# APPLICATION OF EEG MULTISCALE ENTROPY ANALYSIS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A Dissertation

by

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# ABSTRACT

Analyzing electroencephalography (EEG) complexity could provide insight into neural connectivity and its relationships with attention-deficit/hyperactivity disorder (ADHD) symptoms. I calculated multiscale entropy (MSE) within the EEG signal to evaluate the variability in brain activity and tested for differences between adults with ADHD and their peers during resting and go/nogo task states. MSE transitions (MSE-Δ) from the resting state to the active task state also examine the brain's ability to flexibly change from a resting state to an active state. Thirty unmedicated adults with ADHD were compared to thirty match-paired healthy peers on the MSE in the resting and active task states as well as the MSE-Δ. The MSE from Individuals with ADHD was smaller than their peers' in the resting state. Significant differences of the MSE-Δ were also observed between individuals with ADHD and their peers, specifically at frontal sites. Interestingly, individuals without ADHD performed better with decreasing MSE, showing higher accuracy, shorter reaction time, and a smaller standard deviation of reaction time. Significant correlations between MSE-Δ and task measurements were also confirmed in adults without ADHD, while greater MSE-Δ corresponded to better task performance. These findings suggest MSE could not only provide insight into brain activity complexity differences between adults with ADHD and their peers but also allow us to gain a better understanding of the relationship between brain activity complexity and behavioral performance.

# DEDICATION

This dissertation is dedicated to my family : parents, wife, daughter, and cat.

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# CONTRIBUTORS AND FUNDING SOURCES

## Contributors

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# NOMENCLATURE

| | |
|---|---|
| ACC | Accuracy |
| ADHD | Attention-Deficit/Hyperactivity Disorder |
| ASRS | Adult ADHD Self Report Scale |
| C REGION | Central Site |
| CFQ | Cognitive Failures Questionnaire |
| COMP | Comparison Group |
| DDT | Dynamic Developmental Theory |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EDT | Executive Dysfunction Theory |
| EEG | Electroencephalography |
| EEGLAB | MATLAB Toolbox for EEG Analysis |
| ERP | Event-Related Potential |
| F REGION | Frontal Site |
| GO ACC | Accuracy in the Correct Go Trials |
| GO RT | Reaction Time in the Correct Go trials |
| GO RTSD | Standard Deviation of Reaction Time in the Correct Go Trials |
| IC | Independent Component |
| ICA | Independent Component Analysis |
| MCI | Mild Cognitive Impairment |
| MSE | Multiscale Entropy |
| MSE-Δ | MSE Transition from the Resting State to the Active Task State |

| | |
|---|---|
| O REGION | Occipital Site |
| OST | Optimal Stimulation Theory |
| P REGION | Parietal Site |
| RT | Reaction Time |
| RTSD | Standard Deviation of Reaction Time |
| SASICA | Plugin to EEGLAB (Semi Automatic Selection of Independent Components for Artifact) |
| SRMT | State Regulation Model Theory |
| T REGION | Temporal Site |
| TBI | Traumatic Brain Injury |

TABLE OF CONTENTS

Page

LIST OF FIGURES

# LIST OF TABLES

TABLE Page

# 1 INTRODUCTION

## 1.1 Overview of ADHD

### 1.1.1 Description of ADHD

Attention-deficit/hyperactivity disorder (ADHD) is among the most common childhood neurodevelopmental disorders characterized by persistent behavioral symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association (APA), 2000). Such ADHD symptoms describe children's difficulty to keep focus, excess movement not fitting to the setting, and hasty acts occurring at the moment without thought. Each of these characteristics manifests in different settings and impacts on children's daily life and school performance.

ADHD was first identified and described as an abnormal defect of moral control in children by British pediatrician Sir George Still, in which affected children had difficulty in behavior control but displayed a normal intelligence level (Still, 1902). In 1952, the first edition of Diagnostic and Statistical Manual of Mental Disorders (DSM) was issued by APA, which didn't include ADHD. Hyperkinetic impulse disorder was recognized by APA in the second edition of the (DSM-II) in 1968. In the third edition of the (DSM-III) issued by APA in 1980, attention deficit disorder (ADD) was first defined and divided into two subtypes ADD with hyperactivity and ADD without hyperactivity. In 1987, the term ADHD was first introduced in DSM-III-R with the elimination of ADD without hyperactivity. In the 1990s, ADHD started to attract more attention from researchers. The number of children diagnosed with ADHD increased significantly and new medications were developed. With the publication of DSM-IV, the term ADHD was kept with the introduction of three subtypes, including Inattentive Type, Hyperactive-Impulsive Type, and Combined Type. To date, the publication of DSM-V made several modifications to ADHD diagnostic criteria and used the term "presentation" instead of

"subtype" (Epstein & Loren, 2013). Although there's general agreement that ADHD was mostly studied in children, the research of adolescents and adults with ADHD is getting more attention during the past few decades (Riccio et al., 2005; Kooij et al., 2010).

ADHD should be evaluated through a series of interviews by a qualified mental health care professional for parents and the child, who has shown academic or behavioral problems and symptoms like inattention, hyperactivity, or impulsivity. A report from the child's school regarding academics, social, and behavioral functioning is also necessary for ADHD diagnosis. These evaluations would provide necessary information to determine whether the individual meets the criteria for ADHD (Soffer et al., 2008; Sibley & Kuriyan, 2016; Hartung et al., 2019).

According to the American Psychiatric Association, a child needs to meet at least six symptoms of the criteria listed in DSM-V to be diagnosed for inattention and/or hyperactivity-impulsivity. Besides, such symptoms should be present before age 12 years and in two or more circumstances, such as school, home, or work.

### 1.1.2 ADHD impact at an individual level

Based on the statistics results from the CDC (Centers for Disease Control and Prevention (CDC), 2019), the population of children diagnosed with ADHD increases through the decades. According to a national survey in 2016, the estimated number of children diagnosed with ADHD is 6.1 million (9.4%), whose age is between 2 to 17 years old (Danielson et al., 2018). The estimated number of children diagnosed with ADHD varies markedly across different age categories and the effect of ADHD on the life of an individual also varies among different age groups corresponding to different ADHD stages (Kewley, 2001). In preschool, children with ADHD may stand out due to the appearance of poor concentration, high levels of activity, and impulsiveness. During primary school years, children with ADHD would experience academic

failure, rejection by peers, and low self-esteem, who may also face difficulties with family members at home (Harpin, 2005). As children with ADHD enter puberty, there might be a reduction in symptoms related to hyperactivity, as well as symptoms like inattention and impulsivity will remain difficult for individuals with ADHD, because of the change of emotional and social for adolescence, and increase of hormones. Besides the development of a distorted sense of self in the ADHD population (Krueger & Kendall, 2001), higher risk for developing aggressive and antisocial behavior are observed, such as conflict with parents and negative communication (Edwards et al., 2001; Harpin, 2005).

ADHD symptoms won't disappear when individuals grow into adulthood. Recent studies have shown a great portion of individuals diagnosed with ADHD in childhood (50% to 60%) would continue to show symptoms and have difficulties later in life (Gentile et al., 2006; Okie, 2006). According to diagnostic interview data from the National Comorbidity Survey Replication (NCS-R, Kessler, et al., 2006), there are about 4.4% of adults in the US who have ADHD. In adulthood, behavior symptoms of ADHD appear to blur (Riccio et al., 2005) the presentation difference evidenced in children. For example, hyperactivity may manifest as restlessness and inattention may present as low concentration (Sörös et al., 2019). Adults with ADHD are likely to deal with the following difficulties: a lack of motivation, poor attention to details, low frustration tolerance on certain levels, and deficient self-regulation. They would also struggle to complete their education and work, and more likely to engage in substance use and criminal activities (Wender et al., 2001; Mostert et al., 2018).

Compared with the child literature, relatively less is known about ADHD in adults, especially college students. College students with ADHD display an academic profile that differs from most individuals with ADHD (Weyandt & DuPaul, 2006; Woltering et al., 2013), who have

relatively good academic outcomes, appear to be minimally impaired on tests of neuropsychological function compared to their peers (Barkley, 2002; Weyandt & DuPaul, 2006). But college students with ADHD are struggling to complete their college education successfully (DuPaul et al., 2009), who are constantly at greater risk for academic and psychological difficulties (Weyandt & DuPaul, 2006). College students with active ADHD symptoms were found more likely to be engaged in substance use than healthy students (Upadhyaya et al., 2005), such as tobacco, marijuana, and alcohol. Furthermore, in a study by Shaw-Zirt et al., (2005), college students with ADHD showed lower levels of social skills and adjustment compared with the control group.

### 1.1.3 ADHD impact on society

The families of children with ADHD have to deal with a great number of behavior and education problems, which would not only impact on the children, but also the parents and siblings. Such disturbances would require parents to spend more time and energy, which are also frequently associated with extra stress in family and marital functioning (Harpin, 2005). In a survey of 66 families (Podolsk & Nigg, 2001), parents of children with ADHD expressed more role dissatisfaction than the control group. ADHD may cause a chronic and pervasive impact on the child and long-term stress to parents. Families affected by ADHD are at greater risk of mental health problems. Mothers of children with ADHD are found more likely to have depression (Faraone et al., 1995; Lee et al., 2013), but not for fathers (Segenreich et al., 2009; National Research Council, 2009). In Pelham & Lang's study (1999), parents of ADHD children are associated with increased alcohol consumption due to the extra stress.

Several studies (Birnbaum et al., 2005; Zhao et al., 2019; Minkoff, 2009) have indicated that ADHD would not only create increased mental stress on family members but also cause a

significant economic burden on the family. There are two parts included in the economic burden. First, the cost of healthcare management for the family and, secondly, the economy in general, through reduced productivity, increased accidents and increased criminal activity. Raising a child with ADHD for example (Zhao et al., 2019), individuals with ADHD incur a total economic burden throughout child development that is more than five times greater compared with children without ADHD. The rough estimation of the annual societal cost of illness (COI) of ADHD in children and adolescents is $124.5 billion US dollars (Zhao et al., 2019).

The economic burden caused by ADHD in the healthcare system cannot also be ignored, which may be related to frequent prescription refills, doctor visits, and counseling sessions. According to IMS Health, sales of prescription drugs for ADHD treatment have more than doubled, from $4 billion in 2007 to $9 billion in 2012 (Hayden et al., 2016). In one consumer reports survey, thirty five percent of parents mentioned their costs of treating ADHD is completely covered by their child's health plan. Fourteen percent of school-age children covered by Medicaid are diagnosed with ADHD. In other words, taxpayers are paying for ADHD treatment.

Children with ADHD require more attention or supervision from parents at home, who also need help from their teachers in the school. Children with ADHD experience more obstacles in their study than the average student because they have difficulty in paying attention, sitting still, and controlling their impulses. But studies have indicated teachers have a limited understanding of ADHD related behaviors (Ek et al., 2011). With accurate diagnosis and proper understanding of their behavior, children with ADHD would receive help and be treated more effectively in the school (Nelson & Williamson, 2004).

There are several things schools could offer for students with ADHD, such as behavioral classroom management and organizational training. In the standard classroom environment, students are expected to sit still and patiently wait their turn to participate in class activities, which is relatively difficult for children with ADHD. The behavioral classroom management strategies encourage students' positive behaviors in the classroom through a reward system (Morisoli & McLaughlin, 2004; Evans et al., 2014). Organizational training teaches students skills for time management and planning, and methods to organize school materials to improve learning and reduce distractions. Special education and classroom accommodations are also recommended for students with ADHD, which would reduce distractions and workload for students (Moore et al., 2018).

According to a study from Robb et al. in 2011, students with ADHD incur a higher cost to the U.S. education system, amounting to about $5.007 to society per student as compared to $318 for students without ADHD.

In addition to the impact on the family, healthcare system, and education system, there is a long-term risk for children with ADHD to develop antisocial behavior and get involved with criminal activity in their adulthood (Fletcher & Wolfe, 2009; Mohr-Jensen & Steinhausen, 2016). Impulsivity, known as lack of self-control, may be the most important factor for the development of antisocial behavior (Vazsonyi et al., 2017).

In Silva et al.'s study (2014), community correction and incarceration records were more frequent among children and adolescents with ADHD compared with their healthy peers. Furthermore, boys with ADHD were more likely to have a community correction record than girls with ADHD. Early diagnosis and management of ADHD could reduce the over-representation of children with ADHD within the juvenile justice system. In a long-term study of

childhood ADHD on criminal activities (Fletcher & Wolfe, 2009), children who have shown symptoms of ADHD are more likely to get involved in criminal activities and dangerous behavior than other individuals as young adults.

Several studies have shown that ADHD in childhood is a risk factor for substance abuse (Wilens et al., 1998; Wilens, 2004; Biederman et al., 2006; Mochrie et al., 2020), who would get substance dependence more rapidly and last longer than their healthy peers. Several explanations have been found to explain this relationship, such as poor self-regulation, impaired reward system, demoralization experience, and self-medication.

### 1.1.4 Theories regarding ADHD

As mentioned above, ADHD is one of the most common neurodevelopmental disorders, which has a significant impact on individuals, family, and society. There are several psychological theories developed for ADHD (Zentall, 2005; Johnson et al., 2009), including Optimal Stimulation Theory, State Regulation Model Theory, Dynamic Developmental Theory, and Executive Dysfunction Theory.

The Optimal Stimulation Theory (OST) describes an individual's desire for stimulation as a living creature seeking food, which suggests an individual tries to maintain an optimal level of stimulation.

According to Zentall's study (2005), individuals seek stimulation when they are bored and individuals are under stress or anxiety when they are overstimulated. OST suggests hyperactive behavior in individuals with ADHD is for stimulation optimization, not for too much stimulation. Teachers report the most incidents of hyperactivity for students with ADHD in the classroom during periods of inactivity, which is not noted during periods of excessive hyperactivity. In Johnson et al. 's work (2009), students with ADHD performed poorly when the

stimuli were presented slowly and they worked better when the information was presented rapidly.

In the State Regulation Model Theory (SRMT), the non-optimal energetic state is used to explain the deficits in children with ADHD, which is based on research using Cognitive-Energetic Models (Sanders, 1983; Metin, 2013). The SRMT postulates if the children with ADHD have difficulties regulating their energetic state, which is related to the arousal, activation, and effort levels of the children (Van De Voorde et al., 2010). An effort is necessary to perform cognitive tasks and to compensate for suboptimal states of arousal. Children with ADHD might not be able to keep an optimal activation state due to an inefficient effort. Several psychophysiological studies have been carried out to confirm the validity of this theory. Higher heart rate variability and reduced parietal P3 amplitude were found during slow reaction conditions (conditions with increased reaction time and poor performance) among children with ADHD in the go/nogo task experiment, both of which suggest inefficient effort allocation (Börger & van der Meere, 2000; Wiersema et al., 2006).

In the Dynamic Developmental Theory (DDT), the behavioral manifestations of ADHD are explained from a neurotransmitter level through to a societal level, which suggests the two main mechanisms to explain all ADHD core symptoms: “altered reinforcement of novel behavior” and “deficient extinction of inadequate behavior” (Sagvolden et al., 2005). The DDT postulates that the time window for reinforcement to take effect is shorter for individuals with ADHD, which suggests the desired behavior is not reinforced in time and related to several symptoms of ADHD. The DDT also presumes the extinction procedure is faulty and associated with ADHD symptoms because of the lower tonic level of dopamine, which is also tested by several studies (Sagvolden et al., 1998; Aase, H., & Sagvolden, 2005).

Executive Dysfunction is one term that describes deficits in several cognitive functions, such as planning, reasoning, working memory, inhibition control et al. (Alvarez & Emory, 2006; Mesulam, 2002). Executive functioning relates to neural circuits that link the frontal sites with the parietal region, the basal ganglia, and the thalamus (Middleton & Strick, 2002; Bradshaw & Sheppard, 2000). Extensive studies have revealed structural differences between children with ADHD and their peers in fronto-parietal and fronto-striatal circuits (Seidman et al., 2005). The Executive Dysfunction Theory (EDT) postulates the symptoms of ADHD as a result of deficits in executive function control, which is associated with abnormalities in certain neural circuits. Although many studies have adopted the EDT, the understanding of the neural mechanism of ADHD is still limited, due to the poor comprehension of cognitive and motor processes related to tasks (Johnson et al., 2009).

### 1.1.5 Executive function deficits in ADHD

As mentioned in the previous paragraph, executive function is defined as a series of cognitive processes that are necessary for behavior control, such as attention control, inhibition control, working memory, and cognitive flexibility. ADHD is usually characterized by three core symptoms, including inattention, hyperactivity, and impulsivity. Several authors highlight the role of executive function impairments in individuals with ADHD (Barkley, 1997; Castellanos & Tannock, 2002). Furthermore, impairments in several domains of executive function have been observed consistently in the adult ADHD population, including attention, inhibition, reasoning, planning, and working memory (Barkley, Murphy & Fischer, 2010). Due to the lack of support from teachers and parents, adults with ADHD are relying more on their executive function and dealing with more demand for self-regulation, time management, responsible behavior,

organization, social skills, planning for the future (Barkley & Murphy, 2011; Schoemaker et al., 2012; Craig et al., 2016).

Cognitive flexibility, as one executive function, is defined as the mental ability to switch between two different concepts, which plays a key role in individuals' ability to adapt to changing environments (Scott, 1962; Gabrys et al., 2018).

As shown in Figure 1, several domains of executive function act coherently to cognitive flexibility (Dajani & Uddin, 2015), which allows individuals to identify how the surrounding environment has changed by directing attention. After detecting new stimuli, individuals need to inhibit their previous response and generate new strategies, which might involve working memory and switching attention.

In a recent study (Roshani et al., 2020), the ADHD group had significantly low cognitive flexibility and worse task performance than the control group. Several fMRI studies have shown brain regions which are related to cognitive flexibility, are less active in individuals with ADHD (Leber et al., 2008; Wixted et al., 2016).

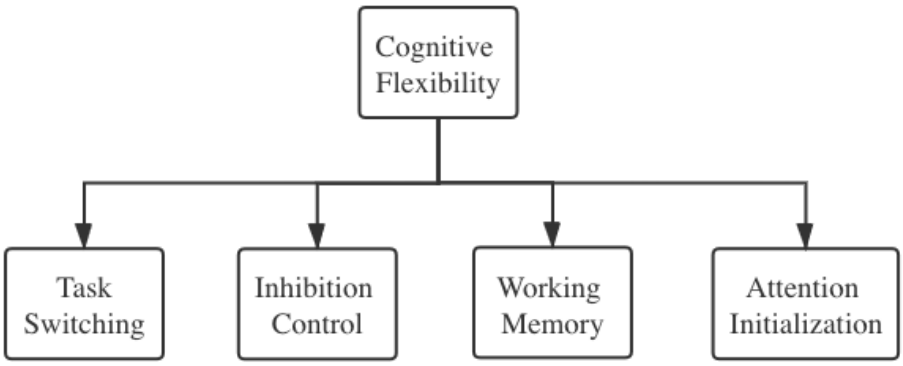


**Figure 1** Cognitive processes, adapted from (Dajani & Uddin, 2015).

Extensive research has been done to investigate the neural mechanism of ADHD and demonstrate abnormal neural connectivity is associated with executive dysfunction symptoms in the ADHD population (Bollmann et al., 2015; Biskup et al., 2016; Petrovic and Castellanos 2016; Kumar et al., 2016). Deficient inhibitory control, such as inhibition of a prepotent response or an ongoing response, has been postulated to be a core deficit in ADHD (Barkley, 1997; Hervey et al., 2004). Deficits in two types of attention (e.g. Selective Attention (Mason et al., 2005) and Sustained Attention (Egeland et al., 2009)) have also been described for individuals with ADHD (Mueller et al., 2017). A better theoretical understanding of the neural mechanisms underlying the difficulties associated with ADHD, and the college student subpopulation, in particular, may inform the development of diagnosis protocol and interventions designed to increase academic achievement in this population (Barkley, 1997).

### 1.2 EEG analysis of ADHD

Electroencephalography (EEG) is a non-invasive neuroimaging technology, which measures electrical activity by placing electrodes on the scalp (Gibbs & Gibbs, 1941; Michel & Murray, 2012; Britton et al., 2016). Characterizing EEG data has provided valuable information on cognition and mental health (Banquet, 1973; Woodman, 2010; Luck, 2014). Since Jasper et al. (1938), electroencephalography (EEG) has been used in ADHD research for more than 80 years, in which a slowing of the EEG rhythms was observed at frontal-central sensors (Lenartowicz & Loo, 2014). Currently, the EEG analysis in ADHD mainly focuses on the temporal (Event-Related Potential, ERP) and frequency domains (Frequency Spectrum).

#### 1.2.1 ERP analysis in ADHD

Event-related potential measures the brain response to a specific sensory, which is achieved by averaging EEG over trials (Sur & Sinha, 2009; Woodman, 2010). Compared with

behavior measurements, ERP could reliably capture the neural activity related to cognitive progress, because (1) The invariable latency and shape of the ERP wave characterize related cognitive progress; (2) The noise contained in the EEG signal can be averaged out by the phase cancellation. Compared with fMRI analysis, ERP has a high temporal resolution. In other words, peak amplitudes or latency features in ERP waveforms could provide insight into time-locked events.

ERP is widely used in studies about cognitive processing deficits in individuals with ADHD (Woltering et al., 2013; Jahanshahloo et al., 2017; Leontyev et al., 2018). Concrete evidence for deficits in inhibitory control in individuals with ADHD is found in the go/nogo experiment, which has been widely used to study the response control process. The previous investigation on the EEG recorded from college students with ADHD during a go/nogo task showed significant reductions in P3 amplitude as well as a trend for reduced N2 amplitude in nogo trials where subjects successfully inhibited a response (Woltering et al., 2013).

### 1.2.2 Neural oscillation in ADHD

Neuronal oscillations are an important mechanism enabling coordinated communications in a neural network (Buzsáki & Draguhn, 2004), which are widely studied in EEG data. In general, there are three kinds of information in neural oscillation, such as frequency, phase, and amplitude. Neural oscillation is normally studied by calculating frequency spectrum over specific frequency bands, including delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–30 Hz), low gamma (30–70 Hz), and high gamma (70–150 Hz) frequency bands. Compared with the ERP approach, the frequency spectrum is able to not only analyze brain activity during the resting state, when there's no time-locked event happening but also analyze event-related brain activity, which requires the time-frequency spectrum analysis. The time-frequency approach

could provide information on the time and frequency domain at the same time with limited resolution (Roach & Mathalon, 2008; Sharma et al., 2017).

In a study related to ours (Woltering et al., 2012), EEG oscillation power during the resting state revealed that college students with ADHD showed a distinct neural pattern, suggesting that oscillatory power, especially alpha band, is a useful index for reflecting differences in neural communication of ADHD in early adulthood. Abnormal oscillatory activity over the alpha band was also found during the attention and working memory tasks (Lenartowicz, 2018). Furthermore, the most robust neural oscillation features associated with ADHD are increased power in the theta band or decreased power in the beta, which is combined and developed as the theta/beta ratio to assist ADHD diagnosis (Barry, 2003; Arns et al., 2013).

### 1.2.3 Disadvantage of tradition EEG analysis

Although traditional EEG analysis approaches could provide valuable information on cognition and mental health (Banquet, 1973; Woodman, 2010; Luck, 2014), there are certain disadvantages for them. The ERP method is unable to analyze EEG components not synchronized by time or phase, which will be averaged out through phase cancellation (Beres. 2017) and the frequency spectrum analysis is not sensitive to non-sinusoidal EEG oscillations, which shows up as harmonics in Fourier transform (Lozano-Soldevilla et al., 2016). Besides these limitations, both of these methods are based on linear operations, such as averaging and Fourier transform, which could not extract nonlinear dynamical features from EEG data. Lack of nonlinear methods of analyzing EEG is a major barrier to understanding dynamic neural processes.

## 1.3 EEG complexity

### 1.3.1 Background knowledge

The brain can be seen as a nonlinear dynamical system at multiple levels, from ionic currents in neurons to constant fluctuations in functionally specialized neural assemblies, to long-range interactions across assemblies through the brain (McKenna et al., 1994; Freeman, 1994; Faisal et al., 2008; Goldman 8et al., 2019). A neural assembly is defined as a group of neurons that are reciprocally connected (Harris, 2012), which would allow the whole assembly to be activated together. Characterization of the nonlinear property of the dynamical system is fundamental to understand brain function.

This dynamical neural network is still poorly understood (McIntosh et al., 2008). In Takahashi's work (2013), the human brain is characterized by "dynamical neural communications in functionally specialized assemblies" and " long-range mutual interactions across these assemblies". Consequently, the application of nonlinear analysis to the brain's activity would provide new insights into its function.

The electroencephalogram (EEG) signal is noisy, constantly varying, and can provide rich information about the underlying neural dynamical system generating thoughts and behavior (Gao et al., 2011). Researchers have typically assumed that variations in the EEG signal represent noise (Frank et al., 1999; McIntosh et al., 2008), however, a growing body of research reveals that the complexity in EEG is essential for several cognitive processes, such as sensory differentiation, learning and decision making (Pinneo, 1966; Garrett et al., 2013; Liu et al., 2019). EEG complexity has proven valuable in characterizing brain dynamics during different mental states (McIntosh et al., 2008; Li et al., 2008; Bassett and Gazzaniga, 2011). As shown in Armbruster-Genç et al. 's work (2016), increased brain signal variability in the left inferior

frontal junction region is correlated with better task performance and higher cognitive flexibility, which has a negative effect on cognitive stability.

There are several EEG complexity measurements used in the research of neuropsychology and mental disorders, such as the Correlation dimension, Omega complexity, Lyapunov exponent.

The correlation dimension is the one most widely used complexity measurement, which represents the degree of freedom of a dynamic system (Boon et al., 2008). A higher correlation dimension during resting state was observed in the lower 2-8 Hz frequency ranges among individuals with Alzheimer's disease (van Walsum et al., 2003).

The omega complexity is considered as one indicator of spatial complexity, which is calculated as “Shannon entropy of the eigenspectrum of the covariance matrix of neural signals” (Wackermann, 1996; Jia et al., 2018). Increased omega-complexity was observed in the 0.5–25 Hz frequency ranges among individuals with Alzheimer's disease (Czigler et al., 2008).

The Lyapunov exponent is one of the most commonly applied tools to predict the influence of perturbations on the solution of a system, which can be considered dynamic measures of attractor complexity (Valenza et al., 2014). An alteration of the Lyapunov exponent was observed during sleep in depression patients (Röschke et al., 1994).

### 1.3.2 Theoretical framework for EEG complexity

A number of theories explain the functionality of EEG complexity, such as dynamic range (Shew et al., 2009), Bayesian optimization (Beck et al., 2008), and itinerant dynamics (Friston et al., 2012) theory.

In the dynamic range theory (Shew et al., 2009), increased brain signal variability indicates a greater dynamic range, which means the brain has a greater range of responses to a

larger range of stimuli. The greater dynamic range could be generally beneficial and allow the brain to adapt to a new environment efficiently. According to Shew et al., (2009), one healthy brain could achieve optimal dynamic range when the balance between synaptic excitation and inhibition is achieved. With a greater dynamic range, the brain could have higher information capacity and processing ability.

Under the theory of Bayesian optimality (Beck et al., 2008), a group of neurons will converge one response that approaches the theoretical optimal selection from a group of potential responses. If a group of neurons fires up at the same time when a specific stimulus is encountered, individuals would be less capable to adjust to different circumstances that involve the same stimulus. In other words, individuals won't be able to make appropriate responses to the same stimulus under different circumstances. Increased brain signal variability relates to a broader probability distribution for networks to make optimal responses, given certain stimulus input. In general, the variability in brain activity could support the neural network to be more reliable and adaptable to converge responses in the existence of stimulus uncertainty.

Finally, in the itinerant dynamic theory (Friston et al., 2012), the brain tends not to settle to any particular state but instead explores from one state to the next across moments, which is described as itinerancy dynamic or wandering dynamic. There are several connectionist conceptualizations of how the itinerancy dynamics emerge and manifest in the complex neural system. For instance, a group of relatively weak attractors, such as Milnor attractors, stay close to each other and enable the itinerancy, while there's no attractor dominating the circumstance (Friston et al., 2012). Another theory refers to the itinerancy dynamics of multi-stability in the system. In such a scenario, the noise related to the attractor, which is stronger than Milnor attractors, would drive the system from one attractor to another across moments. In general, the

itinerancy dynamics would represent the certain flexibility of the brain and drive the system to detect novelty, explore alternative states, and converge optimal responses to stimuli. Increased variability in the brain activity suggests larger itinerancy of the neural system which could translate into more flexible formation and utilization of functional modules. In the proposed study, I will largely adopt the itinerancy theory as it relates to attention to my theoretical framework.

### 1.3.3 EEG complexity during different states

In Pinneo, (1966), brain activity was divided into tonic and phasic activity. The tonic activity represents the brain's default activity and provides the substrate for brain function (Arduini, 1963), which is typically studied through spontaneous brain activity during resting states. The phasic activity represents the stimulus-driven brain activity, which is a relatively small portion of evoked brain activity during active task states (Lashley, 1951). As mentioned by Arieli et al. (1996), "the effect of a stimulus might be likened to the additional ripples caused by tossing a stone into a wavy sea". Many extant studies suggest such "ripples" in brain activity can be a functional extension beyond the tonic and phasic activity. The investigation of EEG complexity during resting and active task states could evaluate the tonic activity and phasic activity respectively.

During the resting state, participants are not performing specific cognitive tasks or responding to external sensory stimuli. The spontaneous brain activity measured on the scalp during the resting state is constructed by electrical activities from distributed sub-networks (Deco et al., 2011). Each sub-network is representing one functional module and the configuration of these functional modules can be seen as a representation of the spontaneous brain network (Deco and Jirsa, 2012).

EEG complexity during resting states has been related to maturation and psychopathology (Li et al., 2008; Fair et al., 2009). For example, EEG complexity during resting states increases with the maturation of the nervous system (Meyer-Lindenberg, 1996; Lippé et al., 2009). Related to mental health, EEG complexity from abstinent heroin addicts, schizophrenia, and the depression groups during resting states was higher than those from healthy subjects (Li et al., 2008; Zhao et al., 2017). Studies show that increased EEG complexity in the resting state may lead to higher sensitivity to negative emotion and reflect distorted sensory perception. Taken together, these findings suggest that increased EEG complexity during resting state may represent larger itinerancy of the brain, suggesting excessive dynamical instability of the perception system (Friston et al., 2012), which might explain a non-optimal degree of cognitive flexibility.

During an active task state, participants are performing cognitive tasks, by processing stimuli or making responses. The evoked brain activity measured on the scalp contains tonic activity and phasic activity, and the phasic activity is largely dependent on the stimuli (McIntosh et al., 2008; Garrett et al., 2013). The evoked brain activity is constructed by electrical activities from distributed functional sub-networks, and the landscape of these functional modules appears driven by task requirements (Knyazev, 2007; Broyd et al., 2011; Sokhadze et al., 2012).

EEG complexity during active task states has also been related to maturation, cognitive performance, and mental health. In a study by McIntosh et al. (2008), the EEG complexity in a face memory task not only increased with maturation but also positively correlated with task performance. In a study on executive function (Grundy et al., 2019), participants performed a bivalency effect task-switching paradigm. Increased EEG complexity was found associated with increased task difficulty and better adaptation to task demands. In a study by Catarino et al.,

(2011), participants with Autism Spectrum Disorder (ASD) and their peers performed the face and chair detection task, in which they were asked to press a button when they saw a repeated image of the corresponding category. In the Autism group, lower EEG complexity was found at temporoparietal and occipital regions compared with the healthy control group. Taken together, these findings suggest that increased EEG complexity during tasks may represent larger itinerancy of the brain to satisfy high-level task requirements, which might suggest an optimal degree of cognitive flexibility and decision optimization (Garrett, et al., 2013).

### 1.4 Multiscale entropy

Multiscale entropy (MSE) is one physiological signal analysis method, which is becoming popular in EEG research. Interpreting the MSE within EEG could extract dynamic features and provide insight into the neural mechanisms of mental disorder, such as ADHD. MSE measures the temporal complexity of finite-length sequences by estimating the sample entropy of the data downsampled by different time scales (Richman and Moorman, 2000; Richman et al. 2004). MSE at small scales and large scales represented information processing within local and distributed neural networks across brain regions, which corresponded to functional connectivity at low and high frequencies (McIntosh et al., 2014; Wang et al., 2018).

Sample entropy was introduced by Richman & Moorman (2000), which captures the unpredictability of the data and evaluates the appearance of repetitive patterns (Escudero et al., 2006). In other words, sample entropy evaluates the conditional probability that two consecutive data sequences, which are similar to each other, will keep the similarity within the same tolerance when the next point is included. Sample entropy would assign high values to random signals and low values to highly deterministic signals.

MSE could access the information represented by the unpredictability in the data over different time scales, in which the coarse graining procedure is necessary. The coarse graining generates new data sequences by averaging the original data points within non-overlapping windows whose length is corresponding to time scales. Regarding the nature of the coarse graining procedure, MSE is designed to evaluate the high frequency temporal complexity across fine scales (e.g., 1-6) and low frequency temporal complexity across coarse scales (15-20), which could reveal local information processing and long-range interaction with other regions respectively (Vakorin et al., 2011; McDonough & Nashiro, 2014; Wang et al., 2016).

**1.5 Innovation and hypothesis**

During the last decade, several studies applied MSE to better understand cognitive functioning and mental health. For example, bilingual individuals were found to have higher MSE than monolinguals in occipital regions during a task-switching experiment (Grundy et al., 2017). Lower MSE was found in patients suffering from traumatic brain injury (TBI), while increased MSE indicated improved behavioral improvement in TBI patients (Beharelle et al., 2012). Furthermore, there's concrete evidence suggesting that individuals with Mild Cognitive Impairment (MCI) had lower MSE than their healthy peers and higher MSE than patients with Alzheimer's disease (McIntosh, 2018).

To the best of my knowledge, MSE has only been applied to a few ADHD studies.

In a study by Chenxi et al. (2016), MSE was used to explore the dynamical complexity of the brain over different scales. Thirteen children diagnosed with ADHD and thirteen gender and age match paired healthy peers were recruited to conduct multi-source interference tasks. MSE in the delta, theta, alpha, and beta frequency bands were calculated across twenty time scales. MSE in the delta and theta frequency bands was higher among children with ADHD compared to their

peers, while MSE in the alpha frequency band was lower. These findings of MSE over different frequency bands could reveal aberrant neural connectivity associated with ADHD, which suggested weakened long-range connection and enhanced local connection.

In Boroujeni et al. 's work (2019), several nonlinear features of EEG were introduced to distinguish children with ADHD and their peers, including Lyapunov exponent, fractal dimension, correlation dimension, sample entropy, fuzzy entropy, and approximate entropy. Fifty children diagnosed with ADHD and twenty six healthy children were recruited to participate in the Continuous Performance Test. EEG data were collected under three different conditions, including eyes closed resting state, eyes open resting state, and cognitive task state. Sample entropy and other nonlinear features were calculated to train classifiers for ADHD diagnosis and yield high accuracy.

Previous studies propose different MSE patterns between children with ADHD and control groups (Chenxi et al. 2016), but whether the difference in MSE is also found between adults with ADHD and their peers has not been explored. Furthermore, there's an urgent need to fill the gap between abnormal MSE patterns and executive function deficits within a theoretical framework. And as far as we know, MSE transition from the resting to active task state has not been reported, which could reveal the transition between tonic activity and phasic activity (Pinneo, 1966; Radulescu, 2010; Mastrovito, 2013). In the current study, college students were recruited to participate in two resting sessions and a series of go/nogo tasks (Woltering et al., 2012; Woltering et al., 2013), while EEG was recorded to investigate the brain signal complexity.

To determine if MSE was a promising candidate for a neurocognitive endophenotype of adult ADHD, my study aimed to calculate and analyze MSE across different mental states, by testing three main hypotheses:

1) In the resting state, MSE from the ADHD group was expected to be lower than that from the comparison group. The MSE in the resting state could provide information about cognitive flexibility (Chén et al., 2019). Cognitive flexibility was found significantly lower in individuals with ADHD than the healthy control group (Roshani et al., 2020), which was also negatively correlated with the level of hyperactivity/inattention symptoms (Farrant et al., 2014). Decreased cognitive flexibility was found to be associated with reduced brain activity variability (Armbruster-Genç et al., 2016), which suggested lower MSE from the ADHD group in the resting state.
2) In the go/nogo task state, MSE from the ADHD group was expected to be higher than that from the comparison group. The MSE in a series of continuous go/nogo tasks could provide information about cognitive stability (Mestanikova et al., 2015). Individuals with ADHD would have difficulty sustaining attention during tasks (Nowacek & Mamlin, 2007). Brain activity variability had a detrimental effect on cognitive stability (Armbruster-Genç et al., 2016), which suggested a larger MSE from the ADHD group in the go/nogo task state.
3) From the resting state to the active task state, the MSE transition in the comparison group was expected to be larger than that from the ADHD group. Individuals with ADHD would have difficulty coming to attention and difficulty sustaining attention (Nowacek & Mamlin, 2007). Furthermore, I presumed individuals with ADHD would not be able to

change their brain flexibly for cognitive tasks, which suggested individuals with ADHD would have a smaller change of MSE than their healthy peers.

Additionally, brain activity variability was found correlated with task performance measurements, such as accuracy, reaction time, and standard deviation of reaction time, for healthy individuals (McIntosh et al., 2008; Armbruster-Genç et al., 2016). MSE in the active task state was expected to be correlated with behavior performance, while this relationship would not be found in individuals with ADHD. Change of MSE from the resting state to an active task state would represent the ability to change the brain to satisfy task requirements, which was expected to be related to behavioral performance in the comparison group.

The application of EEG multiscale entropy analysis in ADHD could evaluate EEG complexity over different time scales and identify their relationships with behavior performance, cognitive flexibility, and cognitive stability. The comprehensive interpretation of the MSE complexity over different mental states could provide insight into the neural mechanism of ADHD.

# 2 METHODOLOGY

## 2.1 Participants

For this study, 73 students were recruited from the University Student Service with attention-deficit/hyperactivity disorder (ADHD). For the healthy comparison group (COMP), 30 healthy students were recruited through campus advertisements. Table 1 shows basic information regarding the sample's demographics.

Inclusion criteria for the ADHD group were (1) A previous diagnosis of ADHD, and (2) Registration at the college Student Disability Services, which required supporting documentation proof. All participants were asked to finish the Adult ADHD Self Report Scale (ASRS v1.1, Kessler et al., 2005) to assess their current symptoms of ADHD. Three exclusion criteria (for control and ADHD group) were defined as (1) Uncorrected sensory impairment; (2) Major neurological dysfunction; (3) Mood affecting medication rather than a prescription for ADHD.

I also used the ASRS and Cognitive Failures Questionnaire (CFQ) to support my classification of ADHD subjects. Participants in the ADHD group had evidence of a DSM-IV diagnosis of ADHD as provided by the university student disability services.

To investigate the difference of MSE between adults with ADHD and their peers, 30 unmedicated college students with ADHD were pair-matched with 30 peers on gender (15 male, 15 female) and age (mean age 23, sd = 3).

**Table 1** Demographic data for all groups

| | COMP | ADHD | All |
|---|---|---|---|
| Male | 15 | 39 | 54 |
| Female | 15 | 34 | 49 |
| Age | 23 (3.4) | 24 (3.6) | 23.7 (3,7) |

### 2.2 EEG data acquisition

The EEG data used for examining the MSE in the resting state and active task state was acquired in one experiment, including two resting sessions and one task session (a series of go/nogo tasks).

Participants were asked to sit in a comfortable chair in front of a screen and wore a 129 - electrode EEG net (Electrical Geodesic Inc., EGI). Participants sat in front of a 17-inch VGA monitor at a distance of approximately 80cm. EEG data were collected by the standard procedure (Ferree et al., 2001; Kappenman and Luck, 2010), which used a 0.1-100Hz bandpass hardware filter, 500 Hz sampling rate, and electrode Cz reference.

After becoming familiar with the environment, instructions on a screen explained the task to participants. There was one resting session before the task session and one resting session after the task session. In each resting session, there were six 40-second intervals (i.e., 240 seconds in total and 120 seconds for eyes-opened or eyes-closed condition). Before each interval, a sound signaled when they were to alternate closing or opening their eyes. Participants were encouraged to relax, prevent excessive blinking, and keep the eyes fixated on a central cross to prevent eye-movements during the eyes-opened condition.

After the first resting session, participants started to perform the go/nogo task, which is identical to the one reported in (Liu et al., 2017). The go/nogo task was presented by E-prime software (Psychological Software Tools, Pittsburgh, PA). Participants were instructed to press a button as soon as a letter appeared on the screen during the go condition and hold their response when a letter was repeated for the second time during the nogo condition. Participants finished a practice block of 21 trials before the actual task started.

The schematic outline of the go/nogo task is shown in Figure 2. Stimulus pseudo-randomly appeared on the screen for at least 450ms or less if the subject pressed the button earlier correctly in the go trial or incorrectly in the nogo trial. After one successful trial, an 800ms clear time was introduced before another stimulus to avoid intertrial influence. After one unsuccessful trial, a red bar appeared in the center of the screen for 300ms as error feedback, which encouraged participants to keep pressing the button as fast as they could, and as a result, build up a strong response tendency. In the case of incorrect go trial, a 500ms clear time was introduced after the red bar appearance. In the incorrect nogo trial, an extra 400ms clear time was presented between the response and the red bar, which was followed by another 500 ms of clear-time.

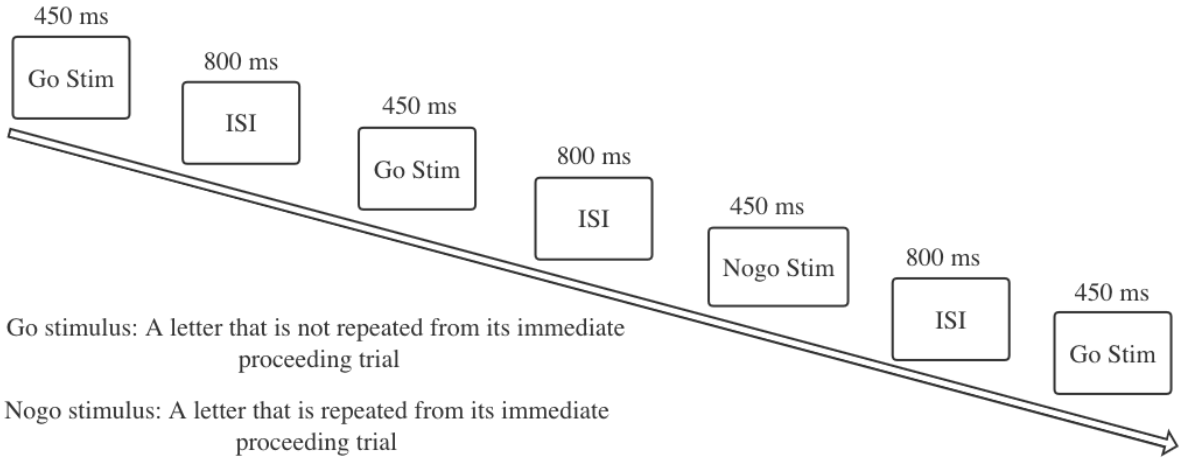


**Figure 2** Schematic outline of the go/nogo task. The maximum duration of go and nogo stimuli is 450 ms. However, the stimulus presentation is terminated as soon as a response is performed, adapted from (Liu et al., 2017).

## 2.3 Clinical measurements

All participants were asked to complete a series of standard questionnaires and tasks to evaluate their current levels of behavioral, cognitive, and social emotional functioning.

The Adult ADHD Self Report Scale (ASRS) is a valid and reliable measurement for evaluating ADHD symptoms in adults, which has eighteen questions based on the criteria used for ADHD diagnosis in the DSM-IV-TR. The ASRS Part A is most predictive of symptoms consistent with a diagnosis of ADHD. Scores for these questions were added up to calculate a final score in this dissertation.

The Cognitive Failures Questionnaire (CFQ) measures self-reported failures in perception, memory, and motor function. There are 25 questions, which ask participants to rank how often these mistakes occur. Its reliability and validity in quantifying the distractibility of individuals have been established in previous research. CFQ scores show temporal stability with good test-retest consistency even after 16 months.

Several behavior measurements of the go/nogo task were selected to evaluate participants' performance, including reaction time (RT), accuracy (ACC), and standard deviation of reaction time (RTSD). All behavior measurements were provided by E-prime software and transferred into Matlab for further analysis.

## 2.4 EEG data processing

After the EEG data was collected, the EEG data was preliminarily divided into three parts, corresponding to two resting sessions and one task session. I cleaned and analyzed the EEG data by following the procedure shown in Figure 3.

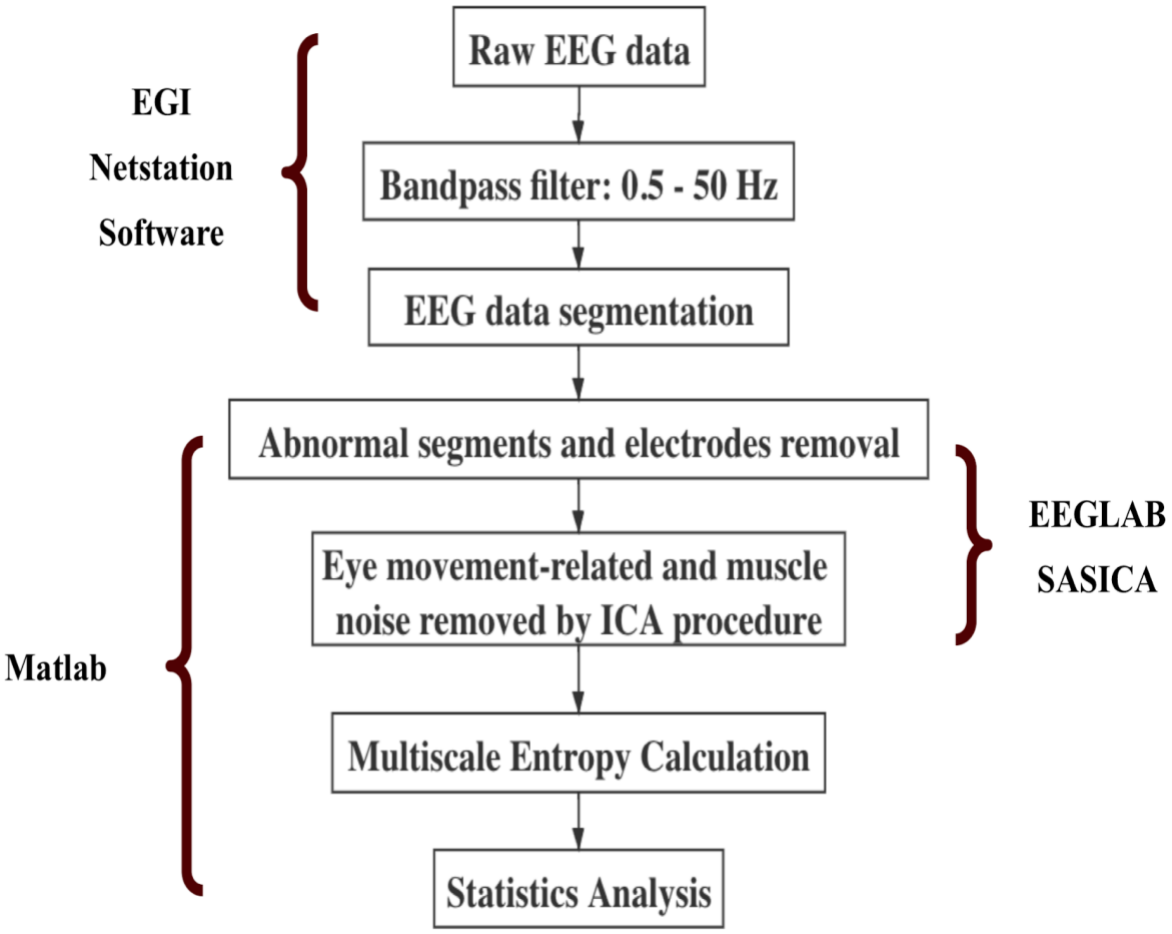


**Figure 3** EEG data cleaning and analysis procedure.

The raw EEG data was filtered through a bandpass filter (0.5 - 50 Hz) to remove the DC noise and high frequency noise in the EGI's Netstation software. Furthermore, the filtered EEG data were segmented into 2-second frames/trials and 1.4-second frames/trials for resting states and active task states correspondingly.

For resting states, I only focused on the EEG data recorded under the eyes-closed conditions in the first resting session because the cognitive task could reshape the neural oscillation in the resting session after the task (Zunini et al., 2013) and there would be less eye-related artifacts in the EEG data under the eye closed situation than that under the eye open situation.

For active task states, EEG data recorded in the task session were segmented from 400 ms before the stimulus onset to 1,000 ms after the stimulus onset. Correct nogo trials were removed which did not have a correct go trial preceding and following them because they might reflect attentional lapses or chronic non-responding. Segmented EEG data was transferred into Matlab. In Matlab, all electrodes that were referenced to Cz during the recording were referenced to an average reference for further cleaning and analysis.

One of the most pervasive problems of EEG analysis is artifacts. Typically, there are two types of artifacts contained in the EEG data, including physiological artifacts (cardiac, muscle, blink, eye movement, respiratory and pulse) and non-physiological artifacts (electrode pop, cable movement, and body movement), as they could contaminate the EEG signal and lead to an unfavorable loss of trials and subjects. To remove artifacts from the EEG, two denoising strategies were applied in sequence, abnormal segment, and electrode removal as well as ICA procedure.

To the best of my knowledge, ICA would extract independent components from the EEG signal and project desired components back to the EEG signal. In the ICA decomposition procedure, there were usually more than one artifact source, which may be contained in multiple ICs. Non-physiological artifacts like electrode pop (shown in Appendix A) were usually contained across all trials and found in most ICs, which made it difficult to be removed by the ICA procedure. The abnormal electrode was verified by a research assistant blind to the study hypothesis and EEG from abnormal electrode was interpolated by EEG from nearby electrodes in EEGLAB (Delorme and Makeig, 2004).

For non-physiological artifacts like cable movement and body movement were usually extremely large-voltage and contained in several trials, which would contaminate many ICs and affect the isolation of other artifacts, like eye movement. In my study, abnormal segments containing extremely large non-physiological artifacts were identified by the research assistant and removed manually (shown in Appendix B)

In my study, I mainly focused on the correct go trials, which accounted for the majority of go/nogo task trials. This resulted in a different number of trials between COMP and ADHD groups in the same condition (see Table 2 for details in trial counts).

**Table 2** Trial count information for each group and condition

| | COMP | ADHD |
|---|---|---|
| Resting State Trials | 56 (4) | 55 (3) |
| Correct Go Task Trials | 149 (30) | 155 (24) |

To remove artifacts and keep as many trials and subjects as possible, physiological artifacts in the EEG data, such as blink, eye movements, or muscle movement were eliminated by the ICA procedure. I utilized the Independent Component Analysis (ICA) module in the EEGLAB to calculate Independent Components (ICs) for the EEG data. To detect, separate, and remove EEG contributions from artifactual sources, the SASICA toolbox (Chaumon et al., 2015) was used to automatically identify ICs with the artifact, followed by a manual identification procedure, as shown in Appendix C. All verified artifact ICs were removed and the remaining ICs were projected back to EEG data.

After the EEG was cleaned, MSE within EEG was calculated for each trial at each electrode over corresponding time scales. The calculation of MSE was done by an open source algorithm in Matlab available at www. physionet.org/physiotools/mse/, which could obtain coarse-grained EEG data by averaging the data points within non-overlapping windows of time scales and calculate sample entropy for each coarse-grained EEG data (Goldberger et al., 2000).

In the sample entropy calculation, the pattern length was set to m = 2, which means, two consecutive data points were used to pattern matching. The simplicity threshold was set to r = 0.5. All coarse-grained EEG data were normalized before the calculation of sample entropy. MSE in the resting state was calculated from scale 1 to 20, while MSE in the active task state was calculated from scale 1 to 14 due to the shorter duration.

To observe how the brain adapts to the task, the MSE transition (MSE-Δ) was obtained by subtracting MSE in the active task state from MSE in the resting state over corresponding scales (scale 1-14) and electrodes.

## 2.5 Statistics analysis

Statistical analysis was conducted in Matlab after MSE and MSE-Δ were calculated. I utilized the 10-10 system and grouped electrodes into 5 clusters at the left and right hemispheres separately (Luu and Ferree, 2005). Each cluster of electrodes represented one brain region as shown in Figure 3. Calculated MSE were averaged within the corresponding brain sites over the left and right hemispheres and checked for outliers. In general, there were five sets of MSE results corresponding to 5 pairs of brain sites.

In general, the group difference of MSE in the resting and task states, and MSE-Δ between individuals with ADHD and their peers were calculated over corresponding time scales within each pair of brain sites.

To find the relationship between task performance and neural measurements, I averaged MSE in the resting and task states, and MSE-Δ across different scale ranges respectively, including fine scales (1-6), mid scales (7-14), and coarse scales (15-20) (Jaworska et al., 2018) and looked into their relationships with behavior measurements as shown in Figure 5. The Pearson's r correlation coefficients were calculated for MSE measurements within each pair of brain sites as shown in Figure 4.

Partial eta-squared values $\eta^2$ were computed to verify the effect size. According to Vacha-Haase & Thompson (2004), partial $\eta^2$ = .01 corresponds to a small effect, partial $\eta^2$ = .10 standards for a medium effect, and partial $\eta^2$ = .25 represents a large effect.

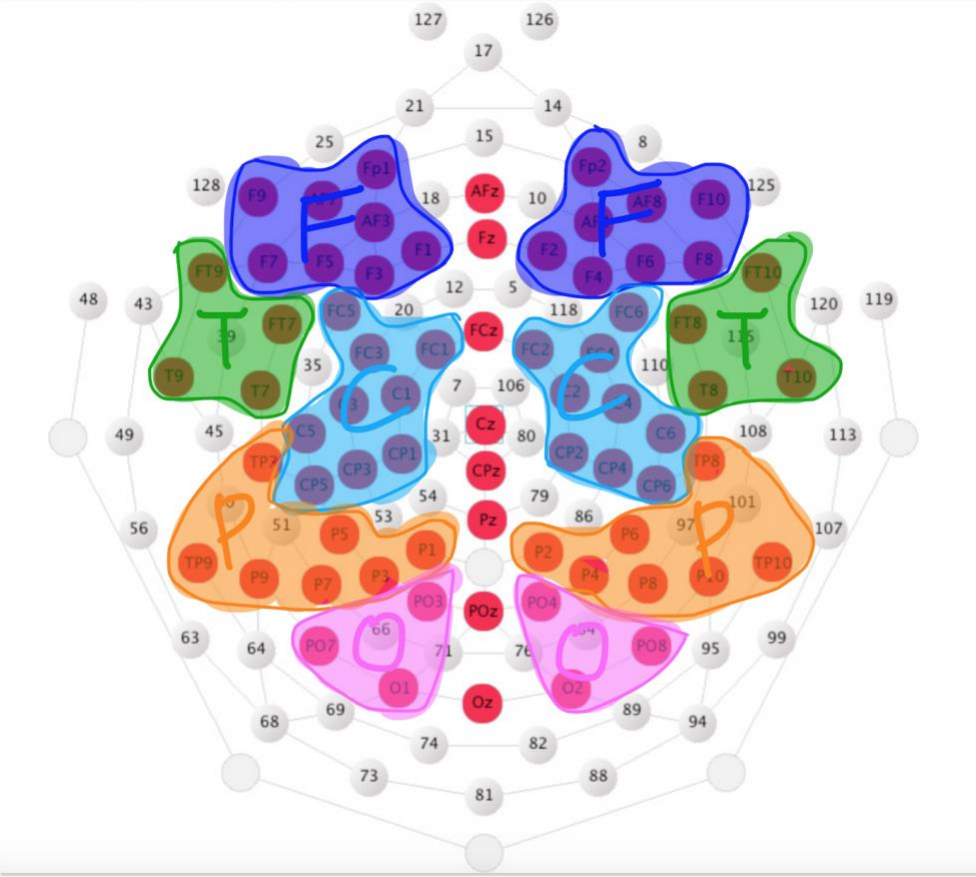


**Figure 4** Electrode clusters represent corresponding brain sites. Deep blue represents the frontal site (F site). Green represents the temporal site (T site). Light blue represents the central site (C site). Orange represents the parietal site (P site). Pink represents the occipital site (O site).

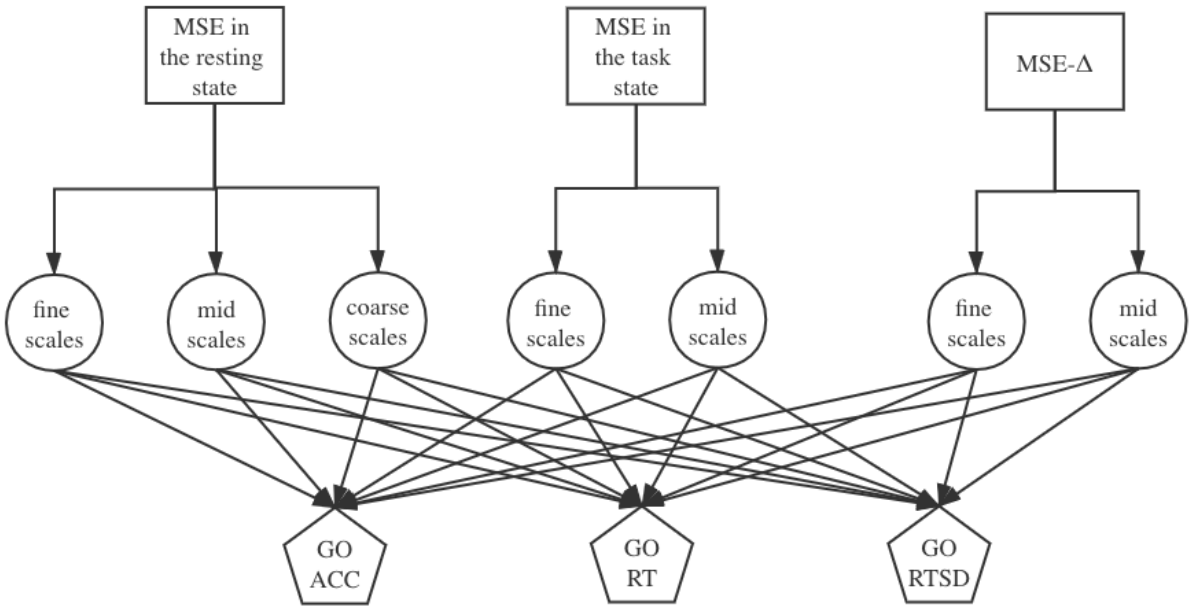


**Figure 5** Relationship between MSE and behavior measurements. GO ACC represents the accuracy in the correct go trials. GO RT represents the reaction time in the correct go trials. GO RTSD represents the standard deviation of reaction time in the correct go trials.

# 3 RESULTS

## 3.1 Behavioral and questionnaire results

I compared the means and standard deviations of the questionnaire and behavioral measurements of the ADHD group and their peers using the statistical tests for group differences in Table 3.

Results showed that the ADHD group reported more ADHD symptomatology and everyday cognitive problems than their peers. The comparison group reported higher accuracy for the go task than the ADHD group, while the ADHD group showed a larger standard deviation of the reaction time for the go task than their peers. No significant group difference in reaction time for go tasks was found.

**Table** 3 Descriptive and differences for questionnaire and behavioral measurements

| | COMP Group | | ADHD Group | | Group Difference | Effect Size |
|---|---|---|---|---|---|---|
| | M | SD | M | SD | p | $\eta^2$ |
| ASRS | 21.87 | 9.15 | 48.53 | 10.03 | $<0.001^{***}$ | 0.666 |
| CFQ | 27.77 | 9.30 | 56.50 | 13.87 | $<0.001^{***}$ | 0.605 |
| GO ACC | 0.93 | 0.05 | 0.89 | 0.06 | $<0.05^{*}$ | 0.095 |
| GO RT | 304.43 | 31.11 | 315.20 | 31.67 | >0.05 | 0.029 |
| GO RTSD | 85.26 | 15.88 | 101.50 | 16.00 | $<0.001^{***}$ | 0.212 |

ASRS is the Adult ADHD Self-Report Scale.

CFQ is the cognitive failures questionnaire.

GO ACC is the accuracy in the correct go trials.

GO RT is the reaction time in the correct go trials.

GO RTSD is the standard deviation of reaction time in the correct go trials.

### 3.2 MSE in the resting state

In the resting state, different MSE distributions between the comparison and ADHD groups could be observed across different time scales and brain regions.

Across all electrodes, MSE in the comparison group was larger than that in the ADHD group across coarse scales (15-20), whereas no difference of MSE was observed across fine scales (1-6) and mid scales (7-14) as shown in Figure 6. Different distributions of MSE were not only found across scales but also observed over different brain sites, which were compared in the topographic distributions of MSE in Figure 7. Furthermore, as compared in Figure 8, MSE from the comparison group was larger than that from the ADHD group across coarse scales in the frontal, central, and temporal sites, but not in the parietal and occipital sites. However, the difference of MSE between the comparison and ADHD groups was only significant at the frontal site across coarse scales, as shown in Figure 9. There's no significant relationship between MSE and behavior measurements in the comparison or ADHD group as shown in Figure 10.

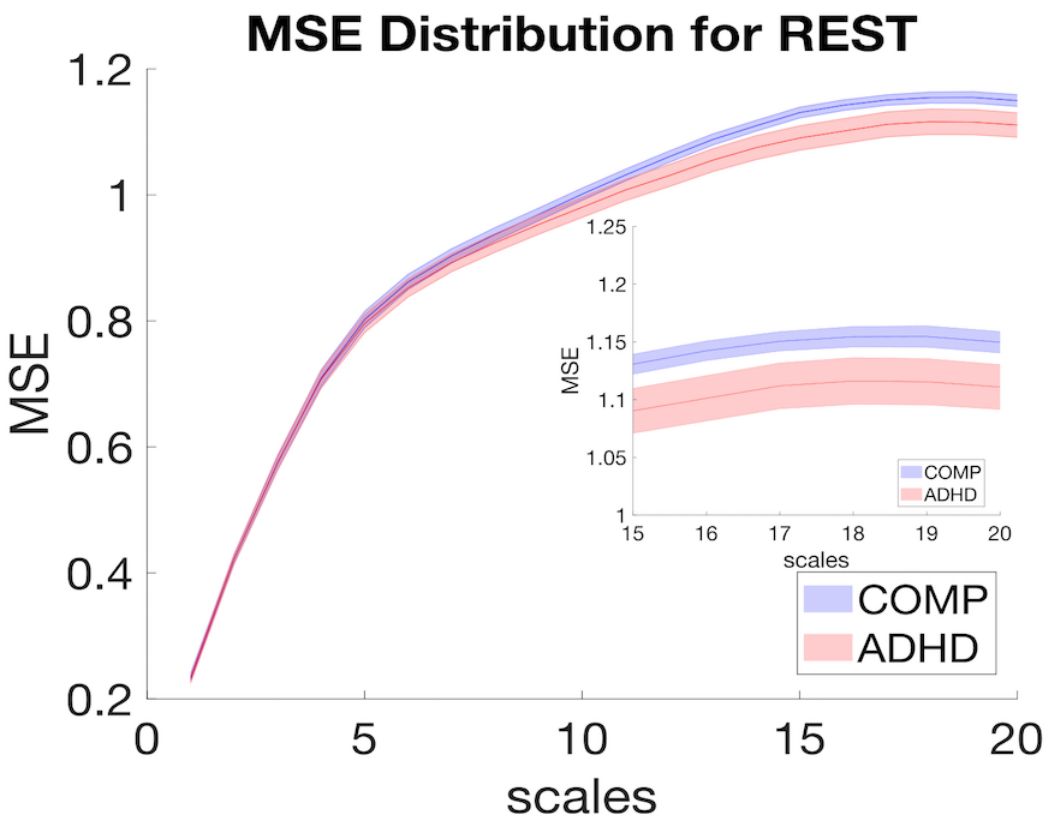


**Figure 6** MSE distribution across scales during the resting state. MSE from the comparison (COMP) group and ADHD group were averaged over all electrodes and compared across scales (1 to 20), with standard error as the shaded area, which was partially enlarged viewed across coarse scales.

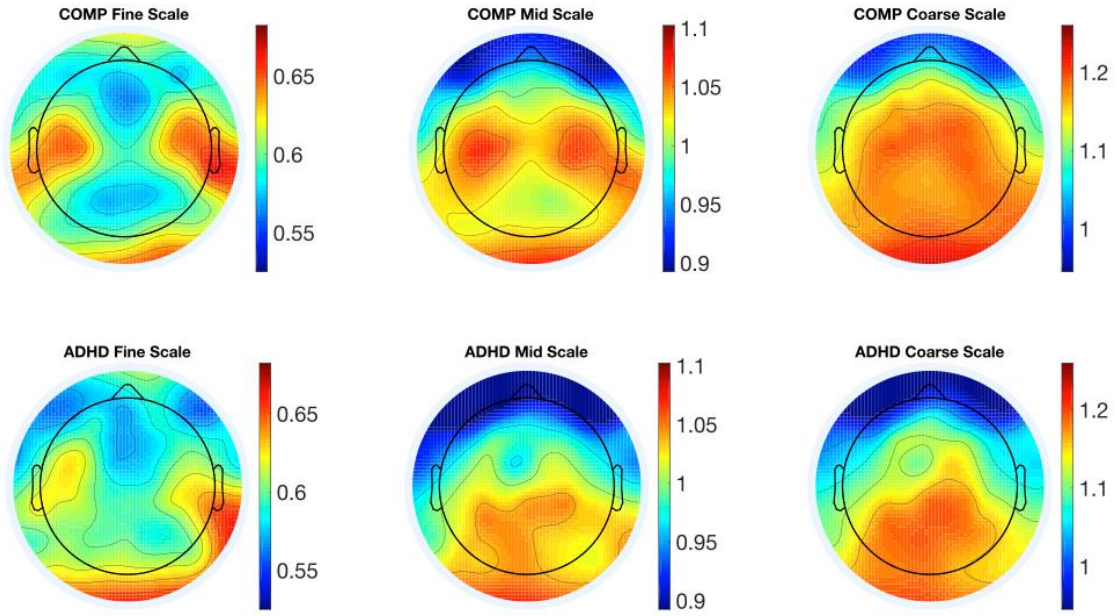


**Figure 7** MSE topographical distribution during the resting state. MSE was averaged over three time scale ranges and compared topographically.

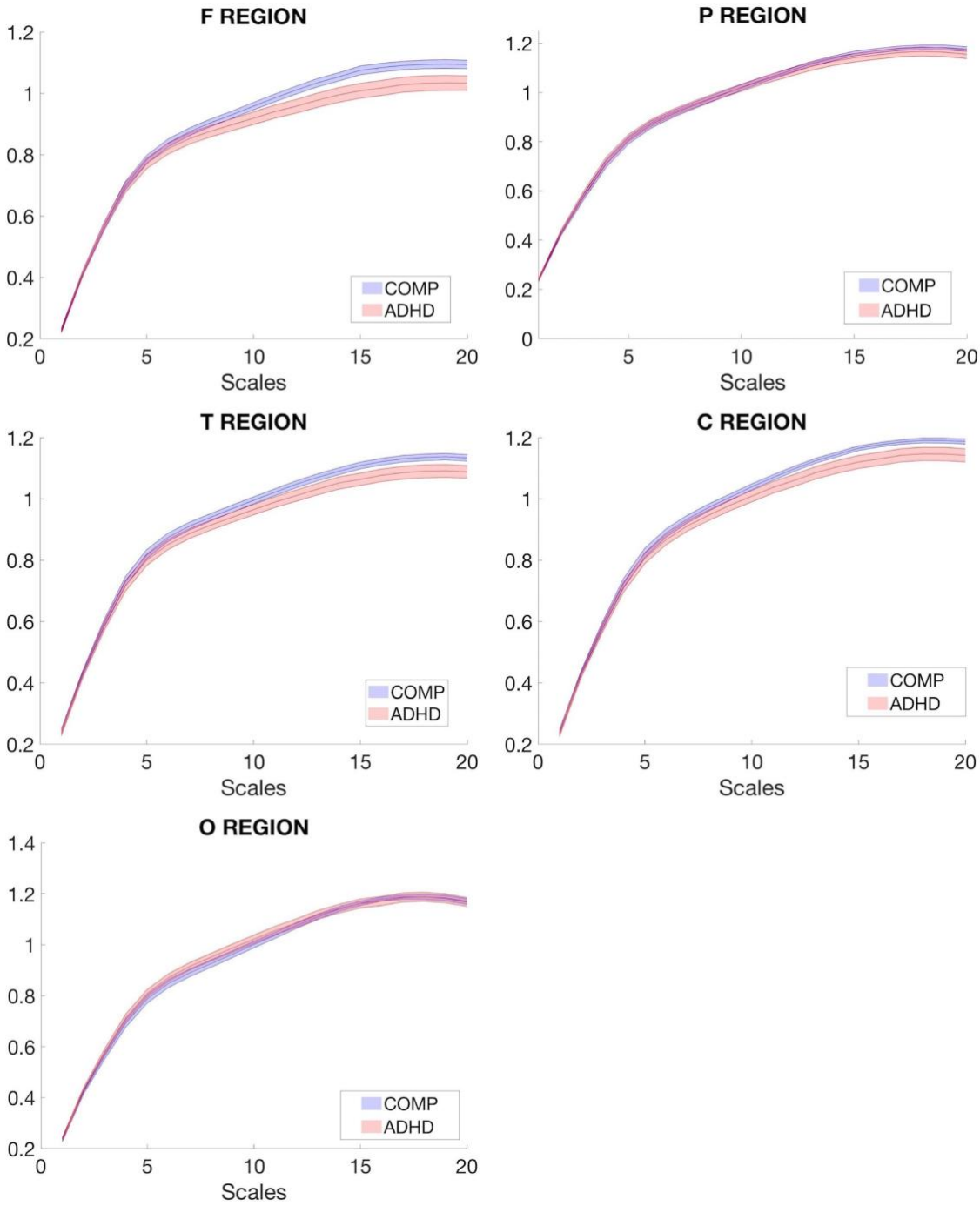


**Figure 8** MSE distribution across scales at different brain sites during the resting state. MSE were averaged within each region and compared across scales with standard error as the shaded area.

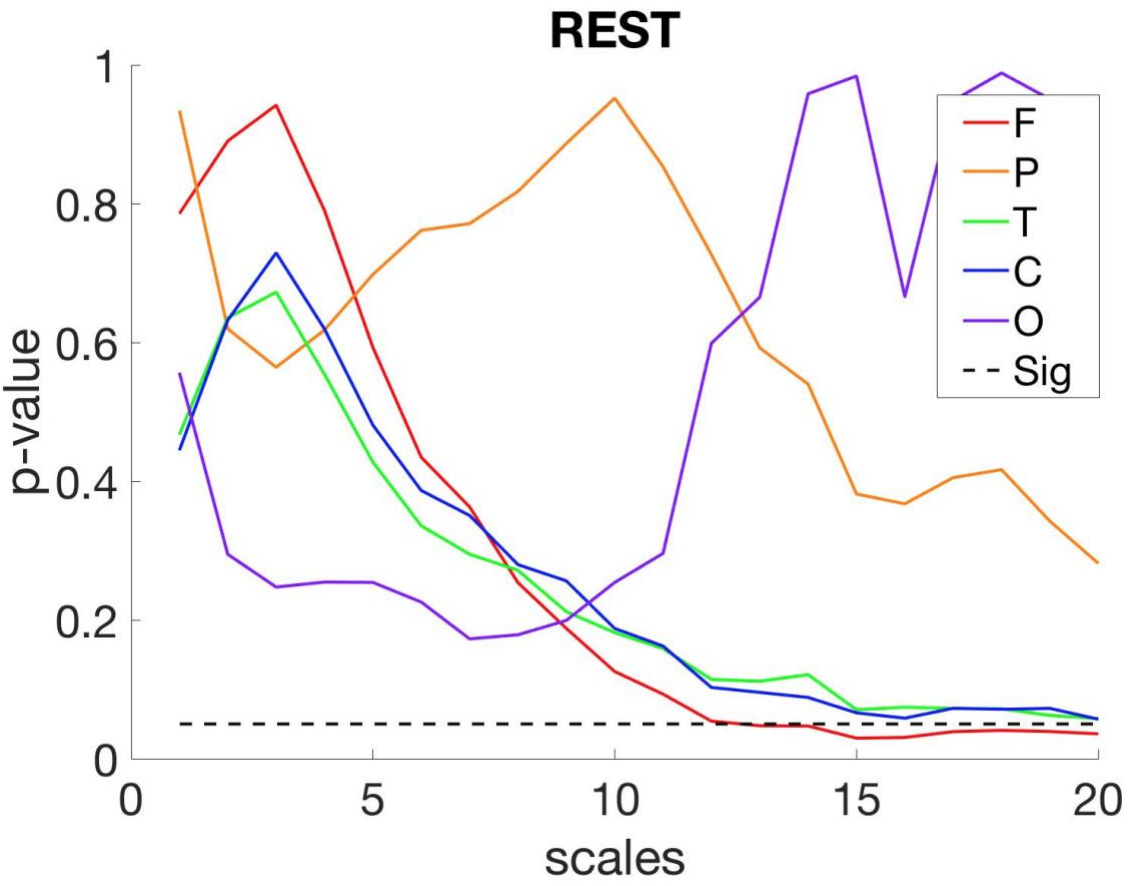


**Figure 9** Group difference of MSE during the resting state. A paired t-test was performed for MSE averaged within each electrode cluster over all scales.

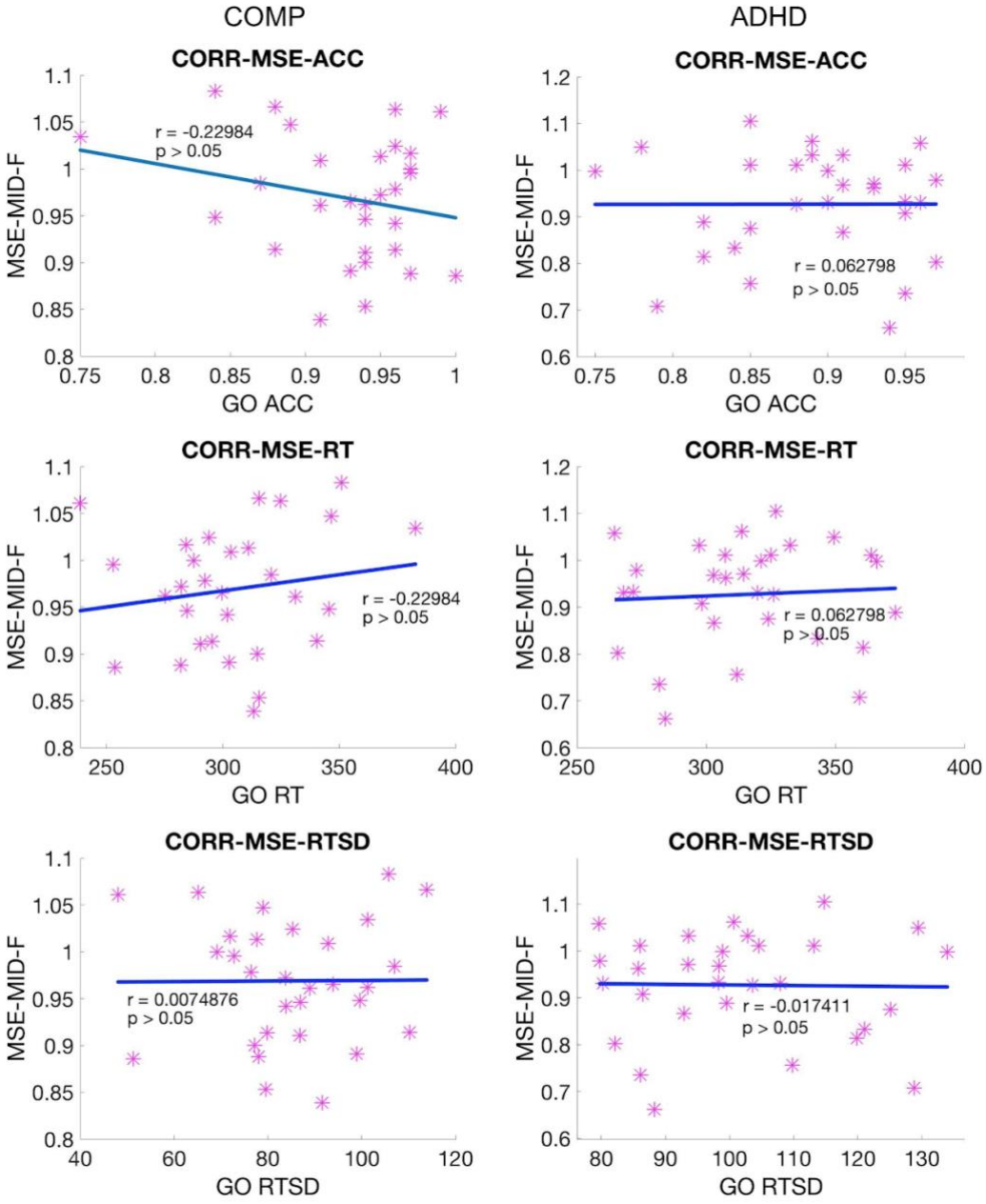


**Figure 10** Correlation between MSE and behavior performance during the resting state. Scatter plots with regression line between MSE averaged across mid scales at the frontal site and three behavior measurements (GO ACC, GO RT, GO RTSD) for both the comparison and ADHD groups.

### 3.3 MSE in the active task state

In the active task state, no significant group difference of MSE between the comparison and ADHD groups was achieved for any scale or any brain site.

Across all electrodes, similar distributions of MSE were observed across fine scales (1-6) and mid scales (7-14) in the comparison and ADHD groups, whereas MSE in the comparison group was smaller than that in the ADHD group across mid scales (7-14), but didn't reach statistical significance as shown in Figure 11. Similar distributions of MSE were not only found across scales but also observed over different brain sites as shown in Figure 12. Furthermore, as compared in Figure 13, MSE from the comparison group was smaller than that from the ADHD group across mid scales in the frontal and central sites, but not in the temporal, parietal, and occipital sites. However, no significant group difference of MSE between the comparison and ADHD groups was achieved as shown in Figure 14. There's a significant negative correlation between MSE and behavior measurements in the comparison group as shown in Figure 15, but not for the ADHD group as shown in Figure 16. Increased MSE across mid scales in the frontal site was associated with lower accuracy (ACC), larger reaction time (RT), and a larger standard deviation of reaction time (RTSD).

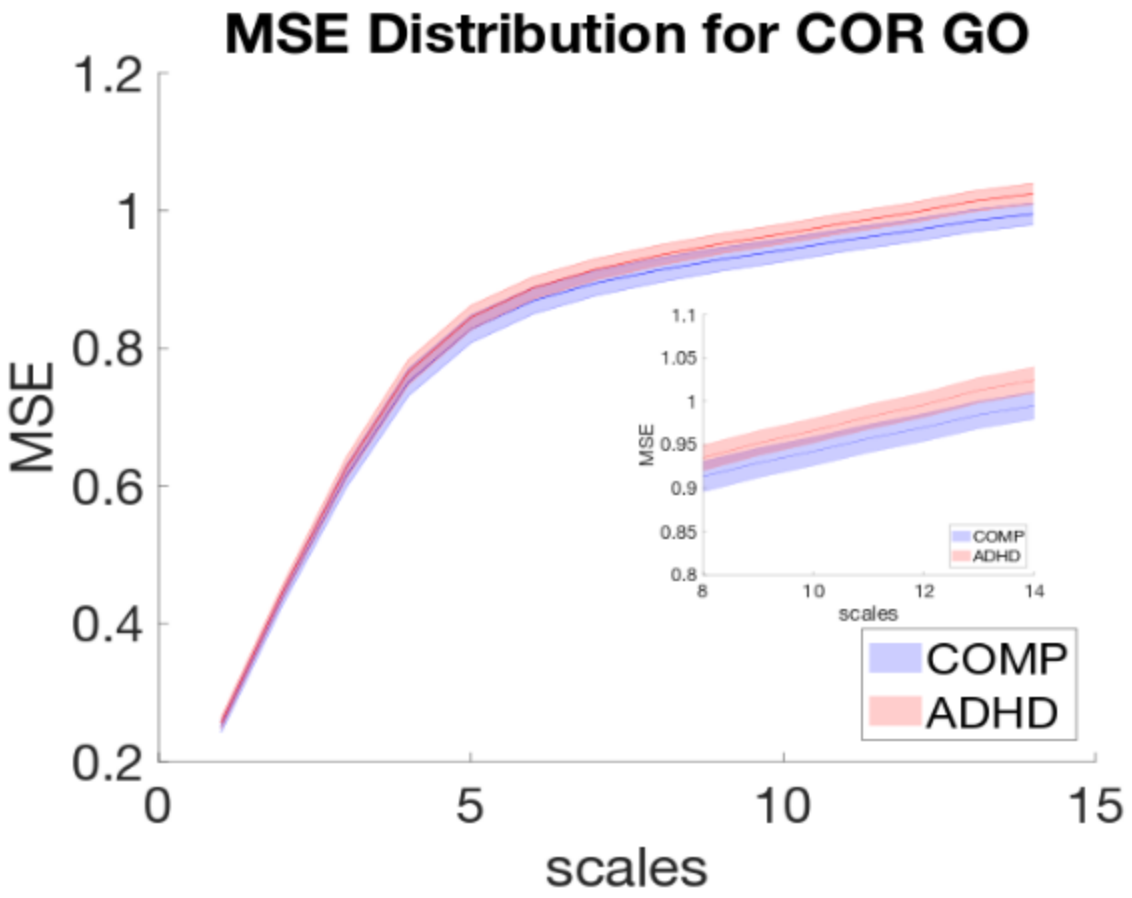


**Figure 11** MSE distribution across scales during the active task state. MSE from the comparison (COMP) group and ADHD group were averaged over all electrodes and compared across scales (1 to 14), with standard error as the shaded area, which was partially enlarged viewed across mid scales.

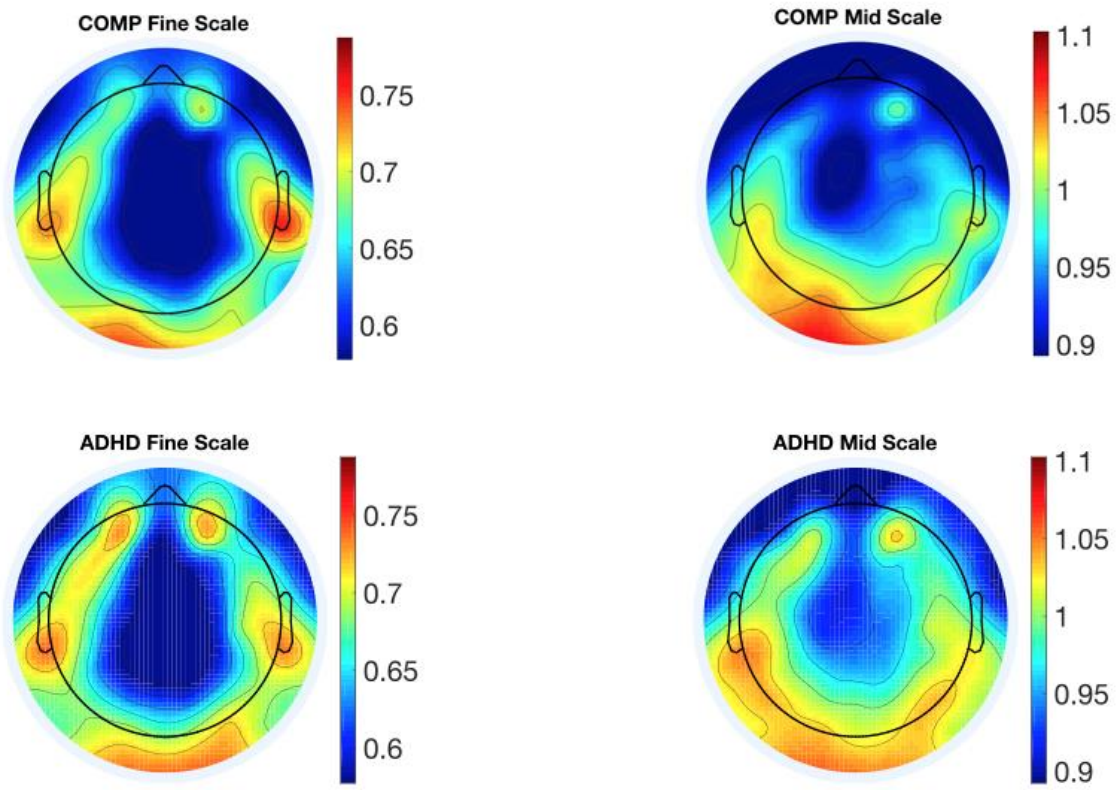


**Figure 12** MSE topographical distribution during the active task state. MSE was averaged over two time scale ranges and compared topographically.

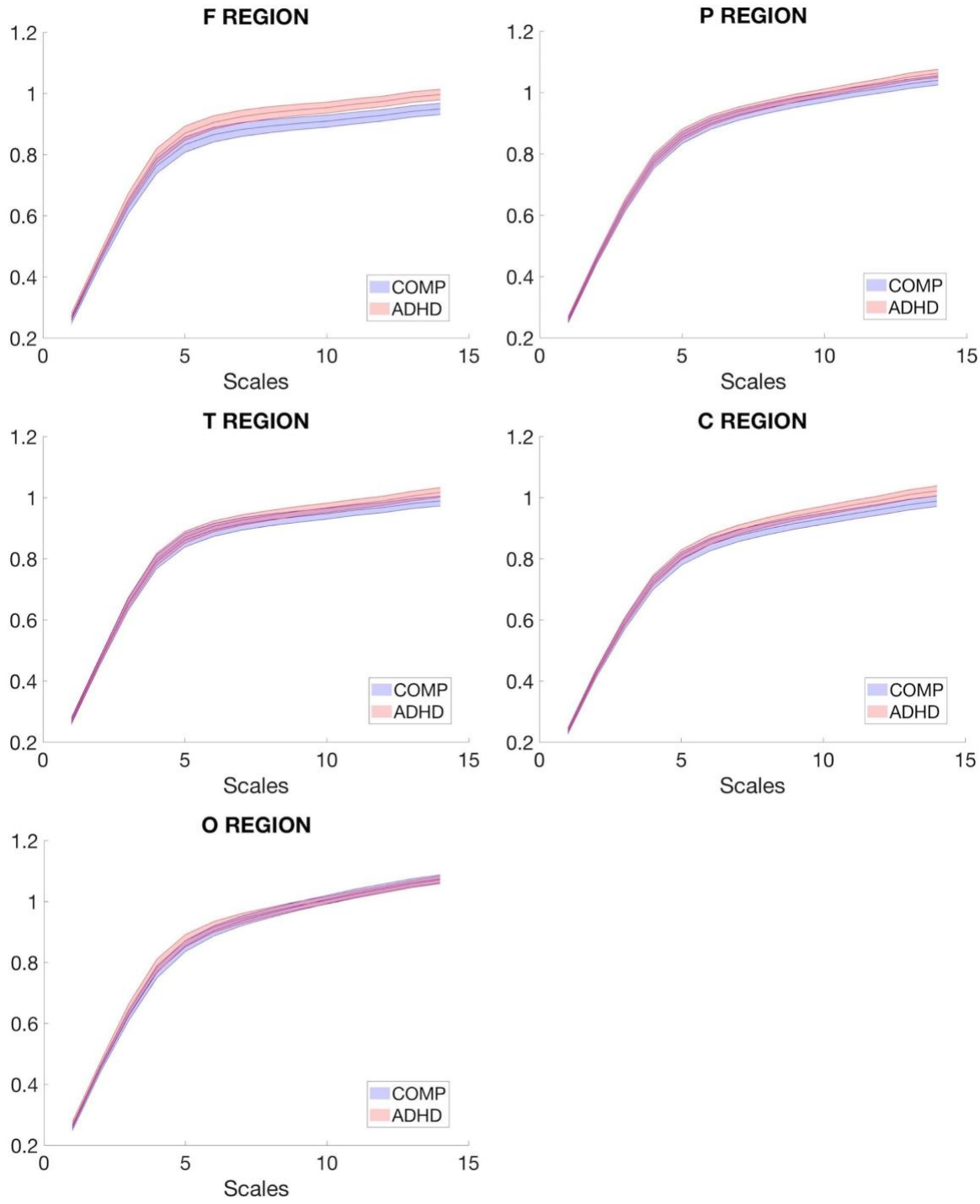


**Figure 13** MSE distribution across scales at different brain sites during the active task state. MSE were averaged within each region and compared across scales with standard error as the shaded area.

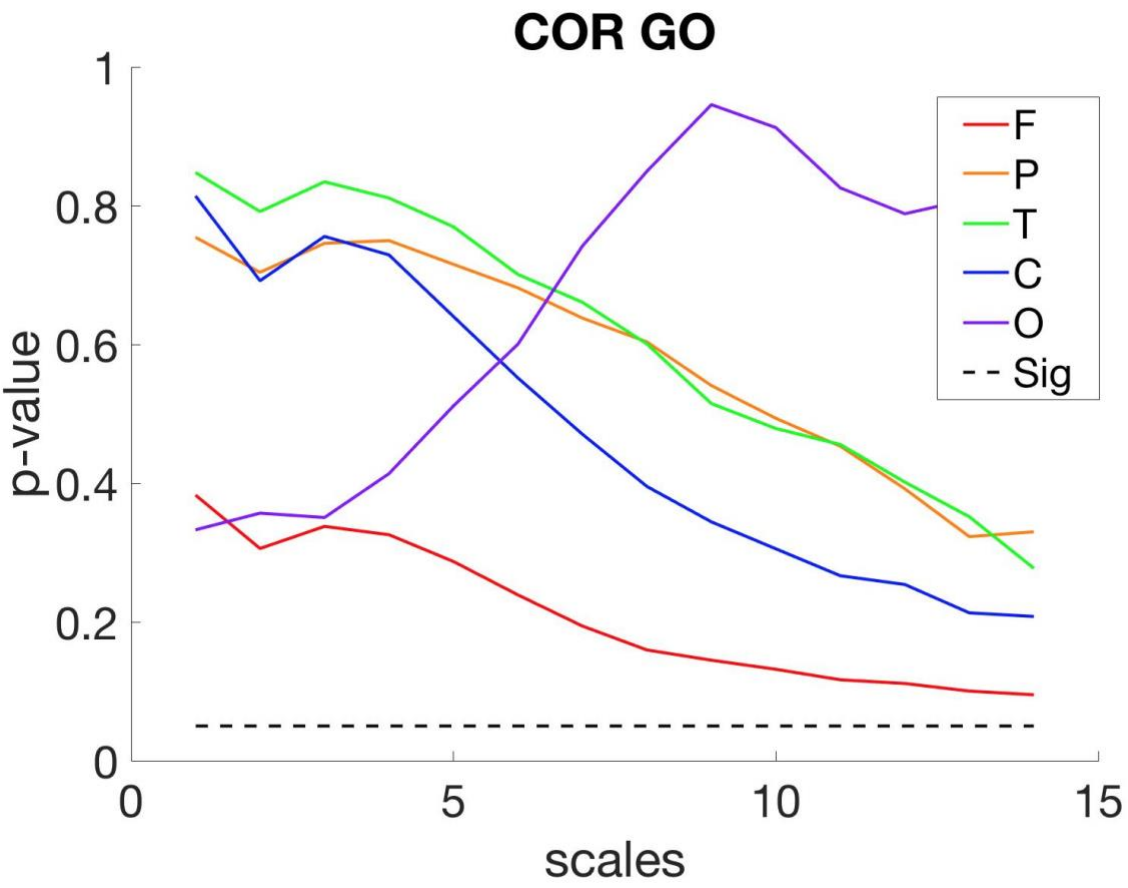


**Figure 14** Group difference of MSE during the active task state. A paired t-test was performed for MSE averaged within each electrode cluster over all scales.

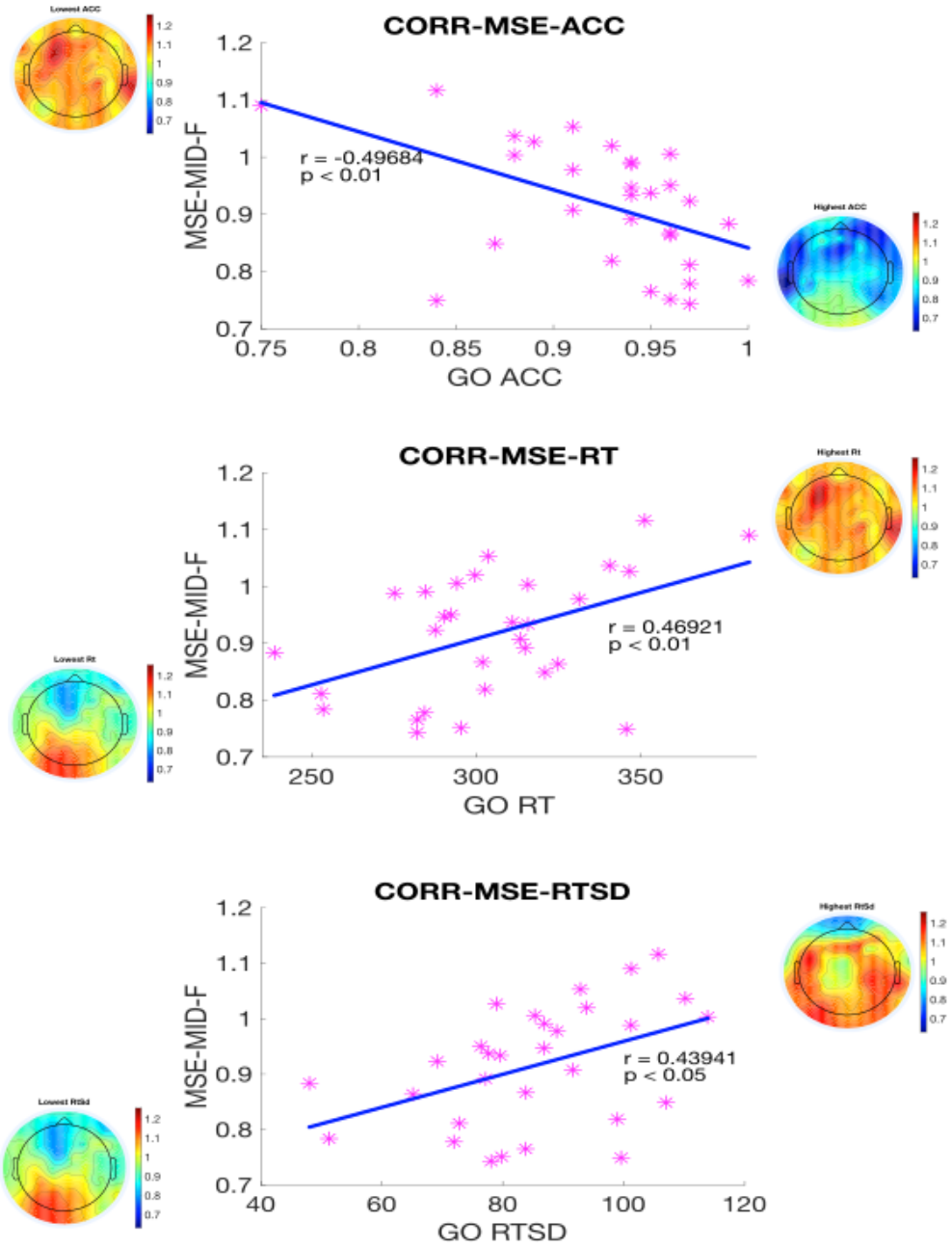


**Figure 15** Correlation between MSE and behavior performance for the comparison group during the active task state. Scatter plots with regression line between MSE averaged across mid scales at the frontal site and three behavior measurements (GO ACC, GO RT, GO RTSD) for the comparison group.

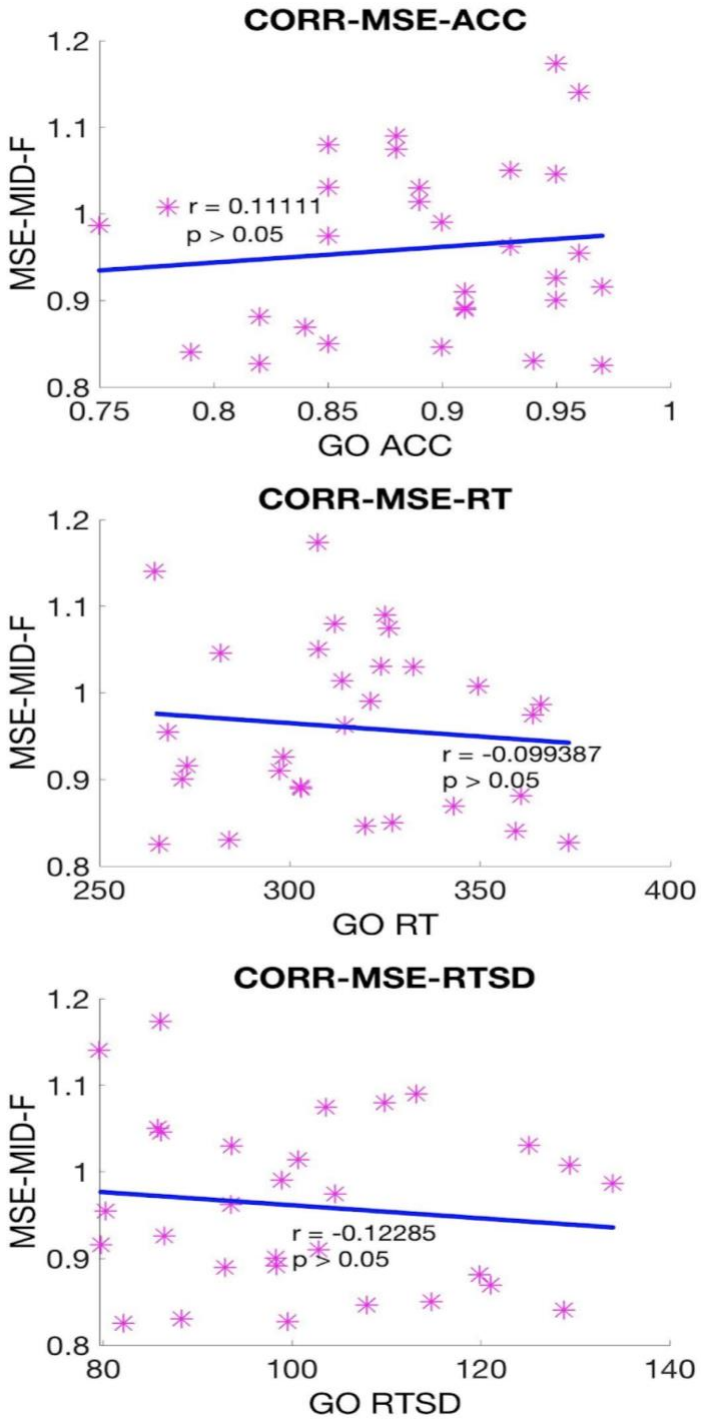


**Figure 16** Correlation between MSE and behavior performance for the ADHD group during the active task state. Scatter plots with the regression line between MSE averaged across mid scales at the frontal site and three behavior measurements (GO ACC, GO RT, GO RTSD) for the ADHD group.

### 3.4 MSE transition from the resting state to task state

From the resting state to the active task state, MSE increased within fine scales and decreased within mid scales for both the comparison and ADHD groups, as shown in Figure 17.

Different MSE transition (MSE-Δ) distributions could be observed between the comparison and ADHD groups across different time scales and brain regions. Positive MSE-Δ represented larger MSE during the active task state, as well as negative MSE-Δ corresponding to larger MSE during the resting state.

Overall electrodes, MSE-Δ in the comparison group was significantly larger than that in the ADHD group across mid scales (7-14), whereas no difference of MSE was observed across fine scales (1-6) as shown in Figure 18. Different distributions of MSE-Δ were not only found across scales but also observed over different brain sites, which were compared in the topographic distributions of MSE-Δ in Figure 19. Furthermore, as compared in Figure 20, MSE-Δ from the comparison group was larger than that from the ADHD group across mid scales in the frontal, central, and temporal sites, but not in the parietal and occipital sites. Especially, over the entire mid scales, a significant group difference of MSE-Δ between the comparison and ADHD groups was achieved for the frontal site, as shown in Figure 21. There's a significant negative correlation between MSE-Δ and behavior measurements in the comparison group as shown in Figure 22, but not for the ADHD group as shown in Figure 23. Increased MSE-Δ across mid scales in the frontal site was associated with lower accuracy (ACC), larger reaction time (RT), and a larger standard deviation of reaction time (RTSD).

For the comparison group during the active task state, the effect of MSE on the task performance (GO ACC) was not significantly mediated via MSE in the resting state. As shown in Figure 24, the regression coefficient between MSE in the active task state and task

performance (GO ACC) was significant, while the regression coefficient between MSE in the resting state and task performance was not. The indirect effect was statistically not significant ($p > 0.05$).

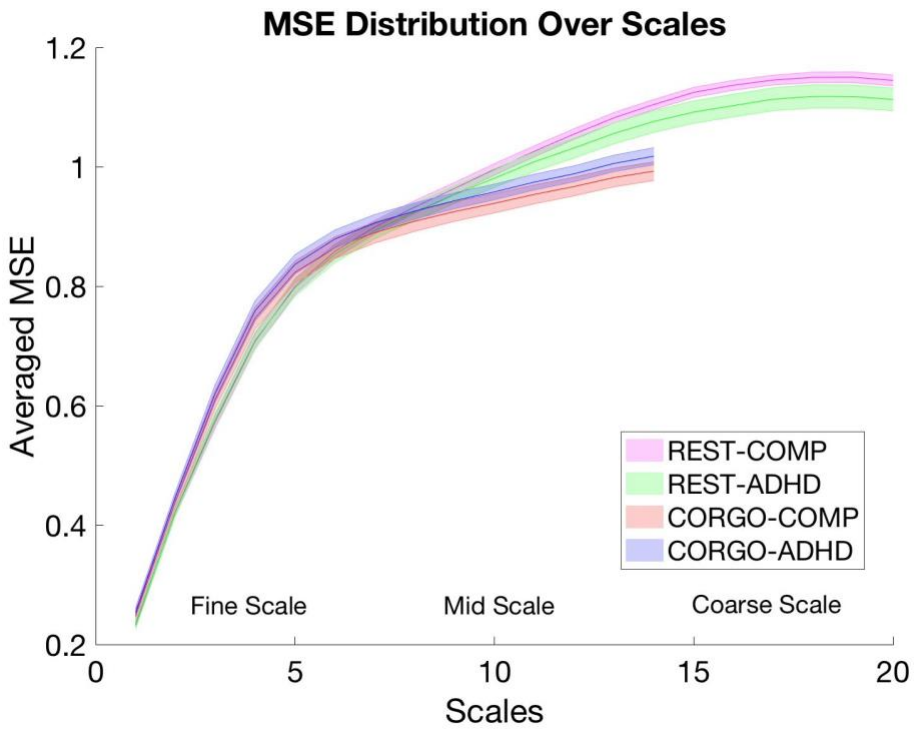


**Figure 17** MSE distribution across scales for the comparison and ADHD groups during the resting and active task states. MSE from the comparison (COMP) group and ADHD group were averaged over all electrodes and compared across scales, with standard error as the shaded area for the resting (REST) and active task (COR GO) states.

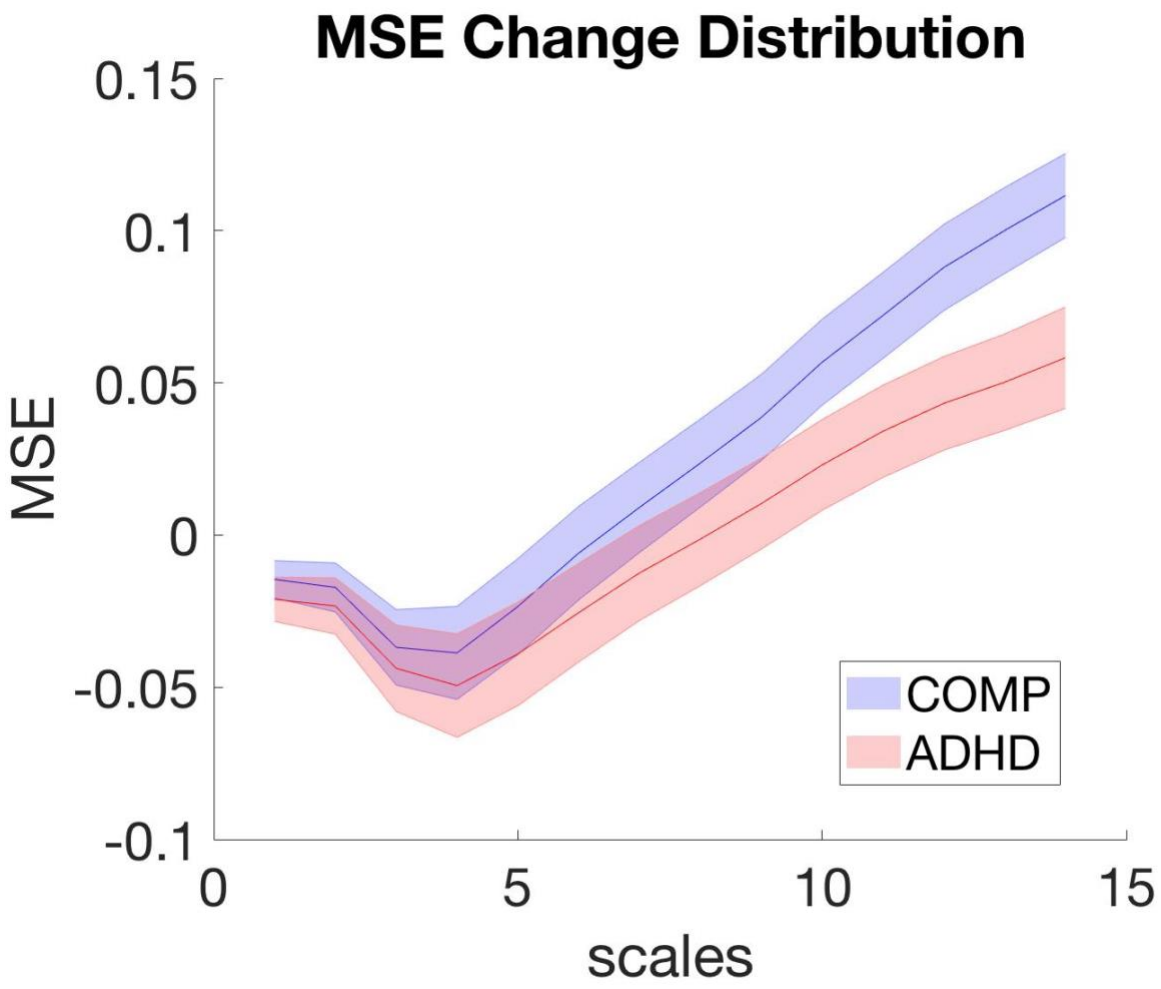


**Figure 18** MSE-Δ distribution across scales. MSE-Δ from the comparison (COMP) group and ADHD group were averaged over all electrodes and compared across scales (1 to 14), with standard error as the shaded area, which was partially enlarged viewed across mid scales.

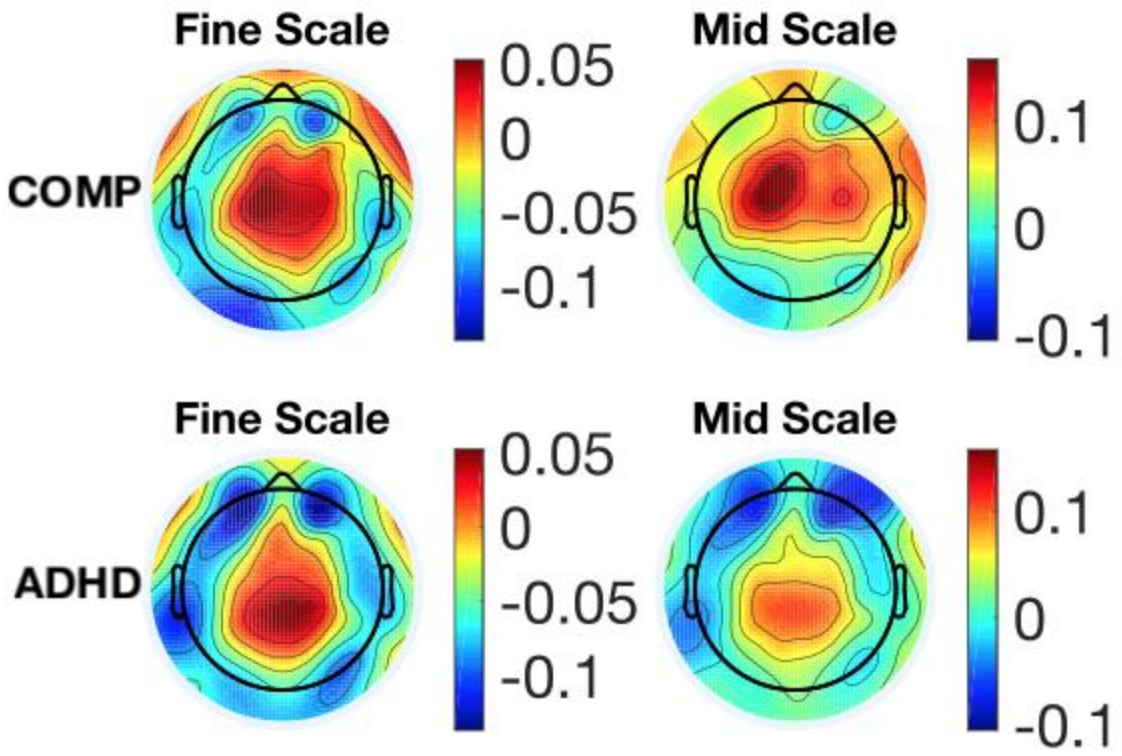


**Figure 19** MSE-Δ topographical distribution. MSE-Δ was averaged over two time scale ranges and compared topographically.

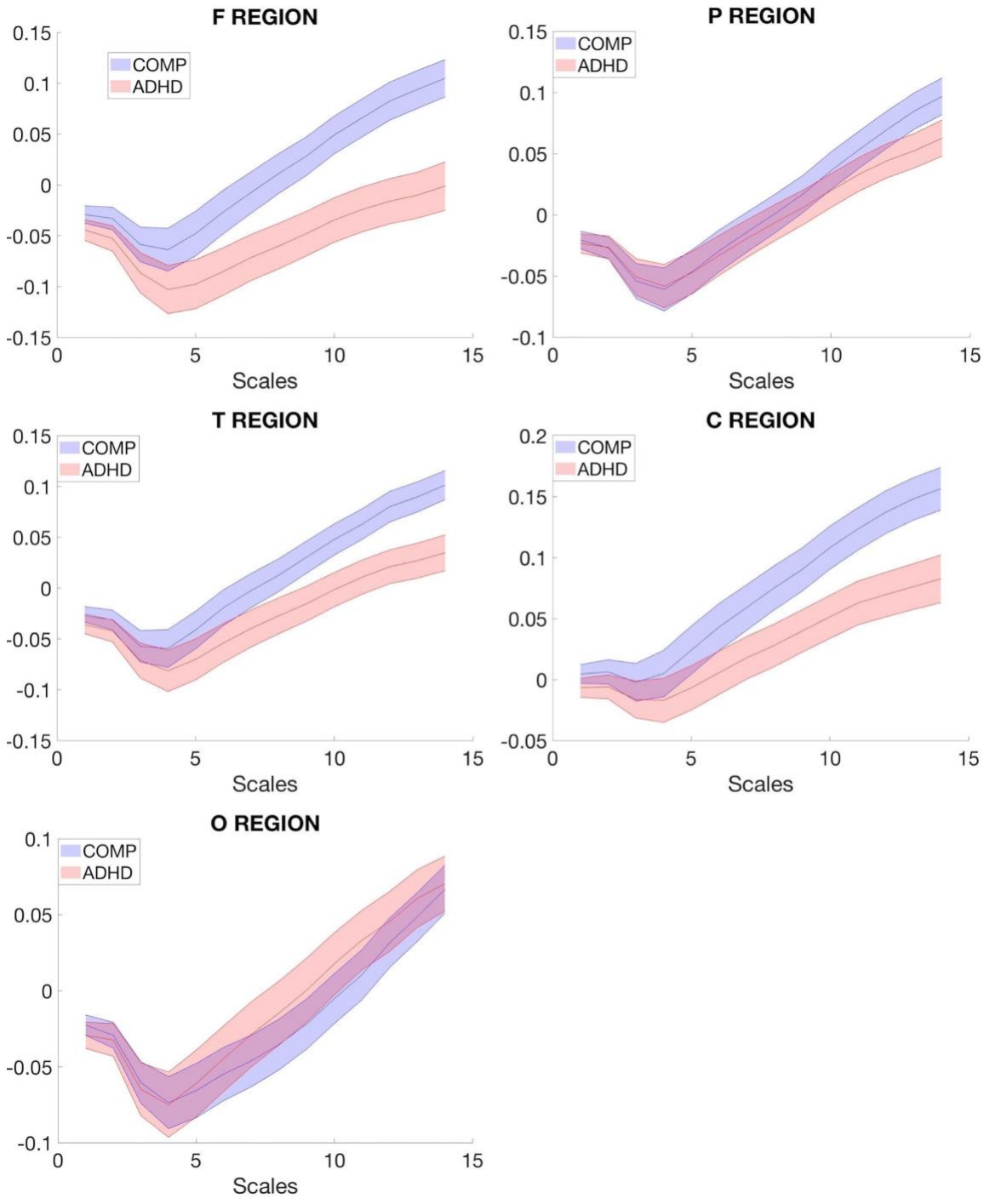


**Figure 20** MSE-Δ distribution across scales at different brain sites. MSE-Δ were averaged within each region and compared across mid scales with standard error as the shaded area.

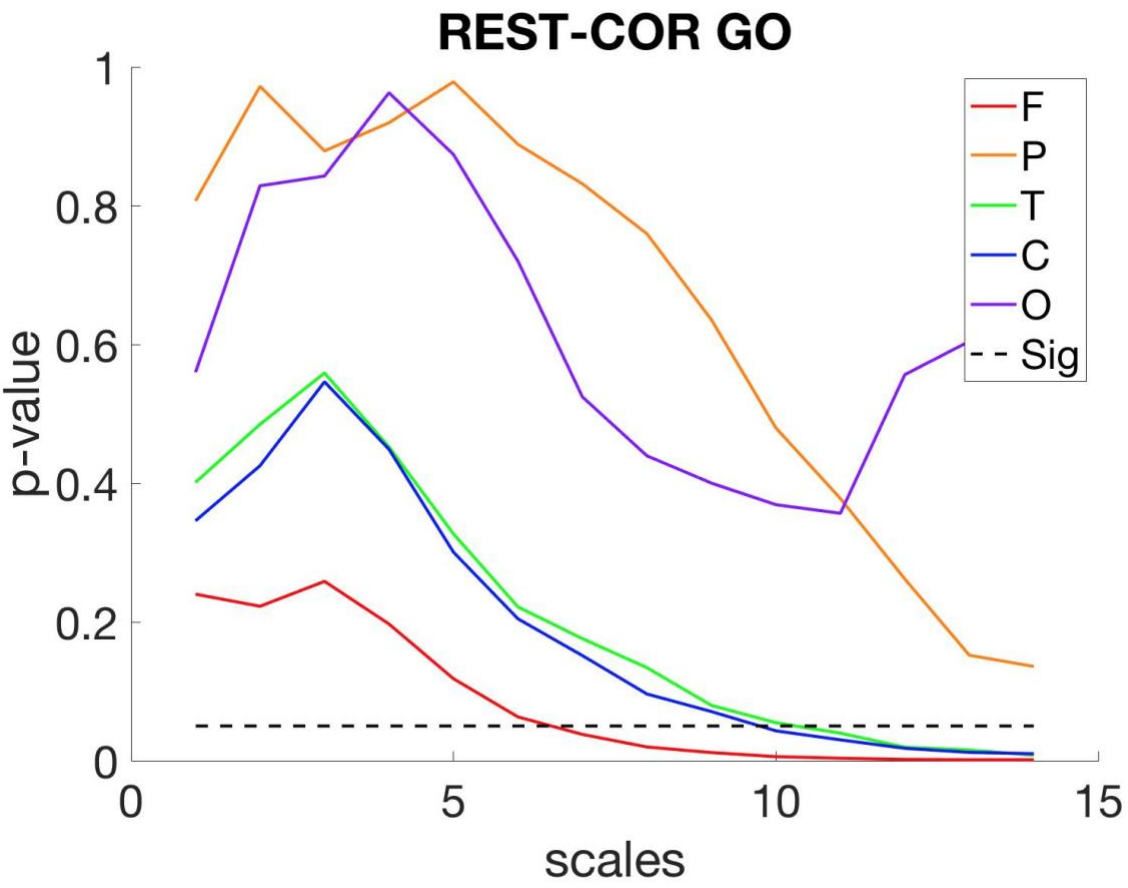


**Figure 21** Group difference of MSE-Δ. A paired t-test was performed for MSE-Δ averaged within each electrode cluster over all scales.

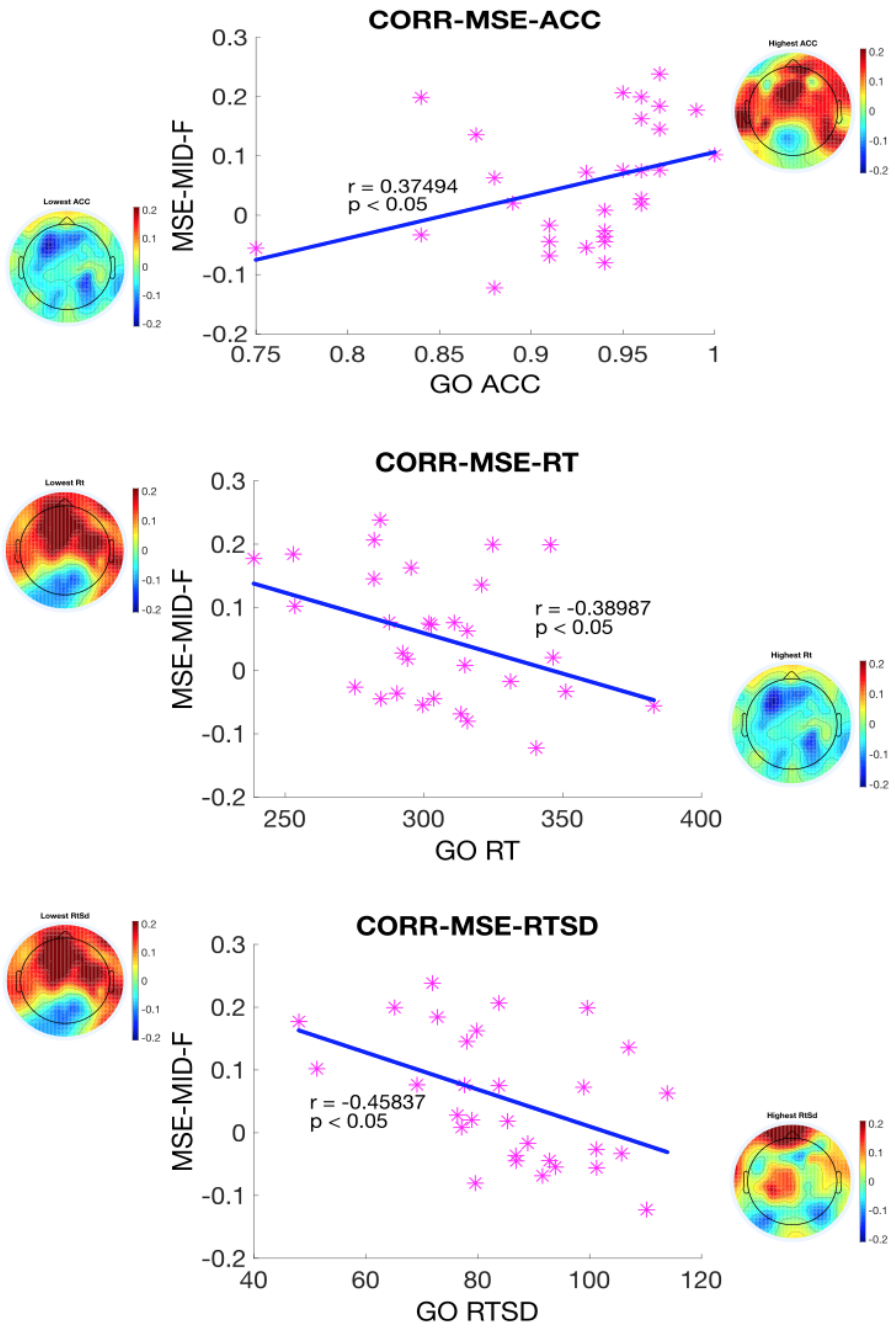


**Figure 22** Correlation between MSE and behavior performance for the comparison group. Scatter plots with regression line between MSE-Δ averaged across mid scales at the frontal site and three behavior measurements (GO ACC, GO RT, GO RTSD) for the comparison group.

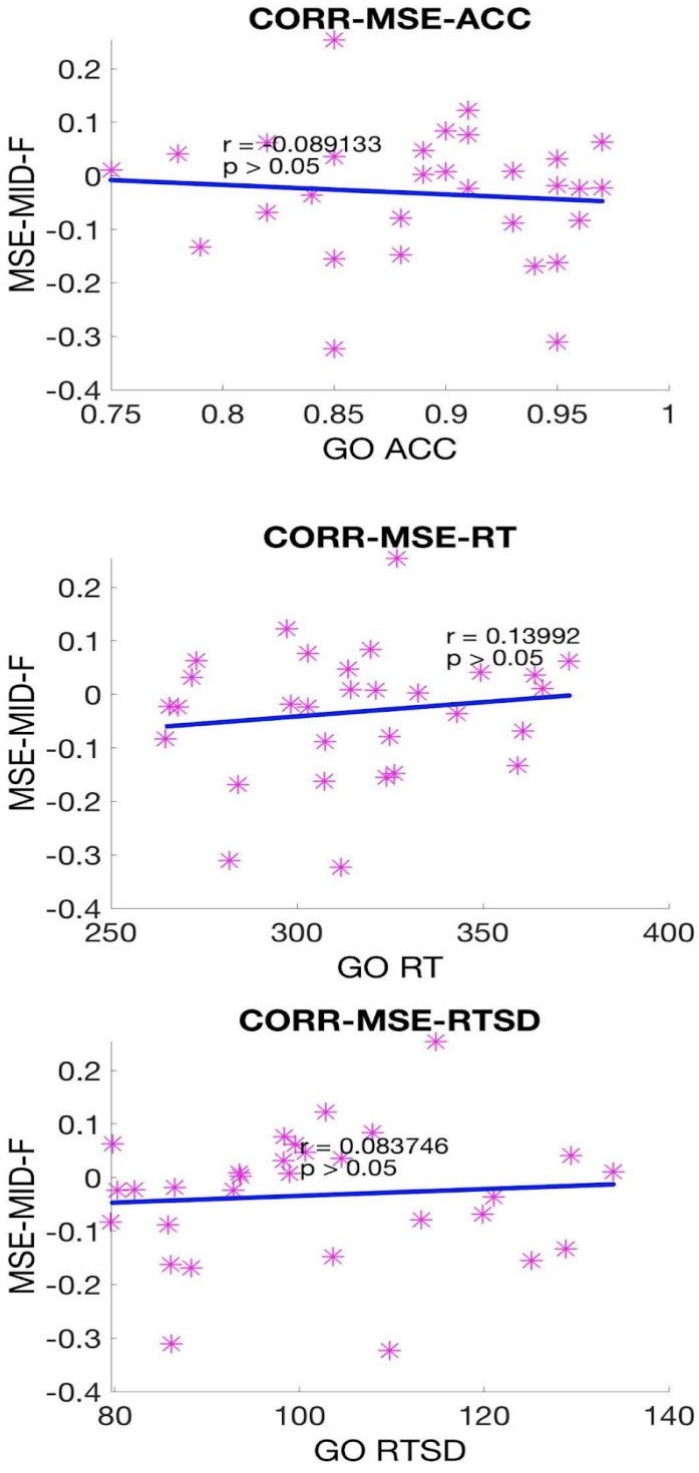


**Figure 23** Correlation between MSE and behavior performance for the ADHD group. Scatter plots with regression line between MSE-Δ averaged across mid scales at the frontal site and three behavior measurements (GO ACC, GO RT, GO RTSD) for the ADHD group.


**Figure 24** Mediation analysis of MSE.

# 4 SUMMARY

The present study aimed to investigate whether and how adults with ADHD differ from their peers in aspects of EEG complexity under different conditions. The ADHD group reported severe impairments on everyday functioning and showed worse task performance. During the resting state, the MSE from the comparison group was larger than that from the ADHD group across coarse scales (15-20) - an effect that was driven by frontal sites. No group differences were found during the active task states. In the comparison group, MSE at frontal sites within the mid scales correlated with all three task performance measurements (GO ACC, GO RT, GO RTSD), showing better performance related to decreased MSE measurements. Furthermore, the transition of MSE from the resting state to the active task state at the frontal site within the mid scales was larger in the comparison group than the ADHD group, and also correlated with task performance in the comparison group with better performance being associated with larger transitions of MSE between states.

## 4.1 Behavioral performance

Performance in the Go/Nogo task (Accuracy, Reaction time, and Standard deviation of reaction time) was compared between the comparison and ADHD groups. Consistent with previous literature, the accuracy (GO ACC) from individuals with ADHD was lower than that from their healthy peers. The small effect size of group differences in accuracy can be explained by the nature of the sample: college students with ADHD. These subjects are relatively high functioning adults with ADHD, especially in their performance on standardized neuropsychological tests (DuPaul et al., 2009; Gu et al., 2018). It's possible the go/nogo task was not sensitive enough to find differences between ADHD and healthy controls for college students.

The lack of group differences in reaction time (GO RT) was consistent with previous publications on go/nogo tasks in children with ADHD (Baijot et al., 2017). This could be explained by the relatively small size of the sample.

Compared with healthy subjects, the standard deviation of reaction time (RTSD) from adults with ADHD was larger than that from their peers with medium effect size. In other words, the ADHD group represented increased intra-individual variability in reaction time for go/nogo tasks. A previous study (Adams et al., 2011) investigated the standard deviation of reaction time in individuals with ADHD during different tasks and linked RTSD to distractibility, which suggested RTSD could be a valid measure of inattention in ADHD (larger RTSD indicated a higher level of inattention syndrome).

**4.2 MSE in the resting state**

When the comparison and ADHD groups were compared, it was first confirmed that smaller MSE at frontal sites within coarse scales during the resting state characterized individuals with ADHD. This could indicate weaker long-range interaction between the frontal site with other regions respectively in the ADHD group (Vakorin et al., 2011; McDonough & Nashiro, 2014; Wang et al., 2016), which was consistent with the executive dysfunction theory, that symptoms of ADHD were associated with abnormalities in frontal-parietal and frontal-striatal circuits (Seidman et al., 2005).

Previous studies on MSE during the resting state has revealed that there was an increase of MSE along with the development of the brain (Wang et al., 2016). Furthermore, smaller MSE during the resting state in the ADHD group could suggest a potential maturational delay of the cortex, which was consistent with behavioral and neuropsychological studies (Shaw et al., 2007; Berger et al., 2013)

Larger MSE across coarse scales in the comparison group could be supported by studies of neural oscillation in the resting state for adults with ADHD. In Woltering et al. (2012), lower

power in the alpha band was found during resting state for adults with ADHD compared to their peers. MSE within coarse scales was associated with EEG around the alpha band, which indicated that smaller MSE across coarse scales was associated with decreased neural oscillations around the alpha band in the ADHD group.

Smaller MSE within coarse scales at frontal sites in the ADHD group suggested lower itinerancy in distributed neural network related to frontal sites, which could be associated with lower cognitive flexibility (Armbruster-Genç et al., 2016) and difficulty to initialize attention (Friston et al., 2012).

There were several studies (McIntosh et al., 2008; Smit et al., 2013; Yang et al., 2013; Li et al., 2018; Szostakiwskyj et al., 2017; Armbruster-Genç et al., 2016; Pscherer et al., 2019) that suggested that the complexity or neural oscillation of brain activity during the resting state could provide insight into cognitive performance, such as sensitivity to stimuli and cognitive stability. Regarding the relationships between behavior measurements and MSE across different scale ranges at different brain sites, no significant correlation could be located, even for MSE within coarse scales at frontal sites..

### 4.3 MSE in the active task state

When the comparison and ADHD groups were compared, there was no significant difference in MSE at any brain sites across any scales in the active task state, which was different from my preliminary hypothesis. Similar MSE distribution between the comparison and ADHD groups suggested similar levels of local information processing and long-range interaction across different brain sites during task engagement.

It's premature to conclude that MSE is not able to characterize ADHD during the active task state. There were several potential explanations for the lack of significance of MSE during the active task state.

Firstly, MSE during the active task state measured the complexity of the neural activity driven by task requirements, including inhibitory and attention control in the go/nogo task. The same task requirement would drive individuals in the comparison and ADHD groups to dedicate a similar amount of neural resources, which might associate with similar MSE distribution (Woltering et al., 2013; Jahanshahloo et al., 2017; Leontyev et al., 2018).

Secondly, the weaker effects of MSE difference may have been presented but have required larger sample size to detect. It is worth mentioning that the difference of MSE between the comparison and ADHD groups was larger at frontal sites than other brain sites, as well as MSE in the comparison were smaller than that in the ADHD (not statistically significant), which was consistent with my hypothesis (Seidman et al., 2005).

When the relationship between MSE and task performance was investigated, MSE in the comparison group within mid scales at frontal sites was found to be negatively correlated with accuracy for go trials (GO ACC), positively correlated with reaction time for correct go trials (GO RT) and positively correlated with the standard deviation of reaction time for correct go trials (GO RTSD), which were not found in the ADHD group.

MSE in the active task state provided insight into functional connectivity corresponding to task requirements and evaluated dynamic itinerancy within certain neural networks (McIntosh et al., 2014; Wang et al., 2018). The negative correlation between MSE and task performance (better accuracy, shorter reaction time, a smaller standard deviation of reaction time) suggested decreased MSE in the active task state were associated with a neural network with high cognitive

stability (Armbruster-Genç et al., 2016), which was consistent with the hypothesis and other studies (McIntosh et al., 2008).

During the active task state, no significant relationships between MSE and task performance could be found in the ADHD group. Although the difference of MSE across mid scales at frontal sites didn't reach statistical significance, the direction of the effects suggested abnormal functional connectivity associated with MSE across mid scales at frontal sites might contribute to the executive function deficits in the ADHD population.

**4.4 MSE transition from the resting state to the active task state**

MSE within fine scales increased from the resting state to the active task state, as well as MSE within mid scales decreased from the resting state to the active task state for both the comparison and ADHD groups. These findings suggested more local information processing and less interaction across different sites for go/nogo tasks.

As previously discussed, the MSE from the comparison group was larger than that from the ADHD group (statistically significant) in the resting state, as well as the MSE from the comparison group was smaller than that from the ADHD group (not statistically significant) in the active task state. When the comparison and ADHD groups were compared, it was confirmed that smaller MSE transitions (MSE-Δ) from the resting state to the active task state within mid scales at frontal sites characterized individuals with ADHD.

Smaller MSE-Δ in the ADHD group indicated their brain could not generate sufficient change of long-range interaction between frontal sites with other regions for cognitive tasks, which was consistent with the executive dysfunction theory for ADHD (Seidman et al., 2005). In other words, participants in the ADHD group were less flexible and adaptable to process tasks.

Previous studies on MSE transition from the resting state to the active task state has revealed that there was an increase of MSE-Δ along with the maturation of the brain (Szostakiwskyj et al., 2017). Furthermore, smaller MSE-Δ in the ADHD group could suggest a potential maturational delay of the brain (Shaw et al., 2007; Berger et al., 2013), which was consistent with previous findings of smaller MSE in the ADHD group during the resting state.

When the relationships between MSE-Δ and task performance were investigated, MSE-Δ in the comparison group within mid scales at frontal sites were found positively correlated with accuracy for go trials (GO ACC), negatively correlated with reaction time for correct go trials (GO RT), and negatively correlated with the standard deviation of reaction time for correct go trials (GO RTSD), which were not found in the ADHD group.

MSE-Δ could provide insight into task-related functional connectivity changes and evaluate dynamic itinerancy change within certain neural networks (McIntosh et al., 2014; Wang et al., 2018). Increased MSE-Δ was positively correlated with task performance (better accuracy, shorter reaction time, a smaller standard deviation of reaction time) and revealed that the more adaptable the brain could be, the better task performance participants could achieve.

No significant relationships between MSE-Δ and task performance could be found in the ADHD group, which could be related to abnormal functional connectivity associated with MSE across mid scales at frontal sites during the active task state.

**4.5 Conclusion**

To the best of my knowledge, this is one novel and comprehensive analysis of EEG complexity for college students with ADHD. The study provides support for the idea that multiscale entropy (MSE) can evaluate brain dynamics in subjects with ADHD under different states, provide insight into neural connectivity, and their relationships with attention-

deficit/hyperactivity disorder (ADHD) symptoms. My findings suggest that the brains of individuals with ADHD have lower cognitive flexibility in the resting state than their healthy peers, as well as lower cognitive stability in the active task state. The brain's ability to change from a resting state to an active state is represented by MSE transition and significantly different between individuals with ADHD and their peers. The comprehensive interpretation of the MSE complexity over different mental states could provide insight into the neural mechanism of ADHD and a potential method to evaluate treatment for ADHD.

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# APPENDIX A

## EEG SIGNAL WITH ARTIFACT FROM ELECTRODE POP

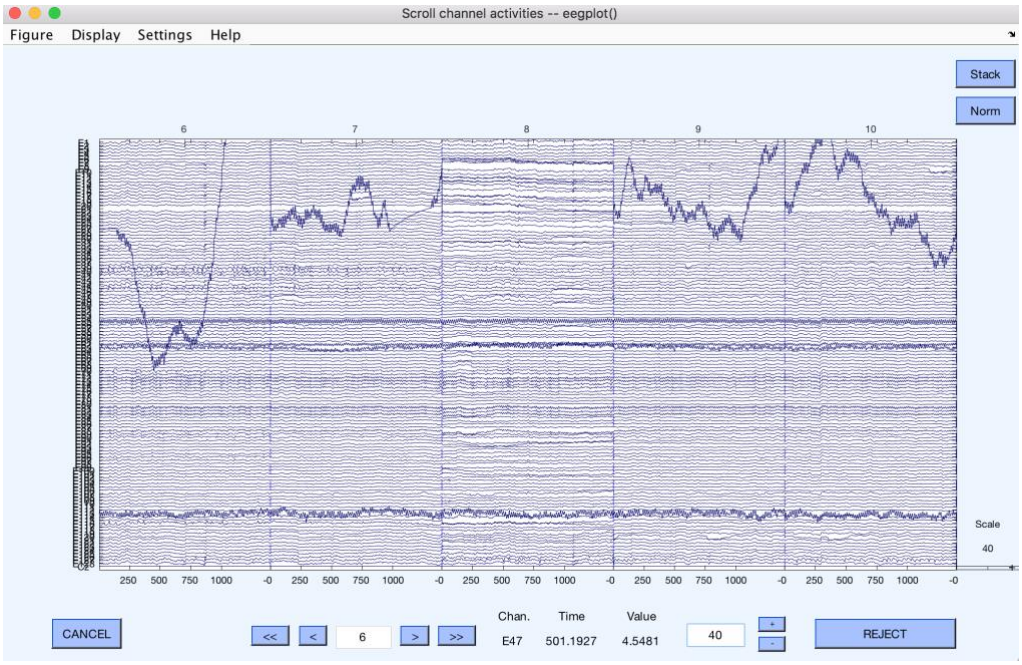


**Figure 25** EEG signal with artifact from electrode pop.

# APPENDIX B

## EEG SIGNAL WITH EXTREME LARGE ARTIFACT IN SEGMENTS

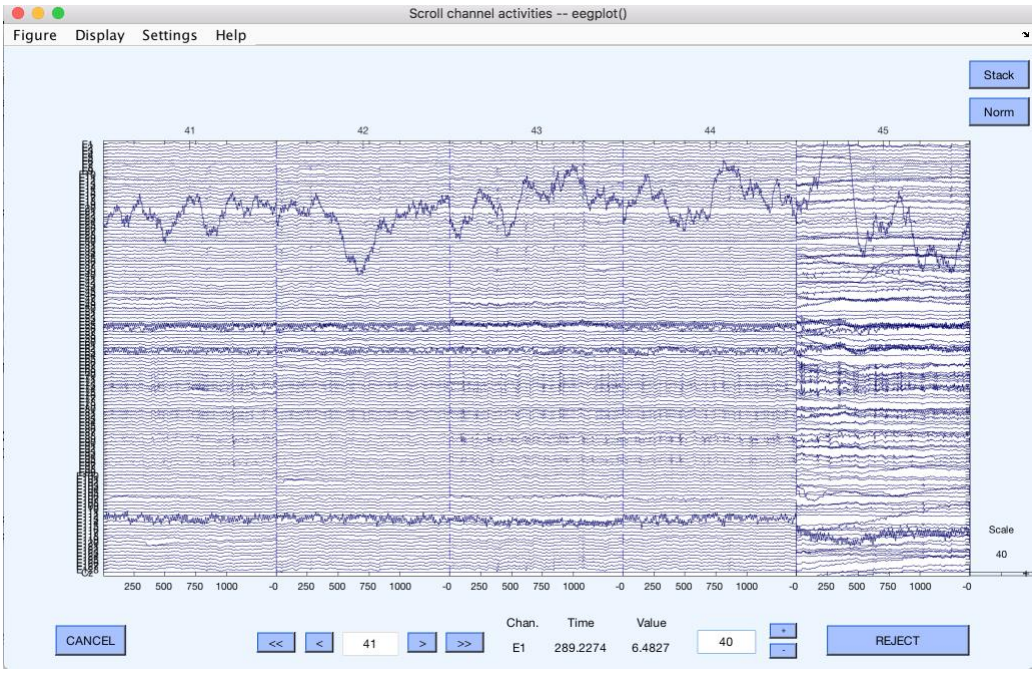


**Figure 26** EEG signal with extreme large artifact in segments.

APPENDIX C

ICA PROCEDURE

(1) After removing abnormal segments and electrodes, I run ICA decomposition in EEGLAB on all electrodes.

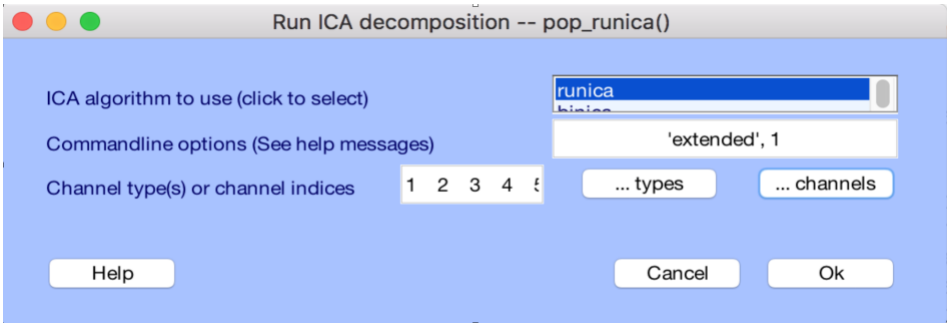


**Figure 27** Run ICA in EEGLAB.

(2) After the ICA decomposition, SASICA (a plugin in EEGLAB) was called to identify ICs with artifacts.

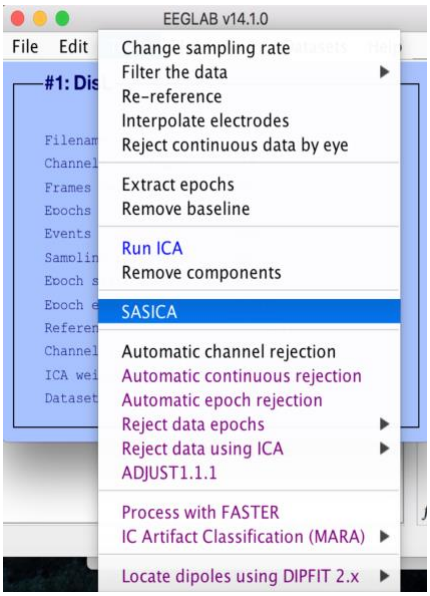


**Figure 28** Run SASICA in EEGLAB.

(3) Parameter selection for SASICA.

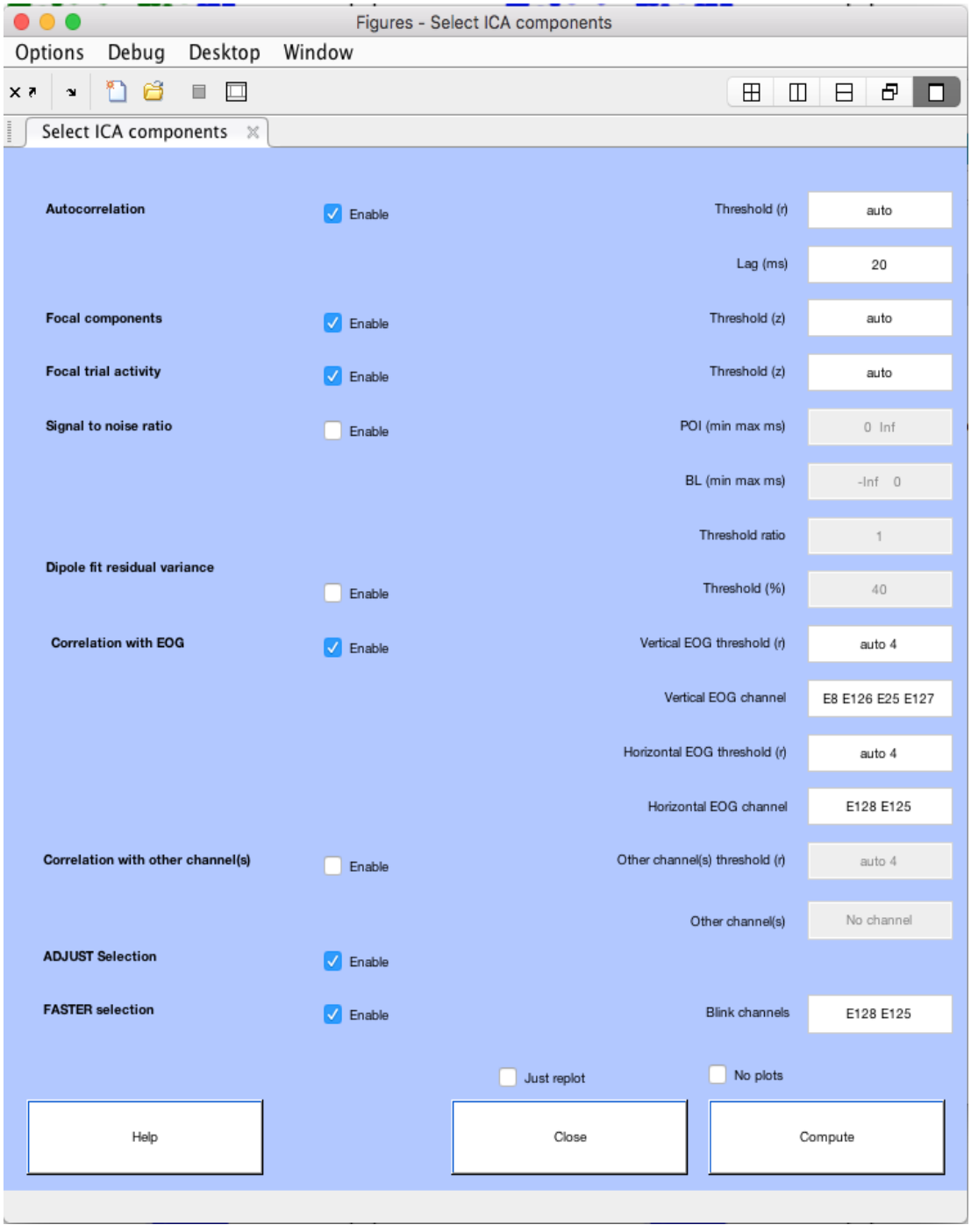


**Figure 29** Parameters in SASICA.

(4) SASICA would automatically identify ICs with artifacts and list corresponding topographies for further verification.

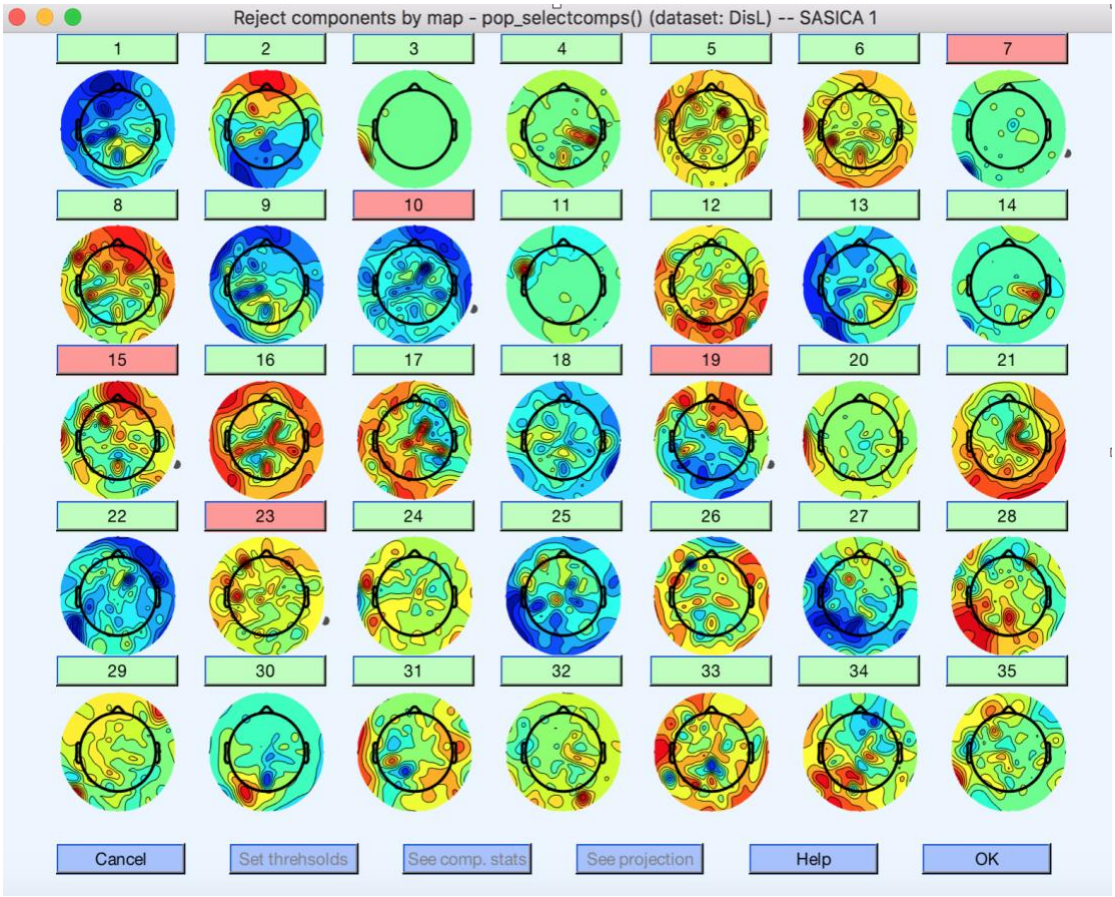


**Figure 30** Topographies of ICs.