups within Alpha and Theta frequency bands. The consistency with which Alpha, Theta, and Delta frequencies generated positive results, in contrast with High Gamma, Gamma, and Beta frequencies, suggests that sample entropy as a marker for ASD in children is most significant within these frequency bands.

The direction of correlations was also consistent across our analysis. Higher levels of entropy were almost universally associated with lower ASD symptomatology and better adaptive functioning. Correlations in our analysis were moderate, ranging from .28 to .41 and were predominantly found within ADOS-2 and Vineland-II scores. Sample entropy was infrequently correlated with measures of intelligence and was never correlated with verbal IQ.

While all of the significant correlations in our study supported the conclusion that higher levels of sample entropy are associated with lower ASD symptoms and better adaptive functioning, one ANOVA result contradicted this trend. The results of the ANOVA for O2 Theta

indicate that sample entropy is significantly higher for the ASDAvg group when compared to both the Typ and ASDLow group. The limited number of participants in our study, along with the high number of analysis performed, suggest that this result may be an anomaly within our sample. Further research is needed to determine the veracity of this result, and determine if sample entropy at the O2 theta measurement is significantly different for children with ASD and average verbal ability.

Age was correlated with sample entropy in three instances, however, on two occasions it was the only significant correlation, and it did not have a consistent direction of correlation as found in behavioral measures. On two occasions lower sample entropy was correlated with higher age, and on one occasion higher sample entropy was correlated with higher age. None of the ANOVA analysis overlapped with significant age correlations. While future research may be interested in exploring the relationship between sample entropy and age, it would appear that the impact of the irregular relationship between age and ASD symptoms in our sample had little impact on the analysis produced.

The results of our study suggest that sample entropy is not a measure capable of identifying individuals with ASD and low verbal IQ. None of the six ANOVA measurements successfully distinguished ASDLow from both the ASDAvg and Typ groups. Additionally, sample entropy was not correlated with verbal IQ at any of 114 measurement points. While our sample was small, and the cutoff for the ASDLow group was a verbal IQ of 85, as opposed to the more common 70, researchers interested in identifying biomarkers of this subgroup may wish to devote resources to alternative avenues of inquiry.

Our study did not demonstrate a relationship between sample entropy and the low verbal subgroup of ASD, but it did demonstrate extensive and consistent correlations between sample

entropy and both ASD symptoms and adaptive behavior. Our results suggest that lower levels of sample entropy are correlated with higher levels of ASD symptoms and lower levels of adaptive functioning. The consistency of these results across a multitude of observations could also be interpreted as indicating that sample entropy is associated with a fundamental neurological process found in ASD.

In addition to the correlational analysis, our ANOVA analysis demonstrated that children diagnosed with ASD, of any verbal ability, can be distinguished from typically developing peers based upon measures of sample entropy. These results confirm and extend the findings in Bosl et al. (2011) which found that sample entropy could be used to distinguish infants and toddlers at high risk of ASD from typically developing counterparts. Our findings have shown that sample entropy may be used as a biomarker to identify ASD among older children, and also suggests that sample entropy may be an indication of underlying neurological processes implicated in ASD. The possibility that sample entropy is related to the etiology of ASD provides another line of inquiry for researchers interested in greater understanding of this disorder.

The results of our ANOVA analysis indicate that ASD and typically developing peers may be distinguished by sample entropy measurements in the prefrontal cortex and parietal lobe. Abnormal processing in the prefrontal cortex has been implicated in ASD, specifically related to core deficits in social cognition (Bicks, Koike, Akbarian, & Morishita, 2015; Paine, Swedlow, & Swetschinski, 2017). Research into the role that sample entropy may play in the etiology of ASD would benefit from replicating studies that use other methods to successfully identify abnormalities in the prefrontal cortex. This would solidify sample entropy as an additional measure to detect underlying neurological processes which contribute to ASD.

Additional considerations for developing sample entropy as a useful measure of ASD involve demonstrating the reliability and stability of this measurement. Reliability of sample entropy measurements of EEG signals could be demonstrated by performing the same analysis on multiple EEG measurements taken at the same time, and over the course of several weeks or months. This would confirm that sample entropy is a reliable measurement of neurological process and allow for longitudinal studies to establish how stable sample entropy is over time.

The stability of sample entropy could be established through measurements taken over the course of years, and such studies would provide a baseline regarding the natural development of sample entropy over the course of an individual's life. Regarding ASD, this baseline would allow for developmental trajectories of ASD, and typically developing peers which incorporate sample entropy measurements in order to understand how this metric may differ between groups. Incorporating sample entropy into these studies could also explore how sample entropy changes in the course of behavioral treatment for ASD.

Our study has several limitations. First, our sample size of 49 was relatively small, and conclusions drawn from our results are necessarily conservative. Further studies are needed to verify the veracity of our findings. Second, our secondary data analysis precluded a better understanding of participant demographics and treatment history. This limited the scope of our initial analysis which provided a better understanding of the composition of our sample.

Despite these limitations, it appears that sample entropy may be a reliable measure of autistic symptomatology for children between 4 and 11 years of age. These results confirm and extend earlier applications of sample entropy to distinguish children at high risk of ASD from typically developing counterparts (Bosl et al., 2011). Our results suggest that further research into sample entropy is warranted to develop this measure into a viable aspect of future studies on

ASD, particularly longitudinal studies attempting to identify developmental trajectories of children with, and without, ASD.

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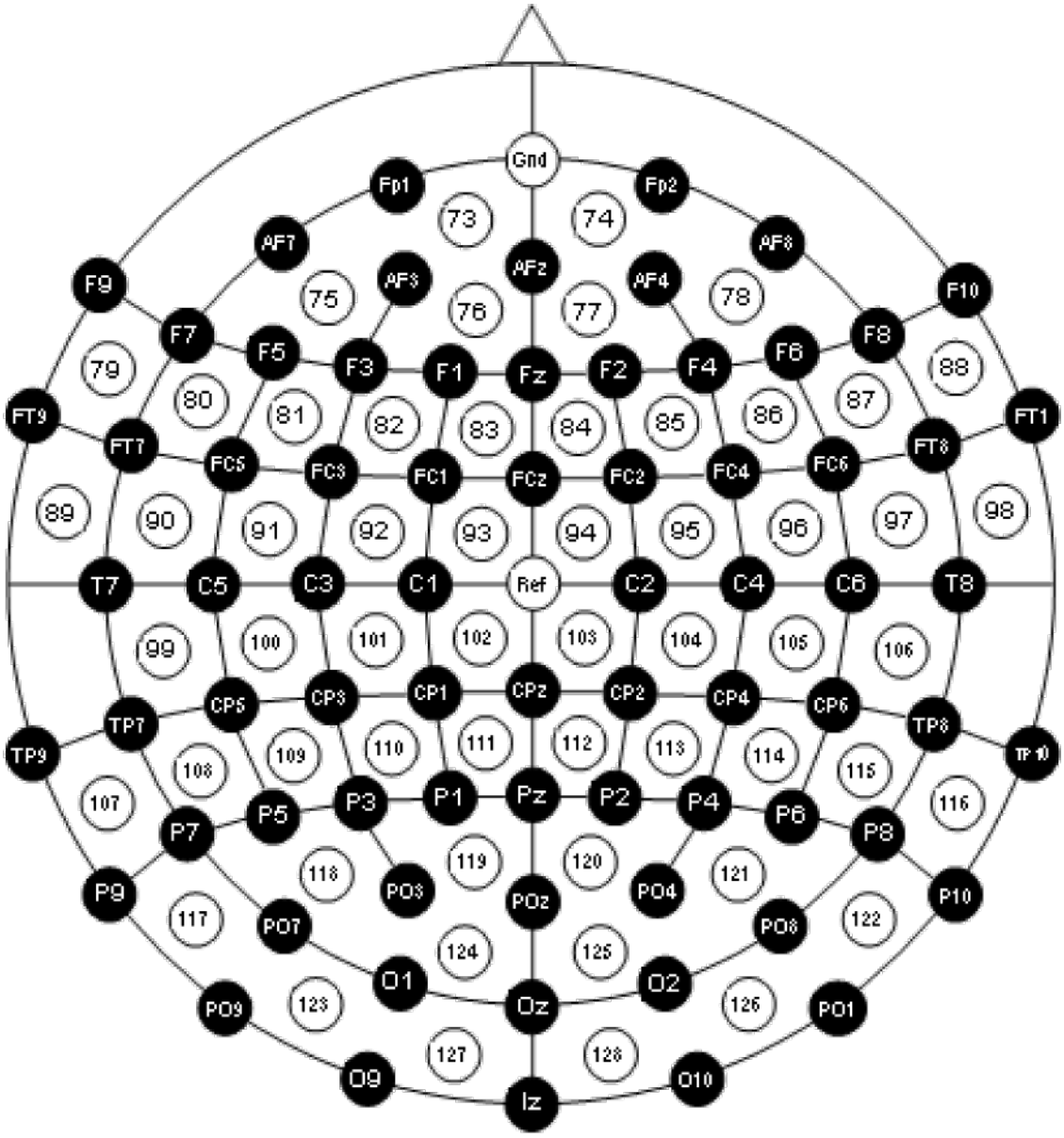
Appendix A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AF7
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Appendix B

Compile Data

Manually import original data file-by-file using Matlab import function. This auto-formats table contents.

Contents

Save imported data

```
writetable(adi200304, 'adi.xlsx');
writetable(ados1201201, 'adosm1.xlsx');
writetable(ados2201201, 'adosm2.xlsx');
writetable(ados3201201, 'adosm3.xlsx');
writetable(dasiiearly03, 'dasey.xlsx');
writetable(dasiischool04, 'dassa.xlsx');
writetable(vinelandsurvey200505, 'vineland.xlsx');
```

Load Data

```
ADI = readtable('adi.xlsx');
ADOSm1 = readtable('adosm1.xlsx');
ADOSm2 = readtable('adosm2.xlsx');
ADOSm3 = readtable('adosm3.xlsx');
DASEY = readtable('dasey.xlsx');
DASSA = readtable('dassa.xlsx');
Vineland = readtable('vineland.xlsx');
EEG_Analysis = readtable('NDAR_data_SE_RQA.xlsx');
```

Implement CleanTables Function

This deletes redundant column headers and standardizes missing values.

```
ADI = CleanTables(ADI);

ADOSm1 = CleanTables(ADOSm1);

ADOSm2 = CleanTables(ADOSm2);

ADOSm3 = CleanTables(ADOSm3);

DASEY = CleanTables(DASEY);

DASSA = CleanTables(DASSA);

Vineland = CleanTables(Vineland);
```

Add Column to Identify Module/Version

```
ADOSm1.Module(:, 1) = 1;

ADOSm2.Module(:, 1) = 2;

ADOSm3.Module(:, 1) = 3;

DASEY.Version(:,1) = "EY";
DASSA.Version(:,1) = "SA";
```

Determine Dx, Language Level and combined

```
%ADOS Module 1 Dx
for i = 1:height(ADOSm1)
    if ADOSm1.scoresumm_compscore(i) >= 4
        ADOSm1.Autism_Dx(i) = 1;
    else
        ADOSm1.Autism_Dx(i) = 0;
    end
end
%ADOS Module 2 Dx
for i = 1:height(ADOSm2)
    if ADOSm2.scoresumm_compscore(i) >= 4
        ADOSm2.Autism_Dx(i) = 1;
    else
        ADOSm2.Autism_Dx(i) = 0;
    end
end
%ADOS Module 3 Dx
for i = 1:height(ADOSm3)
    if ADOSm3.scoresumm_compscore(i) >= 4
        ADOSm3.Autism_Dx(i) = 1;
```

```
    else
        ADOSm3.Autism_Dx(i) = 0;
    end
end
%DAS EY Low IQ
for i = 1:height(DASEY)
    if DASEY.dasii_eyr_verbal_ss(i) < 85
        DASEY.Low_Verbal(i) = 1;
    else
        DASEY.Low_Verbal(i) = 0;
    end
end
%DAS SA Low IQ
for i = 1:height(DASSA)
    if DASSA.dasii_sar_verbal_ss(i) < 85
        DASSA.Low_Verbal(i) = 1;
    else
        DASSA.Low_Verbal(i) = 0;
    end
end
```

This Section has been commented-out because we are not using these features in this analysis

%ADI Minimally Verbal for i = 1:height(ADI) if ADI.funccom_levell(i) == 2 ADI.Minimally_Verbal(i) = 1; else ADI.Minimally_Verbal(i) = 0; end end %DAS SA Poor Expressive Language for i = 1:height(DASSA) if ismissing(DASSA.dasii_sar_wdef_tscr(i)) DASSA.DAS_Poor_Expressive(i) = NaN; elseif DASSA.dasii_sar_wdef_tscr(i) >=10 && DASSA.dasii_sar_wdef_tscr(i) <= 49 DASSA.DAS_Poor_Expressive(i) = 1; else DASSA.DAS_Poor_Expressive(i) = 0; end end x = nan(height(DASEY)); % Initialize NaN matrix to add to DASEY DASEY.DAS_Poor_Expressive = x; % Add column to DASEY to be consistent with DASSA %DAS SA Poor Expressive Semantics for i = 1:height(DASSA) if ismissing(DASSA.dasii_sar_vsim_tscr(i)) DASSA.DAS_Poor_Expressive(i) = NaN; elseif DASSA.dasii_sar_vsim_tscr(i) >=10 && DASSA.dasii_sar_wdef_tscr(i) <= 50 DASSA.DAS_Poor_Expressive_Semantics(i) = 1; else DASSA.DAS_Poor_Expressive_Semantics(i) = 0; end end DASEY.DAS_Poor_Expressive_Semantics = x; %Adds column to DASEY to be consistent with DASSA

Select Total Scores

GUIDs and total scores with inerpretations for all - ADOS includes age and sex

```
ADI_Total = ADI(:, {'subjectkey', 'dbaes_atotal', 'dbaes_ctotal', 'dbaes_dtotal'});
ADOSm1_Total = ADOSm1(:, {'subjectkey', 'interview_age', 'gender',
'scoresumm2_abtotal', 'scoresumm_adtotal', ...
    'scoresumm_overalltotal', 'scoresumm_compscore', 'Module', 'Autism_Dx'});
ADOSm2_Total = ADOSm2(:, {'subjectkey', 'interview_age', 'gender',
'scoresumm2_abtotal', 'scoresumm_adtotal', ...
    'scoresumm_overalltotal', 'scoresumm_compscore', 'Module', 'Autism_Dx'});
ADOSm3_Total = ADOSm3(:, {'subjectkey', 'interview_age', 'gender',
'scoresumm2_abtotal', 'scoresumm_adtotal', ...
```

```
    'scoresumm_overalltotal', 'scoresumm_compscore', 'Module', 'Autism_Dx'});
DASEY_Total = DASEY(:, {'subjectkey', 'dasii_eyr_verbal_ss','dasii_eyr_nonverb_r_ss',
'dasii_eyr_spatial_ss', ...
    'dasii_eyr_gca_ss', 'dasii_eyr_snc_ss', 'Version', 'Low_Verbal'});
DASSA_Total = DASSA(:, {'subjectkey', 'dasii_sar_verbal_ss','dasii_sar_nvr_ss',
'dasii_sar_spatial_ss', ...
    'dasii_sar_gca_ss', 'dasii_sar_snc_ss', 'Version', 'Low_Verbal'});
Vineland_Total = Vineland(:, {'subjectkey', 'communicationdomain_total',
'livingskillsdomain_total', ...
    'socializationdomain_total'});
```

Rename Total Score Columns for DAS and ADOS, which allows for concatenation

```
DASEY_Total.Properties.VariableNames{'dasii_eyr_verbal_ss'} = 'Verbal';
DASEY_Total.Properties.VariableNames{'dasii_eyr_nonverb_r_ss'} = 'Nonverbal';
DASEY_Total.Properties.VariableNames{'dasii_eyr_spatial_ss'} = 'Spatial';
DASEY_Total.Properties.VariableNames{'dasii_eyr_gca_ss'} = 'GCA';
DASEY_Total.Properties.VariableNames{'dasii_eyr_snc_ss'} = 'SNC';
DASSA_Total.Properties.VariableNames{'dasii_sar_verbal_ss'} = 'Verbal';
DASSA_Total.Properties.VariableNames{'dasii_sar_nvr_ss'} = 'Nonverbal';
DASSA_Total.Properties.VariableNames{'dasii_sar_spatial_ss'} = 'Spatial';
DASSA_Total.Properties.VariableNames{'dasii_sar_gca_ss'} = 'GCA';
DASSA_Total.Properties.VariableNames{'dasii_sar_snc_ss'} = 'SNC';
```

Concatenate Versions of ADOS and DAS

```
ADOS_Total = vertcat(ADOSm1_Total, ADOSm2_Total, ADOSm3_Total);

DAS_Total = vertcat(DASEY_Total, DASSA_Total);
```

Remove Duplicate Rows

```
ADI_Total = RemoveDuplicateRows(ADI_Total);

ADOS_Total = RemoveDuplicateRows(ADOS_Total);

DAS_Total = RemoveDuplicateRows(DAS_Total);

Vineland_Total = RemoveDuplicateRows(Vineland_Total);
```

Manually remove rows from Table flagged above

NDARP351LEP

```
DAS_Total.Verbal(12) = 80;                  % Participant had verbal score from EY and
remaining scores from SA
DAS_Total.Version(12) = 'EY&SA';
DAS_Total.Low_Verbal(12) = DAS_Total.Low_Verbal(11); % Transfer Low_Verbal Category
with Vebal Score
DAS_Total = DAS_Total([1:10 12:end], :);
% NDARRC664GBF
DAS_Total = DAS_Total([1:27 29:end], :);    % Participant had EY scores but no SA
scores
% NDARTW441YZ7
DAS_Total.Verbal(31) = 87;                  % Participant had much higher verbal score
from EY. I used this score and ...
DAS_Total.GCA(31) = NaN;                    % kept others from SA, setting GCA to NaN.
Also changed low verbal.
DAS_Total.Version(31) = 'EY&SA';
DAS_Total.Low_Verbal(31) = DAS_Total.Low_Verbal(32); % Transfer Low_Verbal Category
with Vebal Score
DAS_Total = DAS_Total([1:31 33:end], :);
DAS_Total = RemoveDuplicateRows(DAS_Total); % Check for duplicate row warning
```

Join Tables

```
Total = outerjoin(ADOS_Total, ADI_Total, 'MergeKeys', true);
Total = outerjoin(Total, DAS_Total, 'MergeKeys', true);
Total = outerjoin(Total, Vineland_Total, 'MergeKeys', true);
Total = innerjoin(Total, EEG_Analysis);
```

Determine Final Categories

```
for i = 1:size(Total,1)
    if Total.Autism_Dx(i) == 0 && Total.Low_Verbal(i) == 0
        Total.Final_Cats(i) = 0;
    elseif Total.Autism_Dx(i) == 1 && Total.Low_Verbal(i) == 0
        Total.Final_Cats(i) = 1;
    elseif Total.Autism_Dx(i) == 1 && Total.Low_Verbal(i) == 1
        Total.Final_Cats(i) = 2;
    elseif Total.Autism_Dx(i) == 0 && Total.Low_Verbal(i) == 1
        Total.Final_Cats(i) = 4;
    else
        Total.Final_Cats(i) = NaN;
    end
end
%Reorder with Final_Cats at end of scores
Total = Total(:, [1:22, end, 23:end-1]);
```

Save Table

```
writetable(Total, 'ScoresAndEEG.xlsx');
```

End

Convert to Matrices

Contents

Load ScoresAndEEG

```
ScoresAndEEG = readtable('ScoresAndEEG.xlsx');
```

Separate Demographic Information and Scores

```
GUID = ScoresAndEEG(:,{'subjectkey'});
Age = ScoresAndEEG(:,{'interview_age'});
Sex = ScoresAndEEG(:,{'gender'});
Diagnosis = ScoresAndEEG(:,{'Autism_Dx'});
ADOS_Module = ScoresAndEEG(:,{'Module'});
Low_Verbal = ScoresAndEEG(:,{'Low_Verbal'});
DAS_Version = ScoresAndEEG(:,{'Version'});
ADOS = ScoresAndEEG(:,{'scoresumm2_abtotal', 'scoresumm_adtotal',
'scoresumm_overalltotal', 'scoresumm_compscore'});
ADI = ScoresAndEEG(:,{'dbaes_atotal', 'dbaes_ctotal', 'dbaes_dtotal'});
IQ = ScoresAndEEG(:,{'Verbal', 'Nonverbal', 'Spatial', 'GCA', 'SNC'});
Vineland = ScoresAndEEG(:,{'communicationdomain_total', 'livingskillsdomain_total',
'socializationdomain_total'});
Final_Cats = ScoresAndEEG(:,{'Final_Cats'});
```

Convert Scores to Matrices

```
GUID = table2array(GUID);                                % NDAR Identifiers
Age = table2array(Age);                                  % In months, at time of ADOS
Sex = categorical(table2array(Sex));                     % M/F as categorical
Diagnosis = categorical(table2array(Diagnosis));         % Dx as categorical
ADOS_Module = categorical(table2array(ADOS_Module));     % ADOS Module as categorical
Low_Verbal = categorical(table2array(Low_Verbal));       % Low verbal IQ as categorical
DAS_Version = categorical(table2array(DAS_Version));     % DAS Version as categorical
ADOS = table2array(ADOS);                                % SA, RRB, Total, Comparison,
Module
ADI = table2array(ADI);                                  % Sections A, C, D
IQ = table2array(IQ);                                    % Verbal, Nonverbal, Spatial,
GCA, SNC, DAS Version
Vineland = table2array(Vineland);                        % Communication, Daily Living
Skills, Socialization
```

```
Final_Cats = categorical(table2array(Final_Cats));      % All combinations of ASD(+,-) and Low Verbal(+,-) as categorical
```

Convert EEG to Matrices

```
x = find(strcmpi(ScoresAndEEG.Properties.VariableNames,'SampE_C3_cD1')); % Find the column number that begins EEG records
SampE = ScoresAndEEG(:, x: x+113);
SampE2D = table2array(SampE);
SampE3D = SortEEG(SampE2D);
SampE_VariableNames = ScoresAndEEG.Properties.VariableNames(x:x+113);
```

Clear unneeded variables

```
clear ScoresAndEEG
clear SampE
clear x
```

Save workspace variables

```
save('Variables.mat');
```

END

Result of Basic Psych Statistics

Contents

Load Variables

```
clear

load('Variables.mat')
```

Subgroup Indexing

```
TypAvgV = find(Final_Cats == '0');
ASDAvgV = find(Final_Cats == '1');
ASDLowV = find(Final_Cats == '2');
```

```
List_Full = {'Age', 'ADOS_SA', 'ADOS_RRB', 'ADOS_Total', 'ADOS_Comparison', 'ADI_A',
'ADI_C', 'ADI_D', 'IQ_Verbal', 'IQ_Nonverbal', ...
    'IQ_Spatial', 'IQ_GCA', 'IQ_SNC', 'Vineland_Comm', 'Vineland_DLS',
'Vineland_Soc'};
```

Run BasicStats on Complete Sample

```
a = BasicStats(Age);

b = BasicStats(ADOS);

c = BasicStats(ADI);

d = BasicStats(IQ);

e = BasicStats(Vineland);



Total_Psych_Stats = vertcat(a, b, c, d, e);

Total_Psych_Stats = array2table(Total_Psych_Stats);

Total_Psych_Stats.Properties.VariableNames = {'Min', 'Max', 'Mean',
'Standard_Deviation'};
Total_Psych_Stats.Properties.RowNames = List_Full;
```

Run BasicStats on TypAvgV

```
a = BasicStats(Age(TypAvgV, :));

b = BasicStats(ADOS(TypAvgV, :));

c = BasicStats(ADI(TypAvgV, :));

d = BasicStats(IQ(TypAvgV, :));

e = BasicStats(Vineland(TypAvgV, :));



TypAvgV_Psych_Stats = vertcat(a, b, c, d, e);

TypAvgV_Psych_Stats = array2table(TypAvgV_Psych_Stats);

TypAvgV_Psych_Stats.Properties.VariableNames = {'Min', 'Max', 'Mean',
'Standard_Deviation'};
```

```
TypAvgV_Psych_Stats.Properties.RowNames = List_Full;
```

Run BasicStats on ASDAvgV

```
a = BasicStats(Age(ASDAvgV, :));

b = BasicStats(ADOS(ASDAvgV, :));

c = BasicStats(ADI(ASDAvgV, :));

d = BasicStats(IQ(ASDAvgV, :));

e = BasicStats(Vineland(ASDAvgV, :));



ASDAvgV_Psych_Stats = vertcat(a, b, c, d, e);

ASDAvgV_Psych_Stats = array2table(ASDAvgV_Psych_Stats);

ASDAvgV_Psych_Stats.Properties.VariableNames = {'Min', 'Max', 'Mean',
'Standard_Deviation'};
ASDAvgV_Psych_Stats.Properties.RowNames = List_Full;
```

Run BasicStats on ASDLowV

```
a = BasicStats(Age(ASDLowV, :));

b = BasicStats(ADOS(ASDLowV, :));

c = BasicStats(ADI(ASDLowV, :));

d = BasicStats(IQ(ASDLowV, :));

e = BasicStats(Vineland(ASDLowV, :));



ASDLowV_Psych_Stats = vertcat(a, b, c, d, e);

ASDLowV_Psych_Stats = array2table(ASDLowV_Psych_Stats);

ASDLowV_Psych_Stats.Properties.VariableNames = {'Min', 'Max', 'Mean',
'Standard_Deviation'};
ASDLowV_Psych_Stats.Properties.RowNames = List_Full;
```

Write results as table

```
writetable(Total_Psych_Stats, 'Basic_Psych_Stats.xlsx', 'sheet', 'Full_Sample',
'WriteRowNames', true)
writetable(TypAvgV_Psych_Stats, 'Basic_Psych_Stats.xlsx', 'sheet',
'Typical_Avgerage_Verbal', 'WriteRowNames', true)
writetable(ASDAvgV_Psych_Stats, 'Basic_Psych_Stats.xlsx', 'sheet',
'ASD_Avgerage_Verbal', 'WriteRowNames', true)
writetable(ASDLowV_Psych_Stats, 'Basic_Psych_Stats.xlsx', 'sheet', 'ASD_Low_Verbal',
'WriteRowNames', true)
```

```
Error using writetable (line 124)

Unable to write to file 'Basic_Psych_Stats.xlsx'.  Ensure the file is a valid
spreadsheet file and is not password protected.



Error in Results_of_Basic_Psych_Statistics (line 56)

writetable(Total_Psych_Stats, 'Basic_Psych_Stats.xlsx', 'sheet', 'Full_Sample',
'WriteRowNames', true)
```

End

Results of Sex T-tests

Contents

Load Variables

```
clear

load('Variables.mat')
```

Subgroup indexing by sex used in function SexTtest

```
Malei = find(Sex == 'M');           % Male
Femalei = find(Sex == 'F');         % Female
List_Full = {'Age', 'Sex' 'ADOS_SA', 'ADOS_RRB', 'ADOS_Total', 'ADOS_Comparison',
'Diagnosis', 'ADI_A', 'ADI_C', 'ADI_D', 'IQ_Verbal', 'IQ_Nonverbal', ...
    'IQ_Spatial', 'IQ_GCA', 'IQ_SNC', ' Low_Verbal', 'Vineland_Comm', 'Vineland_DLS',
'Vineland_Soc', 'Final_Cats'};
```

Sex Ttest

```
[Ttest, pvalue, ci, stats] = SexTtest(Age);                                    %
Run Age T-test
AgeSexTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];  %
Concatenate Results

[Ttest, pvalue, ci, stats] = SexTtest(Sex);                                    %
Run Sex T-test
SexSexTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];  %
Concatenate Results

[Ttest, pvalue, ci, stats] = SexTtest(ADOS);                                   %
Run ADOS T-test
ADOSSexTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];  %
Concatenate results

[Ttest, pvalue, ci, stats] = SexTtest(Diagnosis);                              %
Run Diagnosis T-test
DiagnosisSexTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = SexTtest(ADI);                                    %
Run ADI T-test
ADISexTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];   %
Concatenate Results

[Ttest, pvalue, ci, stats] = SexTtest(IQ);                                     %
Run IQ T-test
IQSexTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];    %
Concatenate results

[Ttest, pvalue, ci, stats] = SexTtest(Low_Verbal);                             %
Run Low_Verbal T-test
Low_VerbalSexTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = SexTtest(Vineland);                               %
Run Vineland T-test
VinelandSexTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = SexTtest(Final_Cats);                             %
Run Sex T-test
Final_CatsSexTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate Results

Sex_Ttest_Full = vertcat(AgeSexTtestResults, SexSexTtestResults, ADOSSexTtestResults,
DiagnosisSexTtestResults, ADISexTtestResults, ...
    IQSexTtestResults, Low_VerbalSexTtestResults, VinelandSexTtestResults,
Final_CatsSexTtestResults);    % Verically Concatenate all results
```

```
Sex_Ttest_Full = array2table(Sex_Ttest_Full);
% Convert to table
Sex_Ttest_Full.Properties.VariableNames = {'T_test', 'p_value', 'ci_low', 'ci_high',
...
    'value_of_test_statistic', 'degrees_of_freedom', 'standard_deviation'};
% Label Columns
Sex_Ttest_Full.Properties.RowNames = List_Full;
```

Write Results as Table

```
writetable(Sex_Ttest_Full, 'Sex_Ttest.xlsx', 'WriteRowNames', true)
```

End

Results of Age T-tests

Contents

Load Variables

```
clear

load('Variables.mat')
```

Subgroup Indexing by age used in functions below

```
Youngi = find(Age<74);              % Bottom 3rd
Medi = find(Age>=74 & Age<105);     % Middle 3rd
Oldi = find(Age>=105);              % Top 3rd
List_Full = {'Age', 'Sex', 'ADOS_SA', 'ADOS_RRB', 'ADOS_Total', 'ADOS_Comparison',
'Diagnosis', 'ADI_A', 'ADI_C', 'ADI_D', 'IQ_Verbal', 'IQ_Nonverbal', ...
    'IQ_Spatial', 'IQ_GCA', 'IQ_SNC', ' Low_Verbal', 'Vineland_Comm', 'Vineland_DLS',
'Vineland_Soc', 'Final_Cats'};
```

Young Med T-Tests

```
[Ttest, pvalue, ci, stats] = Young_Med_Ttest(Age);
% Run Age T-test
AgeYMTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];        %
Concatenate Results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(Sex);                                  %
Run Sex T-test
```

```
SexYMTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];        %
Concatenate Results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(ADOS);                                 %
Run ADOS T-test
ADOSYMTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];        %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(Diagnosis);                            %
Run Diagnosis T-test
DiagnosisYMTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(ADI);                                  %
Run ADI T-test
ADIYMTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];         %
Concatenate Results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(IQ);                                   %
Run IQ T-test
IQYMTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];          %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(Low_Verbal);                           %
Run Low_Verbal T-test
Low_VerbalYMTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(Vineland);                             %
Run Vineland T-test
VinelandYMTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];    %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Med_Ttest(Final_Cats);                           %
Run Sex T-test
Final_CatsYMTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate Results

YM_Ttest_Full = vertcat(AgeYMTtestResults, SexYMTtestResults, ADOSYMTtestResults,
DiagnosisYMTtestResults, ADIYMTtestResults, ...
    IQYMTtestResults, Low_VerbalYMTtestResults, VinelandYMTtestResults,
Final_CatsYMTtestResults);    % Verically Concatenate all results
YM_Ttest_Full = array2table(YM_Ttest_Full);
% Convert to table
YM_Ttest_Full.Properties.VariableNames = {'T_test', 'p_value', 'ci_low', 'ci_high',
...
    'value_of_test_statistic', 'degrees_of_freedom', 'standard_deviation'};
% Label Columns
YM_Ttest_Full.Properties.RowNames = List_Full;
```

Young Old T-Tests

```
[Ttest, pvalue, ci, stats] = Young_Old_Ttest(Age);
% Run Age T-test
AgeYOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];        %
Concatenate Results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(Sex);                                  %
Run Sex T-test
SexYOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];        %
Concatenate Results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(ADOS);                                 %
Run ADOS T-test
ADOSYOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];        %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(Diagnosis);                            %
Run Diagnosis T-test
DiagnosisYOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(ADI);                                  %
Run ADI T-test
ADIYOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];         %
Concatenate Results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(IQ);                                   %
Run IQ T-test
IQYOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];          %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(Low_Verbal);                           %
Run Low_Verbal T-test
Low_VerbalYOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(Vineland);                             %
Run Vineland T-test
VinelandYOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];    %
Concatenate results

[Ttest, pvalue, ci, stats] = Young_Old_Ttest(Final_Cats);                           %
Run Sex T-test
Final_CatsYOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate Results

YO_Ttest_Full = vertcat(AgeYOTtestResults, SexYOTtestResults, ADOSYOTtestResults,
DiagnosisYOTtestResults, ADIYOTtestResults, ...
```

```
    IQYOTtestResults, Low_VerbalYOTtestResults, VinelandYOTtestResults,
Final_CatsYOTtestResults);    % Verically Concatenate all results
YO_Ttest_Full = array2table(YO_Ttest_Full);
% Convert to table
YO_Ttest_Full.Properties.VariableNames = {'T_test', 'p_value', 'ci_low', 'ci_high',
...
    'value_of_test_statistic', 'degrees_of_freedom', 'standard_deviation'};
% Label Columns
YO_Ttest_Full.Properties.RowNames = List_Full;
```

Med Old T-Tests

```
[Ttest, pvalue, ci, stats] = Med_Old_Ttest(Age);
% Run Age T-test
AgeMOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];        %
Concatenate Results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(Sex);                                    %
Run Sex T-test
SexMOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];        %
Concatenate Results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(ADOS);                                   %
Run ADOS T-test
ADOSMOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];        %
Concatenate results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(Diagnosis);                              %
Run Diagnosis T-test
DiagnosisMOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd'];  %
Concatenate results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(ADI);                                    %
Run ADI T-test
ADIMOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];         %
Concatenate Results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(IQ);                                     %
Run IQ T-test
IQMOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];          %
Concatenate results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(Low_Verbal);                             %
Run Low_Verbal T-test
Low_VerbalMOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(Vineland);                               %
Run Vineland T-test
```

```
VinelandMOTtestResults = [Ttest, pvalue, ci, stats.tstat',stats.df', stats.sd'];    %
Concatenate results

[Ttest, pvalue, ci, stats] = Med_Old_Ttest(Final_Cats);                             %
Run Sex T-test
Final_CatsMOTtestResults = [Ttest, pvalue, ci, stats.tstat', stats.df', stats.sd']; %
Concatenate Results

MO_Ttest_Full = vertcat(AgeMOTtestResults, SexMOTtestResults, ADOSMOTtestResults,
DiagnosisMOTtestResults, ADIMOTtestResults, ...
    IQMOTtestResults, Low_VerbalMOTtestResults, VinelandMOTtestResults,
Final_CatsMOTtestResults);    % Verically Concatenate all results
MO_Ttest_Full = array2table(MO_Ttest_Full);
% Convert to table
MO_Ttest_Full.Properties.VariableNames = {'T_test', 'p_value', 'ci_low', 'ci_high',
...
    'value_of_test_statistic', 'degrees_of_freedom', 'standard_deviation'};
% Label Columns
MO_Ttest_Full.Properties.RowNames = List_Full;
```

Write Results as Tables

```
writetable(YM_Ttest_Full, 'Age_Ttest.xlsx', 'sheet', 'Young_Medium', 'WriteRowNames',
true)
writetable(YO_Ttest_Full, 'Age_Ttest.xlsx', 'sheet', 'Young_Old', 'WriteRowNames',
true)
writetable(MO_Ttest_Full, 'Age_Ttest.xlsx', 'sheet', 'Medium_Old', 'WriteRowNames',
true)
```

End

Results of Psych Correlations

Contents

Load Variables

```
clear

load('Variables.mat')
List_Full = {'ADOS_SA', 'ADOS_RRB', 'ADOS_Total', 'ADOS_Comparison', 'ADI_A', 'ADI_C',
'ADI_D', 'IQ_Verbal', 'IQ_Nonverbal', ...
```

```
    'IQ_Spatial', 'IQ_GCA', 'IQ_SNC', 'Vineland_Comm', 'Vineland_DLS', 'Vineland_Soc',
'Age'};
```

Run Correlation Between all Psych Scores

Don't change order of analysis, it is tied to the Psych_Correlation Function

```
[ADOSco, ADOSp] = Psych_Correlation(ADOS);

[ADIco, ADIp] = Psych_Correlation(ADI);

[IQco, IQp] = Psych_Correlation(IQ);

[Vinelandco, Vinelandp] = Psych_Correlation(Vineland);

[Ageco, Agep] = Psych_Correlation(Age);



% Concatenate all correlations and all p-values into two separate matrices
Correlations = vertcat(ADOSco, ADIco, IQco, Vinelandco, Ageco);
p_Values = vertcat(ADOSp, ADIp, IQp, Vinelandp, Agep);
```

Isolate Statistically Significant Correlations

keep correlations with p-values less than .05 and replace all correlations and p-values with NaN

```
Sig_p_Values = p_Values;

Sig_Correlations = Correlations;

for i = 1:size(Correlations, 1)
    for j = 1:size(Correlations, 2)
        if Sig_p_Values(i,j)> .05
            Sig_p_Values(i,j) = (NaN);
            Sig_Correlations(i,j) = (NaN);
        end
    end
end
```

Convert to tables and only show correlations once - in upper half of tiangle

```
Sig_Correlations = triu(Sig_Correlations);                % Correlation and p-Values
displayed twice in square, this isolates upper half
Sig_p_Values = triu(Sig_p_Values);
```

```
Sig_Correlations = array2table(Sig_Correlations);          % Convert to table
Sig_p_Values = array2table(Sig_p_Values);

Sig_Correlations.Properties.VariableNames = List_Full;     % Add column and row names
Sig_Correlations.Properties.RowNames = List_Full;

Sig_p_Values.Properties.VariableNames = List_Full;         % Add column and row names
Sig_p_Values.Properties.RowNames = List_Full;
```

Write Table to File

```
writetable(Sig_Correlations,'Psych_Correlations.xlsx', 'sheet', 'Correlations',
'WriteRowNames', true);
writetable(Sig_p_Values,'Psych_Correlations.xlsx', 'sheet', 'p_values',
'WriteRowNames', true);
```

End

Sample Entropy and Psych Scores Correlation

Contents

Load Variables

```
clear

load('Variables.mat')
List_Full = {'Frequency Scale' 'Age', 'ADOS_SA', 'ADOS_RRB', 'ADOS_Total',
'ADOS_Comparison', 'ADI_A', 'ADI_C', 'ADI_D', 'IQ_Verbal', 'IQ_Nonverbal', ...
    'IQ_Spatial', 'IQ_GCA', 'IQ_SNC', 'Vineland_Comm', 'Vineland_DLS',
'Vineland_Soc'};
```

Correlations Psych Scores and SampE

```
[Ageco, Agep] = corr(Age, SampE2D, 'rows', 'complete');
[ADOSco, ADOSp] = corr(ADOS, SampE2D, 'rows', 'complete');
[ADIco, ADIp] = corr(ADI, SampE2D,'rows', 'complete');
[IQco, IQp] = corr(IQ, SampE2D, 'rows', 'complete');
[Vinelandco, Vinelandp] = corr(Vineland, SampE2D, 'rows', 'complete');

FullCorrelation = vertcat(Ageco, ADOSco, ADIco, IQco, Vinelandco);
```

```
FullP = vertcat(Ageco, ADOSp, ADIp, IQp, Vinelandp);
```

Only Significant

```
for i = 1:size(FullP,1)
    for j = 1:size(FullP,2)
        if FullP(i,j)> .05
            FullP(i,j) = NaN;
            FullCorrelation(i,j) = NaN;
        end
    end
end
```

Add Frequency Scale to First Row

```
FullCorrelation(2:17,:) = FullCorrelation(1:16,:);

FullP(2:17,:) = FullP(1:16,:);

for i = 1:6
    if i == 1
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "High Gamma";
    elseif i == 2
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Gamma";
    elseif i == 3
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Beta";
    elseif i == 4
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Alpha";
    elseif i == 5
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Theta";
    elseif i == 6
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Delta";
    end
end
FullCorrelation = num2cell(FullCorrelation);
FullP = num2cell(FullP);
for i = 1:114
    FullCorrelation{1,i} = zz{1,i};
    FullP{1,i} = zz{1,i};
end
```

Create Tables

convert correlation coeficients to Table

```
FullCorrelation = array2table(FullCorrelation);

FullCorrelation.Properties.VariableNames = SampE_VariableNames;

FullCorrelation.Properties.RowNames = List_Full;



FullP = array2table(FullP);

FullP.Properties.VariableNames = SampE_VariableNames;

FullP.Properties.RowNames = List_Full;
```

Condense Columns to EEG Scalp Locations

write new columns

```
FullCorrelation.C3 = FullCorrelation{:,1:6};

FullCorrelation.C4 = FullCorrelation{:,7:12};

FullCorrelation.O1 = FullCorrelation{:,13:18};

FullCorrelation.O2 = FullCorrelation{:,19:24};

FullCorrelation.Cz = FullCorrelation{:,25:30};

FullCorrelation.F3 = FullCorrelation{:,31:36};

FullCorrelation.F4 = FullCorrelation{:,37:42};

FullCorrelation.F7 = FullCorrelation{:,43:48};

FullCorrelation.F8 = FullCorrelation{:,49:54};

FullCorrelation.Fz = FullCorrelation{:,55:60};

FullCorrelation.Fp1 = FullCorrelation{:,61:66};

FullCorrelation.Fp2 = FullCorrelation{:,67:72};

FullCorrelation.P3 = FullCorrelation{:,73:78};

FullCorrelation.P4 = FullCorrelation{:,79:84};
```

```
FullCorrelation.Pz = FullCorrelation{:,85:90};

FullCorrelation.T7 = FullCorrelation{:,91:96};

FullCorrelation.T8 = FullCorrelation{:,97:102};

FullCorrelation.P7 = FullCorrelation{:,103:108};

FullCorrelation.P8 = FullCorrelation{:,109:114};



FullP.C3 = FullP{:,1:6};

FullP.C4 = FullP{:,7:12};

FullP.O1 = FullP{:,13:18};

FullP.O2 = FullP{:,19:24};

FullP.Cz = FullP{:,25:30};

FullP.F3 = FullP{:,31:36};

FullP.F4 = FullP{:,37:42};

FullP.F7 = FullP{:,43:48};

FullP.F8 = FullP{:,49:54};

FullP.Fz = FullP{:,55:60};

FullP.Fp1 = FullP{:,61:66};

FullP.Fp2 = FullP{:,67:72};

FullP.P3 = FullP{:,73:78};

FullP.P4 = FullP{:,79:84};

FullP.Pz = FullP{:,85:90};

FullP.T7 = FullP{:,91:96};

FullP.T8 = FullP{:,97:102};
```

```
FullP.P7 = FullP{:,103:108};

FullP.P8 = FullP{:,109:114};

% Delete old rows
FullCorrelation(:,1:114) = [];
FullP(:,1:114) = [];
```

Write as Tables

```
writetable(FullCorrelation,'Psych_Scores_And_EEG_Correlation.xlsx', 'sheet',
'Correlations', 'WriteRowNames', true);
writetable(FullP,'Psych_Scores_And_EEG_Correlation.xlsx', 'sheet', 'p_values',
'WriteRowNames', true);
```

End

ANOVA Analysis

Contents

Load Variables

```
clear

load('Variables.mat')
```

Subgroup Indexing by age used in functions below

```
TypAvgVi = find(Final_Cats == '0');                    % No ASD + Average or High
Verbal IQ
ASDAvgVi = find(Final_Cats == '1');                    % ASD DX + Average or High
Verbal IQ
ASDLowVi = find(Final_Cats == '2');                    % ASD DX + Low Verbal IQ

TypAvgEEG = SampE2D(TypAvgVi, :);
ASDAvgEEG = SampE2D(ASDAvgVi, :);
ASDLowEEG = SampE2D(ASDLowVi, :);
```

List of EEG Locations

```
for i = 1:6
    if i == 1
```

```
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "High Gamma";
    elseif i == 2
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Gamma";
    elseif i == 3
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Beta";
    elseif i == 4
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Alpha";
    elseif i == 5
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Theta";
    elseif i == 6
        zz(1,[i, i+6, i+6*2 i+6*3 i+6*4 i+6*5 i+6*6 i+6*7 i+6*8 i+6*9 i+6*10 ...
        i+6*11 i+6*12 i+6*13 i+6*14 i+6*15 i+6*16 i+6*17 i+6*18]) = "Delta";
    end
end
for i = 1:114
    if (i>=1) && (i<=6)
        zz(1,i) = strcat('C3_', zz(1,i));
    elseif (i>=1+6) && (i<=6*2)
        zz(1,i) = strcat('C4_', zz(1,i));
    elseif (i>=1+6*2) && (i<=6*3)
        zz(1,i) = strcat('O1_', zz(1,i));
    elseif (i>=1+6*3) && (i<=6*4)
        zz(1,i) = strcat('O2_', zz(1,i));
    elseif (i>=1+6*4) && (i<=6*5)
        zz(1,i) = strcat('Cz_', zz(1,i));
    elseif (i>=1+6*5) && (i<=6*6)
        zz(1,i) = strcat('F3_', zz(1,i));
    elseif (i>=1+6*6) && (i<=6*7)
        zz(1,i) = strcat('F4_', zz(1,i));
    elseif (i>=1+6*7) && (i<=6*8)
        zz(1,i) = strcat('F7_', zz(1,i));
    elseif (i>=1+6*8) && (i<=6*9)
        zz(1,i) = strcat('F8_', zz(1,i));
    elseif (i>=1+6*9) && (i<=6*10)
        zz(1,i) = strcat('Fz_', zz(1,i));
    elseif (i>=1+6*10) && (i<=6*11)
        zz(1,i) = strcat('Fp1_', zz(1,i));
    elseif (i>=1+6*11) && (i<=6*12)
        zz(1,i) = strcat('Fp2_', zz(1,i));
    elseif (i>=1+6*12) && (i<=6*13)
        zz(1,i) = strcat('P3_', zz(1,i));
    elseif (i>=1+6*13) && (i<=6*14)
        zz(1,i) = strcat('P4_', zz(1,i));
    elseif (i>=1+6*14) && (i<=6*15)
        zz(1,i) = strcat('Pz_', zz(1,i));
```

```
    elseif (i>=1+6*15) && (i<=6*16)
        zz(1,i) = strcat('T7_', zz(1,i));
    elseif (i>=1+6*16) && (i<=6*17)
        zz(1,i) = strcat('T8_', zz(1,i));
    elseif (i>=1+6*17) && (i<=6*18)
        zz(1,i) = strcat('P7_', zz(1,i));
    elseif (i>=1+6*18) && (i<=6*19)
        zz(1,i) = strcat('P8_', zz(1,i));
    end
end
```

ANOVA

```
bb = NaN(10,1);

cc = NaN(19,1);

anovaTable = ["EEG_Location", "ANOVA_p-value", "MeanDiff/p-value", "Typ_ASDAvg",
"Typ_ASDLow", "ASDAvg_ASDLow"]';
for i = 1:114
    a = TypAvgEEG(:, i);
    b = vertcat(ASDAvgEEG(:, i), bb);
    c = vertcat(ASDLowEEG(:,i), cc);
    d = [a,b,c];
    [p,~,stats] = anova1(d, [], 'off');
    if p <= 0.05
        [p,~,stats] = anova1(d);
        [e,~,h,gnames] = multcompare(stats);
        figure(h)
        yticklabels({'ASD Low Verbal', 'ASD Avg Verbal', 'Typically Developing'});
        f = [gnames(e(:,1)), gnames(e(:,2)), num2cell(e(:,3:6))];
        g = vertcat(zz(1,i),p, "MeanDiff", f(:,3));
        h = vertcat(NaN, NaN, "p-value", f(:,6));
        anovaTable = [anovaTable, g, h];
    end
end
```

Write Table

```
t = array2table(anovaTable);

writetable(t, 'Anova_Results.xlsx');
```

End

PsyD Program Signature Page

This dissertation, written under the direction of the candidate's dissertation committee and approved by members of the committee, has been presented to and accepted by the faculty of the PsyD Program in Clinical Psychology in partial fulfillment of the requirements for the degree of Doctor of Psychology. The content and research methodologies presented in this work represent the work of the candidate alone.

Candidate Signature

Nathan Wright — 7 June 2018

Candidate — Date

Dissertation Committee Signatures

William J. Beal — 7 June 2018

Chair — Date

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Committee Member — Date

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