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# Informatics for EEG biomarker discovery in clinical neuroscience

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Dissertation

**INFORMATICS FOR EEG BIOMARKER DISCOVERY  
IN CLINICAL NEUROSCIENCE**

by

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“And this is what all concerned with global mental health must work to advance. The moral failure of humanity in the past does not mean *we must tolerate this failure any longer.*”

- Arthur Kleinman (2009). Global mental health: a failure of humanity. *Lancet* 374, 603-604.

"Despite the great attention western countries pay to the mind and human consciousness in philosophy and the arts, *disturbances of mental health remain not only neglected but also deeply stigmatised across our societies.*"

- Sartorius, N. (2007). Stigma and mental health. *Lancet* 370, 810-811.

“A key problem is that mental health services in developing nations imitate those in the West, where specialists in clinics or hospitals treat patients. This works well when there are enough specialists, and importantly, enough hospitals. When both are in short supply, *more innovative thinking is needed.*”

- Vikram Patel, Mental health in the developing world: time for innovative thinking, 2010

## **DEDICATION**

I would like to dedicate this work to my partner and the love of my life, Judy, my sweetest friend. Her support, selflessness and joyful love have given me freedom to pursue my intellectual interests with abandon. And to my wonderful children Justin, Brian, Janelle and Kevin, who have kept me young and given me the ability to see the world through child-like eyes.

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# **INFORMATICS FOR EEG BIOMARKER DISCOVERY**

## **IN CLINICAL NEUROSCIENCE**

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### **ABSTRACT**

Neurological and developmental disorders (NDDs) impose an enormous burden of disease on children throughout the world. Two of the most common are autism spectrum disorder (ASD) and epilepsy. ASD has recently been estimated to affect 1 in 68 children, making it the most common neurodevelopmental disorder in children. Epilepsy is also a spectrum disorder that follows a developmental trajectory, with an estimated prevalence of 1%, nearly as common as autism. ASD and epilepsy co-occur in approximately 30% of individuals with a primary diagnosis of either disorder. Although considered to be different disorders, the relatively high comorbidity suggests the possibility of common neuropathological mechanisms.

Early interventions for NDDs lead to better long-term outcomes. But early intervention is predicated on early detection. Behavioral measures have thus far proven ineffective in detecting autism before about 18 months of age, in part because the behavioral repertoire of infants is so limited. Similarly, no methods for detecting emerging epilepsy before seizures begin are currently known. Because atypical brain development is likely to precede overt behavioral manifestations by months or even years, a critical

developmental window for early intervention may be opened by the discovery of brain based biomarkers.

Analysis of brain activity with EEG may be under-utilized for clinical applications, especially for neurodevelopment. The hypothesis investigated in this dissertation is that new methods of nonlinear signal analysis, together with methods from biomedical informatics, can extract information from EEG data that enables detection of atypical neurodevelopment. This is tested using data collected at Boston Children's Hospital. Several results are presented. First, infants with a family history of ASD were found to have EEG features that may enable autism to be detected as early as 9 months. Second, significant EEG-based differences were found between children with absence epilepsy, ASD and control groups using short 30-second EEG segments. Comparison of control groups using different EEG equipment supported the claim that EEG features could be computed that were independent of equipment and lab conditions. Finally, the potential for this technology to help meet the clinical need for neurodevelopmental screening and monitoring in low-income regions of the world is discussed.

## **PREFACE**

The pace of discovery in several fields relevant to the science of brain-behavior relationships continues at a remarkable pace. Integration of these discoveries for the purpose of finding early biomarkers for deviations from typical developmental trajectories offers the promise of new clinically useful assessment tools for neuropsychology. Among these advances is a deeper understanding of the brain as a complex adaptive system, composed of multiple interacting circuits, and how this perspective informs our understanding of the neural correlates of behavior. New computational methods derived from complex systems theory are available for mathematically interpreting electrophysical time series to find key information about brain function. It is becoming increasingly apparent that changes in the brain precede observable behavioral correlates by weeks, months or perhaps even years. These new methods for analyzing functional brain data from electroencephalography (EEG) can now be tested for clinical value. Discovery of brain-based EEG biomarkers of neurodevelopmental disorders, including autism and epilepsy, among many other neuropsychiatric injuries and disorders that follow a developmental trajectory, may open a window of opportunity for intervention that does not exist if diagnosis is based purely on behavioral measures.

This dissertation presents an approach to understanding brain electrophysiology based on complex systems theory together with time series analysis methods for computing relevant properties of brain system parameters. An important component of this methodology involves the use of modern machine learning tools, so-called “big data

analytics” to find the subtle and complex mappings from EEG-derived quantitative neural function to observed behavioral assessments. With the emerging role of Electronic Health Records (EHRs) and biomedical informatics methods for integrating electronic medical data into actionable forms for clinical decision support, the methodology described herein may provide a way to incorporate clinical neuropsychology into more general integrated healthcare that includes brain and mental function on an equal par with “organic” medical conditions. More specifically, the brain-derived quantitative biomarkers presented in this dissertation are mapped to clinical diagnoses to demonstrate potential diagnostic or risk-assessment usefulness for early detection of autism and epilepsy.

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## LIST OF ABBREVIATIONS

BU .....	Boston University
ISO .....	International Standards Organization
MSE .....	Multiscale Entropy
NIMH .....	National Institute of Mental Health
ONC .....	Office of the National Coordinator for Health Informatics
RDoC .....	Research Domain Criteria
RPA .....	Recurrence Plot Analysis
RQA .....	Recurrence Quantitative Analysis

## **BIOMARKERS FOR NEURODEVELOPMENTAL DISORDERS**

### **Clinical Neuroscience and Biomarkers**

The study of brain – behavior relationships was born from efforts to correlate carefully controlled behavioral observations to specific brain regions (Barr, 2008). Early ideas about simple correlations between brain regions and behaviors have given way to more refined and complex ideas that involve brain circuits (see, for example, (Bradshaw, 2001)). The fundamental notion that changes in behavior, whether caused by normal development or pathological disease or injury, must correlate to well defined changes in the brain is a necessary axiom for clinical neuroscience. When we observe cognitive, emotional or motor changes in behavior, it is the brain that has changed in some way, not the gall bladder or kidneys. Even though the new approach to classification of mental disorders contained in the Research Domain Criteria or RDoC program that the U.S. National Institute of Mental Health (NIMH) has been developing emphasizes genetics and neuroimaging (Insel, 2014b), it is based on the same basic axiom: how can observed or assessed behaviors be correlated to brain function. The clinical goal is to devise ways to use easily obtained brain measurements to detect disease or injury and predict behavioral outcomes.

Biomarker discovery in neuropsychiatry is concerned with finding objective physiological measurements that are highly correlated with the presence of mental or neurological disorders or with specific neuropsychological constructs. However, the role of information processing methods for extracting relevant information is easily

overlooked. Traditionally, linear statistical methods have been used to analyze clinical data. New methods for finding information in data, including data mining, pattern recognition and longitudinal trajectory modeling algorithms, have grown rapidly in just the past decade. The easy availability of almost limitless computing power in desktop computers, together with access to enormous data resources through the Internet, have spurred growth in the application to data analytics to many fields of application in business, science, economics and engineering. In this dissertation, advanced computational methods are applied to a rather old source of functional brain information, the electroencephalogram. Digital time series measurements of “brainwaves” can be analyzed with relatively new methods for extracting information from time series. These methods have been largely developed in the mathematical physics community for analyzing complex physical systems. But mapping these complex quantities to behavioral constructs or classes of neuropsychiatric disorders is not easily done without the use of recent and advanced machine or statistical learning algorithms. These two steps are demonstrated in the following chapters.

The mind is an ever-changing pattern of electromagnetic fields, sustained and supported by a biological substrate of neural networks. Brain-behavior relationships, therefore, might reasonably look to the electromagnetic fields supported by the brain and attempt to correlate their relationship to behavior. The challenge with correlating brain electrical activity to behavioral is largely concerned how to quantify electrical fields measured at the scalp surface. Even if one accepts the thesis that the mind is most fundamentally an electrical phenomenon, electrical fields can only be described by

relatively abstract mathematics. Humans can readily picture the meaning of “Broca’s area” or the hippocampus, because these are found in well-defined spatial locations in the brain. An electromagnetic field that is changing over time is not so easy to picture, yet it may contain useful information about how a particular brain region is functioning. The mathematics that describes the changing electrical fields of the brain is a relatively new branch of physics that goes by several names, including dynamical systems theory, complex systems or chaos theory. Fortunately, new statistical algorithms have also become available for mapping abstract mathematical quantities to observations.

Clinical neuroscience may be defined as the application of principles from cognitive and behavioral neuroscience to the clinical practice of neurology, psychiatry and neuropsychology. It is dependent to some extent upon the technology available for measuring and analyzing brain function. If the focus of clinical neuroscience is clinical application, then the tools and methods used must be appropriate for clinical use. Thus, tools used in research laboratories for studying brain function may not be appropriate for use in clinical settings for a number of reasons, including cost, safety and ease of use. This is an important point that is easily overlooked in neuroscience research: the needs of the laboratory scientist may be different from the clinician.

New and improving methods for functional measurement of brain activity together with ubiquitous mobile access to the global Internet are creating tremendous opportunities for studying brain-behavior relationships over developmental trajectories. Low cost, medical-grade quality wireless EEG devices are now available. The discovery

of new methods for utilizing EEG as a clinical tool in neuropsychology may enable new approaches to monitoring functional brain development through the lifespan.

### **Neurodevelopmental Disorders**

Technology for inexpensively and easily measuring brain function through the lifespan in a clinical setting has only recently advanced to the point where it is feasible to consider using in primary care settings. Measurements of brain electrical activity with EEG have long been a valuable source of information for neuroscience research, yet this rich resource may be under-utilized for clinical applications in neurology and psychiatry (Niedermeyer and Lopes da Silva, 2005). The relatively good temporal resolution and direct measurement of potentials produced by neural activity that EEG offers, enables nonlinear time series analysis tools to be used to estimate complex neural network topological differences. Moreover, as will be discussed in much greater detail throughout this dissertation, new methods for analyzing EEG signals, derived from complex systems theory and computational methods, are revealing a tremendous amount of information in EEG signals that has been overlooked. All other functional brain imaging modalities suffer from severe limitations as clinical support tools. Magnetoencephalography (MEG) measures essentially the same brain physics as EEG, but is much more expensive and difficult to use with infants, children, or people with certain medical or psychological conditions, making it much less attractive as a potential clinical screening tool. Functional magnetic resonance imaging (fMRI) measures metabolic response via blood oxygenation levels in neural regions with a time resolution on the order of seconds, with

much finer spatial resolution. fMRI has superior spatial resolution than EEG and can be useful for localizing EEG sources (Lachaux et al., 2007). However, as a routine screening tool, fMRI suffers from the same drawbacks as MEG. Near infrared spectroscopy (NIRS) is an emerging imaging brain imaging method that measures blood oxygenation levels as does fMRI, but is inexpensive, safe and easy to use. NIRS images to about 2 cm below the skull, so lacks the depth and comprehensive fine spatial resolution of fMRI. Like fMRI, the temporal response of NIRS is quite slow, on the order of seconds. This is not a limitation of the device, but a reflection of the fundamental physiology that is being measured. Neural blood oxygenation does not change as quickly as the neurons themselves. For estimates long-range connectivity, diffusion tensor imaging (DTI) is an important tool, but again has severe drawbacks as a clinical screening tool. Between-sensor generalized synchronization calculations with EEG data may enable equivalent cortical information to be estimated (Mizuhara et al., 2005).

Because there is a growing commercial market for EEG devices, even outside of healthcare, it is likely that less expensive and higher quality devices will continue to become available. Leveraging these advances for diagnosis requires novel algorithms to interpret measured electrical activity as the signals produced by an evolved complex dynamical neural network. The potential of neuroelectronics to transform the measurement of brain structure through the analysis of electrical activity may enable methods to unlock the brain's remarkable plasticity to affect personalized neurological therapy, much the same way genomics and bioinformatics are beginning to unlock the potential of personalized medicine in the realm of cell biology. Utilizing EEG as a

routine clinical tool in primary care opens up the possibility of objectively measuring and monitoring brain activity over developmental periods. This will require electronic records to store the data and computational methods for comparing patterns in the EEG data that are relevant or significantly correlated with behavioral changes that are of clinical or developmental interest.

In this dissertation, we present evidence that patterns of electrical activity measured by EEG devices contain information that can detect the presence of neurocognitive dysfunction in children. The approach presented begins with a complex system paradigm that defines the relevant parameters that can be computed to serve as potential biomarkers. Relatively new nonlinear methods for analyzing time series data are presented and described in some detail. We present a theory of the brain as a complex dynamical system and argue that complex system parameters may be relevant to behavioral phenotypes. Nonlinear algorithms provide the methods for computing the complex system features that may be used in a data-driven discovery paradigm to find the mapping or correlation between patterns in the computed electrophysiological features and behavior-based diagnostic assessments.

### **Functional Brain Imaging through the Lifespan with EEG**

The requirements for neuroimaging in carefully controlled scientific research and for clinical application have important and fundamental differences. It is becoming increasingly clear that many neurological and mental disorders, including what are primarily adult brain disorders, follow a developmental trajectory. Some estimates

suggest that 75% of all mental disorders have antecedents in childhood (Insel, 2014a). Importantly, behavioral changes are manifestations of changes in the brain, often starting long before the observable symptoms appear. For example, approximately 80% of the dopamine producing cells involved in Parkinson's Disease must cease to function before the characteristic symptoms become clinically apparent (Insel, 2014a). If this is in general true of neurodevelopmental disorders, then the most leveraged time for intervention is before behavioral symptoms fully emerge, when developmental trajectories might be re-directed in more typical directions. This approach will require simple methods for monitoring brain function and its response to therapy. For routine monitoring of brain function through the lifespan, the measurement techniques must be low cost, easy to administer and fast. At this time, EEG is the only way of measuring brain function that comes close to meeting these requirements.

### **Data-Driven Discovery in Neuropsychology**

A new approach to discovering complex relationships has arisen with the emergence of machine learning methods. Brain-behavior relationships are ideally suited to this scientific paradigm because many human behavioral patterns, and particularly those that are defined to be pathological, are defined with reference to a population. That is, the behavioral traits that define neurological and psychiatric disorders usually require reference to a norm that is determined from a population.

One of the emerging trends in science in the 21<sup>st</sup> century is an approach to scientific discovery based on access to large empirical data sets and the computational

methods for searching for and discovering scientifically meaningful patterns in that data. Data-driven discovery applies machine learning algorithms to data sets composed of high dimensional measurements of large populations to find meaningful clusters of subpopulations. This methodology can be applied to discovering mappings or correlations between neurophysiological measures of brain function and behavioral measures. Thus, machine learning (synonymous with “data mining”, “big data analytics”, or “statistical learning”) can be applied to the task of mapping nonlinear features computed from EEG signals to behavioral traits. That is, machine learning algorithms a powerful tool for discovering brain-behavior relationships.

### **Overview of Chapters**

Chapter 2 presents the theoretical neuroscientific foundation for the approach taken in this dissertation. As a network of neurons that form a highly organized complex, possibly fractal network structure, functional activity of the brain should exhibit the properties and characteristics of a complex dynamical system. This has a number of implications for how the electrophysical time series produced by neural activity should be analyzed. Computational methods for analyzing time series produced by complex dynamical systems are relatively recent and are reviewed for their promise in research and clinical use for understanding brain- behavior relationships.

Chapters 3, 4 and 5 comprise the empirical evidence that the approach described is both experimentally and clinically useful. We first present results using a single measure of complex system dynamics, multiscale entropy, which was first used to

analyze cardiac signals (Costa et al., 2005b; Costa et al., 2008). The multiscale complexity of electroencephalography (EEG) signals is believed to contain information about the architecture of the neural networks in the brain on many scales. Early detection of abnormalities in EEG signals may be an early biomarker for developmental cognitive disorders. In this chapter, results are presented that test the hypothesis that the multiscale entropy (MSE) computed from resting state EEG data can be used as a biomarker of normal brain development and distinguish typically developing children from a group of infants at high risk for autism spectrum disorder (ASD), defined on the basis of an older sibling with ASD. The results indicate that the high risk children exhibit distinct MSE values that enable separation of the typically developing controls from the high risk infants.

Chapter 4 looks at an older population of children, approximately ages 5-11 years and includes children with absence epilepsy, children with autism, and controls. These children were tested in two different settings: the autism subjects and control group were recruited to a research study by the Laboratories of Cognitive Neuroscience at Boston Children's Hospital. The absence epilepsy subjects and associated controls had come to the Epilepsy Clinic at Boston Children's Hospital for testing. This study seeks to investigate two hypotheses: first, the nonlinear EEG analysis that is being performed in this entire dissertation detects real physiological characteristics in the signals, and is not significantly affected by the EEG equipment used or the laboratory or clinical setting where collected. Secondly, this study is a direct comparison of children with absence epilepsy, autism and controls. It is well known that autism and epilepsy commonly occur

together, whether the primary diagnosis is autism or epilepsy (Besag, 2009; Spence and Schneider, 2009; Tuchman et al., 2010). It is not known whether a common pathology underlies both of these disorders, or whether one is causal to the other. A deeper insight into the electrophysiological differences between children with each condition may illuminate the brain-based commonalities or differences between autism and epilepsy.

Chapter 5 is a continuation of the study started in chapter 3. Sufficient numbers of the high-risk children have reached three years of age and can be given a clinical determination of whether or not they are on the autism spectrum. In this study, a broader range of nonlinear dynamical system values are computed from the EEG signals using Recurrence Plot Analysis (Komalapriya et al., 2008; Marwan et al., 2007b; Webber and Marwan, 2015). This chapter investigates the hypothesis that children who are developing autism will exhibit a different trajectory of nonlinear EEG values from age 6 months to 3 years than children who are developing typically. If this is so, then EEG analysis may enable a simple brain measurement that predicts a future behavioral outcome such as autism.

Several questions arise from the previous study of infants who develop autism. These include whether the nonlinear analysis of EEG signals merely distinguishes a typically developing brain from one that has some atypical aspects, or if it actually discriminates autism-specific characteristics. Although a reliable and accurate biomarker is clinically useful even if it is not known why it works, it is important to consider the underlying neurophysiology that might explain more specifically what is different about

the brain signals that are associated with various disorders.

The final chapter brings us full circle. This dissertation began with rather theoretical concepts from mathematics, physics and neuroscience, which were then applied to laboratory and clinical data to demonstrate the usefulness of EEG analysis for clinical neuroscience. The research results are combined with a prescription for how to bring together algorithms, databases, and new low-cost, easy to use functional EEG devices in a way that introduces the possibility of clinical monitoring of brain development through the lifespan.

There is growing awareness that mental, neurological and substance use (MNS) disorders impose an enormous burden of disease on the world's nations. Low income regions of the world bear a large share of the burden due to MNS disorders, including both personal suffering and economic consequences. The regions of the world in most need of care for MNS disorders have the fewest resources to meet those needs, in terms of psychiatrists, psychologists and neurologists. While awareness of the burden of MNS disorders is growing, solutions are difficult to find. Innovative thinking that is does not imitate Western approaches to psychiatric care, which depend on highly trained professionals, is needed. In this final chapter, I propose that the EEG analysis methods described and tested in this dissertation create a low cost approach to monitoring brain function through the lifespan in primary care settings that can be administered by community health workers. More generally, information technology that is available

today, including smart phones and the ubiquitous Internet, can be used as powerful tools for neuropsychological practice and care.

Though this dissertation at times delves deeply into chaos and complexity, and theories of brain function, the goal of this work is clinical practice: to enable new discoveries concerning the brain-behavior relationship to be leveraged to improve brain health throughout the world.

### **Innovation and Expected Impact**

The general hypothesis tested in this dissertation is that nonlinear EEG features computed from relatively short, 30-second segments of data contain information that can be used to detect atypical brain development before the emergence of behavioral symptoms. Early detection of pathological brain developments that precede overt neurological and developmental symptoms is then accomplished by machine learning (ML) comparison with the typical developmental trajectory for a range of neurodevelopmental disorders, including, but not limited to, autism and epilepsy. Unlike most previous approaches to clinical neuroscience, this one depends explicitly on ML algorithms to discover the brain (EEG) – phenotype relationship. The approach required to collect data to test our hypothesis is also appropriate for implementation in clinical practice in low-resource settings because of the availability of low-cost EEG devices that are appropriate for community healthcare settings. Informatics methods, including nonlinear signal analysis and machine learning algorithms, are necessary to correlate EEG measurements to behavioral phenotypes. The neuroinformatics methods developed

and presented herein also point the way to saving brain measurement data for tracking over the lifespan.

Accurate biomarkers that can lower the age of detection and be used by primary and community health workers will have an important impact on the practice of early screening and diagnosis of neurological and developmental disorders that precede behavioral or mental disorders in children, especially in resource-limited settings. Earlier diagnosis may also open up new opportunities for intervention, with resulting improved outcomes.

## EEG PATTERNS AND COGNITIVE PHENOTYPES

### Introduction

The National Institute of Mental Health's Strategic Plan calls for the development of new ways of classifying psychopathology based on observable behavior and neurobiological measures (NIMH, 2008). The goal of this strategy is to discover the fundamental "units of behavior" – cognitive phenotypes - that can be reliably measured and used not only for classification of psychopathological disease, but also for planning therapeutic approaches that target the fundamental neurobiological pathology. In essence, this strategy explicitly states that all neuropsychiatric disorders are brain disorders and lays out a plan for discovering the brain basis for psychological disorders as characterized by cognitive and behavioral phenotypes.

Two goals are actually stated implicitly in the NIMH strategic plan. One is scientific: to discover the brain basis of behavior. The other is clinical and pragmatic: to discover neurobiological measures that are useful for diagnosis and planning therapeutic strategies. Achieving the clinical goal can be done independently of the scientific goal. That is, discovery of clinical biomarkers of developing mental and cognitive disorders does not require that a complete understanding of *why* certain measures are highly correlated with specific pathological outcomes to be useful. Medical practice is full of examples where a procedure or test "works", even though the physiological basis is not fully understood. For example vagal nerve stimulation was accidentally discovered to treat

intractable epilepsy and treatment-resistant depression, though little is known about how this works (Rong et al., 2012).

In this chapter, a single neurophysiological measurement modality is considered: scalp electrophysiology using electroencephalography or EEG. EEG has long been used clinically for confirming the existence of epilepsy, but may contain far more clinically useful information for monitoring brain function over the lifespan than has been realized. At the most fundamental level, brain function is electrical. The neural network that comprises the brain and peripheral nervous system, along with all the specialized cellular structures for propagating electrical impulses, is designed to support exquisitely fine control over the electrical patterns that determine all thought and behavior. It would not be an exaggeration to say that the mind is an ever-changing pattern of electrical fields: brain electrical activity is directly related to every thought and behavior. Measurements of brain electrical activity may thus in principle contain information about cognitive phenotypes, if recurring patterns can be found that correlate with them.

### **Complex Dynamical Systems**

The brain is a complex dynamical system. It may appear so, but this is not an analogy or a model: the brain *is* a complex dynamical system by definition. To be more complete, the brain is an open complex dynamical system, embedded in a body with sensory input from the environment and motor output that enables the brain to sense, respond to and act upon its environment. This has important implications for understanding the relationship between observed behaviors or cognitive phenotypes and

the brain, which is the locus of every behavior, cognitive phenotype and psychopathology that can be observed. The brain is also an adaptive evolving complex system, implying that it's dynamical properties can change over long time periods in response to learning or development.

*Cognitive phenotypes are Dynamical Entities*

A working definition for a cognitive phenotype used in this book is a discrete cognitive or behavioral feature that can be specified with some degree of precision and quantitatively measured. The features of interest are those of most relevance for a classification of neuropsychiatric illness or the indicators of normal neuropsychological functioning. Examples include the language deficiency subtypes associated with autism (Charman et al., 2010; Tager-Flusberg and Joseph, 2003), especially response inhibition and contingency detection.

Although cognitive and behavioral phenotypes are described as static entities, they are in fact *processes* - sequences of actions by a person that recur in a recognizably repeatable fashion and can thus be reliably measured in some fashion. The Society for the Study of Behavioural Phenotype (SSBP), <http://www.ssbp.co.uk>, has proposed a working definition for the phrase *behavioral phenotype* as “a characteristic pattern of motor, cognitive, linguistic and/or social abnormalities which is consistently associated with a biological disorder (Fletcher et al., 2007). An important aspect of this definition is that it describes a *pattern of actions*, not a static structure.

A cognitive or behavioral phenotype may be analogous to units in spoken language. Spoken language is a continuous stream or a trajectory of sound units – phonemes - in time. Combinations of phonemes create words, which in defined combinations create fundamental units of meaning. Translators know that languages cannot be translated word for word, but meaningful units must be conveyed in another language. Similarly, cognitive processes and behaviors are continuous processes in time that can be observed or assessed by delineating the continuous flow of behavior or thought at appropriate points. Identification of fundamental units of behavior requires isolation of a particular sequence of movements or thoughts in the context of a particular situation.

This clarification is important for identifying relationships between cognitive or behavioral phenotypes and dynamic processes in the brain. Cognitive activity that directly reflects (and is in fact caused by) sequences of electrical firing patterns in the brain must be treated as a dynamic process. The relationship is not between static entities, but between a well-defined series of observable behaviors or measurable cognitive activities, and measurable brain dynamics.

### *What is a Complex Dynamical System?*

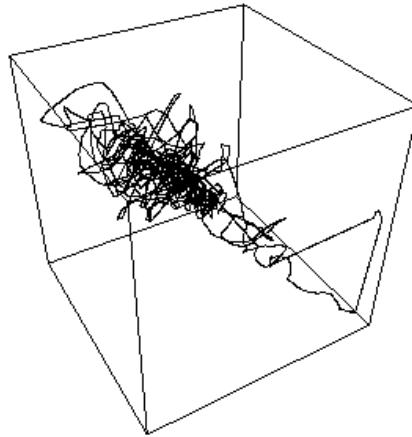
Dynamical systems theory, sometimes called chaos theory, is a branch of mathematical physics that deals with the qualitative and quantitative characterization of long-term properties of complex dynamical systems. A complex dynamical system is a collection of  $N$  components or variables, each described by a single real number value,

that are mathematically or physically coupled and whose values change over time. A convenient way to represent the values of all components is a single vector in N-dimensional space, usually written as a “state vector” of real numbers. Discrete dynamical systems are analogous entities composed of vectors of discrete (integer) values. An example of a state vector is shown:

$$\begin{array}{c} \uparrow \\ \vdots \\ N \\ \vdots \\ \downarrow \end{array} \left| \begin{array}{c} 1.487 \\ 0.984 \\ 0.877 \\ \vdots \\ 0.391 \end{array} \right| \quad (2.1)$$

The state of a complex dynamical system at any given time is represented by the value of the state vector, which is an array of n values at each time. The sequence of state vectors through time comprises the trajectory of the system. The state space of the system is also called the phase space. Isaac Newton carried out the earliest studies of dynamical systems when he formulated his fundamental laws of motion. For a physical system such as the solar system, composed of 10 component elements (8 planets, the sun and the moon - Pluto is no longer considered a planet), the state of the system is given by the three-dimensional location of each body and the three dimensional velocity of each body at each moment. Thus, the state of the entire 10-body system is completely specified by 60 real numbers. The phase space for this system is the space of all possible values of each of the 60 numbers, which is represented by a 60-dimensional vector. If the position

and velocity at every moment could be plotted, these would trace out a trajectory in 60-dimensional phase space.



**Figure 1. A simple trajectory in 3-dimensional phase or state space. Any single point on the line represents the state of the system or the state vector of the system, at a given time.**

The principle activity of neurons for information processing is their continually changing electrical potential, which is continually oscillating or ‘spiking’, with a spiking rate that is believed to be the method used to encode information in single neurons (Kello et al., 2012). Thus, the basic quantitative unit of the dynamic brain might be considered the spiking rate of each neuron in the brain at any given time is a snapshot of the brain’s state at that time. The electrical potential of each neuron could equally be chosen to quantify neural state without changing the following argument. More generally, the entire brain could be represented as a continuous electrical field. This would complicate the mathematical argument here by replacing the discrete dynamical field with a continuous field, but the fundamental argument would remain the same.

In the most general sense, the trajectory of neural electrical values, whether the spiking rate or potential of each neuron must directly reflect all of the movements and behaviors that may be observed in a person. A correspondence between patterns in neural activity and measureable neuropsychological traits – cognitive phenotypes – exists, whether or it can actually be measured in the finest detail or not. Finally, the brain is a *coupled* dynamical system. This means that the future state of any individual neuron depends on not only its current state, but also the state of every neuron in the system.

### *Complex Systems Designed by Evolutionary Processes*

Much of neuropsychology and biological psychiatry research has been focused on localizing brain function. Of course, the brain is spatially organized, but not in as simple a way as we would like. While the effort to map specific brain regions with specific behavioral and cognitive deficits has been successful and clinically useful for many constructs, some higher-level cognitive functions continue to defy localization. For example, recent evidence demonstrates that many neurons in higher order brain regions such as the prefrontal cortex (PFC) are not organized anatomically. Rather, they are said to exhibit mixed selectivity to multiple aspects of cognitive function (Rigotti et al., 2013). Another way of stating this is that the brain functions as a complex system.

Evolutionary or developmental processes in nature construct complex systems. The mammalian nervous system is not specified entirely by the genetic code, but is evolved in a developmental process that is influenced by sensory input from the environment (Lu et al., 2009). An important characteristic of an evolutionary design

process is that the dynamics of the resulting complex system cannot be understood from the component parts and their interactions alone. The whole is more than the sum of the parts, which also imposes a natural scale on the system, below which system functions are lost. Some system functions cannot be found in any single component but exist only when components are combined in a certain functional configuration, which may not be at all apparent from visual inspection of the network topology. However, some components may play critical roles in the system and their function is quite clear. In general, evolutionary design constructs a (complex) system that may look very different from those that an engineer following traditional design principles would concoct (Antonsson and Cagan, 2001). Although attempts have been made to view neurobiological networks in neat modular packages (Hartwell et al., 1999), many interconnections between modules prohibit the black-box modularity that is a hallmark of top-down engineering design (Antonsson and Cagan, 2001).

*The Brain is a Complex Dynamical System*

The state of the brain considered as a complex system composed of individual neurons may be represented succinctly at any time  $t$  as an  $N$ -dimensional vector:

$$\mathbf{B}^t = [n_1, n_2, \dots, n_N], \text{ where } N \approx 10^{11} \quad (2.2)$$

A single floating point number,  $n_i$ , roughly in the range of zero to 1000 hertz, represents the spiking rate or state of a single neuron. This could be generalized to the polarization of the neuron at any time, or even finer detail, and  $N$  would simply be larger. The

superscript  $t$  refers to a specific time  $t$ . Each neuron receives input from many other neurons, perhaps many thousands, and sends its output to other neurons. The connectivity pattern determines what neurons will affect the next state of each neuron. The connections between neurons may change due to learning, and chemical influences may affect synaptic transmission, changing the effective connectivity. Together, the connectivity pattern and various influences that influence neural transmission determine the state transition rule that represents how the brain's state changes through time:

$$\mathbf{B}^{t+1} = F(\mathbf{B}^t) + \mathbf{s}^t \quad (2.3)$$

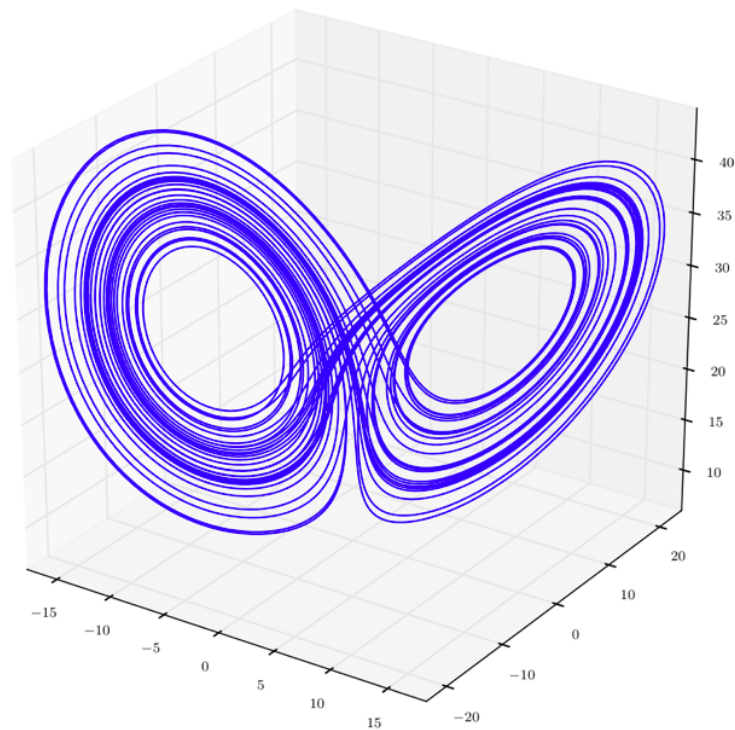
Here,  $F$  is the function that represents how each neuron state will be updated based on the current state of every neuron and the connections to other neurons to give the new state vector at time  $t+1$ .  $\mathbf{s}^t$  represents external sensory inputs, which exert an additional influence on the state of sensory neurons. If we assume healthy individual neurons and neurotransmitters, then the function  $F$  that determines brain function is essentially determined by the connectivity pattern amongst the neurons. Although this is a greatly simplified model of how a biological brain functions, it is nevertheless a realistic representation of how neurons change from one state to the next, and how the whole network of neurons advances through time.

In a general sense, the functioning brain is the state of all  $10^{11}$  neurons at a given time and the trajectory of these neurons through the set of all possible states of the neurons (Kello et al., 2012), which is the phase space of the brain. Note that because neurons are connected in a highly controlled network, every neuron cannot assume an

arbitrary state value at any time. Rather, the state of a neuron is constrained by the state of all neurons to which it is connected, with the influence of neighboring neurons determined by the synaptic strength and the specific neurotransmitter that mediates the connection. These may be either excitatory or inhibitory and this will be represented in our mathematical model by the sign on the entries in the state transition function  $F$ .

### *Phase Trajectories, Attractors and Thought*

The set of all possible brain states is called the phase space of the brain system. In our example, the phase space is represented by all points that can be written as  $10^{11}$  dimensional vectors  $\mathbf{B}^t$ , with each entry  $n_i$  having values in the physiological range of allowable spiking rates (nominally no more than 1000 Hertz). In general, a dynamical system does not assume all the points in its phase space. Rather, it moves through the phase space on trajectories that fill only a small part of the phase space. Figure 2 illustrates a trajectory in a 3-dimensional phase space for a function called the Lorentz attractor. The phase space is delimited by Cartesian coordinates  $(x,y,z)$ , where  $x$ ,  $y$ , and  $z$  are any real numbers. Regardless of what starting point is chosen, the transition rule for the Lorentz system is such that the trajectory settles into the butterfly-like pattern within the phase space, called the *attractor*. The blue lines are the trajectory of this system in phase space and fully describe how the system behaves under any circumstances.



**Figure 2. State space plot of Lorenz attractor. For code to regenerate see: <http://www.node99.org/tutorials/ar/>**

The space that the trajectory occupies is determined by the transition rule  $F$  in equation (2.2). A very simple neural structure, such as the brain of a flatworm, will have a rather limited trajectory in phase space. Indeed, the flatworm has only 312 neurons, so its phase space is rather limited. The number of different states that such a brain may occupy is small relative to a brain made of  $10^{11}$  neurons. The number of behaviors that the organism may exhibit in response to any given stimulus or due to self-generated impulses is therefore also rather small, since every behavior must necessarily reflect a sequence of neural firing patterns. The size of the state space increases combinatorially as the number of neurons, so that  $10^{11}$  neurons yields an enormous number of possible states.

If the vectors represented by equations (2.2) and (2.3) were to be plotted throughout time in an  $N$ -dimensional plot, where  $N$  is the number of neurons or length of the state vector  $B$ , the trajectory would trace out the phase space of the dynamical system. In the context of a brain, we might say that each person, each brain, has a unique function  $F$  that results in a unique dynamical system that traces out its own unique path through time. It responds in different ways to different stimuli. Many people, many brains, respond to similar stimuli in the essentially the same way. For example, all the neural firing patterns – a trajectory through the brain's state space – that correspond to running or chewing, swallowing and digesting food or the saccadic eye movements involved in watching a bird fly past are quite similar in most people. If we could trace out the pattern of the brain in an  $N$ -dimensional plot, the trajectories for each of these cognitive patterns that correspond to specific behavioral processes would be very similar in most people. Neuropsychology, the study of brain – behavior relationships, would not be possible if this was not so.

If the brain is viewed as a dynamical system, the connectivity pattern between neurons is an important determinant of the state transition function, which essentially determines how the brain functions. Research suggests that complex mental disorders are associated with abnormal brain connectivity that may vary between different regions and different scales (Noonan et al., 2009). Estimation of neural connectivity variation or differences might be a useful way to detect abnormal brain function as compared to normal function. This follows from our simple model: the trajectory that a brain follows in state space – dynamical systems language for brain function – is largely determined by

network connectivity. If an N-dimensional plot could be made, a generalization of Figure 2, we might be able to see with our eyes those regions in phase space where normal and abnormal brains differ. Differences in specific regions might correspond to differences in the way two brains respond to seeing emotion in another person's face, for example, or in how the brain responds to specific stimuli. A brain that is subject to seizure might have a region of phase space that looks decidedly unique and different from brains that do not easily have seizures. Again, in dynamical systems language, a brain subject to regular seizures will have many trajectories that fall into a seizure state. A healthy brain has few trajectories that fall into seizure attractors. These include stimuli such as strobe lights or hyperventilation.

A region of phase space into which many trajectories are attracted or move into is called, not surprisingly, an attractor. "Attractors are typical patterns of dynamical, interdependent behaviors of limited dimensionality and carved out from a much larger space of possible patterns and dimensions. These global structural patterns, which emerge from interactions among the system's components through phase space, can be characterized as emergent collectives" (Juarrero, 2010). By definition, then, any situation or stimulus that evokes a similar cognitive or behavioral response must also result in a similar response in the brain; the trajectory of the neural response moves into an attractor of the dynamical system, the brain (Pascanu and Jaeger, 2011). For example, if a person responds to a variety of life events by developing major depression, the "depression" is a kind of attractor – a region of phase space with certain well-defined brain-based behaviors that can be detected by behavioral assessments. Similarly, the trajectory of

brain states moves into the region of phase space that causes depression behaviors. Whenever a person is depressed, parts of their brain are in a specific attractor region of phase space that produces depression-related behaviors.

### **Measuring Complex Dynamical System Properties from Time Series**

The trajectory of neural brain states at each moment of time is a trajectory through phase space and necessarily must directly cause the cognitive states and behaviors at that given moment, unless one posits that the brain alone does not cause all actions and thoughts. That is, the brain state trajectory in time through phase space corresponds directly through some complicated mapping to every thought and behavior at that time, even if the state of every neuron is not measureable, certainly by noninvasive means. However, it may be possible to mathematically infer certain dynamical properties of the attractors in the brain dynamical system from measurements of electrical potentials on the surface of the brain or scalp. Developments in dynamical systems theory demonstrate that such inferences are in principle possible.

#### *Embedding theorems: Reconstructing CDS from Time Series*

Important theorems in mathematics were proved in the 1980s and 1990s regarding what is known as the reconstruction problem. The essence is illustrated in Figure 3.

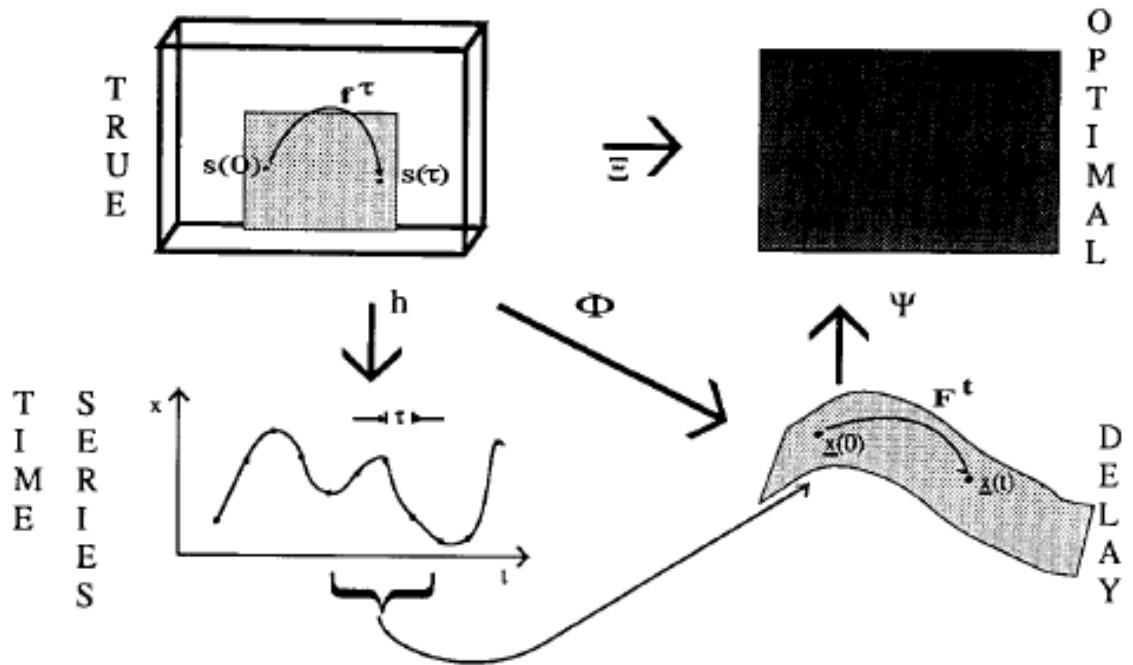


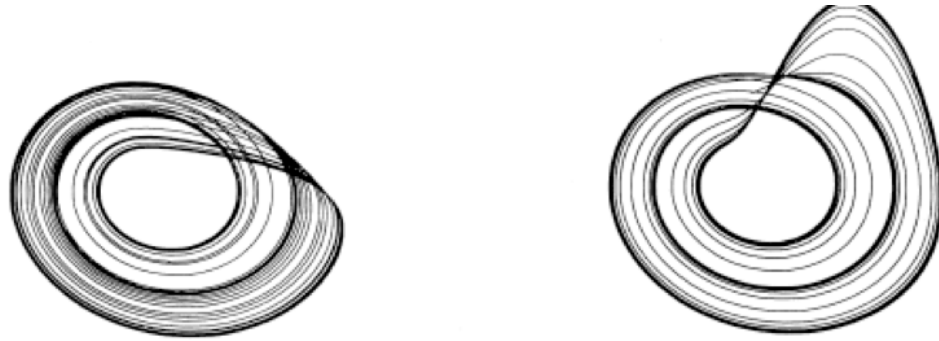
Figure 3. Casdagli's illustration of how dynamical system properties may be inferred from time series measurements (Castagli et al., 1991).

In his explanation of the diagram in Figure 3, Casdagli states that the “true dynamical system  $f$ , its states  $s$ , and the measurement function  $h$  are unobservables, locked in a black box”, as shown in the black square in the upper right. This is an accurate description of the brain as a dynamical system as well. However, the set of values in a time series  $x$  are measureable linear combinations of any set of fundamental components of the true dynamical system, as represented in the lower left graph of Figure 3. The embedding theorems of dynamical systems assert that dynamical properties of the original  $N$ -dimensional system are embedded in the time series  $x$ . This property has potentially profound implications for EEG analysis. It implies that the scalp measurements of an EEG sensor, which are linear combinations of the contribution of many neurons, contain information about all neurons in the system. This does not mean that all the information about all neurons can be extracted from a finite, discrete time series measurement.

Nevertheless, computational methods have been developed by which dynamical properties of the unknown dimensions may be reconstructed. The potential usefulness of this information for detecting pathological brain activity must be explored experimentally to determine its usefulness.

The embedding theorems have profound implications for electrophysiological measurements of groups of neurons using EEGs or other devices. For example, the actual spiking-rate states of all the neurons in the brain are not observable or measureable. If they were, then an exact representation of the state space of the brain and its moment-by-moment dynamics could be measured. The reconstruction theorems state that certain properties of the unobservable multidimensional state space of the brain as a dynamical system can be reconstructed from a one-dimensional time series measurements from EEG sensors. What this implies practically is that the EEG time series contain information about the dynamics of the entire brain. Computational methods that implement the reconstruction theorems may thus be used to compute values that represent dynamical properties of the brain and its attractor states.

A simple example is shown in Figure 4. The phase trajectory of a nonlinear dynamical system, the Rossler equations, is shown, together with its reconstruction from a one-dimensional time series. The diagram shows the attractor of the Rossler dynamical system in two-dimensional Cartesian space. On the right is a reconstruction of the attractor using embedding and reconstruction theorems from a single time series measurement of the sum of  $x$  and  $y$  in the original system.



**Figure 4.** The trajectory mapping out the two-dimensional attractor of the Rossler system is shown on the left. On the right is a reconstruction of the attractor from a single one-dimensional time series.

### *Recurrent Processes, Recurrent Behaviors*

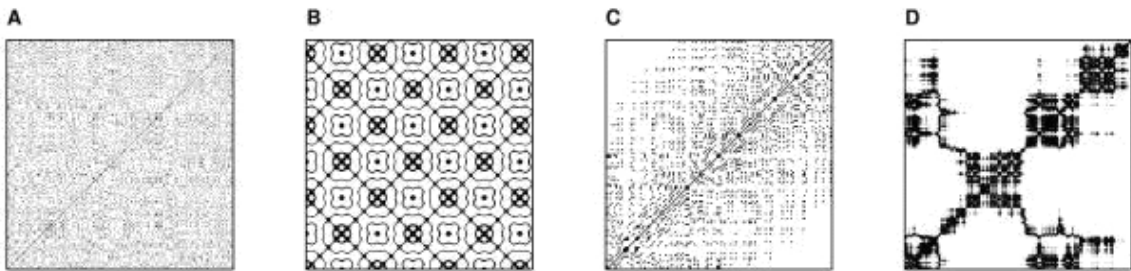
Normal behaviors can only be defined because the way most people respond to given situations is somewhat similar. A normal 2-year-old child will respond to a familiar face such as a parent or sibling with, usually, an emotional reaction, a smile and perhaps attempts to communicate. A child with autism is distinguished from the typical child – and similar to other children with autism – by a different response. These recurrent behaviors are reflected in the brain as well. In dynamical systems language, the state vector of neurons follows a similar trajectory or pattern whenever presented with the same stimulus. The trajectory through phase space of an autistic brain is different from a typical brain in a way that is also recurrent: autistic behaviors can be identified as such because they follow a common, recurring pattern. The problem of finding neural correlates of behavior is one of finding current patterns of neural activity that map to identifiable behaviors.

### *Recurrence Plot Analysis*

A relatively recent and very general approach to nonlinear signal analysis is based on the concept of recurrence plots, introduced by Eckmann in the late 1980's to graphically represent the dynamics of complex systems (Eckmann et al., 1987). Although recurrence plots were originally developed as graphical devices, the concurrent growth of computers for data analysis and research in nonlinear or chaotic systems enabled quantitative statistical analysis of recurrence plots. The methods developed for this analysis have been formalized and are collectively referred to as Recurrence Quantitative Analysis (Marwan et al., 2007b; Schinkel et al., 2009). Recurrence plot analysis is an empirical approach to analyzing time series data and is in principle capable of characterizing all of the essential dynamics of a complex system (Webber and Marwan, 2015).

Recurrence plot analysis is a useful tool analyzing “real-world, noisy, high dimensional data” (Webber and Zbilut, 2005) and is a general empirical approach that can detect macroscopic properties of dynamical systems such as entropy and generalized synchronization. It has proven to be a powerful tool already in physics, geophysics, engineering and biology (Komalapriya et al., 2008; Marwan et al., 2007b). Its use in neuroscience as a method for analyzing neurophysiological time series is in the early stages. Single-trial ERP detection (Schinkel et al., 2009) and state changes before seizure onset (Acharya et al., 2011) are two recent applications.

An illustration of a recurrence plot (RP) for several different time series is shown in Figure 5. The dynamics of each is revealed by a unique pattern in the RP. Recurrence Quantitative Analysis involves computation of features from the RP that are a quantitative characterization of the dynamics of the system from which the parameters were derived.



**Figure 5. Characteristic typology of recurrence plots: (A) uniformly distributed noise, (B) periodic, (C) drift (logistic map corrupted with a linearly increasing term) and (D) disrupted (Brownian motion). From (Marwan, 2012).**

### *Recurrence Quantitative Analysis (RQA)*

The definitions and descriptions of RP parameters given here are derived and explained more fully in the literature (Marwan et al., 2007b; Webber and Marwan, 2015). Recurrence plot statistics are computed from structures in the recurrence plot, analogous to computing object statistics in an image. Statistical analysis of recurrence plots or Recurrence Quantitative Analysis (RQA) is in its infancy. Several statistics have been found useful for characterizing system dynamics and are discussed below. Other relevant statistics remain to be discovered. Significant changes in some RQA values are highly

correlated with and useful for detecting state transitions to new dynamical regimes, such as chaos-order or chaos-chaos transitions (Marwan, 2007). Other changes in RQA values are particularly sensitive to short-time transitions, for instance, those that occur during Evoked Response Potential (ERP) experiments (Schinkel et al., 2007, 2009).

*Recurrence rate (RR)* is a measure of the density of recurrence points in the RP. Specifically, RR is the percentage of recurrent points falling within the specified radius parameter. In the limit  $N \rightarrow \infty$ , RR is the probability that a state recurs to its  $\varepsilon$ -neighborhood in phase space. RR has been found to be useful for detecting evoked response potentials (ERPs) using single trials (Schinkel et al., 2009). RR has a high value for systems whose trajectories often visit the same phase space regions (Marwan et al., 2007b), implying that RR may be useful for detecting regions of hypersynchronization.

### Diagonal Measures

*Determinism (DET)* measures the proportion of recurrent points forming diagonal line structures. The name determinism comes from repeating patterns in the system and is an indication of its predictability. Regular, deterministic signals, such as sine waves, will give very long diagonal lines, while uncorrelated time series, like chaotic processes and random numbers, will give short or no diagonal lines.

The ratio of these first two parameters, DET/RR has been used to discover dynamical changes in physiological time series (Webber and Zbilut, 1994). This will be explored further below in the context of epileptiform activity.

*Line max* ( $L_{max}$ ) is the length of the longest diagonal line segment in the plot, excluding the main diagonal line of identity. This recurrence variable is inversely related to the Lyapunov exponent that is frequently used to characterize system dynamics (Eckmann et al., 1987; Trulla et al., 1996). Positive Lyapunov exponents gauge the rate at which trajectories diverge, and are an indicator of chaos. Thus, smaller  $L_{max}$  indicates a more chaotic (less predictable) signal. Conversely, larger  $L_{max}$  is an indication of predictable signals, which may arise as the result of hypersynchronization of many chaotic oscillators to produce a single, high amplitude oscillation.  $L_{max}$  is the inverse of the divergence (DIV), a statistic that is sometimes computed. Div measures the exponential divergence of the phase space trajectory. Faster divergence results in shorter diagonal lines.

The above measures are computed from the length distribution of diagonal lines in the recurrence plot which encode the main properties of the system, such as predictability and measures of complexity (Marwan et al., 2007b). Vertical lines in the recurrence plot are related to the presence of laminar states in the system. In contrast to the measures based on diagonal lines, these measures are able to find state transitions in chaotic systems, allowing investigation of intermittency, even for rather short and non-stationary data series.

### Vertical Measures

*Laminarity* (LAM) represents the occurrence of laminar states in the system without describing the length of these laminar phases. LAM will decrease if the recurrence plot consists of more single recurrence points than vertical structures (Marwan, 2007).

*Trapping Time* (TT) is the average length of vertical line structures. TT is an estimate of the time the system will remain in a current state or the length of time that the system is “trapped” in a state. It may be related to the length of transient synchronization of component oscillators that contribute to a measured EEG channel.

Other statistics may be derived from recurrence plots, some of which are discussed in (Marwan et al., 2007b). By treating the recurrence plots as shown in Figure 5 as images, it may be possible to apply image classification algorithms to find new characteristic patterns that are associated with distinct time series types or dynamical regimes that have not yet been discovered using statistical measures (Daniusis and Vaitkus, 2008; Norman et al., 2006)

## **From Complex Systems to Cognitive Phenotypes**

Even if the recurrence matrix derived from scalp EEG time series contains all of the essential dynamical information about the brain as a complex dynamical system (Marwan et al., 2007b), the correlation between complicated numerical data derived from the analysis and cognitive or behavioral phenotypes may be subtle and hidden in complicated patterns. A data-driven approach is ideally suited to finding clinical

correlates of cognitive phenotypes in complicated data derived from EEG time series. No *a priori model* is needed. Instead, very general machine learning algorithms are given many examples and are programmed to search for models that best fit the data and explain the phenomenon of interest.

### *Data-driven Discovery: The Fourth Paradigm*

Near the end of the 20<sup>th</sup> century and continuing into the 21<sup>st</sup> century a new approach to discovering relationships in complex data has emerged, under a variety of names, including data mining, data analytics, machine learning or ‘big data’ analysis. This approach to scientific discovery is distinguished from hypothesis-driven data analysis by instead letting the data assume a primary role, then using machine learning algorithms to find the model or hypothesis that best fits the data. It is particularly appropriate for discovering correlations between multisource or complicated sets of data and phenomena of interest when there is no foundational theory to enable models or hypotheses to be determined in advance and tested.

To cite one example, the Neonatal Intensive care unit at the Hospital for Sick Children (SickKids) in Toronto has created a system for early identification of late-onset neonatal sepsis in newborns, a potentially fatal blood infection that occurs in infants. All physiological data that is measured, plus environmental variables, family history and other medical conditions are all collected continuously, resulting in over 10-million data points per infant per day. The predictive analytics enable the presence of infections to be

predicted before symptoms are apparent to neonatologists, allowing early intervention and better outcomes (McGregor, 2013).

Data-driven discovery can find correlations and predictive patterns in data that cannot be found by any other method. This approach requires a move away from trying to understand the deeper cause. Understanding the deeper causes is the goal of scientific research. However, for clinical application, statistically significant and reliable predictive capabilities from data can be life saving, long before causes are understood. This technique is saving lives, even though it is not known what combinations of variables are actually determinative. Causation, expressed in traditional medical terms, is not known. One might argue that the causal pattern is well known to the algorithm; humans are just unable to see the pattern.

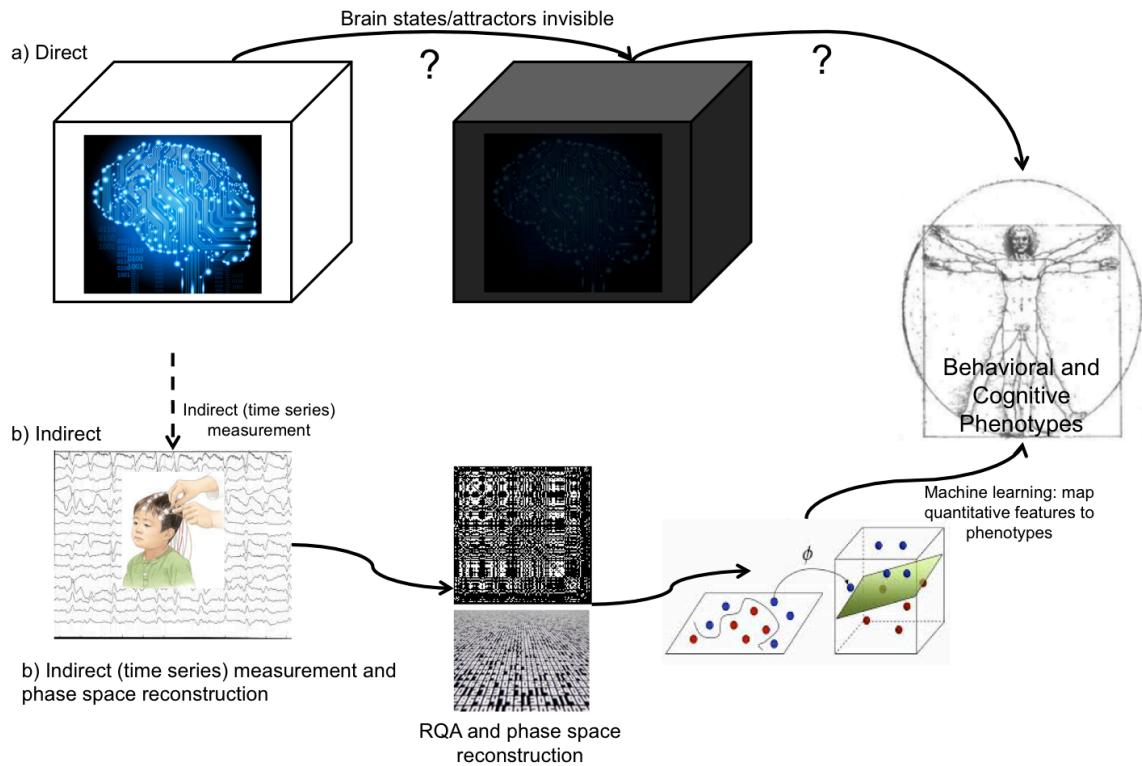
In a philosophical sense, machine algorithm discovery of a model equation that describes a natural process is not so different from human discovery of a ‘law’ of physics. Newton’s law of motion, for example, that says the acceleration of a body (of constant mass) is proportional to the mass of the body and to the applied force is empirically derived. Many experiments were done to confirm its veracity under many conditions. Albert Einstein and the founders of quantum mechanics showed that Newton’s laws of motion were only approximately correct, and that more general laws were actually more accurate. What is called a ‘law’ of nature really falsely assumes that we have insight into a hidden fundamental nature of the universe, when really all we have are empirical observations. This may be controversial, but from a practical viewpoint, a learning

algorithm can also discover Newton's laws of motion from very many empirical observations, as was demonstrated by (Schmidt and Lipson, 2009).

### *Mapping brain dynamics to cognitive phenotypes*

Recurrence Quantitative Analysis (RQA) can be used to compute a number of different nonlinear measures from each of the EEG channels as described above. The recurrence plot for each time series derived from the EEG channels contains considerable information about brain dynamics, state space trajectories and attractors (Marwan et al., 2007b). A typical EEG headset uses 19 sensors in a configuration referred to as the standard 10 – 20 system (Jasper, 1958). Some newer research grade systems use up to 256 sensors (Yamazaki et al., 2013). If six RQA values are computed from each of 19 sensors, the result is 114 numerical values. Hierarchical methods that use wavelet transforms to compute multiresolution time series from each original time series can multiply the number of system features by many times.

Feature extraction is not just a method to enhance machine learning for classification and regression. In this context, the features include the computed nonlinear parameters from recurrence plot and cross recurrence plot analyses for each electrode. If these are arranged in a two-dimensional matrix, with rows for each channel and columns for each measure, then the values for each channel can be treated as a group to determine the location of channels that are most informative for the particular classification or regression task. In this way, the learning algorithm can be used as a discovery tool to localize neural activity that differentiates atypical or pathological regions.



**Figure 6.** The upper pathway is not possible at this time, since brain states are hidden and cannot be measured directly. The lower, indirect pathway illustrates reconstruction of dynamical features using recurrence quantitative analysis. The complicated relationship between patterns in RQ values and behavioral or cognitive measures are determined using machine learning methods.

## Discussion

Measurements of brain electrical activity with EEG are a valuable source of information for neuroscience research, yet this low cost resource may be under-utilized for clinical applications in neurology and psychiatry (Niedermeyer, 2003; Niedermeyer and Lopes da Silva, 2005). When the brain is analyzed as a complex dynamical system, recently developed methods and theorems from dynamical systems theory become applicable and provide powerful new insights into the functional information contained in

scalp electrophysiological measurements. Recurrence plot analysis in particular is an empirical method for analyzing nonlinear time series that, in principle, contains all of the dynamical information about the system that produced the time series. This insight is profoundly important for scalp electrophysiology, as it posits that EEG data contains functional information about the entire brain. The difficulty is that a relationship between the nonlinear time series features and cognitive phenotypes is not readily apparent and may not be explainable in current neurophysiological terms.

The key approach to finding electrophysiological correlates of cognitive phenotypes introduced in this chapter is the employment of machine learning methods. This approach assumes that complicated patterns and relationships in the recurrence plot variables computed from the EEG times series necessarily reflect all cognitive and behavioral activity. Brain states control motor and cognitive output. Machine learning algorithms can find patterns and complex relationships that may be completely opaque to human eyes. However, large datasets may also be required to enable differences in brain function that are biomarkers of serious disorders to be distinguished from the normal range of variation in brain function and behavior that exists among people.

Developments in a number of fields over the past decade have created the possibility of monitoring brain function through the lifespan, recording this information in electronic health records, and monitoring the trajectories for deviations that might indicate emerging disorders. Realizing this possibility will require continued research into the neurophysics of EEG measurements. In addition, research and implementation of

computational methods for extracting this information, storing it in electronic health records, and mining large population databases to discover the biomarkers associated with psychopathology will also be needed. But the tools for moving this technology from the research lab to the bedside are available today. The potential impact of EEG-based functional brain monitoring for pathology is great. If successively developed and implemented on a large scale, it could radically alter the practice of psychiatry, neurology and clinical psychology, with particularly great impact on underserved populations.

## **EEG COMPLEXITY AS A BIOMARKER FOR AUTISM SPECTRUM DISORDER**

### **Abstract**

**Background:** Complex neurodevelopmental disorders may be characterized by subtle brain function signatures early in life before behavioral symptoms are apparent. Such endophenotypes may be measurable biomarkers for later cognitive impairments. The nonlinear complexity of electroencephalography (EEG) signals is believed to contain information about the architecture of the neural networks in the brain on many scales. Early detection of abnormalities in EEG signals may be an early biomarker for developmental cognitive disorders. The goal of this paper is to demonstrate that the modified multiscale entropy (mMSE) computed on the basis of resting state EEG data can be used as a biomarker of normal brain development and distinguish typically developing children from a group of infants at high risk for autism spectrum disorder (ASD), defined on the basis of an older sibling with ASD.

**Methods:** Using mMSE as a feature vector, a multiclass support vector machine algorithm was used to classify typically developing and high-risk groups. Classification was computed separately within each age group from 6 to 24 months.

**Results:** Multiscale entropy appears to go through a different developmental trajectory in infants at high risk for autism (HRA) than it does in typically developing controls. Differences appear to be greatest at ages 9 to 12 months. Using several machine learning algorithms with mMSE as a feature vector, infants were classified with over 80% accuracy into control and HRA groups at

age 9 months. Classification accuracy for boys was close to 100% at age 9 months and remains high (70% to 90%) at ages 12 and 18 months. For girls, classification accuracy was highest at age 6 months, but declines thereafter.

Conclusions: This proof-of-principle study suggests that mMSE computed from resting state EEG signals may be a useful biomarker for early detection of risk for ASD and abnormalities in cognitive development in infants. To our knowledge, this is the first demonstration of an information theoretic analysis of EEG data for biomarkers in infants at risk for a complex neurodevelopmental disorder.

### **Background**

The human brain exhibits a remarkable network organization. Although sparsely connected, each neuron is within a few synaptic connections of any other neuron (Buzsáki, 2006). This remarkable connectivity is achieved by a kind of hierarchical organization that is not fully understood in the brain, but is ubiquitous in nature, called a scale-free network (Barabasi, 2009; Bassett and Bullmore, 2006; Ravasz and Barabasi, 2003) that changes with development. Complex networks are characterized by dense local connectivity and sparser long-range connectivity (Barabasi, 2009) that is fractal or self-similar at all scales. Modules or clusters can be identified on multiple scales. A comparison of network properties using fMRI showed that children and young-adults' brains had similar "small-world" or scale-free organization at the global level, but differed significantly in hierarchical organization and interregional connectivity (Supekar et al., 2009). White matter fiber tracking has revealed that brain development in children

involves changes in both short-range and long-range wiring, with synaptogenesis and pruning occurring at both the local (neuronal) level and the systems level (Supekar et al., 2009). Abnormal network connectivity may be a key to understanding developmental disabilities.

Autism is a complex and heterogeneous developmental disorder that affects the developmental trajectory in several key behavioral domains including social, cognitive and language. The underlying brain dysfunction that results in the behavioral characteristics is not well understood. Complex mental disorders such as autism cannot easily be described as associated with underconnectivity or overconnectivity, but may involve some form of abnormal connectivity that varies between different regions (Noonan et al., 2009). Normal and abnormal connectivity may also change during development, so that, for example, a condition may not exist at 3 months, but may emerge by 24 months. A key to understanding neurodevelopmental disorders is the relationship between *functional* brain connectivity and cognitive development (Johnson, 1993). Measuring functional brain development is difficult both because the brain is a complex, hierarchical system and because few methods are available for noninvasive measurements of brain function in infants. New nonlinear methods for analyzing brain electrical activity measured with scalp electrodes may enable differences in infant brain connectivity to be detected. For example, coarse grained entropy synchronization between EEG electrodes revealed that synchronization was significantly lower in children with autism than in a group of typically developing children (Kulisek et al., 2008), supporting the theory that autistic brains exhibit low functional connectivity. In the

autistic brain, high local connectivity and low long-range connectivity may develop concurrently due to problems with synapse pruning or formation (Belmonte et al., 2004a; Belmonte et al., 2004b). Estimation of changes in neural connectivity might be an effective diagnostic marker for atypical connectivity development.

EEG signals are believed to derive from pyramidal cells aligned in parallel in the cerebral cortex and hippocampus (Sörnmo and Laguna, 2005), which act as many interacting nonlinear oscillators (Nunez and Srinivasan, 2006). As a consequence of the scale-free network organization of neurons, EEG signals carry nonlinear, complex system information reflecting the underlying network topology, including transient synchronization between frequencies, short and long range correlations and cross-modulation of amplitudes and frequencies (Gans et al., 2009). The mathematical relationship between network structure and time series is a subject of current research and may eventually shed further light on the relationship between neural networks and EEG signals.

A great deal of information about interrelationships in the nervous system likely remains undiscovered because the linear analysis techniques currently in use fail even to detect them (Drongelen, 2007). If brain function and behavior are mirrors of each other, as is commonly accepted (Cowan and Kandel, 2001; Hyman, 2007; Kandel, 1998; Singh and Rose, 2009), then biomarkers of complex developmental disorders may be hidden in complex, nonlinear patterns of EEG data. The dynamics of the brain are inherently nonlinear, exhibiting emergent dynamics such as chaotic and transiently synchronized

behavior that may be central to understanding the mind-brain relationship (Varela et al., 2001) or the ‘dynamic core’ (Le Van Quyen, 2003). Methods for chaotic signal analysis originally arose from a need to rigorously describe physical phenomena that exhibited what was formerly thought to be purely stochastic behavior, but was then discovered to represent complex, aperiodic yet organized behavior, referred to as self-organized dynamics (Pikovsky et al., 2001). The analysis of signal complexity on multiple scales may reveal information about neural connectivity that is diagnostically useful (Buzsáki, 2006; Stam, 2005; Varela et al., 2001).

One interpretation of biological complexity is that it reflects a system’s ability to adapt quickly and function in a changing environment (Costa et al., 2005b). The complexity of EEG signals was found in one study to be associated with the ability to attend to a task and adapt to new cognitive tasks; a significant difference in complexity was found between control subjects and those diagnosed with schizophrenia (Li et al., 2008b). Schizophrenic patients were found to have lower complexity than controls in some EEG channels and significantly higher interhemispheric and intrahemispheric cross mutual information values than controls (Na et al., 2002). A study of the correlation dimension (another measure of signal complexity) of EEG signals in healthy subjects showed an increase with aging, interpreted as an increase in the number of independent synchronous networks in the brain (Stam, 2005).

Several different methods for computing complex or nonlinear time series features have been defined and used successfully to analyze biological signals (Chen et

al., 2009; Kuusela et al., 2002). Sample entropy, a measure of time series complexity, was significantly higher in certain regions of the right hemisphere in pre-term neonates who received skin-to-skin contact than in those who did not, indicating faster brain maturation (Scher et al., 2009). Sample entropy has also been used as a marker of brain maturation in neonates (de la Cruz et al., 2007) and was found to increase prenatally until maturation at about 42 weeks, then decreased after newborns reached full term (Zhang et al., 2009).

Living systems exhibit a fundamental propensity to move forward in time. This property also describes physical systems that are far from an equilibrium state. For example, heat moves in only one direction, from hot to cold areas. In thermodynamics, this property is related to the requirement that all systems must move in the direction of higher entropy. Time irreversibility is a common characteristic of living biosignals. It was found to be a characteristic of healthy human heart EKG recordings and was shown to be a reliable way to distinguish between actual EKG recordings and model EKG simulations (Costa et al., 2008). EKG signals from patients with congestive heart disease were found to have lower time irreversibility indices than healthy patients (Costa et al., 2005a). Interestingly, time irreversibility of EEG signals has been associated with epileptic regions of the brain and this measure has been proposed as a biomarker for seizure foci (Gautama et al., 2003). Time irreversibility may be used as a practical test for nonlinearity in a time series.

This study is a preliminary investigation of the difference in multiscale entropy

between two groups of infants between 6 and 24 months of age. The groups include typically developing infants and infants who have an older sibling with a confirmed diagnosis of ASD and who are thus at higher risk for developing autism. ASD is a developmental disorder in which symptoms emerge during the second year of life. Behavioral indicators are not evident at 6 months of age (Ozonoff et al., 2010; Zwaigenbaum et al., 2005; Zwaigenbaum et al., 2007), however, using a novel observational scale to assess ASD characteristics in infants distinguishing characteristics were seen at 12 months (Zwaigenbaum et al., 2005). Another study compared behavioral measures such as frequency of gaze to faces and shared smiles in infants. Again, group differences between those that later developed an ASD and typically developing controls were apparent at 12 months, but not at 6 months (Ozonoff et al., 2010). Only one study investigated behavioral differences at 9 months: infants at risk for ASD showed distinct differences in visual orienting from those with no family history of autism (Elsabbagh et al., 2009). These behavioral observations suggest that important developmental differences are occurring in the brains of typically developing infants and those who will later develop an ASD. Although there have been no other published studies on brain development during the first year of life, one of the most replicated findings, based on retrospective review of medical records, is accelerated growth in head circumference (a valid and reliable proxy for brain growth), which begins at around 6 – 9 months (Courchesne et al., 2003; Courchesne et al., 2007; Elder et al., 2008). If multiscale entropy is a measure of functional brain complexity, then it may be a useful marker for distinguishing differences in brain activity between at-risk and typical infants.

## Methods

### *Participants*

Data was collected from 79 different infants: 46 at high risk for ASD (hereafter referred to as HRA) based on having an older sibling with a confirmed diagnosis of ASD and 33 controls, defined on the basis of a typically developing older sibling and no family history of neurodevelopmental disorders. Testing sessions included infants from ages 6 to 24 months, with some participants tested at more than one age. The study participants were part of an on-going longitudinal study and visits will be evaluated at regular intervals. However, at the time this study was done, most infants had been tested at only one or two visits. Each session was therefore treated as an independent set of data. Thus, the data from an infant that is tested in five different sessions at 6, 9, 12, 18 and 24 months were treated as unique data sets. A total of 143 data sessions were collected from 79 different individuals. The distribution at different ages and risk groups is shown in Table 1. The number of infants who were tested at only one age at the time of this study is shown in Table 2, as well as the number of infants tested 2, 3, 4 and 5 times. Only one infant thus far has been tested at all five ages from 6 to 24 months. For the purposes of this study, all visits were treated as independent measurements. No comparison of different ages or of growth trajectories between individuals is done. Other characteristics recorded include height and head circumference, as shown in Table 1.

Age	6 months		9 months		12 months		18 months		24 months	
Group	HRA	CON	HRA	CON	HRA	CON	HRA	CON	HRA	CON
N	14	16	16	12	23	17	15	7	14	9
Males (59)	6	6	8	4	10	6	8	3	4	4
Females (84)	8	10	8	8	13	11	7	4	10	5
Total (143)	30		28		40		22		23	
DEMOGRAPHIC INFORMATION										
Age (days): mean	189	185	272	273	366	362	549	541	725	727
Std dev	11.7	8.6	5.1	3.6	9.4	9.0	12.4	6.2	9.1	12.4
Height (in): mean	26.5	26.1	27.8	27.2	29.8	29.5	32.1	32.1	34.1	34.8
Std dev	1.9	1.0	0.7	1.6	1.0	1.5	1.7	1.2	1.1	1.2
p-value	0.46		0.18		0.53		0.97		0.24	
Head Circum (mm) mean	434	435	459	447	465	466	484	481	492	493
Std dev	12.7	12.2	13.7	15.8	12.5	18.0	11.4	18.8	16.7	17.2
p-value	0.93		0.04		0.87		0.61		0.53	
MEAN MULTISCALE ENTROPY OVER CHANNEL GROUPS										
Total MSE mean	2.02	1.93	2.07	2.02	2.05	1.87	2.16	1.97	2.07	1.96
Std dev	0.15	0.21	0.20	0.36	0.20	0.35	0.22	0.10	0.14	0.15
p-value	0.17		0.71		0.07		0.01		0.13	
Frontal MSE mean	2.02	1.93	2.12	2.08	2.10	1.94	2.18	2.01	2.08	2.00
Std dev	0.15	0.21	0.20	0.36	0.20	0.35	0.22	0.12	0.11	0.13
p-value	0.04		0.39		0.11		0.04		0.21	
Left Frontal mean	1.94	1.81	1.94	1.91	2.01	1.82	2.06	1.91	2.03	1.88
Std dev	0.15	0.20	0.20	0.31	0.16	0.32	0.21	0.13	0.13	0.15
p-value	0.05		0.72		0.04		0.07		0.03	

**Table 1. Distribution of subjects used in study by age and risk group. Number of male and female infants in each group is shown in parentheses. 79 (46 HRA / 33 CON) different infants participated in this study; some infants participated in multiple sessions at different ages to make a total of 143 recording sessions. Also shown are measured demographic variables (age, height, head circumference) and average MSE values over three regions: whole head, frontal, left frontal. Statistically significant differences between HRA and CON groups are highlighted in boldface.**

The parent Infant Sibling Project study, from which data for this project was taken, was approved by the Committee on Clinical Investigations at Children's Hospital Boston (X06-08-0374) and Boston University School of Medicine (H-29049). Parental written

informed consent was obtained after the experimental procedures had been fully explained.

### *EEG Data Collection*

Infants were seated on their mothers' laps in a dimly lit room while a research assistant engaged their attention by blowing bubbles. This procedure was followed to limit the amount of head movement made by the infant that would interfere with the recording process. Continuous EEG was recorded with a 64-channel Sensor Net System (EGI, Inc.). The net is comprised of an elastic tension structure forming a geodesic tessellation of the head surface containing carbon fiber electrodes embedded in pedestal sponges. At each vertex is a sensor pedestal housing an Ag/AgCl- coated, carbon-filled plastic electrode and sponge containing saline electrolyte. Prior to fitting the sensor net over the scalp, the sponges are soaked in electrolyte solution (6cc KCL/liter distilled water) in order to facilitate electrical contact between the scalp and the relevant electrode. In order to assure the safety and comfort of the infant the salinity of the electrolyte solution is the same as tears. In the event that the solution comes into contact with the eyes no damage or discomfort will occur.

Prior to recording, measurements of channel gains and zeros were taken to provide an accurate scaling factor for display of waveform data. The baby's head was measured and marked with a washable wax pencil in order to ensure accurate placement of the net, which was then placed over the scalp. Scalp impedances were checked on-line using NetStation (EGI, Inc, Eugene OR), the recording software package that runs this

system. EEG data were collected and recorded on-line using NetAmps Amplifiers (EGI, Inc, Eugene, OR) and the NetStation software. The data were amplified, filtered (band pass 0.1-100.0 Hz), and sampled at a frequency of 250 Hz. They were digitized with a 12-bit National Instruments Board (National Instruments Corp., Woburn MA). Typically, 2 minutes of baseline activity were recorded, but depending on the willingness of the infant, recorded periods may be shorter. For this study, continuous sample segments of 20 seconds were selected from the processed resting state data and used to compute multiscale entropy values.

		HRA		CON	
N with 1 time point	6 months	2	21	6	24
	9 months	5		2	
	12 months	4		4	
	18 months	5		2	
	24 months	5		3	
N with 2 time points		16		8	
N with 3 time points		8		5	
N with 4 time points		0		2	
N with 5 time points		1		1	
Total unique infants		46		33	
Total measurements, all visits		82		61	

**Table 2.** The distribution of participants with the number of visits/measurements from the same child at different ages is shown. Overall, 79 infants participated in the study, resulting in 143 measurements sessions.

### *Modified Multiscale Sample Entropy*

A multiscale method for computing the entropy of biological signals was developed by (Costa et al., 2005b). This approach computes the sample entropy on the original time series (or “signal”) and on coarse-scale series that are derived from the original signal. Because biological systems must be adaptable across multiple time scales, measurements of biological signals are likely to carry information across multiple scales.

A multiscale estimation of the information content of EEG signals may reveal more information than the entropy of only the original signal.

Multiple scale time series are produced from the original signal using a coarse graining procedure. The scale 1 series is the original time series. Scale 2 time series is obtained by averaging 2 successive values from the original series. Scale 3 is obtained by averaging every three original values and so on as shown in equation 3.1.

$$\begin{aligned}
 s_1 &: x_1, x_2, x_3 \dots x_N \\
 s_2 &: (x_1 + x_2)/2, (x_3 + x_4)/2, \dots, (x_{N-1} + x_N)/2 \\
 &\vdots \\
 s_{20} &: (x_1 + \dots + x_{20})/20, \dots, (x_{N-20} + \dots + x_N)/20
 \end{aligned} \tag{3.1}$$

Coarse-grained series up to scale 20 are computed for each of the 64 EEG channels. The modified sample entropy (mSE) defined in (Xie et al., 2008) was used to compute the entropy of each coarse grain time series. The mSE algorithm uses a sigmoidal function to compare vector similarity rather than a Heaviside function with a strict cutoff as with the Sample Entropy used for analysis of biological and EKG signals in (Costa et al., 2005b; Costa et al., 2008). The practical effect of using the modified sample entropy is the computed entropy values are more robust to noise and results are more consistent with short time series. In brief, the similarity functions  $A_r^m$  and  $B_r^m$  defined by equations (7) and (9) in (Xie et al., 2008) are computed with  $m=2$  and  $r=0.15$  for each coarse-grained time series defined in equation 3.1. The modified multiscale entropy (mMSE) will then be defined as the series of modified sample entropy values at

each of the coarse grain scales from 1 to 20. The mMSE for scale  $s$  with finite length time series is then approximated by:

$$mMSE(s, m, r) = -\ln \left( \frac{A_r^m(s)}{B_r^m(s)} \right) \quad (3.2)$$

The multiscale entropy for several linear, stochastic and nonlinear time series are shown in Figure 7, along with representative MSE for EEG signals from EEG data used in this study. The purely random white noise signal the completely deterministic logistic equation series have similar MSE curves and visually appear indistinguishable. As discussed in (Costa et al., 2005b), these are quite distinct from normal physiological signals. The EEG signal is the only one of the series in the figure that has an mMSE that increases with scale, indicating longer-range correlations in time. Decreasing entropy in general indicates that a signal contains information only on the smallest time scales. If entropy values across all scales for one time series are higher than for another, then the former is considered to be more complex than the latter. Although the mean mMSE value can be computed and used for comparing the overall complexity of physiological signals, the shape of the curve itself may be important for distinguishing two signals.

### *Time Asymmetry and Nonlinearity*

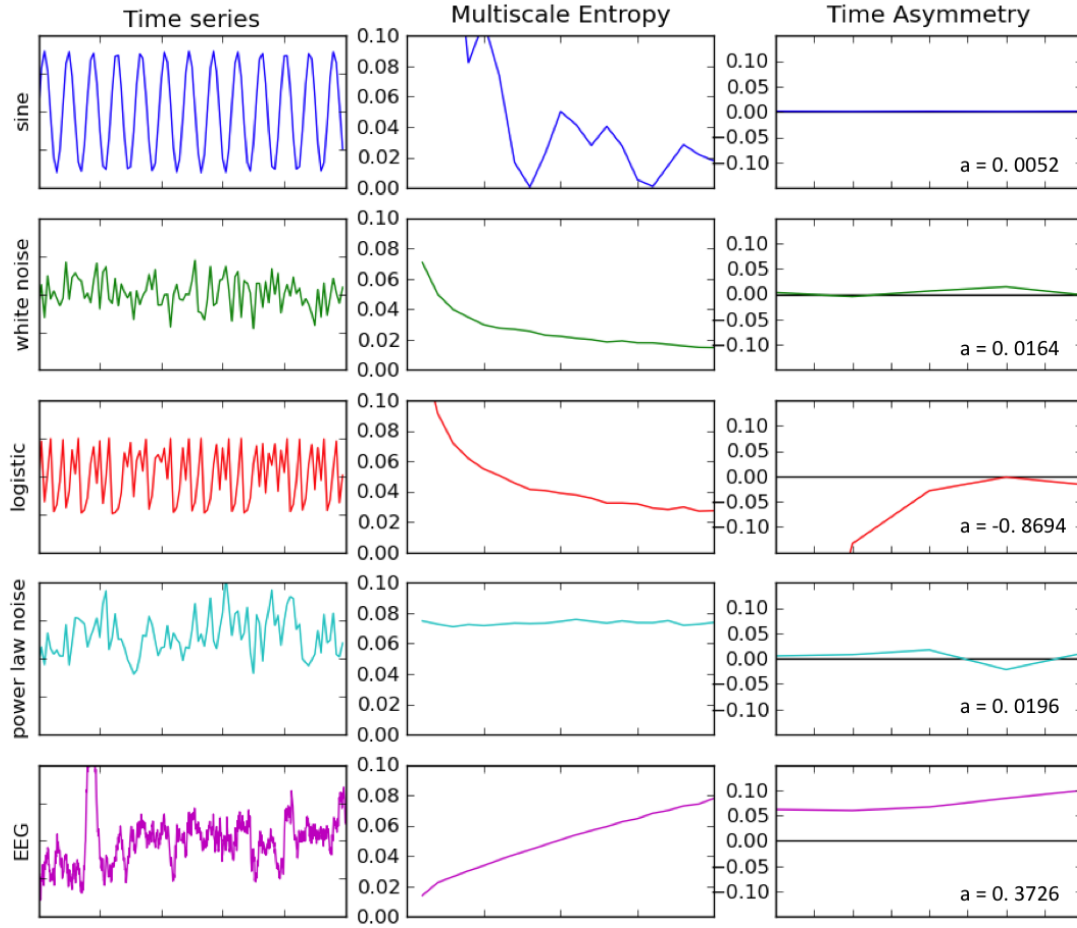
The time irreversibility index ( $t_{rev}$ ) was computed for different resolutions of the EEG time series using the algorithm of (Costa et al., 2008). The third column of Figure 7 shows  $t_{rev}$  for several different linear and nonlinear time series. Of particular note is that only the sine wave time series and both random time series have nearly zero

irreversibility indices, while the index for the nonlinear logistic series and the representative EEG signal are both nonzero on all scales shown.

After computing multiple resolutions of the EEG time series as described above, an estimate of the time irreversibility for each resolution is computed by noting that a symmetric function or time series will have the same number of increments as decrements. That is, the number times  $|x_{i+1} - x_i| > 0$  will be approximately the same as the number of times  $|x_{i+1} - x_i| < 0$ . Thus, an estimate of the time series symmetry (or reversibility) was found by summing increments and decrements and dividing by the length of the series. A reversible time series will have a value of zero. For a series of 5000 points, as used in this study,  $t_{rev} > 0.1$  is a significant indicator of irreversibility and thus of nonlinearity (Schreiber and Schmitz, 1997). This information is used only to indicate that nonlinear information is contained in the EEG time series that is not used in linear analysis methods, suggesting that the mMSE may contain more diagnostically useful information than power spectra analysis alone.

### *Classification and Endophenotypes*

The Orange machine learning package was used for classification calculations (Demsar and Zupan, 2004). Several different learning algorithms were compared (support vector machine, k nearest neighbors and naïve Bayesian) so as to exclude possible overfitting by one method. The significance of the classification results for each method was estimated empirically using the permutation approach described in (Golland and Fischl, 2003).



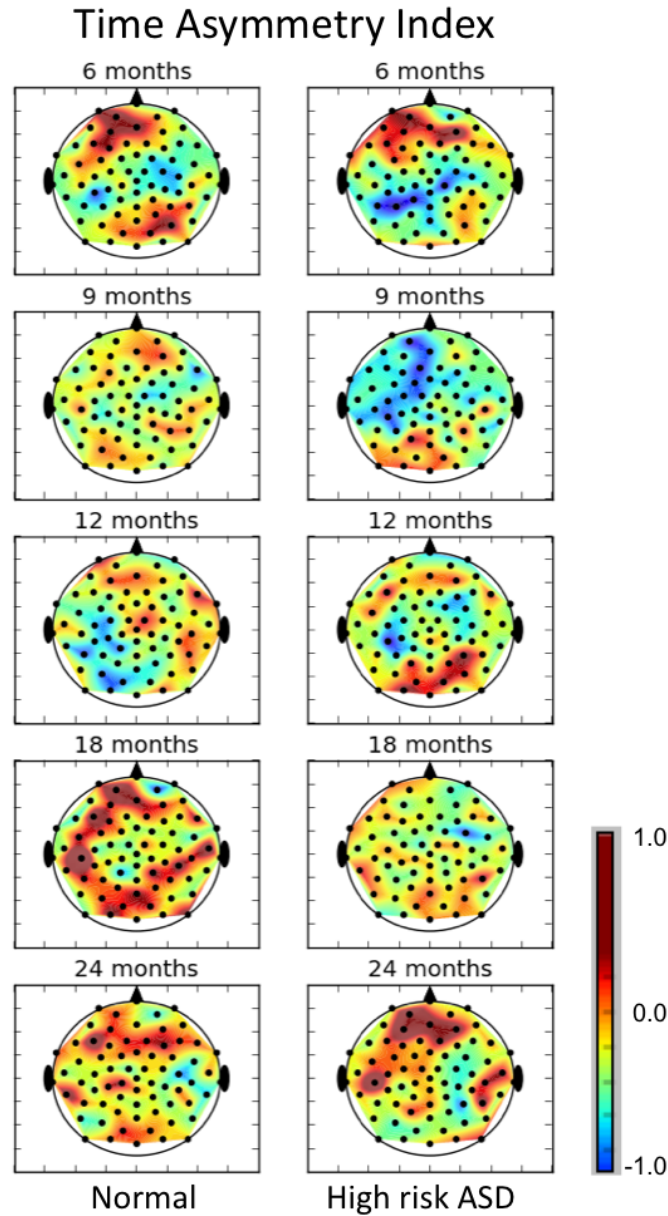
**Figure 7.** Characteristics of five different time series are shown. Column 1 shows the time series amplitudes. Column two is the multiscale entropy, where the horizontal axis is the coarse graining scale, from 1 to 20. Column 3 is the multiscale time asymmetry value. The value of  $a$  in the lower right corner of the time asymmetry plot is the value of the time asymmetry index summed over scales 1 to 5. A non-zero time asymmetry value is a sufficient condition for nonlinearity of a time series.

To keep the feature set smaller while still capturing the overall shape of the mMSE curve, three values (low, high and mean) for each curve were extracted for each of 64 channels, creating a feature set of 192 values (3 x 64). A single sample from the population is represented by these 192 values. Although some data points are from the same infant at different ages, this study should be considered a cross-sectional study in that any relationship between data at two different ages is not used for classification. That

is, the infants in the 6 month EEG data set are considered to be independent of the set of infants used at 9 months, 12 months and so on.

## **Results**

Multiscale entropy and time irreversibility characteristics of five different time series are shown in Figure 8. The example time series amplitudes are shown in the first column. The second column displays plots of the multiscale entropy, where the horizontal axis is the coarse graining scale, from 1 to 20. White noise shows a characteristic decline in entropy with temporal scale, indicating loss of correlation between longer time intervals. Note that the deterministic, but chaotic, logistic equation has an entropy profile similar to white noise, suggesting that signal characteristics that appear as noise may in fact contain significant dynamical information about the system. The physiological (EEG) time series has a unique entropy curve that increases with temporal scale, similar to the cardiac signals observed in EKG readings (Costa et al., 2008; Norris et al., 2008).

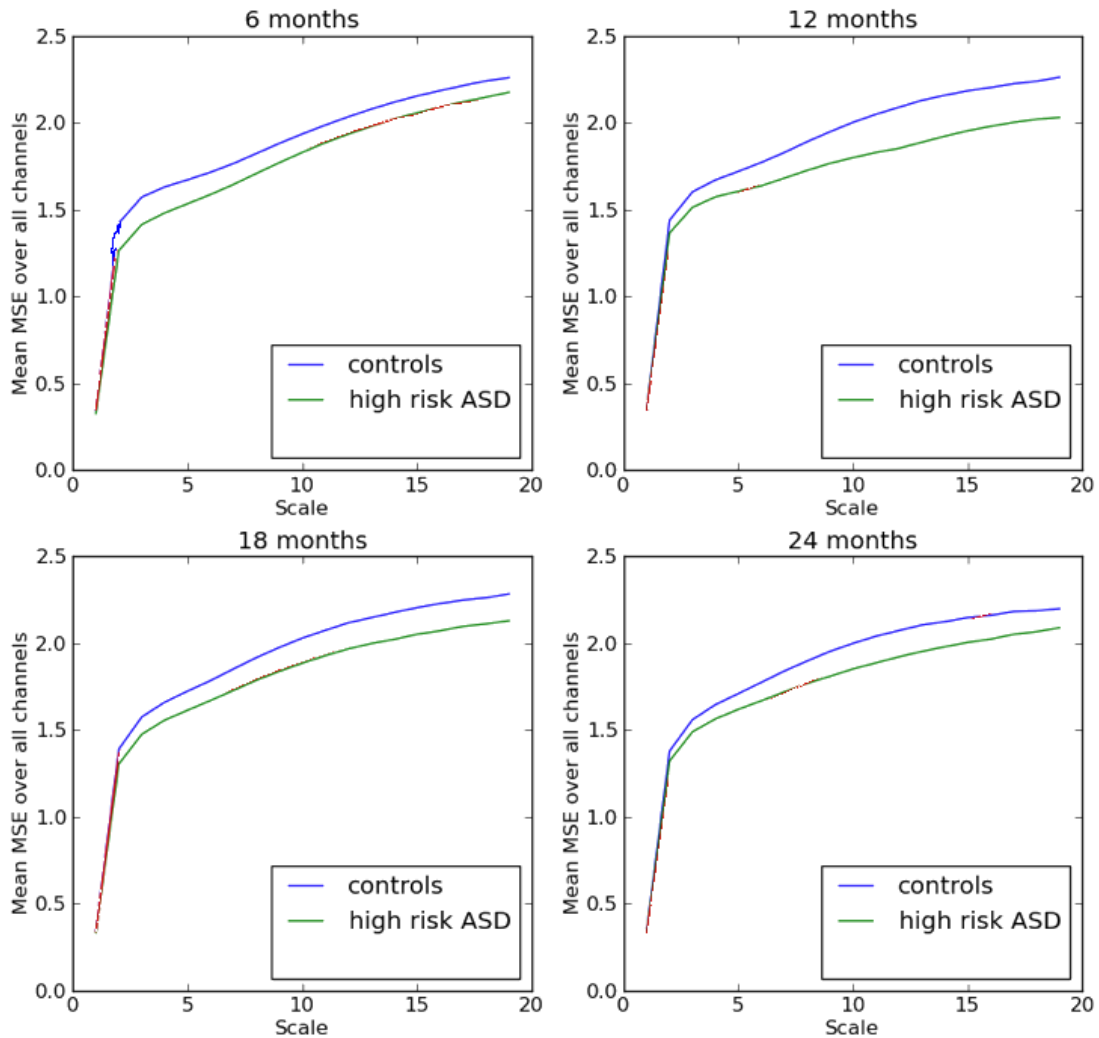


**Figure 8.** Time asymmetry index for normal controls and high-risk groups is shown. The index was averaged over all infants in the group and age category. If time asymmetry varied randomly at channel locations, the fluctuations would average out. The persistence of time asymmetry values different from zero indicates nonlinearity in the signal.

The third column of Figure 7 is the multiscale time asymmetry value. The value of  $a$  in the lower right corner of the time asymmetry plot is the value of the time asymmetry index summed over scales 1 to 5. A non-zero time asymmetry value is a sufficient

condition for nonlinearity of a time series. Although white noise and the logistic curve have similar entropy profiles, the time asymmetry index distinguishes the nonlinear, chaotic signal from noise. The EEG signal shown here clearly contains nonlinear characteristics, based on the nonlinear time asymmetry index.

Using all of the EEG data, time asymmetry was first calculated to determine the degree of nonlinearity present in the signals. Figure 8 shows the time asymmetry index for all 64 channels of the resting state EEG for control and high-risk groups by age. The value of the time asymmetry index in the scalp plot is determined by averaging the index value over all members of that age and risk group. Since the value may take on positive or negative values, and will be near zero for time-reversible signal, the persistence of the nonzero values in this plot is an indicator of signal nonlinearity. The multiscale entropy and  $t_{rev}$  values have independent physiological meaning (Costa et al., 2008). Since apparent differences exist between controls and the high-risk group at all ages for both MSE and  $t_{rev}$ , these two quantities together may provide a more sensitive biomarker for developmental age and atypical development. However, in this study only the multiscale complexity is used to classify the high risk group.



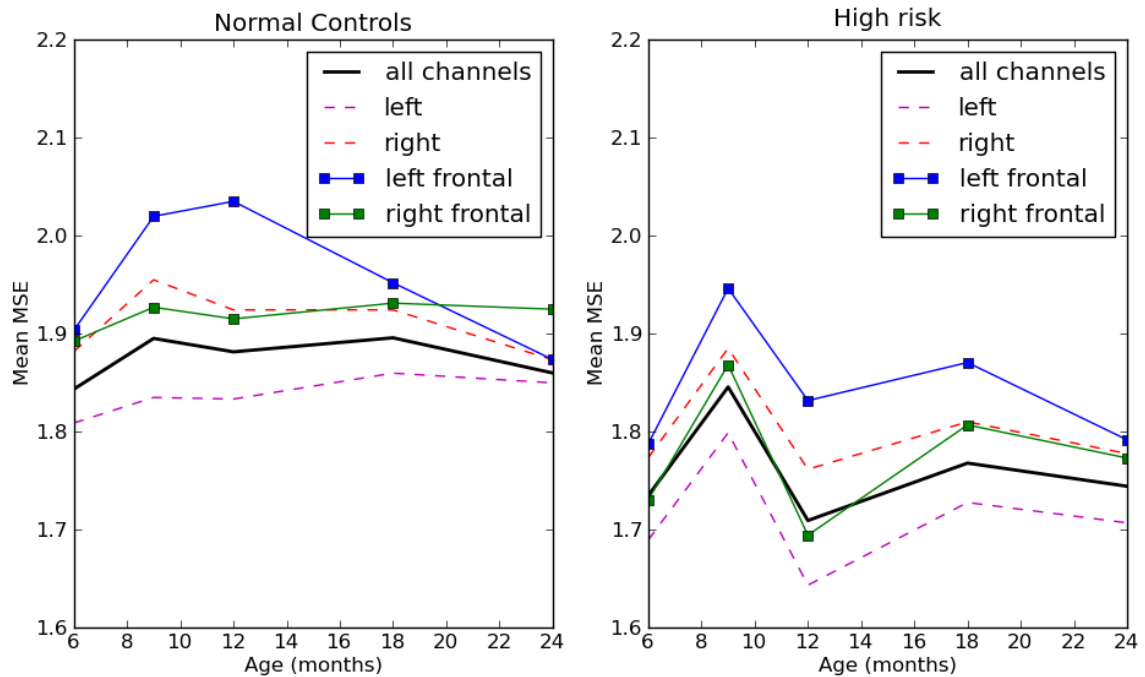
**Figure 9. Multiscale entropy (MSE) is computed for each of 64 channels and for each of the risk groups and averaged over the sample population to produce the MSE plots for ages 6 to 24 months.**

In order to make some general comparisons of EEG complexity between risk groups and different ages, mMSE curves were averaged over all members of sub-groups by both age and risk group. Figure 9 shows that the HRA group has a consistently lower mean complexity over all channels across all scales and at all ages. The group average mMSE value versus age is shown for infants in each of the two risk groups in Figure 10. The bold black line is the mean MSE value averaged over all 64 EEG channels. Left and

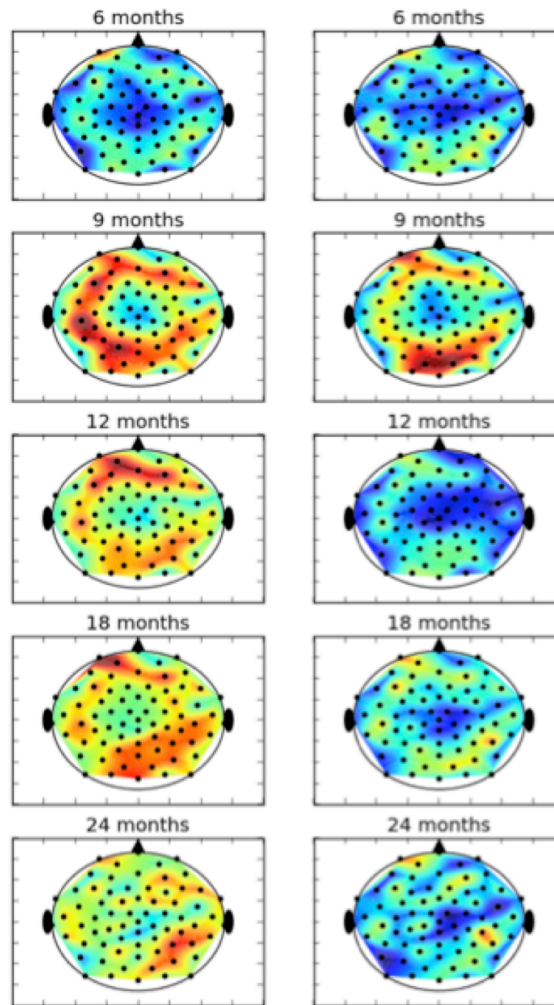
right laterality were determined by averaging all left-side and all right-side channels separately. Similarly, mMSE values for four left-frontal and four right-frontal channels were averaged and plotted versus age. Note that the data in Figure 10 is treated as if drawn from a cross-sectional study, as described previously. Mean values, standard deviations and statistical significance (p-values from t-test) for the channel averages are given in Table 3. Differences between group averages are significant at 18 months for overall mean mMSE, the differences are significant for the left frontal region at all except 9 months. Of note is that significant differences are not found at 9 months for any of the three MSE averages in Table 1, although head circumference is significantly different only at 9 months. As discussed below, when all mMSE data is considered without averaging (that is, mMSE curves, at each channel), machine learning algorithms find the greatest classification accuracy at 9 months. Although it appears in Figure 10 that the most prominent difference between the normal and HRA groups is the *change* in mMSE from 9 to 12 months, significance levels were not computed for changes in this study because measurements at each age use different populations of infants.

Several features are immediately apparent. A general asymmetry in mMSE is seen in both control and high-risk groups, although this appears to decline from 12 to 18 months as the left and right hemisphere and frontal curves come closer together at 18 months. EEG complexity changes with age, but not uniformly. In the controls, the overall EEG complexity, shown by the solid black line, increases from 6 to 9 months then decreases slightly from 9 to 12 months before increasing again from 12 to 18 months. Left and right channels and the right frontal channels all follow this same pattern, though

left and right hemisphere complexity is not symmetric. The left frontal channels follow a different pattern, increasing strongly until 12 months then declining after that. The complexity curves for the high-risk group follow a similar pattern, but the overall complexity is lower and the increases and decreases are much more exaggerated. Perhaps even more distinct is the left frontal curve in the high-risk group. It follows the same pattern as all other regions, unlike the left frontal curve in the controls.



**Figure 10.** The change in mean MSE over all channels is shown for each age. Averaging over all channels reveals that in general MSE is higher in the normal controls than in the high risk group, but regional differences cannot be seen. Numerical data, including statistical significance of group differences, is contained in Table 5.



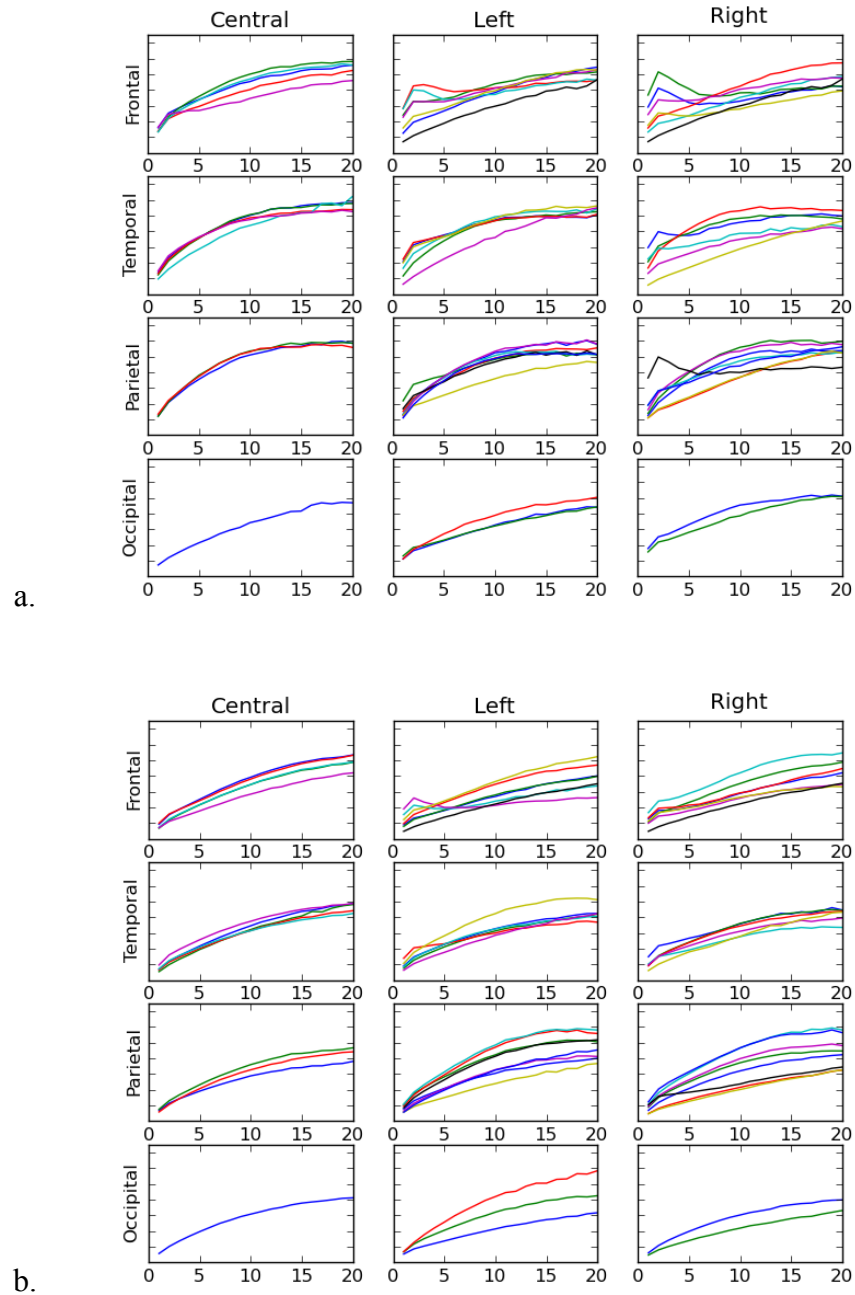
**Figure 11.** MSE in each EEG channel averaged over all infants in the control or high-risk group at each age.

Since the complexity changes seem to vary with EEG channel, a better picture of complexity development with age and between risk groups can be seen in a scalp plot. Figure 11 shows the mean mMSE value for all EEG channels by risk group and age. The complexity values here are computed by averaging the mMSE over all coarse grain scales for that channel as in Figure 8. Complexity variation with age and between risk groups is immediately apparent. One or two channels of the left frontal region appear to increase in complexity continuously with age in the controls, as does the right parietal/occipital

region. The entropy in the high-risk group is lower than in the control group overall. Although the pattern of complexity change from 6 to 9 months appears similar in both groups, the high-risk group shows a marked decline in overall complexity from 9 to 12 months.

Height, head circumference and (exact) age in days at the time of testing are included in Table 5. Group means, standard deviations and significance levels are shown. The only significant group difference in these variables is in head circumference at 9 months – the HRA group has a larger mean head circumference than the typically developing controls.

Statistical averages can sometimes obscure meaningful information in complex and highly varying time series. The scalp plots shown in Figure 11 reveal differences between risk groups and ages, but may not use all the information available in the mMSE calculations. For example, the complete mMSE curves on 20 resolutions or scales are shown in Figure 12 for individual 9-month old infants; 12.a is an infant from the control group and 12.b is for an infant from the high-risk group. Curves are grouped by brain region, with 64 curves in all. The purpose of these graphs is simply to illustrate that the shape of the mMSE curves can vary between channels and individuals in distinct ways and this will not be seen in average values. We note that the low spatial scale entropy in the frontal region of the infant from the control group is especially high while this feature is lacking in the infant from the high risk group. Although differences between these two examples are apparent, it may be quite difficult to compare 64 mMSE curves for a large



**Figure 12. MSE curves for all 64 channels, grouped by brain region. a. 9-month normal control infant. b. 9-month high-risk infant. Higher low-spatial-region (corresponding to high frequency) entropy in the frontal region is one distinct difference in the normal controls.**

number of subjects in each group and determine the differences. In order to use all 64 x 20 or 1280 multiscale entropy values for each subject, a multiclass support vector

machine (SVM) algorithm was used to perform supervised classification of the control and HRA groups.

a. Males and Females

Age (months)		6	9	12	18	24
Accuracy (p-value)	knn	0.67 (0.06)	<b>0.77</b> (0.02)	0.53 (0.38)	0.72 (0.12)	0.53 (0.47)
	SVM	0.63 (0.16)	<b>0.77</b> (0.00)	0.53 (0.71)	0.65 (0.56)	0.55 (0.64)
	Bayes	<b>0.70</b> (0.05)	<b>0.72</b> (0.03)	0.68 (0.06)	<b>0.80</b> (0.04)	0.57 (0.33)

b. Males only

Age (months)		6	9	12	18	24
Accuracy (p-value)	knn	0.40 (0.64)	<b>0.90</b> (0.00)	0.70 (0.16)	<b>0.90</b> (0.03)	-
	SVM	0.30 (0.42)	<b>1.00</b> (0.00)	0.75 (0.12)	0.75 (0.81)	-
	Bayes	0.35 (0.58)	0.75 (0.10)	0.75 (0.09)	<b>0.90</b> (0.05)	-

c. Females only

Age (months)		6	9	12	18	24
Accuracy (p-value)	knn	<b>0.80</b> (0.03)	0.60 (0.20)	0.48 (0.58)	0.35 (0.88)	0.40 (0.89)
	SVM	<b>0.80</b> (0.02)	0.40 (0.54)	0.35 (0.97)	0.55 (0.78)	0.75 (0.53)
	Bayes	0.75 (0.07)	0.65 (0.19)	0.47 (0.54)	0.45 (0.73)	0.50 (0.92)

**Table 3. Supervised learning classification using three different methods: k nearest neighbors (knn), Support Vector Machine (SVM), and Naïve Bayes classification. 10-fold cross validation was run using the computed MSE values on 64 channels for each subject within each age group. P-values were estimated empirically using a permutation of class labels approach, as described in the text. A. males and females together; b. males only; c. females only. Too few 24-month old boys were available for cross validation.**

Using a 10-fold cross validation, subjects were classified into either control or high-risk groups using three different learning algorithms as described previously. Since the complexity of all channels is changing rapidly from 6 months to 24 months, classification within age groups was done rather than comparing the two groups using infants across the entire age spectrum. Machine classification calculations were done for boys and girls

together at each age as well as separately. The results of these simulations are shown in Table 3. Classification by age and gender are shown with accuracy and significance estimates for three different machine learning algorithms: k-nearest neighbors (kNN), support vector machine (SVM) and naïve Bayesian classifier (Bayes).

The significance of the classification accuracy was assessed empirically using the permutation strategy described in (Golland and Fischl, 2003). This approach is common for estimating the significance of learning algorithms when the number of features greatly exceeds the number of training examples. If the class labels are randomly permuted, a new classification accuracy can be computed using 10-fold cross validation, to serve as a baseline. For this study, 100 random permutations were run with a 10-fold cross validation for each machine classification calculation. The p-value was determined by counting the number of random classifications for which the accuracy was equal to or higher than the accuracy for the true labels.

Using  $p=0.05$  as a significance cutoff, HRA and control groups can be classified at 9 months for boys and girls together and for boys separately with accuracies of nearly 80% and well over 90%, respectively. For boys considered alone, the classification accuracy remains relatively high at 9, 12 and 18 months, though the result at 12 months is not statistically significant. For girls, separation of the two groups is most accurate and significant at 6 months, possibly indicating a gender difference in developmental trajectories. These results suggest that a familial endophenotype may be present at around 9 months that enables HRA infants to be distinguished from normal controls. The

differences seem to decline after 9 months, especially in girls, with some evidence that it may persist in boys until 18 months (Table 3.b). Since approximately 60% of the HRA infants are expected to not be diagnosed with an ASD (20% will likely be diagnosed with another disorder, although not an ASD; (Zwaigenbaum et al., 2007), this is not surprising. Increasing heterogeneity in rates of development and behavioral characteristics of the high risk group with age may be partly responsible for the drop in accuracy. Further study and subclassification with future data will be needed to explore gender differences in brain development using entropy calculations.

In order to determine if the significant group differences in mean head circumference were predictors of individual class status, two additional calculations were done. First, head circumference was added as one more feature to the MSE values. The prediction calculations were repeated. The predictive accuracy of the classifiers was unchanged from the results obtained with MSE alone. This might have been because the changed MSE values were a direct reflection of head size differences in some way, so classification was done with head circumference alone. Somewhat surprisingly, classification accuracy was not significant and nearly random. When examining the group values, it appears that the rather large individual variability within each group accounts for this. We conclude that head circumference does not contribute to classification accuracy at any of the ages tested.

## Discussion

The primary goal of this study was to explore whether measures of EEG complexity might reveal functional endophenotypes of ASD and thus be potential biomarkers for risk of ASD at very early ages before the onset of clear behavioral symptoms. Our findings show significant promise for the specific measure of multiscale entropy that was used to compare high and low risk infants between the ages of 6 and 24 months. Differences in mean mMSE over the entire scalp and especially in the left frontal region were significant at most ages measured, except at 9 months. The trajectory of the curves between 6 and 12 months in figure 10 appear to be as informative as information at any specific age. This result makes the relative high accuracy at 9 months of the machine classification using all of the mMSE curves as feature vectors particularly notable. This is a period of important changes in brain function that are foundational for the emergence of higher level social and communicative skills that are at the heart of ASD. A number of major cognitive milestones typically occur beginning at around the age 9 months and perhaps earlier in girls. These include, for example the development of the ability to perceive intentional actions by others (Behne et al., 2005), as well as loss of the ability to perceive speech sound distinctions in non-native languages (Rivera-Gaxiola et al., 2005) and loss of the ability to discriminate individual monkey faces (Pascalis et al., 2002). These latter developments are especially significant because they reveal how *socially-grounded experiences* influence changes in the neurocognitive mechanisms that underlie speech and face processing. Thus, (Marcus and Nelson, 2001) argued that infants mold their face processing system based on the visual experiences they encounter

just as their speech processing skills are molded to their native language (Kuhl, 2000, 2007). This model assumes a narrowing of the social-perceptual window through which language and faces are processed which, in turn, results in an increase in cortical specialization. In a prospective study, (Ozonoff et al., 2010) found that social communicative behaviors in infants that later developed ASD declined dramatically between 6 and 18 months when compared to typically developing infants.

We hypothesize the following developmental sequence may explain the data in Table 3. At six months no significant behavioral differences have been noted between typically developing infants and those who develop autism in prospective studies (Ozonoff et al, 2010; Zwaigenbaum et al., 2005). Thus few differences are expected in electrophysiological data at 6 months, as is seen in Figure 10 and Table 3. However, if girls are considered separately, differences in mMSE appear to be significant at 6 months. If the multiscale entropy calculations from the EEG signals are indeed a biomarker for endophenotypes of autism familial traits, then by 9 months of age, many infants in the high-risk group will display unique characteristics in their MSE profiles that enable them to be distinguished from the controls. Those in the high-risk group who do not have multiple risk factors and later develop normally, would not be expected to exhibit abnormalities in their mMSE profiles throughout the developmental period. These will account for the HRA infants in our study who are classified similarly to our typical controls. This hypothesis will be tested when sufficient numbers of infants in the HRA group have reached 2 to 3 years of age and a diagnosis of ASD or typically developing can be made.

Developmental abnormalities from 6 to 12 months are particularly distinct in the two groups (low and high risk for ASD), allowing the groups to be classified quite accurately, although some overlap between the HRA and control groups should be expected at all ages. From 12 to 24 months, the distinction between the two groups declines. This likely reflects the trend for some fraction of high-risk infants to develop toward more typical cognitive and behavioral function even though they may carry endophenotypes that share common complexity profiles at an earlier age with other high-risk infants who will later develop an ASD diagnosis.

Rather than analyzing entropy at single age points, using a trajectory of entropy values from 6 to 24 months might be more informative. Although EEG complexity has been shown in several studies to increase with age (Janjarsjitt et al., 2008; Lippe et al., 2009; Zhang et al., 2009), the increase is neither monotonic nor uniform across different brain regions. The abnormalities in brain development that lead to autistic characteristics may not be immediately apparent by inspecting relevant brain activity, even if the data contain diagnostically significant information. For example, a recent study of the relationship between cortical thickness and intelligence found no correlation between absolute cortical thickness at any particular age and intelligence. However, a specific *pattern* of developmental changes in cortical thickness was highly correlated with intelligence (Shaw et al., 2006).

One of the characteristics of the high-risk group is heterogeneity: this group includes infants who will go on to develop an autism spectrum disorder and those who

are within the normal range genetically, developmentally and behaviorally, as well as those in-between who carry mild autistic-like traits. Further study with this cohort as they grow and develop will enable this hypothesis to be tested. Rather than binary classification into typical controls and heterogeneous high-risk groups, classification by actual behavioral assessments will allow a more accurate test of the efficacy of using the mMSE to measure brain function.

### **Conclusions**

Abnormal brain connectivity either locally, regionally, or both may be a root cause of a number of behavioral disorders, including ASD (Belmonte et al., 2004a) and changes in local complexity is believed to be related to brain connectivity (Sakkalis et al., 2008). Local neural network connectivity undergoes rapid change during early development and this may be reflected in the multiscale entropy of EEG signals, which is one measure of signal complexity that has been associated with health and disease (Costa et al., 2005b). A number of recent studies have demonstrated a link between brain connectivity and complexity and EEG signal complexity may provide valuable information about the neural correlates of cognitive processes (Sauseng and Klimesch, 2008). Early markers for neurological or mental disorders, particularly those with developmental etiologies, may be the growth trajectories of complexity, as measured by multiscale entropy curves. The results shown in this paper suggest that infants from families with a history of ASD have quite different EEG complexity patterns from 6 to 24 months of age that may be indicators of a functional endophenotype associated with ASD

risk. Differences between mean mMSE averaged over all channels or in frontal regions in the two groups are significant at all ages except 9 months. Machine classification based on mMSE curves in each channel as a feature set is able to determine group membership, particularly at 9 months of age. The classification accuracy decreases after 12 months, possibly due to the influence of normal brain development and the development of normal characteristics in many of the high risk subjects. Classification accuracy for boys alone appears to still be significant and relatively high at 18 months. More data about the future outcome of the HRA infants and the computation of additional features, such as laterality of entropy, together with behavioral and cognitive assessments as the cohort of subjects in this study grow, may enable the high risk population to be sub-classified more accurately. Future longitudinal analysis of data from this cohort will allow growth trajectories to be compared, as well as the future outcome of the high risk children. Deeper understanding of the relationship between these neurophysiological processes and cognitive function may yield a new window into the mind and provide a clinically useful psychiatric biomarker using complexity analysis of EEG data.

## **CHAPTER FOUR: MULTISCALE EEG ANALYSIS: BIOMARKERS FOR AUTISM AND ABSENCE EPILEPSY**

### **Abstract**

Background: Autism spectrum disorders (ASD) and epilepsy co-occur in approximately 30% of individuals with a primary diagnosis of either disorder. As many as 60% of people with an ASD may exhibit epileptiform activity, even when active epilepsy is not present. Although autism and epilepsy are considered to be different disorders, the relatively high comorbidity suggests the possibility of common neuropathological mechanisms. Both are believed to be neural connectivity disorders. We posit that atypical neural connectivity patterns may be a common, and related, cause for both. Recent research in network theory has shown a relationship between network structure and nonlinear signal features, thus providing a link between EEG measurements and neural network structure. Our hypothesis is that the EEG signal features, as computed with multiscale recurrence quantitative analysis (RQA), reveals similarities and differences between ASD and absence epilepsy. Specifically, the epileptic brain should exhibit lower chaos than controls, allowing pathological synchronization that results in seizures.

Methods: Data from 92 children were examined retrospectively in this study, collected from two different projects. Twenty-four (24) patients with absence epilepsy and 26 controls were collected from the Boston Children's Hospital (BCH) Epilepsy Center. Eighteen (18) children with a clinical diagnosis of autism and 23 controls were chosen from the Laboratories of Cognitive Neuroscience (LCN) at BCH. Thirty-second segments

of baseline, resting state EEG without visible spikes or abnormalities were selected from all subjects. RQA values were computed for each of 19 EEG channels in the standard 10-20 configuration. Support Vector Machine (SVM) algorithms were used in a cross validation study to determine the classification accuracy using RQA values as features.

Results: Significant differences were found between absence and control groups, ASD and control groups, and between absence and ASD groups. No significant differences were found between the two control groups. Classification algorithms were able to distinguish 3 groups (absence, ASD, control) with high ( $> 90\%$ ) accuracy. Importantly, the machine learning algorithms were not able to classify the two control groups, suggesting that the RQA values were related to characteristics of the EEG data itself, and not to differences in laboratories or equipment. While RQA values from absence cases differed from controls in all scalp locations, absence and ASD cases had the most significant differences in left temporal and right parietal regions. In most scalp regions, ASD values were intermediate between the control values and absence values.

Conclusions: Significant differences were found in the nonlinear RQA values computed from alert, resting state EEG segments from children with absence epilepsy, ASD and controls. Controls had highest measures of chaos, with absence cases exhibiting the lowest values. These values may be useful as screening biomarkers for emerging absence epilepsy or ASD. The finding that ASD values were intermediate between absence cases and controls suggests a common pathological continuum in neural network structures.

## **Background**

Autism spectrum disorder (ASD) and epilepsy are common neurodevelopmental disorders that account for a significant proportion of child and adult neurologic burden of disease (Tuchman et al., 2013). Although autism and epilepsy are considered to be different disorders, these two spectrum disorders co-occur frequently. Approximately 30% of individuals with a primary diagnosis of ASD have active epilepsy (Besag, 2009; Tuchman et al., 2010), with reports ranging from 5% to 46% (Spence and Schneider, 2009). Up to one-third of children with a primary diagnosis of epilepsy may also meet the criteria for a diagnosis of autism (Clarke et al., 2005). Together, co-occurrence rates of epileptic seizures and autism symptoms are found at prevalence rates ranging from 20% (Tuchman and Cuccaro, 2011) to 30% (Parmeggiani et al., 2010; Tuchman et al., 2010).

ASD constitutes a heterogeneous developmental syndrome that is usually characterized by a triad of impairments that affect social interaction, communication skills, and a restricted range of interests and activities (Harstad et al., 2015; Volkmar and McPartland, 2014). Behavioral signs of ASD tend to become observable after 18 to 24 months, in some cases marked by significant regression after typical development. ASD is not a single disorder, but rather a spectrum of various subtypes with different (largely unknown) causes and developmental trajectories, including several common comorbid conditions such as epilepsy. The most recent figures indicate 1 in 68 children now born the US will develop an ASD diagnosis (Baio, 2014). Evidence suggests a similar prevalence of ASD and related disorders throughout the world, although the lack of

evidence from the majority of the world's population suggests a critical need for further research and capacity building in low- and middle-income countries (Elsabbagh et al., 2012a).

Epilepsy is also a heterogeneous disease classification that is characterized by an enduring predisposition to generate epileptic seizures, evidenced by at least two unprovoked seizures occurring at least 24 hours apart, and by the neurobiological, cognitive, psychological, and social consequences of this condition (Fisher et al., 2014). Epilepsy in the US occurs in approximately 0.6% in children and 1% in adults for all epilepsies (Kobau et al., 2012). Childhood absence epilepsy is a subtype of generalized idiopathic epilepsy. The hallmark of an absence seizure is an abrupt loss of consciousness, usually without motor impairment that may last a few seconds to half a minute (Glauser et al., 2010). Both epileptiform discharges and seizures are a manifestation of absence epilepsy.

A link between epileptiform discharges and developmental disorders, particularly language disorders, has been found even when 'subclinical' discharges without epilepsy are found (Deonna and Roulet, 2006). Even in the absence of epilepsy, reports of epileptiform activity in electroencephalograms (EEGs) in up to 60% of children with autism have been reported (Spence and Schneider, 2009). The incidence of epileptiform abnormalities was positively correlated with the severity of autistic symptoms may be associated with higher likelihood of epileptiform abnormalities (Mulligan and Trauner, 2013).

Complex spectrum disorders such as autism and epilepsy are associated with atypical neural connectivity on many scales (Noonan et al., 2009). Evidence for disrupted cortical connectivity in autism continues to accumulate (Kana et al., 2011), with excessive local connectivity within neural assemblies and deficits in long-range connectivity between functional brain regions. This model is thought to be consistent with observed impairments in autism, such as reduced motor coordination and visuo-perceptual abnormalities (Belmonte et al., 2004a). Similarly, atypical neural network dynamics is likely to be fundamental to the etiology of epilepsy (Kramer and Cash, 2012). Patients with mesial temporal lobe epilepsy (mTLE), for example, were found to have altered brain network properties, along with smaller degree of connectivity. The authors suggest that the observed alterations “may be used to define tentative disease markers” (Liao et al., 2010).

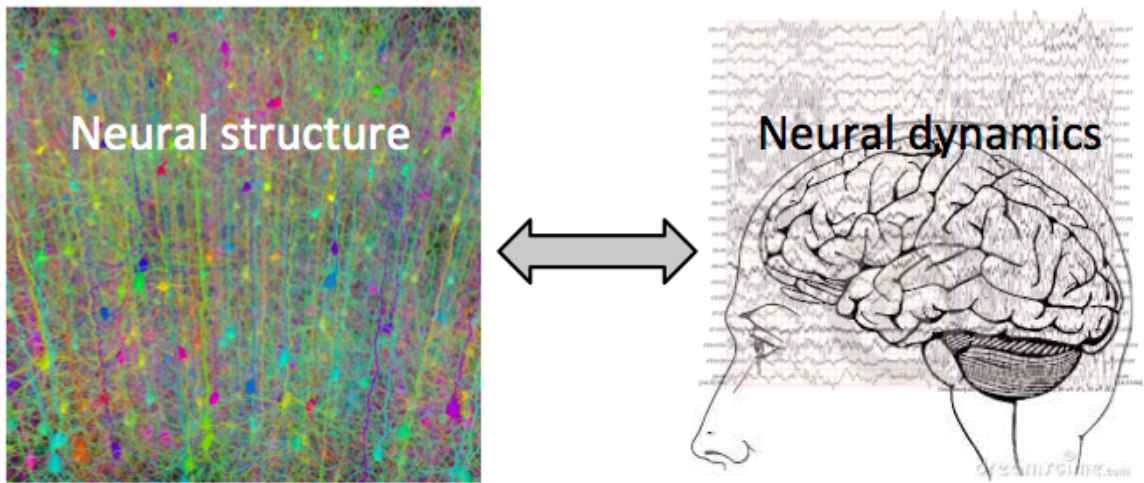
Increasingly detailed neural imaging studies reveal that abnormal neural connectivity is implicated in many mental and neurological disorders (Takahashi, 2013). In particular, autism spectrum disorders (ASD, or simply ‘autism’) and the epilepsies (or ‘epilepsy’) have both been described as neural connectivity disorders (autism: (Assaf et al., 2010; Belmonte et al., 2004a; Minshew and Keller, 2010; Sato et al., 2015); epilepsy: (Coben and Mohammad-Rezazadeh, 2015; Douw et al., 2010; Englot et al., 2015; Gong et al., 2014; Liao et al., 2010)). By this it is meant that the behavioral characteristics that define autism and the unprovoked seizures of epilepsy are caused by characteristic differences in neural structure from typical neural network topology.

Autism and epilepsy have also been described as dynamical disorders. Epilepsy has been described as a dynamical disease (Lopes da Silva et al., 2003; Milton, 2010; Osorio et al., 2010). Using dynamical models of neural networks, computational modelers attempt to understand the relationship between the structure of the nervous system and the dynamic abnormalities generated by epileptic neural populations (Milton, 2010). Similarly, autism has been analyzed from the perspective of complex dynamical systems (Bosl et al., 2011; Catarino et al., 2011; Megremi, 2014; Perez Velazquez and Galan, 2013; Sato et al., 2015).

The two concepts, neural connectivity and neural dynamics, are related. The neural networks that make up the brain appear to exhibit a very peculiar kind of structure or topology, a hierarchical, fractal network connectivity pattern. This complex network forms the structural substrate for distributed interactions among specialized brain systems (Hagmann et al., 2008). Studies of complex networks reveal that they can exhibit a kind of “spatial chaos” in which network properties can change drastically with small changes to key network connections, analogous to the sensitive dependence of chaotic time series on initial conditions (Motter and Albert, 2012). The clinical implication is that computing dynamical features of the brain from EEG time series may be used to infer atypical neural connectivity that is associated with either epilepsy or autism.

The remarkable realization that is emerging is that features of brain electrical signals that can be computed from scalp EEG measurements contain information about the underlying neural network topology (Donges et al., 2012; Gao et al., 2009; Gao and

Jin, 2009; Li et al., 2008a; Zanin et al., 2012). Although neural network topology cannot be measured directly, the electrical time series produced by networks of neurons and measured by EEG sensors exhibit complex dynamics, contains information about the network (Donges et al., 2012; Marwan et al., 2002; Mocenni et al., 2010; Schinkel et al., 2009). Periodic series and noisy series have been found to convert into regular and random networks, respectively, while chaotic time series produce networks with hierarchical, fractal or scale-free structures (Gao and Jin, 2009). Furthermore, different aspects of the dynamics of a time series are associated with topological indices of the network. Quantitative features derived from EEG time series can be used to distinguish different dynamical regimes (Gao and Jin, 2009). The implications for neural connectivity disorders such as autism and epilepsy are that EEG analysis can reveal neural network pathologies that are related to functional and behavioral symptoms associated with the disorders. We explore this possibility in this paper. We hypothesize that aberrations in neural network topology are fundamental causes of autism and epilepsy, and any commonalities in network topology will be reflected in common nonlinear EEG features.



**Figure 13. Neural dynamics produces scalp electrical fields that contain information about the neural structure that produces the electrical fields. Left image: Simulated pyramidal neural network, from (Cuntz et al., 2010).**

Since both ASD and epilepsy fundamentally involve neural connectivity abnormalities, similar topological abnormalities may be a common source of symptoms of both disorders. The electrical signals produced by neural networks are believed to contain information about network structure (Raghavendra et al., 2009; Stam, 2005; Zavaglia et al., 2008) that can be analyzed using novel analysis methods from nonlinear systems theory, including chaotic signal processing (Fuchs et al., 2007; Janjarsjitt et al., 2008). Thus a comparison of EEG features that carry information about network dynamics may reveal fundamental similarities or differences between autistic and epileptic brain function.

This paper presents two primary results, both resulting from a relatively new nonlinear signal analysis method called recurrence quantitative analysis (RQA). First, we demonstrate that RQA analysis of 30-second EEG segments can be used to distinguish children with absence epilepsy or ASD from typical controls and from each other.

Secondly, the comparison of similarities and differences in the analysis of the ASD and absence patients suggests similarities and differences in the neural structures that underlie each disorder. These results suggest a potential use for EEG in clinical settings as an early screening tool and method for monitoring therapeutic progress.

## **Methods**

### *Participants*

**Study setting:** This study was performed in two different settings within Boston Children's Hospital. Epilepsy patients and a contrast group were seen in a tertiary reference epilepsy unit at the Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital. Autism patients were recruited for a research study in the Developmental Medicine department at Boston Children's Hospital.

**Study design:** We performed a quantitative retrospective study to evaluate the use of multiscale nonlinear features derived from RQA analysis of EEG segments as biomarkers for absence epilepsy and autism spectrum disorders.

**Ethical approval:** The Institutional Review Board at Boston Children's Hospital granted approval for this study. Given its retrospective nature, the need to obtain individual informed consents was waived.

Patients: Subjects for this study were drawn from two different settings: the BCH Epilepsy Center and the Laboratories for Cognitive Neuroscience (LCN) under the direction of Charles A. Nelson in the Developmental Medicine Division at BCH.

The main demographic features of all subjects are summarized in Table 4. Twenty-four absence cases and 18 ASD cases are included, along with 49 controls from both labs: 24 from the BCH Epilepsy Clinic and 23 controls from the Laboratories of Cognitive Neuroscience.

Parameter	BCH Epilepsy Clinic		Lab Cog Neuro (LCN)	
	Absence N=26	Control 1 N=24	ASD N=18	Control 2 N=23
Mean age in years (std dev)	8.6 (1.7)	7.74 (4.3)	8.8 (1.9)	8.6 (1.4)
Gender (male/female)	13/13	9/15	16/2	21/2

**Table 4. Numbers and demographic features of the study population.**

*BCH Epilepsy clinic:* A database of patients undergoing routine electroencephalograms (EEG) performed at the BCH Epilepsy center was reviewed retrospectively and two populations of subjects were identified: patients with typical absence seizures (abs) and patients that underwent an EEG for different reasons but were eventually determined to not have epilepsy (contrast group). All subjects selected from the Epilepsy Center met the following inclusion criteria: 1) normal neuropsychological development, and 2) no other EEG abnormalities than those consistent with generalized absence epilepsy. Diagnosis was confirmed by documented seizures on EEG, and the diagnosis of typical absence

seizures was confirmed after careful evaluation of the clinical and EEG features by at least one board-certified clinical neurophysiologist.

The epilepsy contrast group met the following criteria: 1) at least one EEG study because of the clinical suspicion of seizures, 2) normal routine EEG study after visual inspection, 3) very low-risk of a diagnosis of epilepsy after a thorough electro-clinical evaluation. Causes for performing an EEG study in controls included daydreaming, syncope, night terrors or sleepwalking.

EEG segments of 30 seconds duration each were selected from EEG sample files. EEG data was sampled at 200 Hz for all Epilepsy Center subjects. From the absence cases, an experienced neurologist used visual review to select 30-second samples containing no spikes or evidence of epileptiform activity. Similarly, 30-second segments were selected from the contrast group after visual review. All EEG samples collected in the Epilepsy Center were from awake subjects that were normal on visual analysis. For all subjects, segments of equal length were collected on 19 channels located according to the standard 10-20 system, as shown in Figure 14.

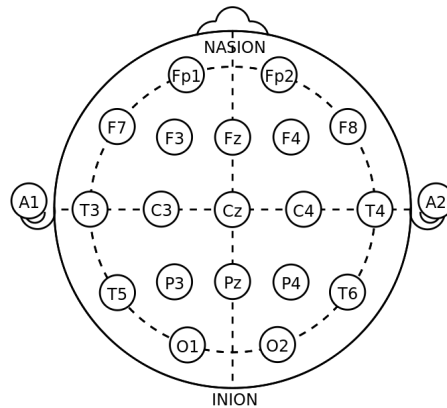
*LCN Autism Study Subjects:* The autism study group of participants included 18 children with an autism spectrum disorder (ASD) (mean age = 9.0 years; SD = 1.7; 16 males, 2 females) and 23 typically developing children (mean age = 8.6 years; SD = 1.4; 12 males, 11 females). Participants were recruited from a list of families who had expressed interest in research participation. ASD diagnosis was confirmed by clinical diagnosis as reported by the parent and/or by meeting criteria on the Autism Diagnostic Observation Schedule

(ADOS) in a research setting conducted within the past year. Written informed assent was obtained from each participant and one of their parents, and verbal assent was confirmed from each participant prior to the experiment.

All LCN electrophysiological recording was completed in an electrically and sound-shielded testing room with low lighting. Children were seated on a chair approximately 60 centimeters in front of the experimental monitor. Continuous baseline EEG was recorded before children were presented with images or other stimuli. Only baseline data was used in this study.

#### *Data Analysis, Feature Selection and Classification*

Continuous EEG was recorded using a high density 128-channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR) and referenced to vertex (Cz). The electrical signal was amplified with a 0.1 to 100 Hz band-pass, digitized at 500Hz, and stored on a computer disk. The data were analyzed offline by using NetStation 4.4.1 analysis software (Electrical Geodesics Inc., Eugene OR). EEG data were digitally filtered using a 30hz low-pass elliptical filter. After using an artifact detection tool standard to the NetStation software package to exclude segments with eye saccades and blinks, the remaining segments were visually scanned by an experimenter blind to study group. For comparison to the subjects examined in the BCH Epilepsy Center, only 19 channels were selected from the sensor net, corresponding to the positions shown in figure 4.1.



**Figure 14. The standard 10-20 montage (Jasper, 1958). The 19 scalp locations shown here were used for all subjects in the Epilepsy Center. In LCN, these channels were selected from a larger montage of 128 sensors.**

EEG signal analysis: Each of the EEG samples was processed in an identical manner by the following steps. Thirty-second segments were selected from EEG data for each subject. Average referencing was computed and used for all EEG time series.

Recurrence quantitative analysis (RQA) values were computed for all of the scales derived from each EEG channel. Software for computing recurrence plot statistics is publicly available from a web site (Marwan, 2012). Seven of the most commonly used recurrence plot values used in the analysis (RR, DET, LAM, L\_max, L\_mean, L\_entr and TT) are discussed below. Multiscale sample entropy was also computed and included in this set of EEG signal features and is denoted by SampE. The methods used for computing multiscale sample entropy are discussed in a previous paper (Bosl et al., 2011). Thus, eight features or values were computed for each EEG sensor time series.

A more complete discussion of RQA analysis may be found in the literature (Marwan et al., 2007b; Webber and Zbilut, 2005). Multiscale time series were derived

from the original EEG signals using the multiscaling procedure described in (Costa et al., 2005). RQA values were computed on all scales 1 to 32 for each subject at each EEG electrode. Examples of multiscale curves are shown in Figure 15. As a simple way to characterize the multiscale curve, the mean value of the multiscale curve was computed. Thus, the set of features computed for each subject consists of 8 values at each of 19 channels or 152 features.

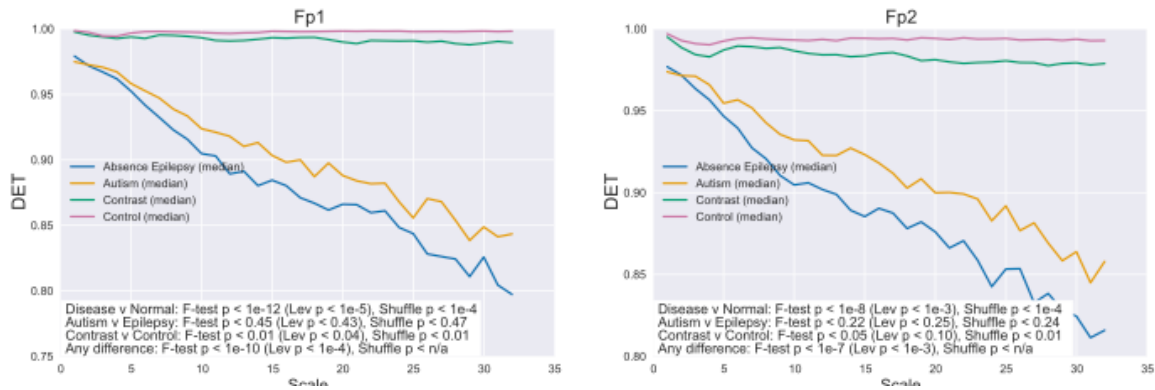
Feature selection and classification was performed using a recursive feature elimination algorithm that uses a support vector machine (SVM) method as described in (Guyon et al., 2002). The algorithm used is `rfe` in the Python open source machine learning package `scikit-learn` ([www.scikit-learn.org](http://www.scikit-learn.org)). The initial feature set includes the mean value of the multiscale curves from all channels and all RQA values, as shown in the graphs in Figures 16-23.

## Results

### *Multiscale RQA Plots*

Multiscale RQA plots were computed for each of the 19 sensor locations in the standard 10-20 configuration shown in Figure 14. The multiscale time series were derived from the original EEG segments using the averaging method described in (Costa et al., 2005b). We note as before that for scales that are powers of 2 (1, 2, 4, 8, 16 and 32) the averaging scheme presented is identical to the Haar wavelet transform. Multiscale curves were computed for the following RQA values: RR, DET, LAM, L<sub>entr</sub>, L<sub>mean</sub>,

L\_max and TT. In addition, the modified multiscale sample entropy (SampE) used in (Bosl et al., 2011) was also computed. Collectively, these are referred to as ‘signal features’ or simply features hereafter. Examples of the multiscale curves at Fp1 and Fp2 for the DET measure are shown in Figure 15. Multiscale curves for all of the signal features at a selection of the 19 sensor locations are shown at the end of this chapter. We note that the two control groups are visually quite similar for every location and feature, while curves for the absence and ASD are distinctly different in many of the sensor locations and signal features.



**Figure 15.** Multiscale curves are shown for L\_max values at Fp1 and Fp2. P-values for the significance of group differences are derived from the median value over all scales.

### *Multiscale feature comparisons*

Each multiscale curve can easily be viewed as a single object. Although methods for comparing curves based on mean value, slope and various shape parameters is possible, we chose in this study to use the mean value of the multiscale curve to represent the entire curve for simple comparisons between curves. Using the mean values only

resulted in many group differences that met the strict Bonferroni-corrected criterion of  $p < 10^{-4}$ , derived by dividing the commonly used significance cutoff of 0.05 by  $19 \times 8$  (19 sensors, 8 features) and rounding down to the nearest power of 10. Significant group differences between absence and control subjects, ASD and controls, and absence versus ASD groups were found.

<b>Classification</b>	<b>Most significant sensors</b> (Strict Bonferroni corrected significance level of $10^{-4}$ used)	<b>Most significant features</b>
<b>Absence vs. controls</b>	All except F7, C3, Cz, T8	RR, DET, LAM, L_max, SampE
<b>ASD vs. controls</b>	Fp1, Fp2, T7, P8, O1, O2	RR, DET, LAM, L_max, L_ent, SampE
<b>Absence vs. ASD</b>	Fz, Cz, Pz, C3, C4, P3, P4, O1	L_max
<b>Control 1 vs. Control 2</b>	No significant differences	No significant differences

**Table 5.** The significance of group differences was computed using the two-tailed t-test for each sensor location and each signal feature.

An important first result found was that the two control groups were indistinguishable. They did not have any significant differences at any sensor location for any signal feature. Furthermore, it was found in classification calculations, discussed further below, that classification methods could not distinguish between control groups. When the absence and ASD groups were compared to each control group separately, the results were the same: either absence or ASD groups could be classified with high accuracy when compared to either control group. For this reason, the control groups were combined for all other group comparisons.

*Absence versus controls*

		RR	DET	LAM	L_max	L_mean	L_entr	TT	SampE
Frontal	Fp1	-12	-10	-8	-27		-14		-18
	Fp2	-9	-8	-6	-17		-12		-11
	F7								-4
	F3				-7				-4
	F4				-9				
	F8	-8	-7	-6	-9		-10		-11
Central	Fz				-5		-6		-15
	Cz								-6
	Pz				-5		-5		-10
	C3								
	C4								
Temporal	T7	-5	-7	-7	-18		-10		-16
	T8								
Parietal	P7				-7		-6		-10
	P3				-7				-5
	P4								
	P8		-5	-5	-11		-9		-15
Occipital	O1	-5	-7	-6	-13		-11		
	O2	-5	-8	-7	-15		-11		

Table 6. Log base 10 P-values for absence epilepsy versus controls. Numbers in the table are exponents of 10. Thus, -12 indicates  $p < 10^{-12}$ . Only entries that are less than  $10^{-4}$  are filled, illustrating where the most significant group differences are found. Yellow highlights are sensor locations that have significant differences from controls for 4 or more features.

The absence group differed significantly from the control at most sensor locations across the scalp for one or more signal features when comparing the mean value of the curve across all scales. We note again that the EEG segments were from inter-ictal cases and did not exhibit epileptiform activity. L\_max and SampE were the most significantly different, as shown in Table 6. Of the eight features, only two (L\_mean and TT) did not meet the significance criterion of  $p < 10^{-4}$  at any location for any feature using mean values. We note that if slope is considered, then group mean slopes for some sensor locations for L\_mean and TT are significantly different.

Differences in signal features between absence and control subjects are distributed

across the scalp, with L\_max and SampE differing most consistently. Of note, the greatest differences between absence and control groups were found in the orbitofrontal (Fp1, Fp2), right dorsolateral (F8), occipital (O1, O2) and left temporal (T7) regions.

#### *ASD versus controls*

The ASD group also differed significantly from the control groups. Similar signal features were significant as to the absence-control comparison, but scalp locations were not as widely distributed. Table 7 reveals that the most significant differences were at scalp locations in the orbitofrontal (Fp1, Fp2), left temporal (T7) and occipital (O1, O2) regions.

		RR	DET	LAM	L_max	L_mean	L_ent	TT	SampE
Frontal	Fp1	-13	-13	-13	-21		-12		-17
	Fp2	-11	-8	-6	-13		-9		-9
	F7								
	F3								
	F4								
	F8	-6	-5	-4			-7		-6
Central	Fz								-7
	Cz								
	Pz								
	C3								
	C4								
Temporal	T7	-6	-9	-6	-11		-8		-12
	T8								
Parietal	P7								
	P3								
	P4								
	P8				-5		-5		-7
Occipital	O1	-5	-6	-6			-6		-10
	O2	-4	-8	-8	-6		-6		-12

Table 7. Log base 10 P-values for ASD versus controls. Numbers in the table are exponents of 10. Thus, -12 indicates  $p < 10^{-12}$ . Only entries that are less than  $10^{-4}$  are filled, illustrating where the most significant group differences are found. ASD subjects differ from controls particularly in orbitofrontal (Fp1, Fp2), left temporal (T7) and occipital (O1, O2) regions.

### *Absence versus ASD*

Although the absence and ASD groups differed from controls in similar locations, when compared to each other the only significant group differences were found in the L\_max features in central locations. Table 8 illustrates this.

		RR	DET	LAM	L_max	L_mean	L_ent	TT	SampE
<b>Frontal</b>	<b>Fp1</b>								
	<b>Fp2</b>								
	<b>F7</b>								
	<b>F3</b>								
	<b>F4</b>								
	<b>F8</b>								
<b>Central</b>	<b>Fz</b>				-5				
	<b>Cz</b>				-5				
	<b>Pz</b>				-5				
	<b>C3</b>				-4				
	<b>C4</b>				-5				
<b>Temporal</b>	<b>T7</b>								
	<b>T8</b>								
<b>Parietal</b>	<b>P7</b>								
	<b>P3</b>				-5				
	<b>P4</b>				-5				
	<b>P8</b>								
<b>Occipital</b>	<b>O1</b>				-5				
	<b>O2</b>								

**Table 8. Log base 10 P-values for absence versus ASD subjects. Numbers in the table are exponents of 10, as in previous tables.**

The absence and ASD groups differed from each other primarily in central regions. One interpretation of this is that absence features differ from controls in most scalp regions whereas ASD atypicalities are focused in orbitofrontal, left temporal and occipital regions.

For all group comparisons, and for the feature ranking calculations discussed below, L\_max is the most useful feature for differentiating the absence, ASD and control groups. Thus, group mean multiscale values for L\_max are shown in Table 9 for each

sensor location and each group. The red values are those that are significantly different from the control values. The yellow highlighted values are those that differ significantly

Region	Sensor location	L_max p-value for abs-ASD difference	L_max value		
			Abs	ASD	Con
Frontal	Fp1		234	278	715
	Fp2		227	274	648
	F7		285	419	409
	F3		431	576	642
	F4		402	577	636
	F8		288	433	574
Central	Fz	$10^{-5}$	521	693	687
	Cz	$10^{-5}$	520	672	632
	Pz	$10^{-5}$	458	613	643
	C3	$10^{-4}$	491	652	577
	C4	$10^{-5}$	460	645	609
Temporal	T7		309	458	716
	T8		297	420	406
Parietal	P7		356	495	610
	P3	$10^{-5}$	438	611	635
	P4	$10^{-5}$	431	605	466
	P8		364	463	661
Occipital	O1	$10^{-5}$	324	495	633
	O2		327	479	658

**Table 9.** This table highlights where the most significant group differences are found between absence, ASD and control groups. Yellow shading indicates locations where absence and ASD groups differ significantly. Red numbers differ significantly from controls.

between absence and ASD groups. L\_max is lowest in the absence group at every location. L\_max values for the ASD group are intermediate between absence and controls at most locations, though higher than the controls at F7, Fz, Cz, C3, C4, T8, and P4. With the exception of T8, these are also the locations where absence and ASD groups differ most significantly.

In summary, the above results reveal three important results:

- (1) The two control groups are indistinguishable on the basis of the signal features discussed in this paper, even though they were measured in different settings using different EEG equipment.
- (2) The absence and ASD groups each differ significantly from the control groups in many sensor locations and for 5 of the 8 signal features.
- (3) Absence and ASD groups differ significantly from each other primarily in centrally located regions on the L\_max feature.

#### *Machine learning classification*

The real value of the signal features derived and discussed above is revealed if they can be used as features for machine learning classification algorithms. A recursive feature elimination algorithm was used to rank the features and a standard Support Vector Machine (SVM) classifier was then used to classify each of the groups when compared to controls, as well as to compare the control groups to each other. A 10-fold cross validation procedure was used. The feature elimination and SVM algorithms used are the rfevcv method in the python scikit-learn package (<http://scikit-learn.org>). Table 10 shows results for the classification calculations.

Classification	Classification			Empirical p-value	Highest ranked features
	Accuracy	Sensitivity	Specificity		
Absence versus controls	1.00	1.00	1.00	< 0.01	L_max, TT
ASD versus controls	0.97	1.00	0.94	< 0.01	L_max, TT
Absence versus ASD	0.75	--	--	< 0.01	L_max
Control 1 versus Control 2	No significant differences, groups cannot be classified.				

**Table 10. Classification results for pairs of groups. Empirical p-values are computed using the method of shuffled labels as described in (Golland and Fischl, 2003). One hundred trials were used for empirical p-values.**

The empirical p-values were computed using the method of shuffled labels as described in (Golland and Fischl, 2003). One hundred trials were used for empirical p-values. The mean and standard deviation of accuracy values using shuffled labels were less than 0.01 in all cases. That is, in 100 trials with shuffled labels, the cross validation accuracy never equals or exceeds that obtained when correct labels are used.

Although it would seem that the highest ranked features would be those are statistically the most different in two groups, for classification this may not be the case. The reason is that a variable such as TT, though not statistically different in any pair of groups, may introduce an added, independent dimension to another variable such as L\_max. Together they may distinguish group members more clearly than either alone. The highest ranked features for classification are those that are found to contribute the most information to the classifier.

In summary, the absence and ASD groups can be classified from either or both control groups with nearly perfect accuracy. Although there is some overlap between the absence and ASD groups, the classification accuracy of 75% is significantly better than chance, as demonstrated by the shuffled label test used to compute the empirical p-value.

### **Discussion**

The goal of this study was to determine if the nonlinear dynamical measures computed from short EEG segments using multiscale recurrence plot analysis would reveal similarities in signal features between children with ASD (with no evidence of seizures) and children with absence epilepsy. Further, we tested the hypothesis that RQA analysis would enable classification of children with epilepsy or autism from controls and from each other. A secondary aim was to compare control groups from two different settings using different EEG equipment as a test of the robustness of this approach.

Three general findings resulted. First, we found highly significant differences in the multiscale RQA (mRQA) curves between absence, ASD and control groups. Machine learning classifiers were able to distinguish absence and ASD groups from controls with nearly 100% accuracy. Secondly, the two control groups were indistinguishable using mRQA values. Not only were there no significant control group differences in any of the values or scalp locations, but also machine learning algorithms were unable to distinguish the two control groups using any combination of the mRQA features. This is an important finding, because learning algorithms can find differences that may be due to

factors unrelated to those of interest, such as equipment differences. Finally, the most significant spatial locations that differentiated the absence and ASD groups from controls and from each other may give some insight into the neuronal dynamics that characterize these conditions. We discuss each of these findings in more depth below.

### *Comparison of Control Groups*

Our initial expectation was that the control groups would be significantly different from each other on at least some measures, since we thought that differences in laboratory versus clinical settings and the different EEG equipment would introduce systematic differences in the multiscale RQA values. This was not the case. The two control groups had indistinguishable RQA values at every sensor location and for every dynamical variable. Furthermore, in a 10-fold cross validation scheme, machine learning classifiers were unable to differentiate the two control groups with accuracy better than random chance (50%). This was in stark contrast to the nearly perfect classification accuracy when either absence or ASD groups were classified with either or both control groups.

### *Detection of absence epilepsy and ASD*

Cognitive processes are the result of transient synchronization of local and distributed neuronal assemblies (Rapp et al., 2015). Neuronal oscillations must balance the need for transient synchronization and the pathological, runaway hyper-synchronization that results in an epileptic seizure. The Lyapunov exponent is a measure

of the amount of ‘chaos’ a time series exhibits. The more chaotic a signal is, the higher the Lyapunov exponent is, the more quickly it diverges from an initial trajectory when slightly perturbed. Because of their greater propensity to diverge from an initial starting point, chaotic signals can entrain and synchronize only transiently before diverging from each other. Lower chaos is generally an indication of an unhealthy physiological condition (Costa et al., 2005b).

Absence epilepsy subjects revealed significantly different values at nearly all scalp locations in some of the mRQA values, and particularly  $L_{\max}$ .  $L_{\max}$  is related to the largest Lyapunov exponent of a time series. Smaller  $L_{\max}$  indicates less chaotic signals that may synchronize for longer periods, increasing the probability of hypersynchronization over larger neuronal assemblies. Thus, lower  $L_{\max}$  is consistent with the absence epilepsy group.

As shown in Table 9, the absence group has lower  $L_{\max}$  values than the controls at every sensor location. The ASD group is mixed: at some locations it has a higher  $L_{\max}$  value than controls, though all but one are statistically insignificant group differences. At several key locations (Fp1, Fp2, T7, P8, O1, O2) the  $L_{\max}$  values of the ASD group are significantly lower than controls.

Note that, consistent with larger  $L_{\max}$  values, the absence subjects have much larger average trapping time (TT) values, though the variability of TT values is greater, hence group differences are less significant. Larger TT values indicate that the time series remain in a similar state for longer periods (the time they are ‘trapped’ in a state is

longer), which is consistent with lower chaotic activity. This might be interpreted as creating a greater probability of massive entrainment and hypersynchronization.

For DET and LAM features, visual inspection of Figures 17 and 18 reveals that the slope over all scales seems to be significantly different between controls and cases, whether absence or ASD. Similarly for other features, shape appears visually to be important for differentiating groups, beyond the mean value of the curves. The shape of the multiscale curves is an indication of differences in signal activity over many scales (or frequencies), which may reflect functional differences in local and distributed neuronal assemblies in the absence, ASD and control groups.

#### *Scalp Location of Most Significant Features*

The ASD group differed significantly from controls for most features at Fp1, Fp2, T7, P8, O1, O2, as noted previously. At these locations, the L\_max values for ASD were midway between the absence and control values, as for many other features (see Figures 16-23). This finding suggests that a common pathology may be involved that results in lesser or different symptom manifestations in ASD when compared to absence epilepsy cases.

Interestingly the ASD and absence groups differed from each other in centrottemporal sensor locations only. At most locations where significant differences were noted between ASD and controls, the ASD values were midway between the absence and control values. A seizure represents a brain state that has a high degree of

periodicity and loss of complexity. Since seizures may involve a synchronization process that entrains multiple frequency bands leading to large amplitude, highly periodic and low complexity activity, we speculate that the propensity to have seizures is represented by multiresolution dynamics. In biological systems, a lower level of chaotic dynamics is often associated with pathological conditions (Catarino et al., 2011; Costa et al., 2005a; Goldberger, 1997; Takahashi et al., 2010; Zhang et al., 2009). Although the complete neurophysiological implications of recurrence plot analysis for physiological signals have not been extensively explored in the literature, some general meaning can be derived.

Occipital spikes may be common in children with neurodevelopmental disorders, particularly as age-dependent benign epilepsies. They appear to be more common in children with autism or autistic regression and possible seizures. The effects of the epileptiform discharge on cognitive functioning may result from extension into temporal and parietal lobes, rather than occipital disturbances per se (Nass et al., 1998). From a physics perspective, spiking activity represents sufficiently long local synchronization to create a visual peak. Increased synchronization may be revealed by lower  $L_{\max}$  values, as discussed previously, even when spikes are not visually present in the EEG record. We note that the occipital regions had consistently lower  $L_{\max}$  values and significant differences from controls in both absence and ASD groups.

### *Feature Selection and Classification*

Classification results shown in Table 10 were derived from 10-fold cross validation calculations. Feature ranking and selection were done using a recursive feature

selection algorithm as implemented in the widely used, open source scikit-learn package (Abraham et al., 2014). Recursive feature selection is used with a Support Vector Machine (SVC) classifier algorithm to recursively remove features that have low scores as SVC support vectors and build a model based on remaining features.

The feature selection method not only enables efficient selection of features for the classification process, but also gives an indication of where the most important group or class differences are found in combinations of data values. In the classification calculations shown in Table 10, two important points stand out. First, both absence and ASD groups can easily be distinguished from the controls with nearly perfect accuracy. The absence and ASD groups cannot be classified quite as well, with an accuracy of 75%, perhaps suggesting a common pathology and fundamental similarities in neural network structures.

### *Confounding Factors and Further Study*

The absence data and controls need to be interpreted in the clinical setting from which data was acquired. Several confounding factors require further study. The control subjects from the BCH Epilepsy Clinic used in this study may have a variety of neurological disturbances that have not fully emerged. They presented in the clinic initially because of some neurological concerns, though none was known to have a diagnosis of epilepsy or autism spectrum disorder. A larger set of subjects, including controls without neurological impairments and children with confirmed ASD or absence epilepsy, will be essential for determining the features that are most useful for detecting

the presence of absence epilepsy, ASD, or other disorders and distinguishing them reliably from normal EEGs or other neurological conditions. Importantly, the controls derived from the Laboratories of Cognitive Neuroscience were carefully screened for any known history of neurological or mental disorders. The statistical equivalence of the two control groups found in our analysis gives greater confidence in the appropriateness of both control groups.

The gender distribution between in the four groups differed. Control group 1 was 38% male, while control group 2 was 91% male. The statistical similarity of these two groups on nearly all measures used suggests that gender was not a significant factor in our analysis. The Absence group was 50% male while the ASD group was 89% male. Because the balance of male/female differed in the two control groups, and the results of our analysis are the same regardless of which control group was used, also suggests that gender was not a significant factor. Nevertheless, further studies of gender differences with larger study groups may be useful for gaining further insights. Early studies of EEG complexity differences in children at risk for developing autism based on family history did suggest gender differences (Bosl et al., 2011).

For this initial study, patients with absence epilepsy were selected because they represent a common diagnosis in the epilepsy population, are relatively easy to characterize clinically and electroencephalographically, and constitute one of the most homogeneous groups of patients with epilepsy. Additionally, there are no clear structural brain abnormalities on structural MRI imaging, and there is no EEG slowing which may

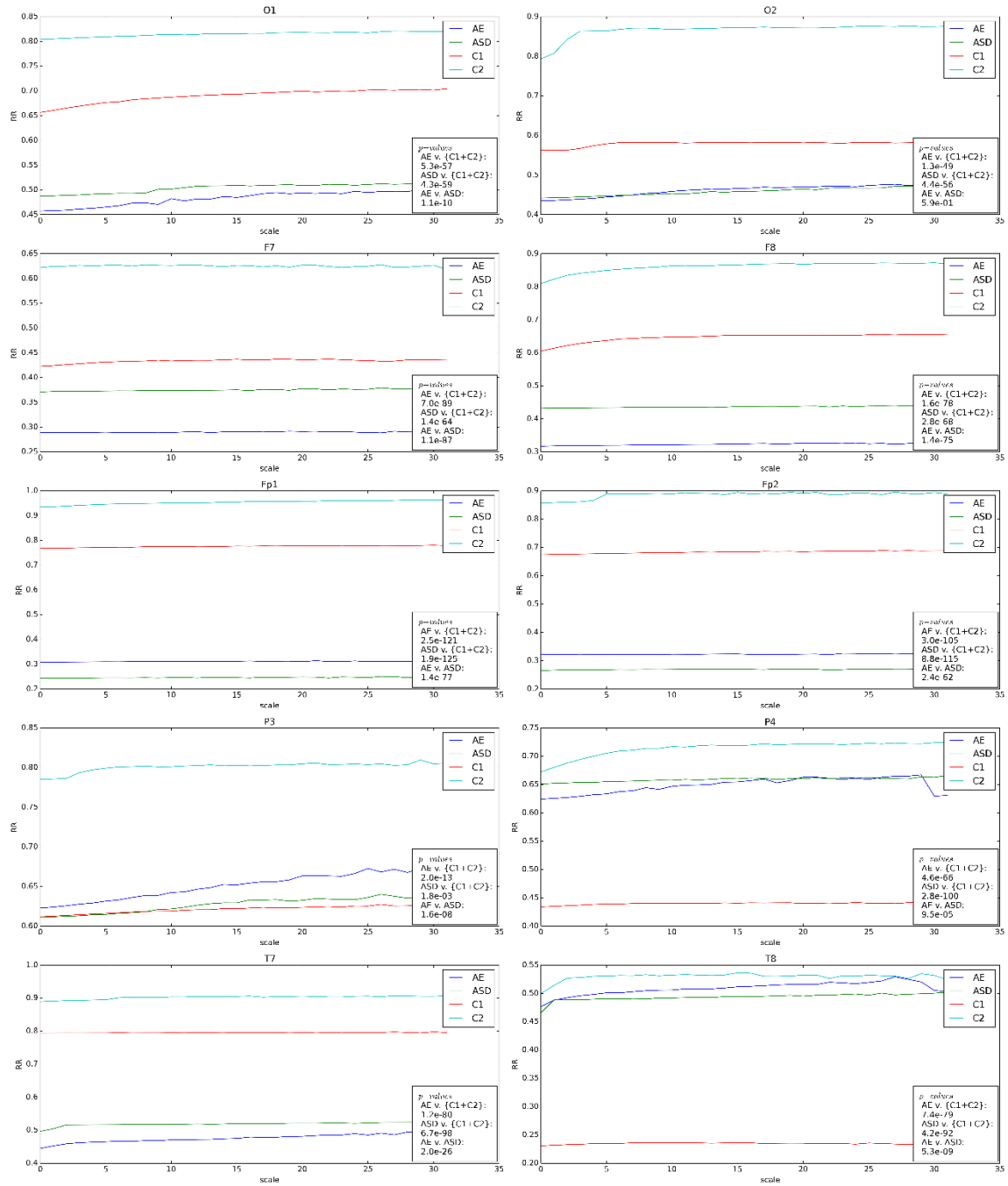
confound results in other epilepsies or seizure types. Whether these findings will be applicable to other patients with different types of epilepsy will require additional data sets with patients who have clearly identified epilepsy syndromes. We hypothesize that if mRQA analysis is detecting the dynamics of an epileptic brain, then different epilepsies will reveal different spatial distributions than those seen for absence patients, and they should distinguish the different epilepsies.

### *Multiscale Decomposition*

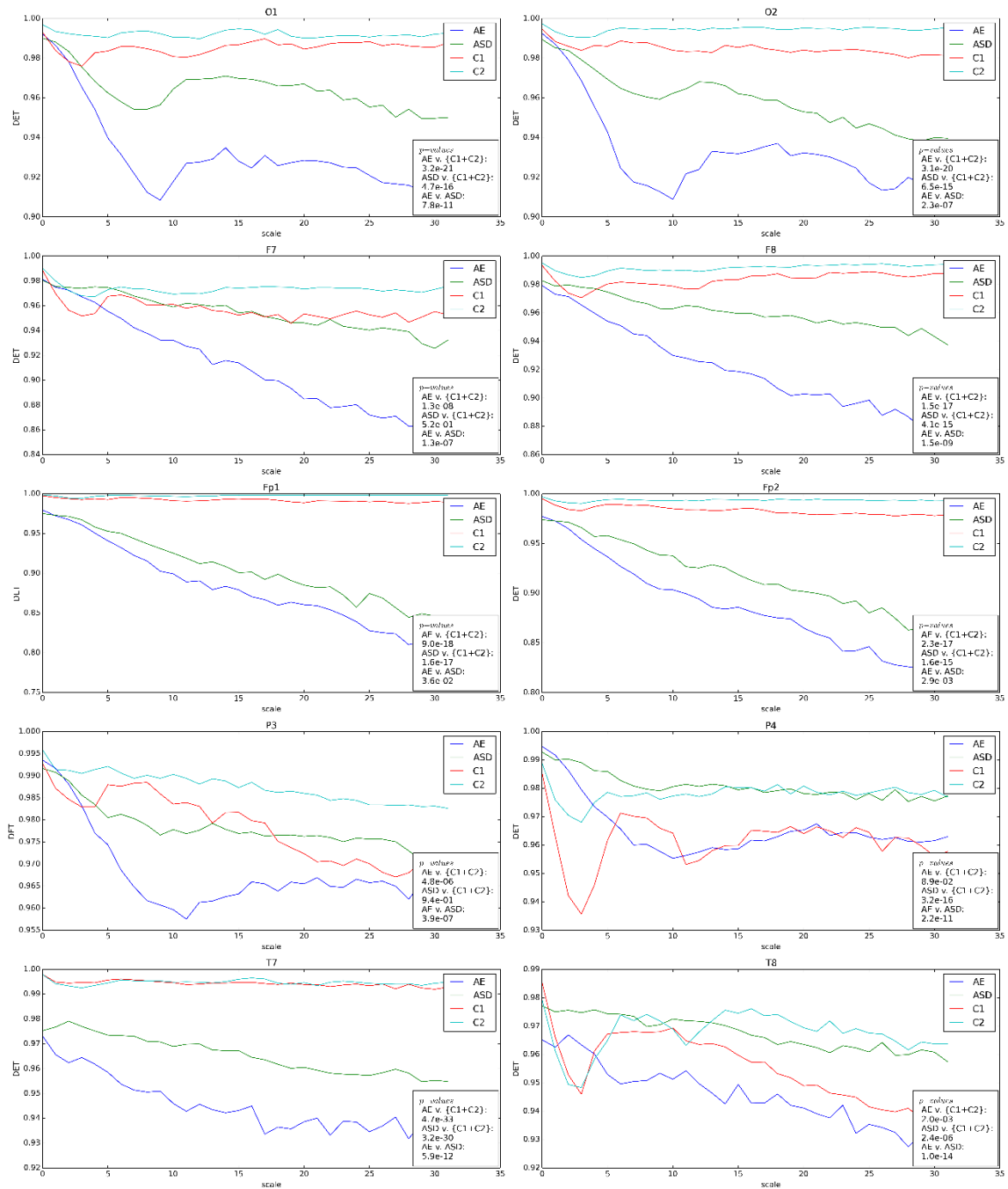
Synchronization of relatively local neuronal assemblies involves high frequency neuronal oscillations that are analogous to the lower scales in a multiscale decomposition. Higher scales are representative of slower frequencies that are involved in distributed cell assemblies that may span the cortex. Accumulating evidence suggests that information and processing is integrated across these multiple spatial and temporal scales, and that a hierarchy of mutually-interacting oscillations would be well-positioned to regulate this multi-scale integration (Rapp et al., 2015). This would suggest that more information from the multiscale curves, such as slope and shape parameters, might differentiate the absence, autism and control groups even more completely than the mean value of the curve over scales alone. Children with tuberous sclerosis complex (TSC) commonly manifest seizures and ASD characteristics. Significant differences in the high-frequency spectral content of EEG have been observed in children with TSC when compared to typically developing children (Stamoulis et al., 2015). This population of children may provide another means for testing the results found in this study.

## Conclusions

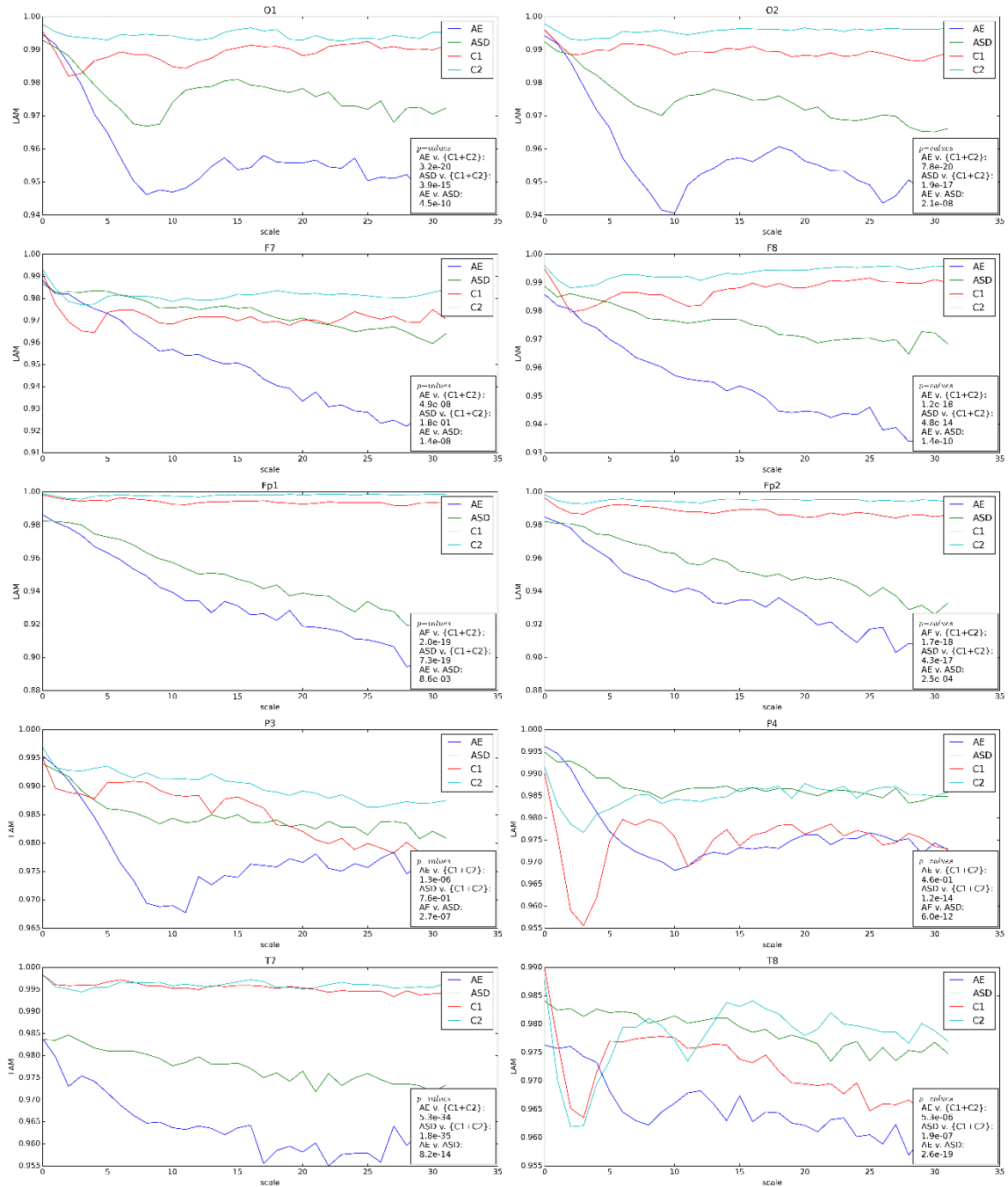
Our results demonstrate that EEG complexity, as measured by RQA analysis, may contain sufficient information to detect epilepsy, autism and possibly a variety of neurodevelopmental disorders (as represented by the control group) and distinguish children with these disorders from typically developing children. The signal feature that is most highly ranked in the epileptogenicity determination,  $L_{max}$ , is related to the Lyapunov exponent, which may be related to how easily neural oscillators can synchronize, which is related to epileptiform or spiking activity and to seizures. The similar scores on the autism group and contrast group, and significantly different from the typically developing group, suggests that this measure is associated with neurological impairment of some form. Our results suggest that the computed RQA values are related to fundamental differences in the EEG neural generators and are independent of the EEG equipment used and the laboratory or clinical conditions under which the data are collected. This has important implications for the clinical use of EEG analysis as a biomarker for neurological impairments.



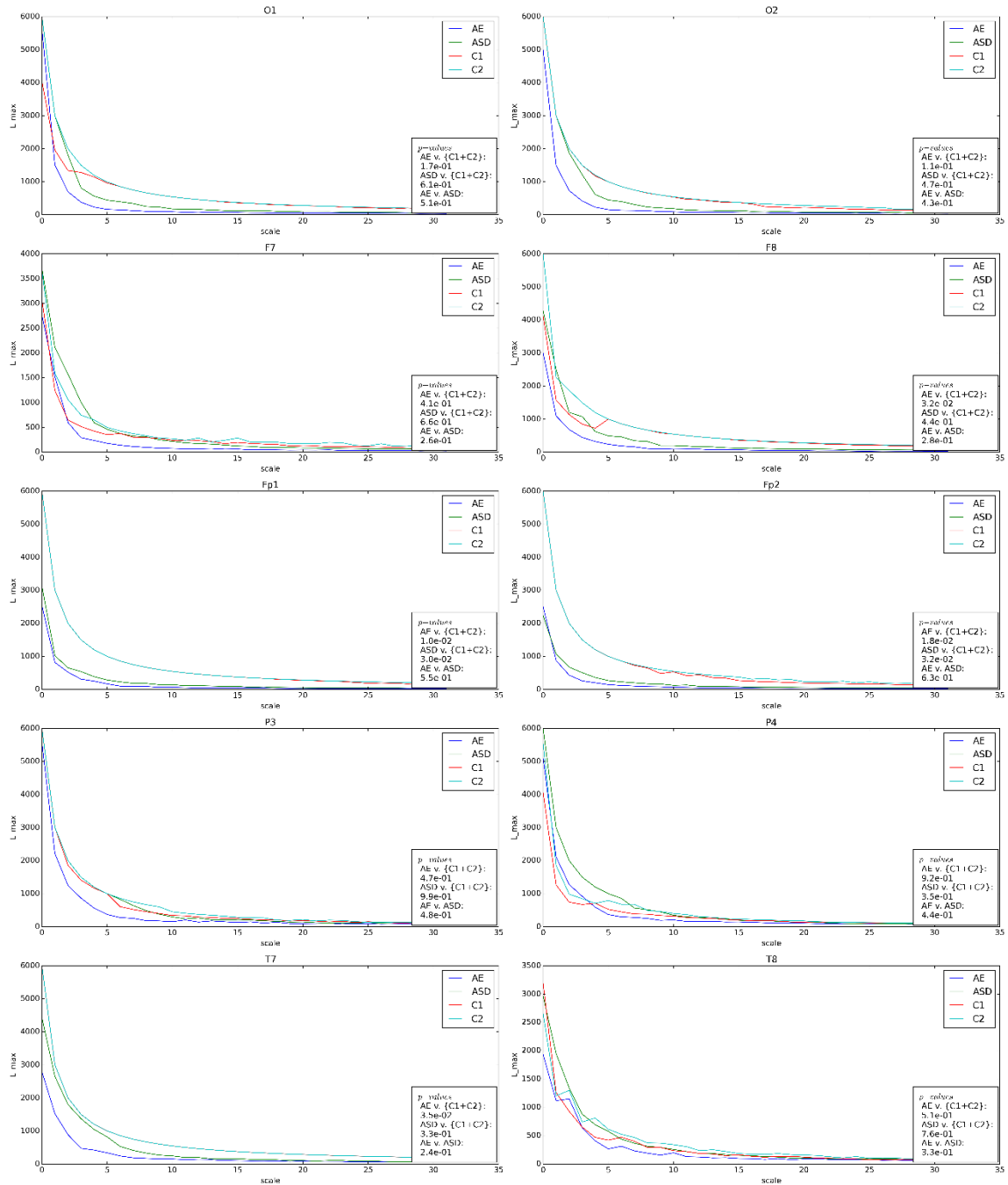
**Figure 16. Recurrence rate (RR) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



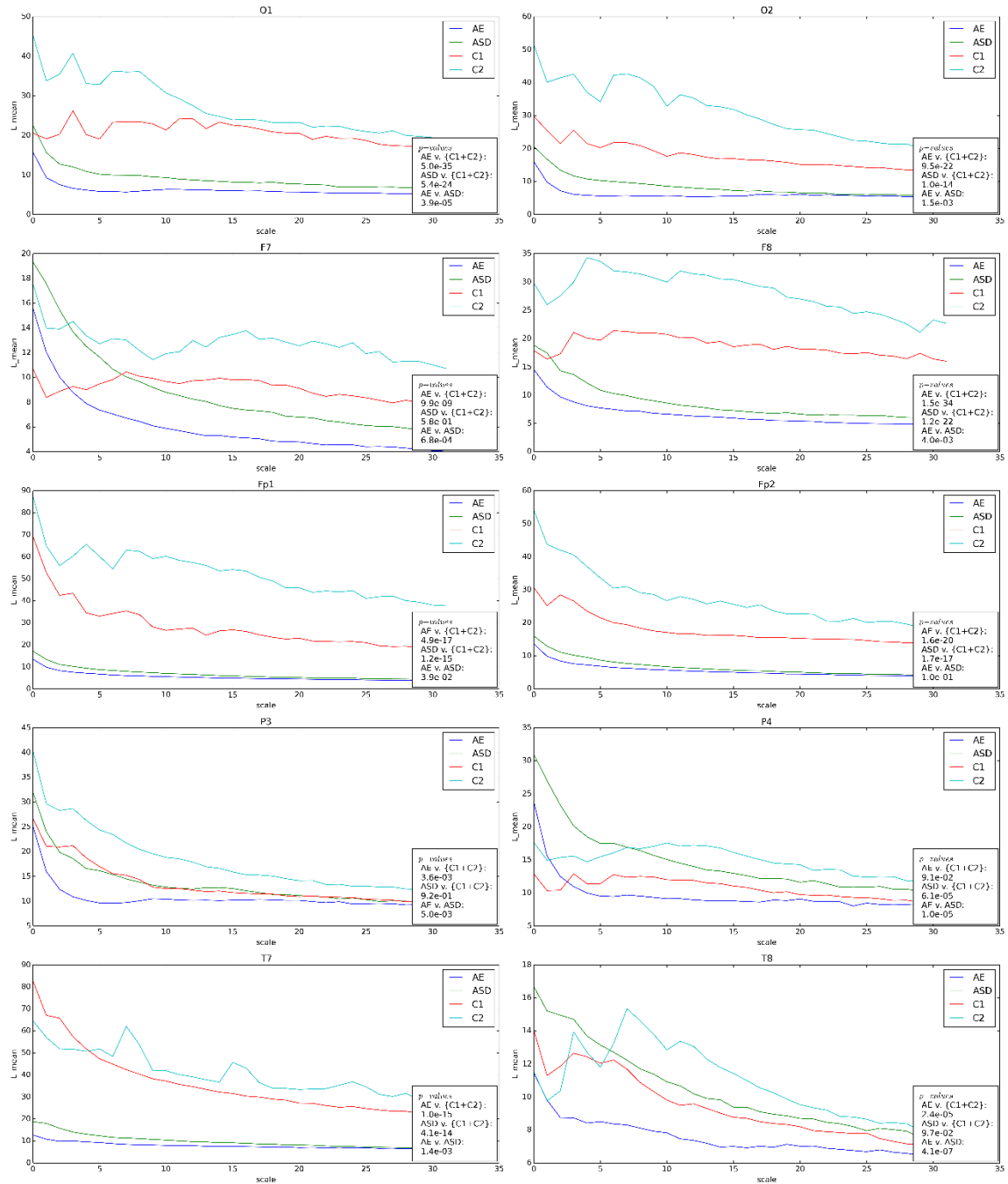
**Figure 17. Determinism (DET) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



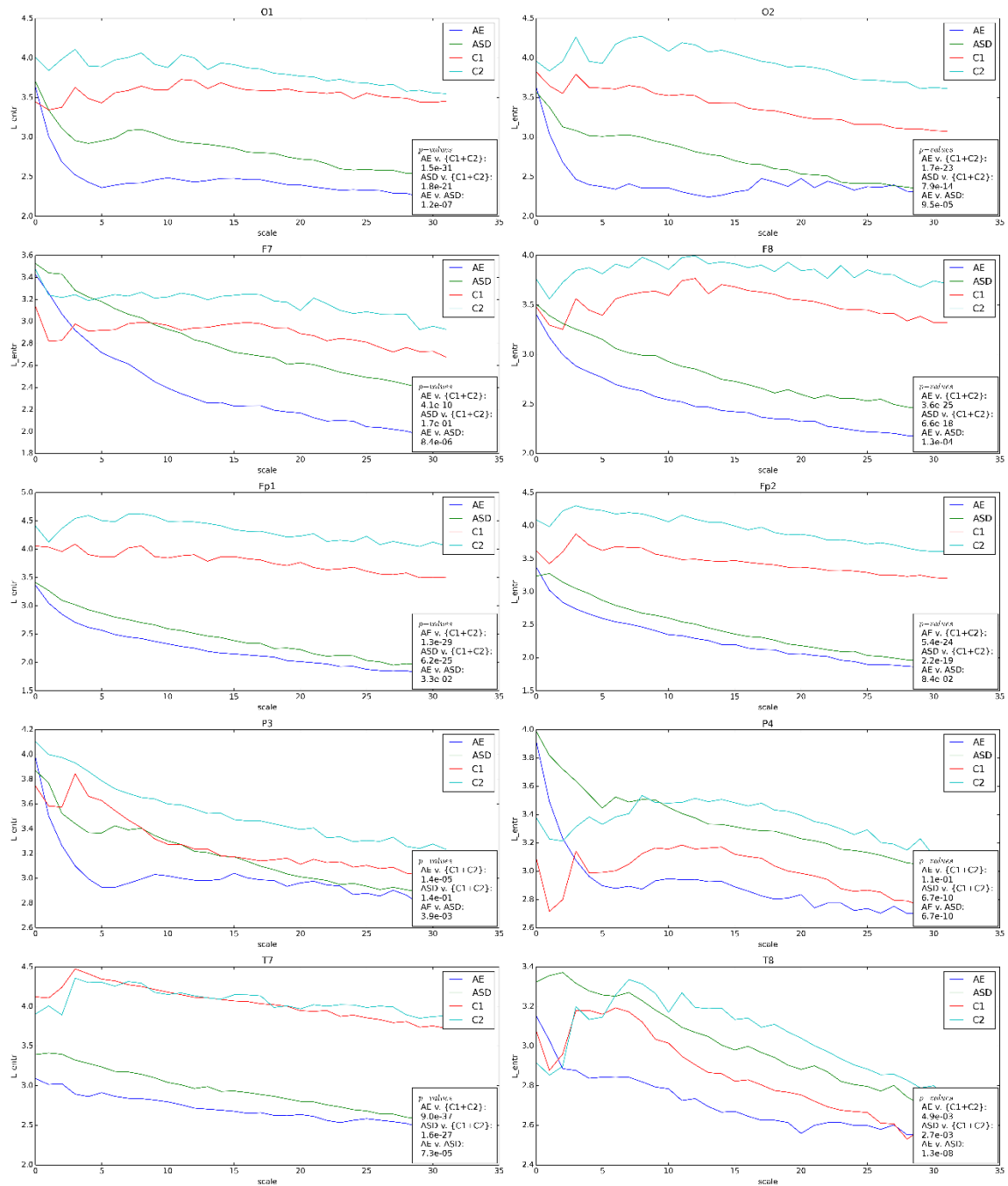
**Figure 18. Laminarity (LAM) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



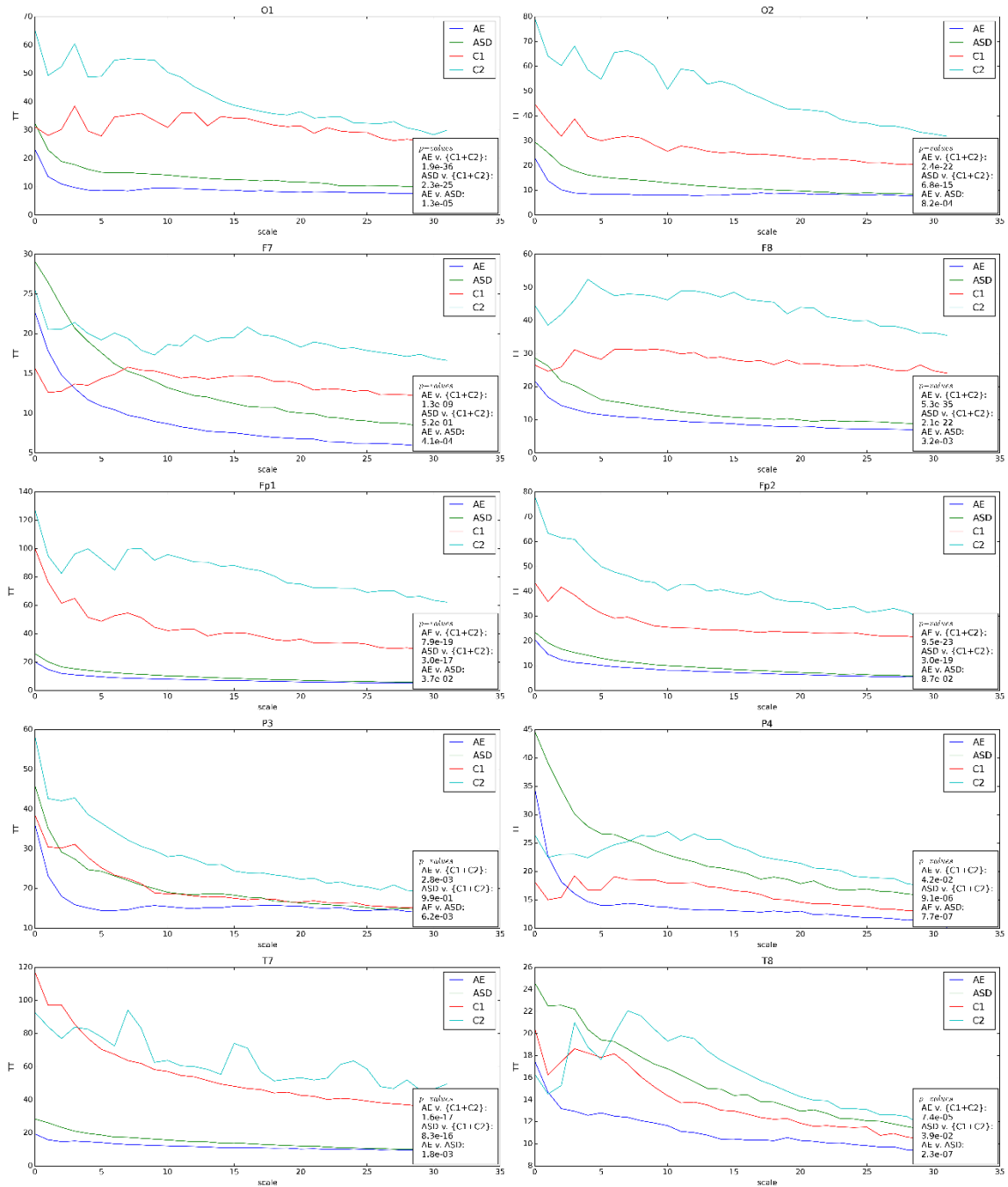
**Figure 19. Maximum (diagonal) line length ( $L_{max}$ ) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



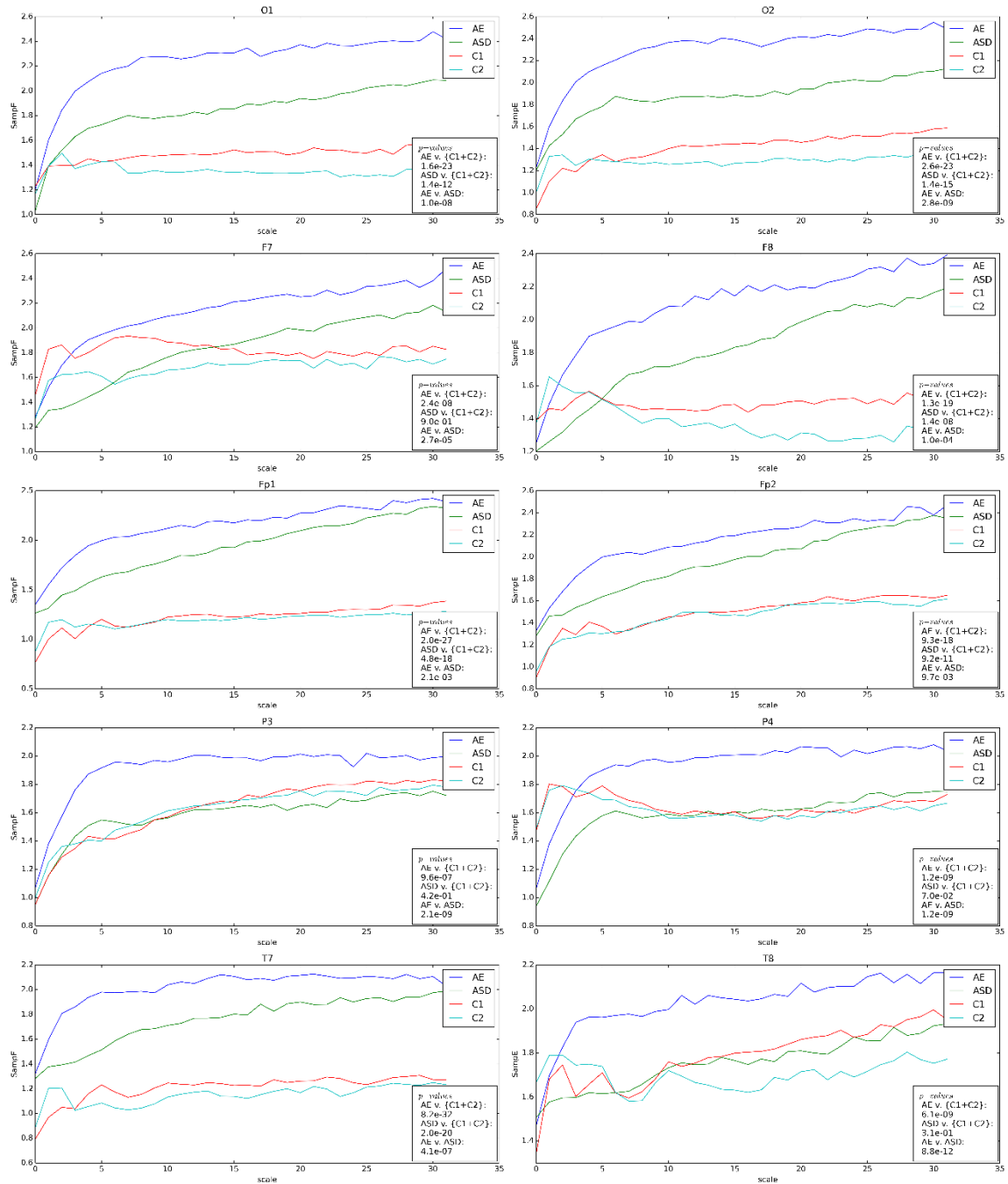
**Figure 20. Mean (diagonal) line length ( $L_{mean}$ ) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



**Figure 21. Entropy of diagonal lines ( $L_{entr}$ ) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



**Figure 22. Transit time (TT) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**



**Figure 23. Sample entropy (SampE) values for four groups: Absence epilepsy (AE), ASD, control 1 (C1) and control 2 (C2) are shown at ten different sensor locations.**

## **CHAPTER FIVE: EARLY AUTISM DETECTION WITH EEG BIOMARKERS AND INFORMATICS ANALYSIS**

### **Abstract**

**Background:** The prevalence of autism in the United States continues to increase, with the CDC recently estimating that 1 in 68 children born today will develop an autism spectrum disorder. Autism imposes an enormous burden on children in developing countries as well. Finding biomarkers for early screening and risk assessment that can be integrated into primary care practice are high priorities for high and low-income countries. EEG is a relatively low cost brain measurement tool that is being increasingly explored as a potential clinical tool for monitoring atypical brain development associated with autism. In this study, we use an expanded set of complex system measures to follow up on a previous study in which we use nonlinear analysis and modern analytics to find biomarkers for autism in a population of high-risk infants.

**Objective:** The goal of this study is to test the hypothesis that EEG complexity, derived from nonlinear time series analysis based on multiscale recurrence plot analysis, will reveal significant differences between typically developing controls and high risk children that are later diagnosed with an autism spectrum disorder (ASD). Furthermore, EEG-derived complexity will enable quantitative estimates of ASD severity by predicting ADOS test scores up to 15 months in advance. This is a follow-up study to the earlier proof-of-principle study discussed in the previous chapter that examined a single complexity measure, multiscale entropy (MSE), as a biomarker for autism.

**Methods:** Recurrence plot analysis is an empirical approach to analyzing time series data and is in principle capable of characterizing all of the essential dynamics of a complex system from real-world, noisy, high dimensional data. We used this method to compute complexity values from EEG measurements from high-risk infants at 6, 9, 12 and 18 months. Machine learning algorithms were then used to predict a 36-month outcome of autism at each of these ages. Additionally, a quantitative severity score was computed from the EEG complexity and used to estimate an ADOS score in the high-risk siblings who were not determined to be on the autism spectrum, but may exhibit the broader autism phenotype.

**Results:** Using a cross-validation paradigm, prediction of the 36-month outcome was poor using 6-month EEG measurements, but was nearly 100% accurate at 9, 12 and 18 months. Predictions of autism severity, as measured by the ADOS test, were significantly correlated with the actual ADOS scores, and exhibited similar variability in typically developing, high-risk siblings who were not diagnosed with autism, and children who later developed an autism diagnosis.

**Conclusions:** The complexity of EEG signals, computed from children 9 to 18 months using multiscale recurrence plot analysis, may be a clinically useful biomarker for autism spectrum disorders and for the broader autism phenotype in high risk children.

### **Background**

A recently released report by the US Centers for Disease Control (CDC) estimated that the prevalence of autism spectrum disorders (ASDs) in the United States is 1 in 68, a significant increase over an estimate two years ago of 1 in 88 (Baio, 2014). In

testimony before the United States Committee on Foreign Affairs entitled “Global Perspectives on Autism – A Growing Public Health Crisis”, Andy Shih, Vice President of Public Affairs for Autism Speaks, stated that some form of autism now affects about 1 percent of the world’s population, “a prevalence that is higher than AIDS, diabetes and cancer combined” (Shih, 2011). While the causes for the changing prevalence numbers may be debated, it is clear that ASDs impose a large disease burden on individuals, families and society in both rich and poor regions throughout the world.

Autism is a disorder that is defined clinically by the presence of a triad of behavioral traits that generally do not appear before 24 to 36 months of age. Because autism is behaviorally and not biologically defined, a formal diagnosis of ASD cannot reliably be made until a child is 2 years old or older (Turner 2007, Sutera 2007). As a result, intervention efforts miss a critical window for earlier diagnosis, prevention and treatment. There is increasing evidence that the behavioral symptoms that define autism may be manifestations of earlier abnormalities in neurodevelopment that span multiple domains (Insel, 2014a). This has fueled the search for early neural correlates or biological indicators of ASD that could identify ASD in the prodromal phase, although varying developmental trajectories in infants at high risk for ASD cause heterogeneous outcomes that make this a difficult endeavor.

Research from infant siblings indicates that ASD manifests in one of three prodromal patterns: early onset (i.e. around the first birthday), late onset (i.e. after the first birthday) or a regressive pattern (a period of normal development followed by a loss

of previously acquired skills). At age 14 months, about half of the children with ASD who were followed from an early age showed no difference from typically developing infants in social behavior such as shared positive affect and initiation of joint attention. Such late-onset cases were “essentially indistinguishable from those without ASD on the social and communication skills” (Yirmiya, 2010).

Other studies show that some children with ASD develop typically over the first two years but then regress in communication and social domains. Furthermore, there is undeniable overlap between normal and abnormal early development: some children who are in fact typical may exhibit delays in language and social behavior, whereas some children at risk for ASD may exhibit some proficiency in language and social behavior during early development. (Pierce 2009, Zwaigenbaum 2005, 2007, 2009). The diversity of presentations of ASD make early differential diagnosis difficult even for specialists, and particularly so in primary care settings which may be the only contact that many children have with their medical system.

### *Need for Biomarkers in Primary Care*

Discovery of relatively easy to implement early screening biomarkers for ASD that can be integrated into primary care practice for routine screening is considered a high priority in pediatric care. The American Academy of Pediatrics Bright Futures practice guide outlines an approach to address developmental and mental health care for children of all ages and in particular screening tests starting as early as 12 months. Delivering the full range of services recommended in the guide requires considerable time from multiple

specialized clinicians, which are not easily implemented in routine primary care settings. Such services are generally not available to underserved populations, nor are such levels of service affordable by low-income populations even when in principle available, resulting in large disparities. For example, compared with parents of white children with ASD, parents of Latino children with ASD were 1.5 times as likely to report difficulties getting needed referrals, twice as likely not to have a usual source of care, and almost three times more likely to have unmet routine healthcare needs (Parish et al., 2012).

The 2012 IACC Strategic Plan Update cited the innovative use of EEG data in our previous study as a potential biomarker and quantifier of ASD risk in the first year, suggesting that this may be a promising approach to very early identification of ASD in at-risk populations ((IACC), December 2012). In that study, a cohort of infants at high risk for developing autism based on having an older sibling with autism, was compared to typically developing controls (Bosl et al., 2011). As ASDs have a prevalence of slightly less than 1% in the general population, the prospective study of the evolution of ASD from birth to diagnosis in a population-based sample would be prohibitively expensive. Therefore, prospective studies have been confined to high-risk groups. The baby sibling design is based on the increased risk of mothers of children with autism having a second child who will develop an ASD. Initially the increased risk was estimated to be about 5% to 10%. However, prospective studies have shown the incidence to be closer to 18% (Ozonoff 2011).

We previously showed that multiscale entropy, a particular nonlinear feature

computed from resting state EEG signals, was a useful feature for distinguishing high risk siblings from typically developing controls and thus might be a useful biomarker for early detection of ASD risk (Bosl et al., 2011). However, the eventual outcome of the high risk infants was not known at that time. The infants studied in our previous report have passed 36 months of age and were given a formal evaluation by a licensed clinician for the presence of ASD.

### *Continuation of Pilot Study*

This present study is intended as a follow-up to our previous multiscale entropy study discussed in chapter 3. The primary goal of this work has a clinical focus and is motivated by a neurodevelopmental perspective: our objective is to discovery clinically useful biomarkers for ASD within easily measured EEG segments. Our focus on EEG as a tool for functional brain measurements is partly motivated by work in underserved populations throughout the world, where screening tools for early detection of ASD and other developmental disorders could have a major impact, but must be low cost and easily integrated into primary or community care practice to be useful (Bakare et al., 2012; Collins et al., 2011). As mentioned earlier, brain developments are likely to precede behavioral manifestations, thus measuring brain electrical activity may reveal deviations from a typical trajectory months or years before the behavioral manifestations become apparent. If ASD symptoms are a manifestation of an atypical developmental process, then a relatively simple method for monitoring neurodevelopmental trajectories may open a window for intervention that will otherwise be missed. Early detection may

also enable new preventive interventions to be explored and may provide a way to monitor the effects of therapeutic interventions.

In Chapter 3, a single measure of signal complexity called multiscale entropy was computed for each EEG signal. A very general approach to nonlinear signal analysis called recurrence quantitative analysis (RQA) is now being used to analyze complex dynamical systems. RQA is an empirical approach to analyzing time series data and is in principle capable of characterizing all of the essential dynamics of a complex system and is useful for analyzing “real-world, noisy, high dimensional data” (Webber and Zbilut, 2005). It has proven to be a powerful tool already in physics, geophysics, engineering and biology (Komalapriya et al., 2008; Marwan et al., 2007b). Its use in neuroscience is just beginning. It may be capable of detecting significant state changes in brain function that are associated with chronic neurological and mental dysfunction.

Thus, the multiscale RQA values used in this paper are a generalization of the multiscale entropy method used in the earlier study to characterize brain activity through EEG analysis. We refer to the multidimensional RQA variables that are computed for each EEG signal collectively as simply the EEG “*complexity*”. The goal of this study and the cohort of infant siblings are identical to our previous study: to use complex systems analysis to find clinically useful early biomarkers of brain activity that indicate a future diagnosis of autism.

## **Methods**

### *Participants*

Data were collected from 97 different infants: 46 at high risk for ASD based on having an older sibling with a confirmed diagnosis of ASD and 33 controls. All study subjects came from monolingual, English speaking households (English spoken  $\geq 80\%$  of the time). Infants who had an older sibling with ASD (not due to a known genetic disorder such as fragile X syndrome or tuberous sclerosis) were designated high risk (hra). The older siblings all received an expert clinical community diagnosis that was confirmed by study personnel using the Social Communication Questionnaire (SCQ; [Rutter et al., 2004](#)) or the Autism Diagnostic Observation Schedule- Generic (ADOS-G; [Lord et al., 2000](#)) for siblings older than 48 months.

Low-risk control infants had at least one typically developing older sibling and no known first-degree relatives with ASD or neurodevelopmental disorders, based on a detailed screening interview. The study participants were part of an on-going longitudinal study and for this analysis visits were evaluated at regular intervals. A total of 190 lab encounters were collected from 97 different individuals. The distribution at different ages and risk groups is shown in Table 11. For the purposes of this study, all visits were treated as independent encounters. Thus, the data from an infant that is tested in five different sessions at 6, 9, 12, 18 and 24 months were treated as unique data sets.

The larger Infant Sibling Project study, from which data for this project was taken, was approved by the Committee on Clinical Investigations at Children's Hospital

Boston (X06-08-0374) and Boston University School of Medicine (H-29049). Parental written informed consent was obtained after the experimental procedures had been fully explained.

<b>Age</b>	<b>con-typ</b>	<b>hra-typ</b>	<b>asd</b>
6	23	18	5
9	17	22	6
12	18	21	9
18	7	14	4
24	10	14	2
<b>Total visits</b>	75	89	26

**Table 11. Distribution of visits by age for typically developing controls (con-typ), high risk siblings that were determined to be typically developing at a 36 month evaluation (hra-typ), and high risk siblings or controls that were determined to have an autism spectrum disorder at 36 months (asd). These three groups are independent.**

#### *Clinical Evaluation at 36 Months*

If a subject meets the cutoff criteria for ASD on the ADOS (total score greater than 7), then a video of the child during ADOS testing session is sent to a licensed clinical psychologist for review. In addition to watching the ADOS testing session, the psychologist is given scores from the Mullen Scales of Early Learning (Measure of cognitive ability, language and motor development) to assess any further delays in development. If needed, the psychologist will also watch the Mullen test session to determine if the concerning behaviors observed in the ADOS are consistent across tasks.

The child must meet the minimum criterion on the ADOS and have a clinical judgment of ASD to be considered ASD positive. The clinician makes a determination if

the child should be grouped as ASD positive or typically developing. Non-spectrum developmental disorders may also be noted, but such children were excluded from this study. If the clinician sends back the clinical judgment of ASD positive, it also includes a sub-category of ASD possible, ASD probable or ASD definite. All of these determinations are considered ASD positive in this study.

### *EEG Data Collection*

Infants were seated on their mothers' laps in a dimly lit room while a research assistant engaged their attention by blowing bubbles. This procedure was followed to limit the amount of head movement made by the infant that would interfere with the recording process. Continuous EEG was recorded with a 64-channel Sensor Net System (EGI, Inc.). The net is comprised of an elastic tension structure forming a geodesic tessellation of the head surface containing carbon fiber electrodes embedded in pedestal sponges. At each vertex is a sensor pedestal housing an Ag/AgCl- coated, carbon-filled plastic electrode and sponge containing saline electrolyte. Prior to fitting the sensor net over the scalp, the sponges are soaked in electrolyte solution (6cc KCL/liter distilled water) in order to facilitate electrical contact between the scalp and the relevant electrode. In order to assure the safety and comfort of the infant the salinity of the electrolyte solution is the same as tears. In the event that the solution comes into contact with the eyes no damage or discomfort will occur.

Prior to recording, measurements of channel gains and zeros were taken to provide an accurate scaling factor for display of waveform data. The baby's head was

measured and marked with a washable wax pencil in order to ensure accurate placement of the net, which was then placed over the scalp. Scalp impedances were checked on-line using NetStation (EGI, Inc, Eugene OR), the recording software package that runs this system. EEG data were collected and recorded on-line using NetAmps Amplifiers (EGI, Inc, Eugene, OR) and the NetStation software. The data were amplified, filtered (band pass 0.1-100.0 Hz), and sampled at a frequency of 250 Hz. They were digitized with a 12-bit National Instruments Board (National Instruments Corp., Woburn MA). Typically, 2 minutes of baseline activity were recorded, but depending on the willingness of the infant, recorded periods may have been shorter. For this study, continuous sample segments of 30 seconds were selected from the processed resting state data and used to compute multiscale entropy values.

Data were initially taken in this study with 64 channel nets, then later with 128 channel nets. In order to compare data taken from both nets, and looking forward to future studies comparing these results with children from the Boston Children's Hospital neurology clinics where standard 19 channel systems are used, a decision was made to use only 19 sensors or channels from the common 10-20 scalp locations, as shown previously in Figure 14. Data from sensors at these locations were the only data used for this study. An additional 8 "channels" were constructed by subtracting left-right pairs, element by element in the time series. The purpose was to include laterality differences as features. For example, subtracting the raw time series F7 from F8 created the new F7-F8 difference channel.

### *Recurrence Quantitative Analysis*

A brief discussion of some of the most commonly used recurrence quantitative analysis variables is given here. A more complete and mathematical discussion of recurrence plot variables that can be computed is given in (Marwan et al., 2007a). We note that RQA was initially developed in the context of physical system, thus much of the terminology reflects physical systems. For example, ‘laminarity’ is a term that has physical meaning for fluid flow and is commonly used to distinguish turbulent flow from smooth or laminar flow. The meaning of these terms in the context of neural systems will require future research.

<b>RQA Variable</b>	<b>Symbol</b>	<b>Description</b>
Recurrence rate	RR	The probability that a system state recurs in a finite time. RR has been found useful for detecting evoked response potentials (ERPs) using single trials (Schinkel et al., 2009).
Determinism	DET	DET comes from repeating patterns in the system and is an indication of its predictability. Regular, deterministic signals, such as sine waves, will have higher DET values, while uncorrelated time series, such as chaotic processes and random numbers, will cause low DET.
Laminarity	LAM	Laminarity represents the frequency of occurrence of laminar states in the system without describing the length of these laminar phases. More frequent appearance of laminar states may relate to more frequent “seeds” for synchronized dynamics (Hirata and Aihara, 2011), which may be related to epileptiform spiking on an EEG trace.
Max line length	L_max	Lmax and related measures Vmax and Wmax are related to the largest Lyapunov exponent of a chaotic signal, which is a dynamic complexity measure that describes the divergence of trajectories starting at nearby initial states, (Gomez and Hornero, 2010). Lower values are typically associated with pathological conditions (Goldberger, 1997; Peng et al., 2009).

Entropy derived from diagonal lines	L_entr	These are three measures of entropy derived from the diagonal, vertical and horizontal lines of the recurrence plot, respectively. They are related to, but not identical to, other measures of entropy, such as the sample entropy used in our previous study (Bosl et al., 2011)
Entropy of vertical lines	V_entr	
Entropy of horizontal lines	W_entr	
Trapping time	TT	Trapping time is an estimate of the time that a system will remain in a given state - “trapped” state. Thus, lower TT values may be an indication of more frequent transitions between dynamical states and less system stability.

**Table 12. Recurrence Quantitative Analysis variables and their interpretation.**

### *Classification*

The Orange machine learning package was used for classification calculations (Demsar and Zupan, 2004). Several different learning algorithms were compared: support vector machine (svm), k nearest neighbors (knn) and naïve Bayesian (bayes) so as to exclude possible overfitting by one method.

### *Significance Testing*

The significance of the classification results for each method was estimated empirically using the permutation approach described in (Golland and Fischl, 2003). These are reported as ‘empirical p-values’ along with classification accuracy results. The basic idea for estimating empirical p-values is to randomly shuffle the diagnostic labels and then proceed to do the cross validation in the usual manner. This shuffling and re-classification is done many times. For the estimates below, one hundred random trials were done. Each time the random accuracy from the cross validation equals or exceeds that obtained from the true classification, the p-value is incremented by one. The final p-

value is obtained by divided the summed value by the total number of trials.

### *Feature Selection*

Feature selection was performed using a simple ranking algorithm initially developed for high dimensional data sets, such as gene expression arrays (Haury et al., 2011; Zhou and Wang, 2007). The initial feature set consists of the 8 computed RQA values shown in table 2. These are used to compute multiscale RQA values, using the same multiscaling algorithm used to compute multiscale entropy (Bosl et al., 2011). Multiscale RQA values are computed for each of the 19 sensor locations plus 8 left-right difference values for a total of 27 sensors. The multiscale values for each sensor location constitute a multiscale curve. Only the area under the curve, mean value and the initial value are used. Thus, the entire initial feature set consists of  $8 \times 27 \times 3$  or 648 features. For classification calculations, the 10 highest-ranking features are selected using the simple ranking algorithm referenced above (Haury et al., 2011; Zhou and Wang, 2007). This is in accordance with a common practice of using feature sets that are not larger than about 10% of the sample population size. Larger feature sets start to degrade accuracy due to the relatively small population sizes relative to the feature set. Feature sets with fewer than 10 features also show decreasing classification accuracy as important information may be missed when too few features are used.

## Results

The infants in this study belong to one of three groups, based on the 36 month clinical outcome and family history, as described in the methods section: (1) **asd**: those determined to be on the ASD spectrum, (2) **hra-typ**: siblings at high-risk who are determined to not be on the ASD spectrum, and (3) **typ**: controls who are determined to be typically developing. Note that those in the hra-typ group may not be considered typically developing in all of the three primary autism diagnostic categories – they do not meet the threshold for an ASD diagnosis. Initial classification calculations use the two end-point groups, asd and typ in cross validation paradigm. These two groups are then used as the training set for a classifier that is then used to classify and score the intermediate hra-typ group members. The groups are summarized in table 13.

Group Label	Family history	36 month clinical assessment
typ	None; control group	Typically developing
hra-typ	Sibling with ASD	Do not meet criteria for ASD diagnosis – may exhibit broader autism phenotype
asd	Sibling with ASD	ASD diagnosis

**Table 13.** The high risk siblings were divided into two groups: those that had a 36-month diagnosis of ASD (asd) and those that did not meet the threshold for an ASD diagnosis (hra-typ).

### *Binary classification with controls and ASD outcomes*

A prediction of the 36 month binary outcome, asd or typ, was computed using a leave-one-out cross validation. The cross validation used multiscale RQA values computed from the unfiltered EEG, as described in the methods section above. Results

are shown in table 3. The age in column one is the age at which the resting state EEG was taken and used to predict the 36 month outcome. Several different classification methods were used to test for consistency.

In summary, significant classification accuracies of greater than 90%, with similarly high sensitivity and specificity, were obtained using multiscale RQA features at 9, 12, and 18 months of age, but not at 6 months. We note that the empirical p-values are exactly 0.0 after 100 trial classifications with shuffled labels, for every method at ages 9 to 18, demonstrating that the classification accuracy was unlikely to be due to chance alone. Sensitivity with the SVM method was 100% at 9, 12, and 18 months.

Age	N asd / typ	Method	Acc	Sens	Spec	Randomized labels test p-value (100 trials)
6	5 / 23	knn	0.86	0.2	1.0	0.25
		bayes	0.82	0.60	0.87	0.04
		svm	0.78	0.00	0.96	1.0
9	6 / 17	knn	0.90	0.67	1.0	0.00
		bayes	0.90	1.0	0.88	0.00
		svm	<b>1.0</b>	<b>1.0</b>	<b>1.0</b>	<b>0.00</b>
12	9 / 18	knn	0.89	0.78	0.94	0.00
		bayes	0.82	0.89	0.78	0.00
		svm	<b>0.96</b>	<b>1.0</b>	<b>0.94</b>	<b>0.00</b>
18	4 / 7	knn	1.0	1.0	1.0	0.00
		bayes	0.88	0.75	1.0	0.00
		svm	<b>1.0</b>	<b>1.0</b>	<b>1.0</b>	<b>0.00</b>

**Table 14. Predictive classification of 36-month outcome based on clinical diagnosis. The age represents the age at which EEG analysis was done with classification based on 36 month outcome.**

For clarity, we summarize the results of Table 14 by noting that using the SVM method, sensitivity for ASD is 100% at 9, 12, and 18 months, with corresponding specificity also 100% at 9 and 18 months and 94% at 12 months. Complexity differences between these two groups are clear, as will be shown graphically in the following figures.

### *Quantitative Estimate of Severity and Predicted ADOS Scores*

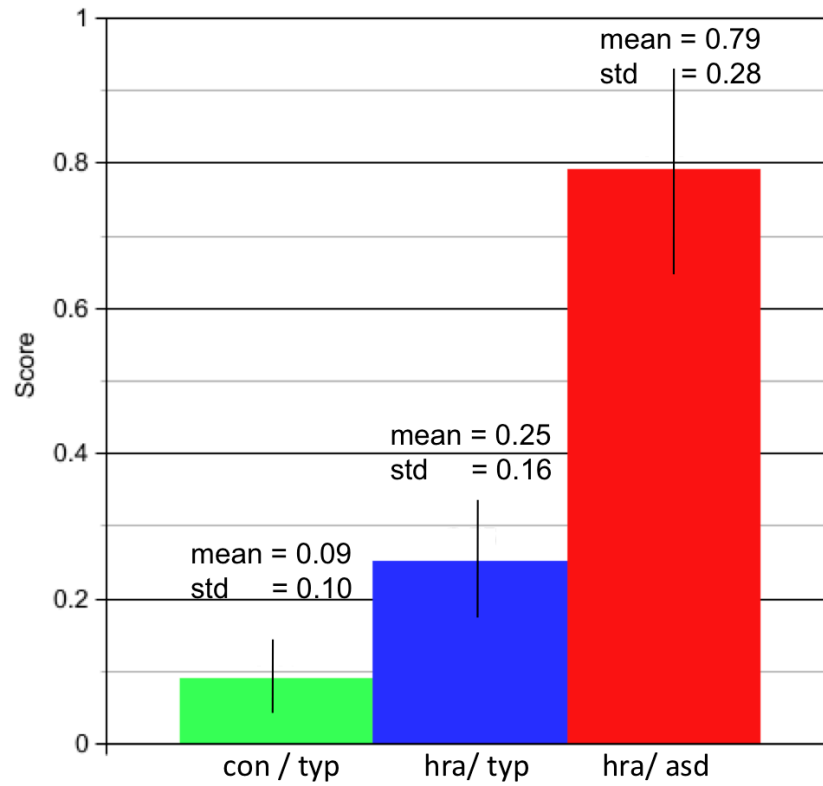
The svm method computes a hyperplane that divides the training set into classes that are maximally separated by some measure. This allows a quantitative estimate of how close or far each member of a test set is from the plane. A detailed discussion of a severity score or predicted ADOS severity score is derived from the SVM algorithm is given in Appendix A. In general, the EEG complexity is used to predict an ADOS severity score using the SVM algorithm. As discussed earlier, EEG complexity refers to the multidimensional RQA values that quantify the complexity of the EEG time series segment. We do not try to reduce this complexity measure to a single dimension that can easily be correlated to a specific neural function or characteristic.

In the following, the training phase of the classification is always performed using only the two end groups, typ and asd. This is to avoid possible confusion that may be created if the hra-typ group is used, since children in this intermediate group may exhibit the broader autism phenotype but still be diagnosed as typically developing.

In our first experimental calculation, an SVM classifier was trained using all typ and asd subjects from 6 to 24 months, with leave-one-out cross validation calculation.

The score for each subject in the test or predictive part of the cross validation was computed by the method described in Appendix A. This will be referred to as the predicted ADOS score in the following.

Scores for the intermediate group consisting of typically developing children from the high risk group, denoted ‘hra-typ’, were then computed using the asd and typically developing controls as the training set. Thus, none of the hra siblings were included in the training set. Normalized mean scores for each group are shown in figure 15. This suggests that the multiscale RQA features contain quantitative group information about autism severity. The group difference in scores between typically developing controls and typically developing high-risk siblings is statistically significant, suggesting that the broader autism phenotype may be detected in the RQA analysis of EEG signals.



**Figure 15.** The training set used to generate this plot consisted of all typically developing controls (con / typ) and the high-risk infant siblings that had a positive clinical diagnosis of autism spectrum disorder at 36 months (hra / asd). The test set consisted of all high-risk infant siblings that were determined to be typically developing at 36 months (hra / typ). Scores represent the distance from the classification hyper plane learned by the SVM algorithm from the training set. P-value for con/typ versus hra/typ =  $7.8e-12$ .

### *Quantitative Prediction of ADOS Scores in Individuals*

Next, rather than computing group means, prediction of ADOS severity scores is attempted using the approach described in appendix A for individuals by age. The method involves computing the distance of each subject from the separating plane in the SVM classifier. It is thus an estimate of the distance of a subject from the furthest endpoints in the typ and asd groups, with distance measured in the feature space. Actual ADOS severity scores are plotted alongside predicted ADOS scores. Two ADOS scores were available in this study for each infant: one at 18 months and one at 24 months. In

general, these scores are consistent. However, because not all scores were available for infants at both ages, and to account for observer variability, the 18 and 24 month ADOS scores were averaged to obtain the actual scores plotted here.

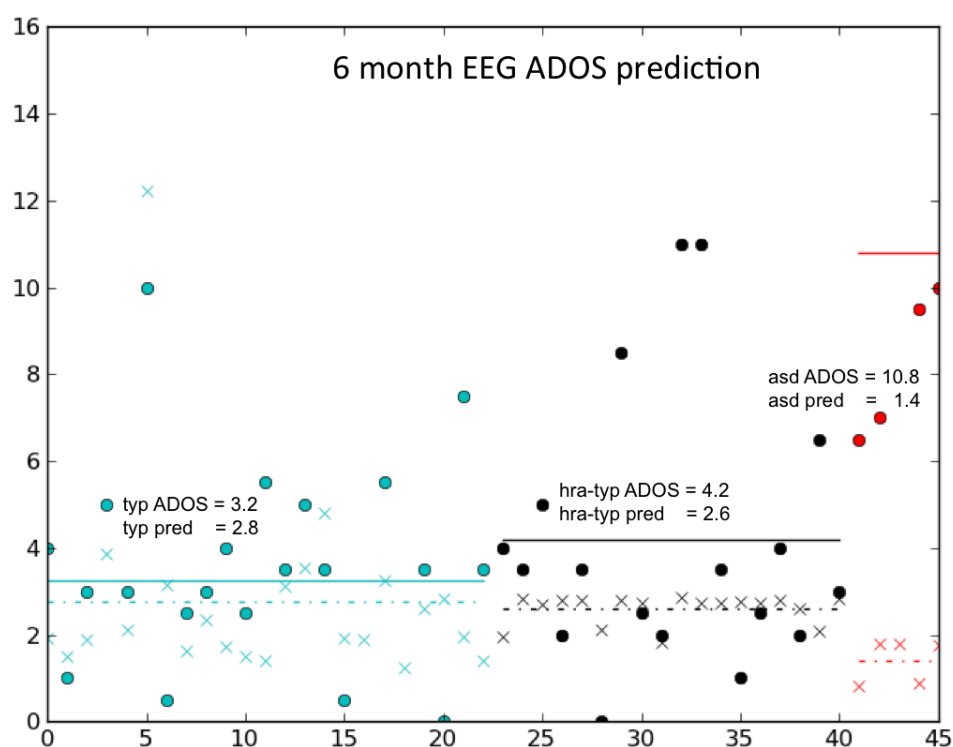
The predicted severity scores are computed from the SVM classification model by age. The training set for classification consists of all subjects for which EEG data is available at a given age (6, 9, 12, and 18 months). The SVM algorithm enables calculation of a normalized score from 0.0 to 1.0 between the two groups. In this case, the two groups are infants from the control group that are later determined to be typically developing at 36 months (typ), and infants from the high risk group that are later determined to be on the autism spectrum (asd). In the leave-one-out cross validation, the SVM algorithm computes a score for the test subject between 0.0 (the typ endpoint) and 1.0 (the asd endpoint). Scores above 0.5 are classed as asd, otherwise typ. The score for each test subject is saved. Using the entire training set, each of the subjects in the high risk group that was determined to be typically developing (hra-typ) was also scored. The normalized scores were multiplied by 14, the highest ADOS severity score among our population, to give a “EEG-derived severity score”.

Age of EEG data (months)	Pearson correlation: ADOS score and predicted score	Significance
6	0.15 (none)	0.32
9	0.66 (strong)	0.80e-7
12	0.35 (moderate)	0.016
18	0.60 (strong)	0.0014

**Table 16. Correlation between ADOS severity scores (18 month and 24 month average) and EEG-derived severity score based on typ-asd classification model.**

As Table 16 illustrates, the correlation between EEG-derived severity scores and the actual ADOS summary scores are moderate to strong, and highly significant, for predictions made using EEG measurements at 9, 12, and 18 months. The 6-month EEG predicted scores are not correlated with actual ADOS scores, consistent with previously discussed inability to predict the 36-month outcome from 6-month EEG data.

The plots in Figure 25 show individual EEG-derived severity and ADOS scores graphically. Using 6-month EEG data, all subjects have similar EEG-derived severity scores (shown as Xs) that are close to the typ scores, with relatively low scatter, which does not reflect the actual ADOS scores (shown as solid dots).



**Figure 25.** Predicted ADOS scores (Xs) determined from 6-month EEG data from each of the 3 groups are plotted along with actual ADOS scores (solid circles). Solid (actual scores) and dashed (predicted scores) lines show the mean score for that group. Predicted ADOS scores at 6 months are all similar to controls.

The situation changes when 9-month and later EEG data is used, as found previously for classification. The EEG-derived severity scores of the each of the groups (typ, hra-typ and asd) are correlated with the actual ADOS scores, and the variability of the actual assessed ADOS scores is mirrored by the predicted scores.

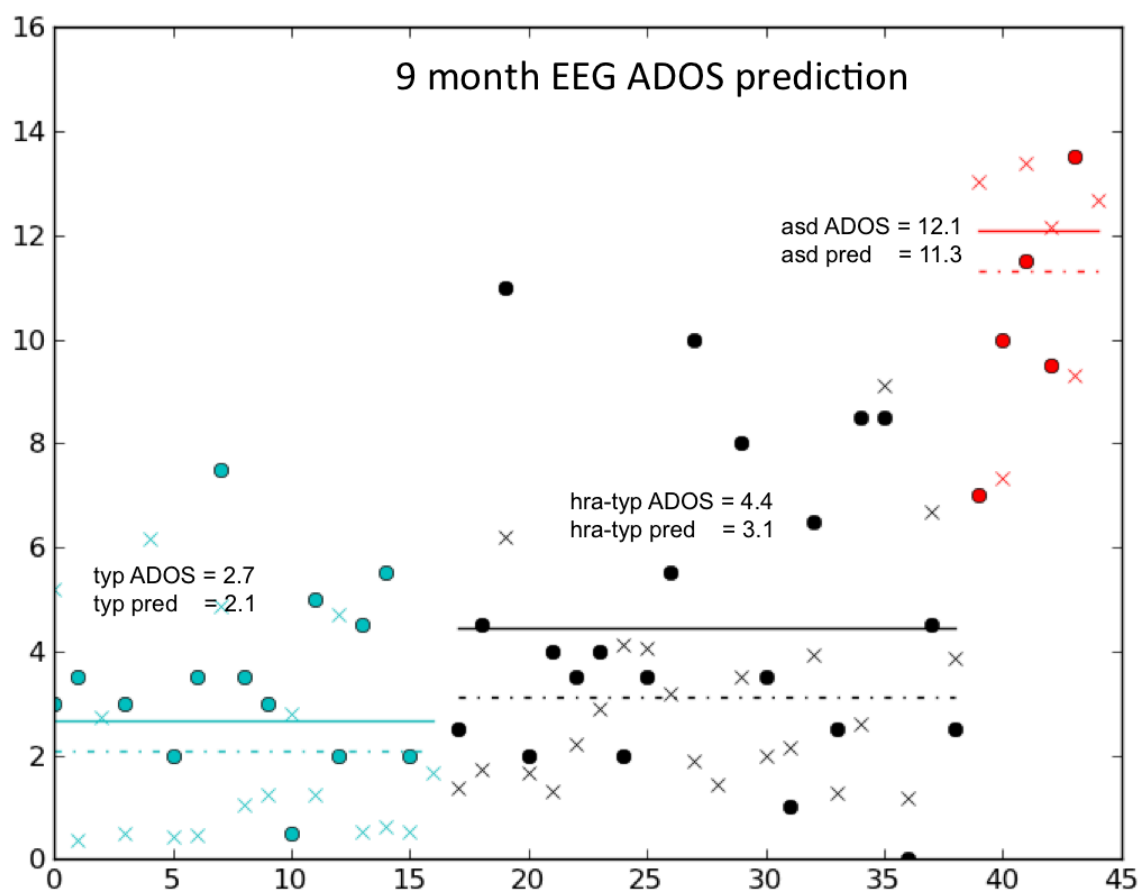


Figure 26. Predicted ADOS scores (Xs) determined from 9-month EEG data from each of the 3 groups are plotted along with actual ADOS scores (solid circles). Solid (actual scores) and dashed (predicted scores) lines show the mean score for that group.

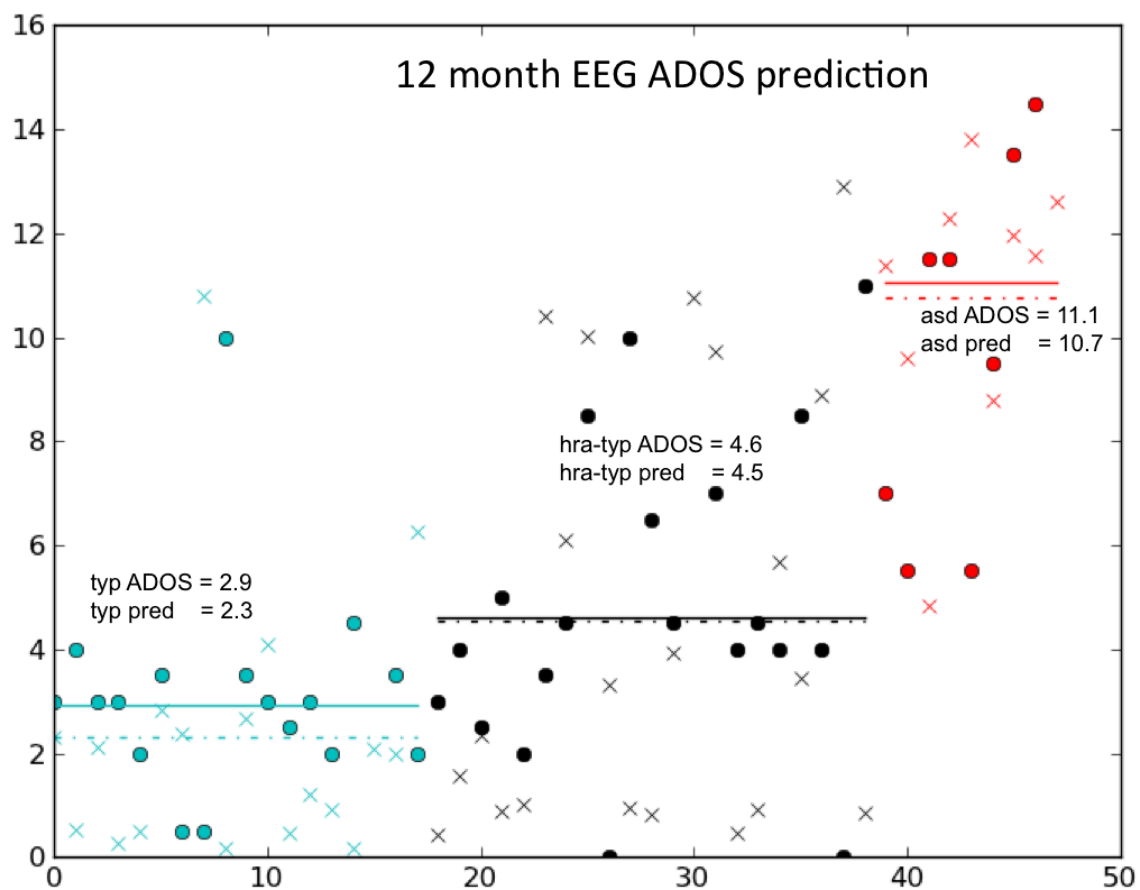
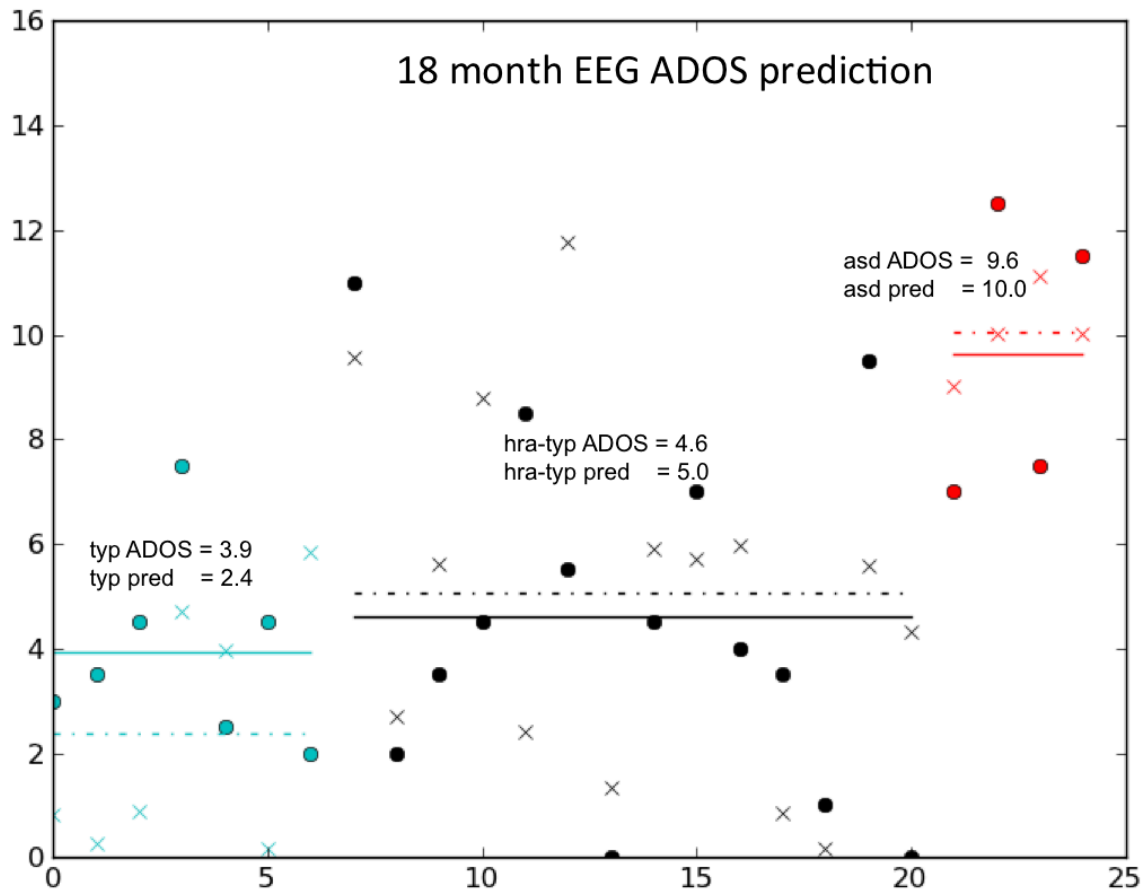


Figure 27. Predicted ADOS scores (Xs) determined from 12-month EEG data from each of the 3 groups are plotted along with actual ADOS scores (solid circles). Solid (actual scores) and dashed (predicted scores) lines show the mean score for that group.



**Figure 28.** Predicted ADOS scores (Xs) determined from 18-month EEG data from each of the 3 groups are plotted along with actual ADOS scores (solid circles). Solid (actual scores) and dashed (predicted scores) lines show the mean score for that group.

As the age of the EEG data used for predicting the ADOS scores increases, the predicted and actual ADOS scores, and the variability of scores within each group, become closer. When ADOS scores are predicted with 12 month and 18 month EEGs, the difference within each group between predicted and actual becomes statistically insignificant.

## **Discussion**

### *Importance of Biomarkers*

Discovering methods for very early detection of autism spectrum disorders is a priority research area for a number of organizations throughout the world (Gokcen et al., 2014; Happe et al., 2006; Smith, 2011). The growing prevalence of ASD in the US is widely advertised and deeply concerning. Less well known is the enormous burden that ASD imposes on children in economically disadvantaged regions of the world. While striking progress has been made in preventing deaths among children under 5 years of age, neurodevelopmental disorders, and particularly autism, are now emerging as major public health challenges. Though the causes of autism are likely diverse, it is becoming increasingly clear that significant adversity early in life can cause disruptions to the developing brain and lead to a higher risk of cognitive, social and neurological disorders (Abubakar et al., 2008; Abubakar et al., 2009; Bakare et al., 2012; Mung'ala-Odera and Newton, 2007). In regions of the world where malaria is still a major concern in young children, cerebral malaria is a major risk factor for neurodevelopmental impairment in young children (Boivin et al.; Carter et al., 2005; Carter et al., 2003; Kihara et al., 2006).

Methods that can be used widely for early detection of ASD in primary and care settings is a high priority for identifying those that need services as early as possible (Brito et al., 2010). However, autism presents several diagnostic problems. First, the behaviors by which it is currently defined do not appear until long after the brain developments that lead to those behaviors have occurred. Thus, the most leveraged time

for intervention is lost with behavior-based screening tools. Secondly, the behaviors that characterize autism spectrum disorders are diverse. Evidence continues to mount suggesting that autism-like characteristics are distributed throughout the population (Gokcen et al., 2014; Happe et al., 2006). An additional complication arises from the paucity of early screening instruments that are valid in cultures outside of mainstream North American and European communities – including large and diverse immigrant populations within these regions. Discovery of biologically-based biomarkers for mental and cognitive disorders is a driving force behind the National Institutes of Health Research Domain Criteria (RDoC) program (Insel et al., 2010; Morris and Cuthbert, 2012; Sanislow et al., 2010).

Recently, performance-based measures such as atypical eye contact (Bedford et al., 2012; Paul et al., 2011; Wagner et al., 2012), unusual vocalization (Paul et al., 2011), or fixation on geometric patterns (Pierce et al., 2011) have highlighted the many potential early markers of ASD risk. Many brain recording (ERP) and imaging techniques such as DTI (Elsabbagh et al., 2012b; Elsabbagh et al., 2012c) and sleep fMRI (Pierce et al., 2011) are very expensive, time consuming and not appropriate for infants, but have shown great promise to identify brain correlates of prodromal ASD. Recent advances in the technology of EEG monitoring (wireless infants caps) now allow the introduction of these measures into primary care clinical settings.

An accurate biomarker that can lower the age of diagnosis will have tremendous impact on the practice of early screening and diagnosis. Furthermore, if reliable methods

can be developed to lower the age of diagnosis, and if insight is gained into the biological mechanisms that underlie the disorder, it may be possible to develop intervention strategies that can be implemented during the first year of life. The methods developed in this project will further introduce the possibility of monitoring the effectiveness of personalized interventions. This is the motivating goal and primary aim of this research: *to find clinically useful, objective, biologically-based biomarkers for the early detection of autism*. Understanding the neurobiological explanation for precisely why these biomarkers are effective is an important, but secondary goal.

### *Study Population*

A prospective study of the association between very early biomarkers and later outcome is the ideal approach to the development of an evidence-based screening program. Nevertheless, a small, carefully selected population such as the infant sibling population used for this study has several limitations. The diversity of autism characteristics leaves open the question of whether the results shown here are detecting autism-specific characteristics, or if a broader atypical neurodevelopmental pattern is being detected. Our population is from an English-speaking, Boston-based population. It is yet to be determined if the brain electrophysiological patterns discovered here are also predictive of autism behaviors in other cultures. The ASD cases used in this study have a strong genetic component, based on the sibling design used. ASD is likely to have many diverse causes and risk factors, including as-yet unknown, complex genetics, nutritional, environmental and social factors. Although the results presented here are promising,

much larger and more diverse populations must be studied before the clinical applicability of this approach to EEG analysis can be determined.

### *Complexity and 'Big data' Analytics*

Unlike most approaches to the cognitive neuroscience of autism, this approach used in this study depends explicitly on a model-free or machine learning paradigm to discover the brain (EEG) – phenotype relationship. This approach, recently dubbed the “fourth paradigm” of scientific research (Hey et al., 2009) depends on the use of machine learning algorithms to find patterns or regions of high dimensional data sets that are significantly correlated with phenomena of interest. Fundamentally, it is no different from the earliest experimental science, which collects data and human eyes look for relevant patterns. The only difference is that human eyes (or mind) cannot see relevant patterns that involve hundreds of variables.

Our hypothesis is that the “complexity” of EEG signals, with complexity defined by a general nonlinear time series analysis approach referred to as recurrence quantitative analysis, contains information about brain function that is significantly correlated with a future diagnosis of ASD. Our results support this hypothesis. The finding that a more complicated measure of brain function, rather than a single variable or biological parameter, is consistent with the view of autism as an “an emergent disorder that is characterized by the loss of social communication skills in the period between 9 and 24 months ... defined on the basis of alterations in the developmental trajectories across multiple domains” (Tager-Flusberg, 2010).

We suggest that our approach differs from a traditional single-variable hypothesis driven approach only in that the variables of interest that characterize the EEG complexity are higher dimensional. Nevertheless, the hypothesis is straightforward: the dynamical complexity of the brain in children in whom autistic characteristics are developing follows a different trajectory than in typically developing children. The complexity is measured by computing recurrence quantitative analysis, a proven technique for quantifying complex system characteristics. Because it is difficult for humans to visualize in more than 3 dimensions, we employ a machine learning technique, SVM, to find the plane that distinguishes ASD from typically developing phenotype.

The finding that high risk siblings that later develop an ASD diagnosis is consistent with other recent findings with high risk siblings. Behavioral symptoms were not apparent at 7 months in one study, but emerged by 14 months (Elsabbagh et al.). A distinct temperament profile that included increased negative affect and reduced tendency for physical contact (“cuddliness”) was found to be detectable by 14 months, but not at 7 months (Clifford et al., 2012). Ozonoff found that some infants who developed ASD at 3 years did not exhibit any deficits in social or communication behaviors compared to typically developing infants at 6 months of age (Ozonoff et al., 2010). Using a study sample drawn from the same population of infants as this study, significant group differences in the development of lateralized ERP response to speech were found between 6 and 12 months in the control and high risk sibling groups (Seery et al.), which supports further the hypothesis that brain developments associated with a later diagnosis of autism are occurring in this age range. It is possible that all of these prodromal

*behavioral* patterns are preceded by neural correlates that are changing before 12 months.

The high accuracy of the cross validation predictions, and the significance level determined by the empirical p-value calculations suggests that the complexity measure employed in this study reflects real differences in the brains of children who are developing autism. Nevertheless, describing precisely what those differences are in neurobiological concepts may prove difficult. The brain is a complex system, and in many respects functions as a system rather than as a collection of independent, localized components. As suggested previously, ASD is an emergent disorder involving multiple domains. Further research in the biophysics of neural computation and in analysis of complex system time series is needed to bring scientific clarity. Nevertheless, the clinical utility of these findings is quite clear, even in the absence of complete neuroscientific explanation.

The results presented in this study may represent a lower bound on the predictive accuracy obtained. The feature selection method used was chosen for its simplicity and reports in the bioinformatics literature that it is effective for many applications (Haury et al., 2011; Zhou and Wang, 2007). However, if the highest ranked features contain similar information, then it may be that different combinations of features contain more information about the developing brain. Feature selection will require further research.

#### *Broader Autism Phenotype and Predicted Severity*

Siblings who do not develop ASD are more likely to share some of the characteristic features, usually at a less severe level, of the ASD phenotype (Happé et al.,

2006). Reviews of the broader autism phenotype may be found in (Ozonoff et al., 2014; Pickles et al., 2013). Research suggests that features of autism are not restricted to individuals diagnosed with autism spectrum disorders (ASDs), and that there is pronounced variation within the general population relating to ASD traits, which reflect similar (though less severe) social-cognitive and emotional features to those observed in ASDs (Gokcen et al., 2014). Cognitive tests in another study revealed similarities between children with autism and typically developing siblings on standard intelligence tests, suggesting that the common cognitive profile could be an intermediate phenotype of this syndrome (Gizzonio et al., 2014). Studies of older children have found that siblings and parents are more likely to show mild impairments in language (Lindgren et al., 2009; Ruser et al., 2007), non-verbal communication (Ruser et al., 2007), theory of mind (Baron-Cohen and Hammer, 1997; Dawson et al., 2005) and face processing compared to controls (Dawson et al., 2005).

The prediction of symptom severity or predicted ADOS score presented in this paper may be useful not only as a means for gauging the severity of future symptoms, but may be useful for detecting the broader autism phenotype. We note that the method used for predicting severity scores used in this study did not depend on ADOS scores at all. Rather, the two end groups, typ and asd, were used to train a classifier, which was then used to compute the distance of each of the intermediate hra-typ members from the endpoints. The average value and standard deviation of the computed hra-typ values was remarkably close and correlated with the actual range of ADOS values in this group. Additional research with much larger datasets will be needed to confirm the usefulness of

this predicted severity score.

### *Comorbid Conditions*

Children with ASD exhibit a number of clinically significant difficulties in many neurodevelopmental domains ((Jones et al., 2013), including attention (Leitner, 2014; Swanson and Siller, 2014), mood (Matson and Williams, 2014), learning and cognitive function (Gizzonio et al., 2014), and other life skills .

It cannot be determined from these results if the EEG analysis method employed here is detecting autism-specific characteristics of brain development, or a general neurodevelopmental deviation from a typical trajectory. Much larger population sizes with data and subjects from widely distributed clinics with a population of children will be necessary to test whether different atypical developmental problems.

### **Conclusions**

The results presented in this paper are consistent with and greatly extend our previous study with this cohort of infants. Analyzing EEG signals as time series from a complex dynamical system shows that a 36-month outcome of ASD or typically developing can be predicted at 9, 12 and 18 months with high accuracy (at or close to 100% in all three cases) for infants in families with a history of ASD. No prediction is possible at 6 months using this approach.

Perhaps even more importantly, it appears that EEG complexity, as determined using

multiscale RQA, enables a severity score for ASD symptoms to be predicted. Both the typical controls and the high risk siblings groups exhibit computed severity scores that have similar means and distributions to the actual ADOS scores.

Before the approach presented in this study will be useful as an early screening tool for ASD, larger and more diverse populations of subjects will need to be tested to determine if ASD-specific characteristics are being detected, or if a general neuropathology that deviates from typical is detected.

The nonlinear signal analysis method presented here for computing features from EEG segments contains information that enables statistically significant predictions of a 36 month clinical diagnosis of autism by 9 months of age, but not at 6 months. Whether this is because differences at 6 months are not present, or they are subtler and require much larger datasets to tease out remains to be determined.

We present these results as a potentially useful tool for risk assessment, leaving the much more difficult scientific question about why the dynamical information extracted by recurrence plot analysis appears to effectively map electrophysiology to developing behavioral and cognitive phenotypes. Larger studies using clinical populations of children should be performed with the methods described in this paper in order to determine as quickly as possible if this might be clinically useful for early risk screening. Simultaneously, carefully designed theoretical studies are needed to elucidate more fully the meaning of the complexity measurements found by RQA analysis that appears to detect emerging autistic characteristics.

## **ADDRESSING THE GLOBAL BURDEN OF NEURODEVELOPMENTAL DISORDERS (NDDS) USING NEUROTECHNOLOGY**

### **The Global Burden of MNS Disorders**

Mental, neurological, and substance use (MNS) disorders, or simply “mental disorders” impose the largest burden of all chronic disease classes in the world (Collins et al., 2011; Idro et al., 2010; Prince et al., 2007). Though long overlooked as healthcare priorities globally, mental disorders are an enormous economic burden on nations, particularly low income nations, where the lack of capacity to deal with the problem leads to personal suffering for patients, which also affects caregivers, families and communities. Yet, the burden may still be underestimated because current measures fail to take into account the connectedness of mind and body. Many chronic medical conditions have comorbid mental and cognitive conditions, leading to poor outcomes. Similarly, mental conditions can cause a number of poor health outcomes, creating a range of serious chronic diseases that require medical care. As the World Health Organization (WHO) constitution states: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Thus, there is no health without mental health.

*Social and Economic Burden*

Mental disorders not only affect the well being of individuals, but also their families, communities and societies. Mental disorders do not respect income or social conditions: mental illness accounts for a larger proportion of disability in high-income countries than any other group of illnesses. For example, an estimated 25% of adults in the United States reported having a mental illness in the previous year (Reeves et al., 2011). The economic burden imposed by these disorders, in high and low income nations alike, includes loss of gainful employment, with the attendant loss of family income; the requirement for care giving, with further potential loss of wages; the cost of medicines; and the need for other medical and social services. These costs are particularly devastating for poor populations (WHO, 2008). Unfortunately, economic burden leads to a huge loss of resources that could have been saved, which is unfortunately rarely considered in developing countries.

A functioning mental healthcare system also helps to reduce poverty (WHO, 2008). Homelessness and incarceration in prisons are common occurrences for people with mental health conditions, which exacerbate their marginalization and precariousness. Rates of mental illness among the homeless can be greater than 50% (Fazel et al., 2008) and studies reveal that more than one third of the prison population have mental health conditions (Kleinman, 2009). People with mental health conditions often lack educational and employment opportunities. Not surprisingly, severe mental illness is associated with unemployment rates up to 90%, the highest rates of all

disabilities (WHO, 2008). Moreover, mental health conditions in a single individual can lead entire families into poverty and thus hinder economic development (Chisholm et al., 2007a).

### *Effects of War and Conflict on Mental Health*

War, armed conflict and terrorist attacks introduce a significant cause of mental health burden in many parts of the world. A particularly high burden is borne by low-income regions, where indirect effects of conflict greatly exacerbate the damage. Armed conflict causes widespread injury and illness that contribute to a breakdown of health services just when they are most needed.

The mental health effects of war may be greatest burden among children, who then suffer with disability resulting from depression, anxiety symptoms, psychoactive substance use problems, malnutrition and failure to thrive in younger children and other consequences for a lifetime, especially in Africa. Displacement from homes, loss of family, destruction of schools and social structures important for psychosocial development may all be consequences of war and contributors to the damage to young minds. Higher rates of mental health problems, such as PTSD and depression, have been documented among child soldiers. These are further influenced by post-conflict risk and protective factors (Betancourt et al., 2010). A strong association between maternal symptoms of depression, anxiety and PTSD and symptoms of PTSD in their children was found in a Middle Eastern region afflicted by conflict (Feldman and Vengrober, 2011).

In addition to the direct effects of war on mental health, recent evidence suggests that an epigenetic intergenerational transfer of the effects of mental stress from parents to offspring (Devakumar et al., 2014). Interestingly, stress levels caused by psychological trauma in mothers can affect their unborn babies similarly to under-nutrition, possibly mediated by changes in the hypothalamic-pituitary-adrenal (HPA) axis (Holsboer, 2000).

While the ultimate solution to trauma-induced mental disorders is the cessation of conflict, the creation of low cost approaches to early detection may help to alleviate some of the impact and reduce long-term burdens by enabling early interventions.

*Moral Imperative: A Failure of Humanity*

Mental healthcare is more than just a public health issue and economic burden it represents a moral failure. The current state of care for mental health patients in the world, in both rich and poor regions of the world, has been called a *failure of humanity* (Kleinman, 2009). The lives of people with mental disorders, particularly in resource poor societies, are deprived of basic human rights. As Kleinman (2009) eloquently argues, “the widespread stigma of mental illness”, which prevails in countries as disparate as China, India, Kenya, Romania, Egypt, as well as selectively in the United States, “marks individuals with severe psychiatric disorders as virtually non-human. None of the world's major religions—no matter how strong is its message of support on behalf of the most marginal and vulnerable sufferers—has been able to break this cycle of misery. Nor have modern anti-stigma campaigns and mental health laws.” Although greater awareness of mental disorders as treatable, medical conditions has led to

improvements in care some countries and some situations, widespread stigma, racial disparities and misunderstanding prevail. The conditions under which people with mental disorders live in both rich and poor regions continue to be deplorable. In addition to restrictions on the right to work and to education they live in unhygienic and inhuman conditions, suffer physical and sexual abuse, neglect, and harmful and degrading treatment practices in health facilities. They are often denied civil and political rights and the right to participate in normal public life (WHO, 2008).

Mental health affects progress towards the achievement of several Millennium Development Goals, such as promotion of gender equality and empowerment of women, reduction of child mortality, improvement of maternal health, and reversal of the spread of HIV/AIDS” (Prince et al., 2007). For this reason the next iteration of the MDGs will take mental health into more specific consideration.

### **Barriers to Treatment: The Need for Innovative Solutions**

Despite growing awareness of the personal, social and moral burden of mental disorders globally, solutions are not easily found. While effective interventions are known for many of the most prevalent mental disorders, a large proportion of people with such problems do not receive treatment and care (Rebello et al., 2014). A large multi-country survey supported by WHO showed that 35–50% of serious cases in developed countries and 76–85% in less-developed countries had received no treatment in the previous 12 months. A review of the world literature found treatment gaps to be 32% for schizophrenia, 56% for depression, and as much as 78% for alcohol use disorders. Many

population-based studies have shown that more than 95% of people with epilepsy in many resource-poor regions do not receive adequate treatment (WHO, 2008). These numbers are strikingly high, particularly when known interventions exist that could enable many of these people to manage their health and greatly reduce the impact of the disorder.

The gap in mental health services between what is already known about treating these disorders, and the number of people who actually receive care, is quite large and cannot be resolved by extending current approaches that have been primarily developed in western countries. It will be essential to adapt known treatments and therapeutic approaches to local cultures and empirically document their effectiveness (Becker and Kleinman, 2012). Integration of mental health services into existing healthcare systems, using available healthcare workers, with a view to provision of holistic health care through the lifespan, will be required. Three specific barriers are often identified that must be overcome for this goal to be realized. These are described here, and then the potential for information technology to overcome these barriers is presented.

Perhaps the greatest barrier to development of mental health services has been the lack of attention to mental health as a serious public health issue among national leaders. This impacts financing available for mental health care. Governments have allocated relatively small amounts for mental health within their health budgets, and interest among NGOs and philanthropic organizations is lacking (Saraceno et al., 2007). Epidemiological data to inform policy makers is a first step to motivating governments – and empowering

reluctant leaders - to reallocate resources to accomplish the changes needed to improve mental health services. Importantly, epidemiological data, presented publicly and widely, may also be an antidote to the widespread stigma associated with mental disorders. Indeed, it has been found that mental health professionals and family members contribute to continuing stigma as much as anyone in society (Gray, 2002).

Another barrier concerns the organization of mental health services. The western approach concentrates mental health resources, and professionals, in large institutions, usually near big cities. These resources are generally inaccessible to rural populations. Those that are able to access these facilities are often isolated from their families and communities, are more expensive than community-based services, and are associated with inhumane conditions and increase stigma (Saraceno et al., 2007). Integration of mental health services effectively with primary and community care services is an important goal for overcoming the urban institutional model of mental healthcare. In many countries, the systems that provide primary health care are overburdened with high patient loads and lack of supplies. Moving mental health services to primary care settings is of course limited by the limited training of primary care providers in mental health care (Saraceno et al., 2007).

The lack of specialists with advanced training in behavioral health is often cited as the primary barrier to better mental healthcare in many regions of the world, including low- and high-income countries. A lack of trained personnel or lack of access to psychiatric and neurological services can prevent attention to the enormous burden of

mental disorders on many levels, tying together all of the barriers discussed. Capacity building with low-cost, easy to use screening and diagnostic tools is of paramount importance for overcoming all of these barriers (Bakare et al., 2012).

Innovative use of information technology can help to build capacity and overcome all of these barriers to expanding high quality mental healthcare among underserved populations. Before discussing the technology itself, a brief review of mental disorders as developmental brain disorders is given. This provides a foundation for considering mental disorders in the context of comprehensive, life-course management of general health and well being in community and primary care settings.

### **Mental Disorders are Developmental Brain Disorders**

Recognizing that mental disorders are brain disorders will go a long way toward removing the stigma associated with these conditions. This perspective also makes the integration of mental healthcare into primary care settings seem obvious. Most mental disorders follow a predictable developmental trajectory over time. The symptoms that define the disorder emerge over time, exhibiting neurodevelopmental etiologies. Half of all mental and neurological disorders of adulthood may have antecedents in childhood and 75% emerge before age 25 (Insel, 2014a). Changes in brain function must necessarily precede observed changes in behavior or the emergence of symptoms of mental disorders. This follows logically from the simple fact that the brain is the seat of all human thought and action. It is becoming increasingly evident that the brain is quite robust at preserving normal function. For example, 50% to 70% of dopaminergic neurons

in the substantia nigra – the part of the brain involved in Parkinson’s Disease, must be destroyed before symptoms of Parkinson’s Disease begin to become observable (Cheng et al., 2010). If this principle holds generally for most or all mental disorders, then clearly the most leveraged opportunity for invention to prevent or reduce the severity of these diseases, in terms of both personal suffering and economic impact, is childhood. Managing chronic disorders to achieve a normal quality of life necessarily *requires* that care be moved into distributed community and primary care settings.

Large amounts of money are spent on high-end brain research with expensive and complex equipment, with the promise of a future breakthrough that may cure specific mental disorders. The “cruel paradox” is that “while we chase the receding holy grail of future basic science breakthrough, we are shamefully neglecting the needs of patients who are suffering right now” (Frances, 2014).

Innovative adaptation of existing technology can enable mental disorders to be managed in a life course approach to healthcare in primary care settings. Many mental disorders, if detected early and treated as chronic disorders, can be managed, allowing a reasonably normal quality of life with existing treatments. There is unfortunately a lag in the applications and implementation of existing interventions that can improve people’s lives today. We do not need to wait for a breakthrough discovery to produce a “magic pill” to realize such a promise.

### Information Technology for Improving Mental Healthcare

Table 17 lists the primary barriers to improved mental healthcare in underserved populations along with information technologies that may be particularly useful for overcoming these. Examples of these uses are given and described further in the text below. These examples have either been developed as pilot demonstration projects or student class projects, if at all, and are presented in part to inspire new translational research projects to scale up these ideas into working clinical implementations.

Barriers	Technology	Examples
Lack of trained health workers	Community screening apps Mobile EEG-based screening	TQQ implemented in Sana mobile app Portable EEG with app connected to OpenMRS
Organization of services	Electronic Health Record (EHR) Electronic and online training materials	Connecting screening surveys to OpenMRS Use of online instructional materials to train community workers.
Lack of information at State and policy making level	SMS survey	MIT/USF Spring 2014 Global Health Informatics Project: Autism in East

Africa		
MIT/USF Spring 2014		
Public attitudes, stigma	SMS messaging, social media	Global Health Informatics
		Project: Autism in East Africa
		Africa

**Table 17. Existing information technology and how each may be used to overcome major barriers to better and more widely available mental healthcare services. (OpenMRS = electronic open medical record system ([www.openmrs.org](http://www.openmrs.org))).**

### *Mobile Apps for Task Shifting*

The single largest barrier to scaling up efficacious treatments for mental disorders is the enormous scarcity and inequality in the distribution of skilled human resources in low-resource settings. In many countries the scarcity of human resources and training is simply overwhelming. Delivery of mental healthcare traditionally requires specialists that simply are not available to deliver core services in many regions of the world (Kakuma et al., 2011). Three levels of mental health workers are typically identified: specialists, including psychiatrists, neurologists, psychiatric nurses, psychologists, and occupational therapists; non-specialist professionals, which includes physicians, pediatricians, nurses; and other professionals, which may include teachers, social workers and community health officers. While many professionals, such as teachers and community health officers, may be available, few have the training necessary to assess patients adequately.

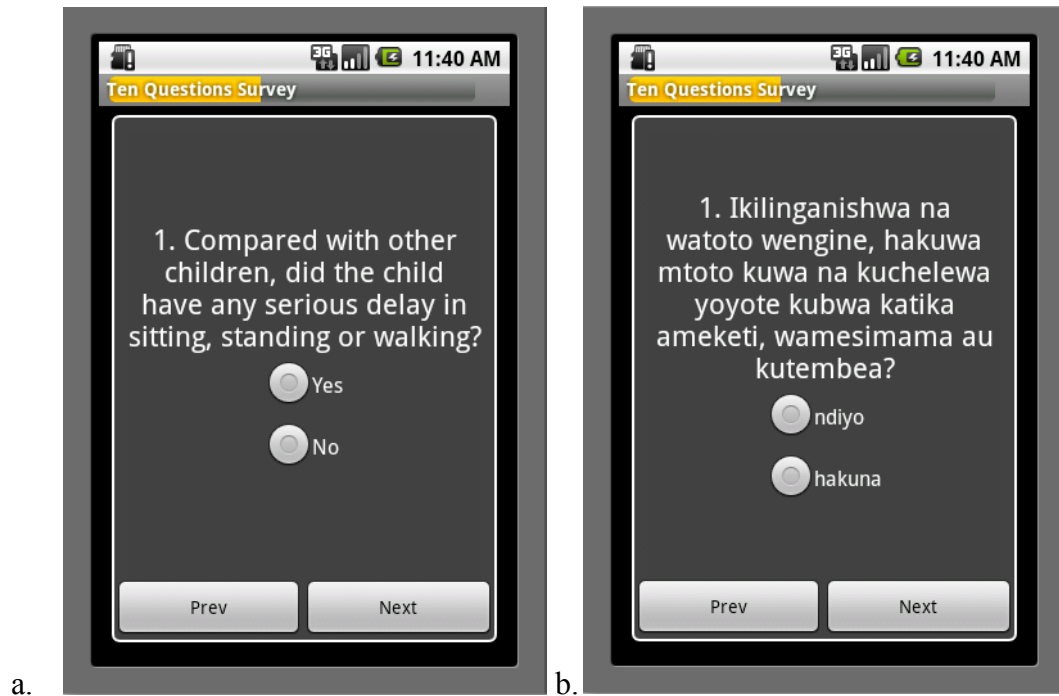
One approach to overcoming this shortage involves task shifting, which refers to the strategy of rational redistribution of tasks among available caregivers. The concept

involves highly trained healthcare specialists sharing specific tasks with health workers having less training and fewer qualifications in order to make more efficient use of the available human resources (Patel, 2012).

Technology can play a critical role in task shifting. “Transferrable technology” is a term that was introduced by (Holtzman et al., 1987) to describe technologies that can be effectively devolved from highly trained professionals to those with a lesser level of training (Nell, 2000). This concept is similar to task shifting, but focuses on the clinical task being performed rather than the persons carrying out the task. An example of how technology might be used for task shifting in mental healthcare can be illustrated with the Ten Questions Questionnaire (TQQ), a set of questions developed to rapidly screen children living in resource-poor countries, aged 2-9, for the most common moderate to severe neurodevelopmental disorders (Mung'ala-Odera et al., 2004). The TQQ can be used to compare the epidemiology of neurodevelopmental disorders in different parts of the world and to screen for moderately/severely impaired children in resource-poor countries. The low positive predictive values mean that other assessments are required for confirmation. The TQQ was augmented with 13 additional questions for detecting autism spectrum disorders (ASD) in Ugandan children. The 23-question screening tool (23Q) was found to be modestly successful in identifying a subgroup of children at especially high risk for developing autism spectrum disorders (Kakooza-Mwesige et al., 2014).

An example of transferrable technology for mental health screening among pediatric populations is illustrated in Figure 29. One of the TQQ questions is shown in

the figure in both English and Kiswahili spoken in Kenya. The questions were implemented in the Sana Android framework, which can collect data on a mobile device and upload the data to a medical database. Sana apps are designed to send data to an OpenMRS electronic medical record system ([www.openmrs.org](http://www.openmrs.org)), but others can also be implemented. With a small amount of training time, community workers can be trained to ask questions from an electronic form and type in the answers, which are then saved on the phone and uploaded to the internet when network connectivity becomes available. Remote computers can analyze and score the answers, followed by automatic feedback to the health worker. Additionally, epidemiological data becomes available as the population data accumulates. Because the questions in the survey can be controlled and updated remotely, it also becomes possible to adjust questions as needed. For example, additional questions could be added to the TQQ, such as the questions that are found in the 23Q, and immediately made available to all community health workers using that app. This enables lightly trained community workers to use the latest tools that are continually evaluated and updated in a central location by more specialized experts. This prototype awaits full implementation and field testing.



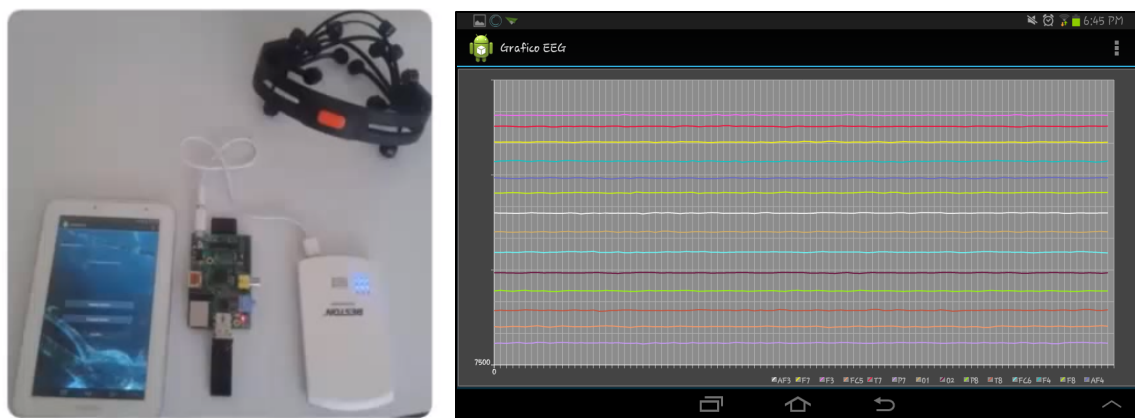
**Figure 29.** Mobile apps created with the Sana framework ([www.sanamobile.org](http://www.sanamobile.org)) by Bosl (unpublished) are illustrated here. One of the questions from the Ten Questions Questionnaire used to screen children for major neurodevelopmental disorders is shown here in both English (a) and Kiswahili (b).

The need for mental health specialists, particularly psychiatrists and neurologists, will continue even if task shifting is implemented extensively. Using mobile technology will enable the expertise of a few specialists to be transferred to many community workers.

### *Portable EEG Diagnostics*

A mobile system for collection of clinical and EEG data has been designed to support the initial assessment of neurological problems (Insuasty et al., 2014). The system demonstrates the possibility to collect data in a community clinic setting, upload data to a remote server where it may be reviewed by a specialized health professional

(medical doctor, specialist nurse, for example). Apart from the capacity to complete a standard medical assessment survey such as the TQQ, the system allows the capture of EEG signals by connecting a portable EEG device through Bluetooth. The information collected is stored in the mobile device and automatically sent (if an Internet connection is available) to the Medical Health Record application (OpenMRS) in order to be assessed by a specialist. The management functionality of the survey and its synchronization with OpenMRS are supported by the Sana platform. For the management of EEG signals, an Android application called NeuroSana was developed, as shown in Figure 30. Three principles guided the development of the system: openness, low cost, interoperability, which are important attributes for technology deployment in low income nations. The hardware and software were mainly supported by open source platforms and interoperability standards, e.g., Bluetooth, XML and the European Data Format (EDF) which is a simple and flexible format for the management of multichannel biological and physical signals such as electroencephalograms or electrocardiograms.



**Figure 30.** Shown here are an EEG device, mobile phone with hardware to capture EEG signal, and example signal display using the NeuroSana software described in (Insuasty et al., 2014).

*SMS (text) Messaging for Public Education on Autism*

Autism Spectrum Disorder (ASD) is a complex lifelong neurodevelopmental disorder, which is characterized by impaired social communication, impairment of language and abnormal behaviors. It has profound influence on the social functioning of the affected person and their family. It's impact is quite large due to its growing prevalence: “67 million people, (approx. 1 percent) of the world's population are affected by Autism Spectrum Disorder, a prevalence that is higher than AIDS, cancer and diabetes combined” (Smith, 2011).

Misinformed perceptions of ASD and its causes are aggravated in most African countries by many factors, including all of the barriers previously discussed. In many countries this dearth of knowledge and support is compounded by lack of a specific term to describe ASD. In cultures that are gregarious, there is often little tolerance for people who are unable to engage socially. Such perceptions are hard to shift, especially when children with ASD are frequently seen as blighted or bewitched – as a consequence of their parents' wrongdoing.

A pilot project was designed and tested by a group in the MIT Global Health Informatics program and led by William Bosl in the Spring of 2014 to evaluate the effectiveness of using SMS (text) messaging as a tool for participatory surveillance to measure public understanding of autism and related disorders in Kenya.

The project was intended as a pilot study of a larger goal to engage a Kenyan edutainment television program, Makutano Junction (MJ), with a viewership of 11 million in East Africa. The goal is to have MJ profile an *autism storyline* within a broadcast series. Questionnaires will be embedded in MJ's established SMS and leaflet information service to measure the impact such a storyline has had on knowledge, attitudes and claimed practices towards those affected by ASD.

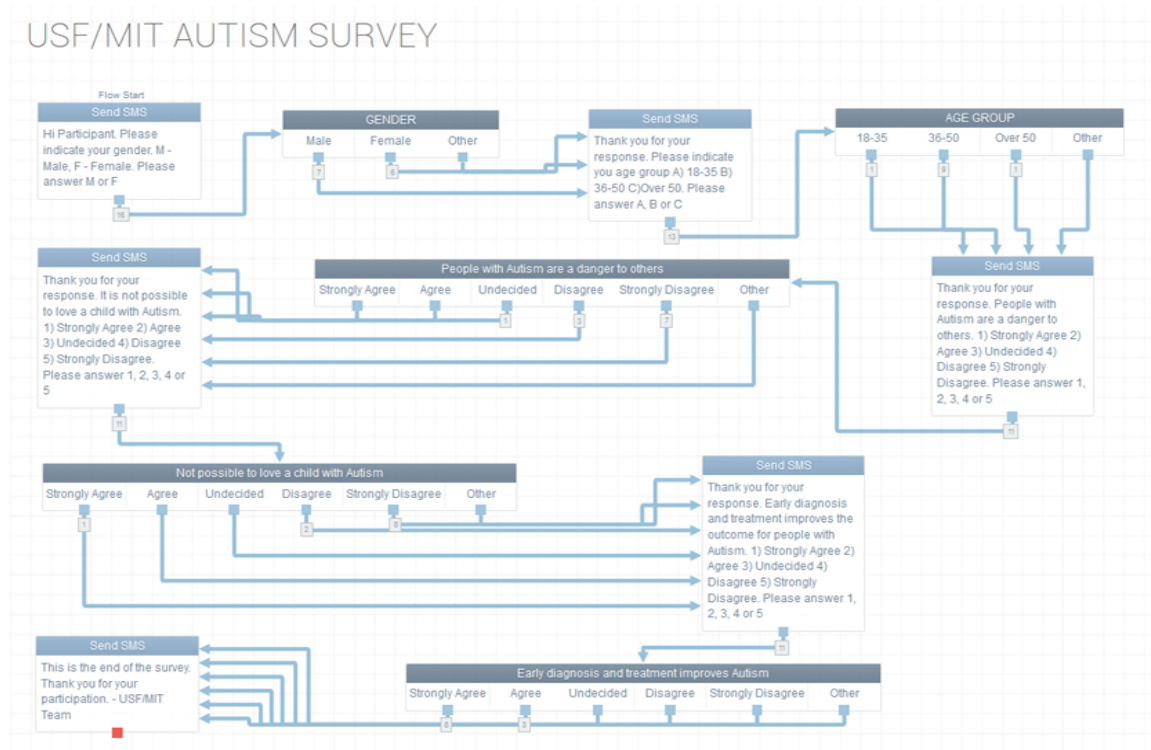
Using a commercially available SMS messaging service called Textit (<http://textit.in>) and mobile, bidirectional communications, a survey was designed and tested on a small population of students. The survey is designed to evaluate the effectiveness of targeted programming and the use of SMS technology as a methodology for participatory surveillance. SMS messaging is intended be used to support public information delivered through broadcasts by sending targeted messages to survey respondents.

TextIt is a platform for visually building SMS applications and sending text messages through a simple Android phone as a small-scale aggregator. For scaling up to very large populations, the TextIt application will be converted to the SMS aggregation facilities of Mediae Company for Education and Development. Figure 31 illustrates one of the survey questions that are sent via SMS. Responses from respondents are automatically accumulated by the Textit system and basic statistical analysis results are made available. More involved analytics can be run on large population data after the pilot stage when large data sets are collected.



**Figure 31. SMS messaging used for epidemiological surveys and for broad information campaigns to educate the public and reduce stigma.**

The findings from these impact assessments will be useful in planning future *Makutano Junction* shows to address related issues concerning mental health. Given that these findings will be representative of a cross-section of the community from three countries within East Africa, they will provide key insights on how to challenge stigma, reduce the isolation of those affected by ASD, and implement best practices for long-term support. Importantly, successful execution of this project on a large scale will provide information on mental health, and a means for collecting on-going data, that can be used by policy makers for planning and allocating resources for ASD and other mental health services.



**Figure 32.** Data flow design used for creating the pilot SMS survey to measure the effectiveness of an autism educational campaign on the public's knowledge of autism.

### *Electronic Health Records (EHRs)*

An important emerging theme in mental healthcare is the need to incorporate a life-course approach to the treatment of mental disorders, recognizing their developmental course and the need to monitor the course over time (Collins et al., 2011). This life-course approach requires that mental healthcare be integrated into routine primary care, which also opens up the possibility of early detection and intervention using a community and peer counseling care approach. Because of the need for primary care health workers to implement such integration, tools for task shifting are needed. Furthermore, some kind of electronic record must be kept for each patient that includes an objective assessment of the relevant associated symptoms, which then enables the

effectiveness of treatments to be monitored. An alternative is OpenMRS, an open-source, robust EHR platform that is supported by a global network of developers that has been used in over forty countries in the world (Fraser et al., 2012).

Electronic screening tools are needed in primary care settings to initially identify a behavioral health risk or condition, and are used in behavioral health settings to track patient's progress and outcomes. Integrated care requires the use of standard behavioral health screening and assessment tools, delivery of treatments, and evaluations of progress across care settings. Participants in a roundtable meeting in the U.S. Office for the National Coordinator for Health Information stressed the need for clinical decision support tools related to behavioral health (RTI\_International, 2012). This need is especially acute in low resource settings for task shifting. However, a search of the literature found no examples of actual implementation of EHRs in low resource settings specifically for screening and monitoring of mental health conditions. This is an area ripe for pilot and demonstration projects.

### **Steps to Adoption in Low Resource Settings**

Several questions must be answered at the level of local or national health ministries when considering the cost of scaling up mental health services in low income regions. A recent study assessed the resource needs and costs associated with scaling up a package of essential interventions for mental health care over 10 years. The core package for this project comprised pharmacological and psychosocial treatments of three mental disorders – schizophrenia, bipolar disorders, and depression – and brief interventions for

one risk factor – hazardous alcohol use. The results suggested that the extra cost of scaling up mental health services over 10 years to provide extensive coverage of the core package should be feasible in absolute terms, although challenging (Chisholm et al., 2007b). Estimates were approximately US\$2 per person per year in low-income countries and \$3-4 in lower middle-income countries, which were considered to be modest compared to the requirements for scaling-up of services for other major contributors to the global burden of disease (Chisholm et al., 2007a).

Studies that have attempted to estimate costs have been done, but appear to not yet take into account innovative uses of technology for task shifting, early detection, or life-course monitoring and treatment. While such estimates are difficult to make before the technology has been implemented, we suggest that economic estimates that attempt to incorporate the impact of innovative uses of technology, as described in this paper, might help to spur government investment in new technology development for this task. Integrated mental healthcare is feasible using emerging health informatics because the innovations needed for such integration into other health care platforms “are consistent with many efforts to strengthen the capacity of primary care systems to address multiple health priorities more broadly” (Patel et al., 2013)

## **Conclusions**

Mental disorders impose a significant disease burden on rich and poor nations of the world alike. The burden extends well beyond the suffering of the patients, affecting caregivers, families and communities. It can be a cause of poverty, and poverty

exacerbates mental disease by limiting access to therapeutic interventions that are known to be effective. Perhaps most compelling of all, the current state of mental healthcare globally has been called a moral failure of humanity due to the atrocious conditions under which many people with mental disorders are forced to endure.

Innovative adaptation of existing technology can enable cost-effective diagnosis and management of mental disorders in primary and community care settings. Many mental disorders, if detected early and treated as chronic disorders, can be managed, allowing a reasonably normal quality of life with existing treatments. The single largest barrier to mental healthcare in resource-poor settings is the enormous scarcity and inequality of skilled human resources in low-resource settings. One approach to overcoming this shortage involves task shifting, which refers to the strategy of rational redistribution of tasks among available caregivers. Information technology is an important enabler of task shifting. Several examples were presented in this chapter showing how mobile devices, including phones and EEGs, together with the growing universal accessibility of the Internet and cloud-based database resources, are being developed to meet the need for better mental healthcare globally. It is hoped that this chapter will provide some guidance and inspiration to health technology students and research groups to engage with mental health providers to create new tools to meet this enormous challenge.

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