NEURAL BASES FOR TEMPERAMENTAL EFFORTFUL CONTROL DEFICIT AND ITS RESPONSE TO TRANSCRANIAL DIRECT CURRENT STIMULATION IN AUTISM SPECTRUM DISORDER

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Neural Bases for Temperamental Effortful Control Deficit and its Response to Transcranial Direct Current Stimulation in Autism Spectrum Disorder

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CERTIFICATE OF ORIGINALITY

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental condition that characterizes impairment in communication and social interaction with the presence of repetitive stereotypic behavioral patterns and interests. These clinical features are heightened in autistic individuals as a result of dysfunctional temperamental effortful control (EC), which employs executive attention skills for suppressing a dominant response and/or to initiate a subdominant response for planning and/or recognizing errors. EC encompasses attentional control, inhibitory control, and cognitive flexibility subcomponents that aid in activating, modulating, or withdrawing tendencies pertinent to chosen behavior. Although EC deficits in autism have been arbitrated with parents' or caregivers' perception in Western populations, the exact neural underpinnings and the magnitude of EC impairment in the Chinese-Hong Kong population remain elusive. Additionally, individuals with ASD presented with abnormal structural and functional neural systems, including the prefrontal cortex, which is responsible for supervising attention, inhibitory control, and cognitive flexibility functions. Reversal of such abnormal brain functions requires intervention to modulate underlying neural activities, which can be accomplished using transcranial direct current stimulation (tDCS). Given that this doctoral thesis includes a combination of four interlinked studies,

Study one aimed to synthesize available whole-brain fMRI studies on EC components, including attention control, inhibitory control, and cognitive flexibility, separately using SDM-PSI software. The study compared the brain activation pattern between individuals with autism and healthy controls (HCs) while controlling for age and further examines the aging effect on task-induced brain activation during each EC component. The results showed that there was a significant deactivation of brain regions in autism patients compared to HCs in all EC components. Notably, hypoactivation was evident in the left inferior frontal gyrus, left fusiform gyri, left precentral gyrus, right cerebellum crus II, right

superior occipital gyrus during attentional control; left anterior cingulate gyrus, right angular gyrus during inhibitory control; and left anterior cingulate gyrus, left inferior frontal gyrus, left precuneus during cognitive flexibility tasks. Meta-regression analysis revealed age-increased deactivation in the right precentral gyrus and left inferior gyrus during attention control; the left anterior cingulate during cognitive flexibility was found in ASD.

Study two examined the relationship between EC and prefrontal cortex activation and connectivity in children with high-functioning ASD. Thirty-nine right-handed children (ASD n = 20; HC n = 19) aged 8-12 years were recruited. The EC level was assessed with the Early Adolescent Temperament Questionnaire-Revised (EATQ-R), and PFC functioning, in terms of activation and connectivity during the n-back task, was recorded using functional near infrared spectroscopy (fNIRS). Children with ASD showed a significant deficit in EC, executive, and socioemotional functions compared to HC. The ASD group also showed significantly increased overall PFC activation and reduced right frontal connectivity during the n-back task. Among children with ASD, the EC level correlated significantly with neither PFC activation nor connectivity and correlated with social functioning only. This study demonstrated EC deficits and altered PFC functioning in children with ASD, but the exact neural basis of EC deficits remains to be determined.

Study three investigated the relationship between EC and prefrontal cortex activation and connectivity in adolescents and adults with high-functioning ASD. Twenty-seven right-handed individuals (ASD n = 14; HC n = 13) aged 15-22 years were recruited. The EC level was assessed with the Early Adolescent Temperament Questionnaire-Revised (EATQ-R) and Adult Temperament Questionnaire (ATQ), and PFC functioning, in terms of activation and connectivity during the Wisconsin Card Sorting Test (WCST), was assessed using functional near infrared spectroscopy (fNIRS). The ASD group showed a significant deficit in EC, executive, and socioemotional functions compared to the HC group. The ASD group also

showed significantly reduced intra- and interfrontal connectivity during the WCST. Among individuals with ASD, the EC level correlated significantly with neither PFC activation nor connectivity and correlated with attentional (reaction time task) and social functions. This study demonstrated EC deficits and altered PFC functioning in adolescents and adults with ASD, but the exact neural underpinnings of EC deficit remain to be clarified.

Study four compared the effect of cathodal and sham tDCS on temperamental EC, social behaviour, information processing speed, and PFC functional connectivity in individuals with ASD. Thirty right-handed individuals (tDCS n = 15; sham n = 15) aged 14-21 years were recruited. Early Adolescent Temperament Questionnaire (EATQ), Adult Temperament Questionnaire (ATQ), Social Responsiveness Scale (SRS-2), neuropsychological tests tapping information processing efficiency, and fNIRS PFC connectivity at rest were measured before and after tDCS intervention. Results showed that only the repetitive cathodal tDCS improved activation control of EC, social function, information processing efficiency, and resting state functional connectivity of the right medial prefrontal cortex (PFC). Such cathodal tDCS on functional connectivity enhancement in the right medial PFC was further associated with information processing efficiency and cognitive flexibility skills which might explain a potential neurophysiological mechanism underlying the desirable behavioral modifications.

These findings have offered valuable evidence regarding the neural bases for temperamental EC deficits in autism. Findings have further extended that Chinese-Hong Kong individuals with high-functioning ASD have EC deficits, and such deficits have been associated with social, emotional, and attentional skills in ASD. Additionally, findings also provided preliminary evidence that the repetitive cathodal tDCS could be an effective intervention for enhancing activation control of EC, social skills, cognitive flexibility, information processing speed, and resting state functional connectivity of the medial PFC.

LIST OF PUBLICATIONS ARISING FROM THE THESIS

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DEDICATION

TO THE BABIES AND TODDLERS OF OUR FAMILY INCLUDING MY SON (K. U. Charvadhiyan), DAUGHTER (K. U. Krithvika), AND MY NIECES (B. R. Rakshana, S. S. Sivani, B. R. Mugilvalavan, and H. N. Sidhaarthika) FOR WHOM THIS RESEARCH WORK MAY INSPIRE AND SERVE AS A MOTIVATING FACTOR FOR THEIR ACADEMIC EXCELLENCE. SPECIAL DEDICATION TO MY PARENTS, FAMILY MEMBERS, ALL TEACHERS, INSTITUTIONS, AND COLLEGUES WHO IMPART KNOWLEDGE IN ME FOR SUCCESSFUL COMPLETION OF THIS DOCTORAL (PHD) STUDY.

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LIST OF ABBREVIATIONS

Abbreviations	Expansions
ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview - Revised
AG	Angular Gyrus
AMED	Allied and Complementary Medicine Database
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid
ANOVA	Analysis of Variance
ANT	Attention Network Test
AR-IRLS	Autoregressive Iterative Reweighted Least Squares
ASD	Autism Spectrum Disorder
ASI	Animal Sorting and Inhibition
ATEC	Autism Treatment Evaluation Checklist
ATQ	Adult Temperament Questionnaire
BDNF	Brain Derived Neurotrophic Factor
BOLD	Blood Oxygenation Level Dependent
BRIEF	Behavior Rating Inventory of Executive Function
cAMP	Cyclic Adenosine Monophosphate
CANTAB	Cambridge Neuropsychological Test Automated Battery
CARS	Childhood Autism Rating Scale
CBQ	Children's Behavior Questionnaire
Ccor	Corticocortical
CStr	Corticostraital

DAN	Dorsal Attention Network
DAWBA	Development and Well-being Assessment
DISC-IV	Diagnostic Interview Schedule for Children
DISCO	Diagnostic Interview for Social and Communication Disorders
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM-5	Diagnostic Statical Manual of Mental Disorders (5th Edition)
E/I	Excitatory/Inhibitory
EA	Executive Attention
EAATs	Excitatory Amino Acid Transporters
EATQ-R	Early Adolescent Temperament Questionnaire - Revised
EC	Effortful Control
ECS	Effortful Control Scale
EF	Executive Function
ERT	Emotion Recognition Task
FEF	Frontal Eye Field
fMRI	functional Magnetic Resonance Imaging
fNIRS	functional Near Infrared Spectroscopy
FPN	Fronto-Parietal Network
FT	Flanker's Task
FWHM	Full Width at Half Maximum
GABA	Gamma Aminobutyric Acid
GLU-Rs	Glutamate Receptors
GNG task	Go/No-Go Task
GS	Glutamine Synthetase

HADS	Hamilton Anxiety and Depression Scale
HbO	Oxygenated Hemoglobin
HbR	Deoxygenated Hemoglobin
HC	Healthy Controls (Group)
IES	Inverse Efficiency Score
IFG	Inferior Frontal Gyrus
IOG	Inferior Occipital Gyrus
IQ	Intelligent Quotient
IT	Intra Telencephalic
L/R	Left/Right
LC-NE	Locus Coeruleus - Norepinephrine
mA	milli Amphire
MFG	Middle Frontal Gyrus
MNI	Montreal Neurological Institute
MOG	Middle Occipital Gyrus
MTT	Multitasking Test
n.s	nonsignificant
NIRS-SPM	Near Infrared Spectroscopy-Statistical Parameter Mapping
NMDA	n-Methyl-d-asparate
OCD	Obsessive Compulsive Disorder
PCG	Precentral Gyrus
PFC	Prefrontal Cortex
PKA	Protein Kinase A
PRISMA	Preferred Reported Items for Systematic Reviews and Meta-analysis
RBS-R	Repetitive Behavior Scale -Revised

ROIs	Regions of Interests
RTI	Reaction Time Task
SADS	Social Avoidance and Distress Scale
SCQ	Social Communication Questionnaire
SDM-PSI	Seed-based d-mapping - Permutation of Subject Images
SDT	Signal Detection Theory
SFG	Superior Frontal Gyrus
SMN	Somato Motor Network
SOG	Superior Occipital Gyrus
S-R	Stimulus-Response
SRS-2	Social Responsiveness Scale - 2nd Edition
tACS	transcranial Alternating Current Stimulation
TD	Typically Developing (Control Group)
tDCS	transcranial Direct Current Stimulation
TEA-Ch	Test of Everyday Attention for Children
tES	transcranial Electric Stimulation
TFCE	Threshold Free Cluster Enhancement
TMS	Transcranial Magnetic Stimulation
TMT	Trial Making Test
tPCS	transcranial Pulsed Current Stimulation
tRNS	transcranial Random Noise Stimulation
VAN	Ventral Attention Network
VN	Visual Network
VSCC	Voltage Sensitive Calcium Channels
WCST	Wisconsin Card Sorting Test

CHAPTER 1: GENERAL INTRODUCTION

1.1. Overview

Autism spectrum disorder (ASD) is a heterogeneous condition that affects neurodevelopmental function related to social communication and behavior, thereby demonstrating communication impairment and persistence of ritualistic stereotypic behavioral manifestations (American Psychiatric Association, 2013). The exact causes of ASD are still imperceptible; however, genetic predispositions and exposure to environmental hazards during fetal development are believed to be underlying etiological factors (Betancur, 2011; Lai, Lombardo, & Baron, 2014). The prevalence of ASD has been growing consistently across the globe (Kim et al., 2011), reaching 1 out of 54 children at present (Maenner et al., 2020). Among the earlier diagnoses of individuals with ASD, only 17% achieved good outcomes in the socio communicative domain, which measures independency, employability, and companionship while the individuals reach the adolescent phase (Steinhausen, Lauritsen, & Mohr, 2016). In turn, adolescents with ASD with poor socio communicative outcomes experience problems interacting with people and securing employment, which pose a great challenge for independent living (Henninger & Taylor, 2013). From a neuropsychological perspective, socio communicative impairment emerges from defective temperamental effortful control (EC), which typically regulates, adapts, and attends task-oriented stimuli from given circumstances (Eisenberg, Smith, Sadovsky, & Spinrad, 2004). Although EC function was found to be dysfunctional in autism, the majority of the studies were conducted in Western children; therefore, it is still uncertain whether Chinese Hong Kong individuals with ASD show similar dysfunctional patterns of EC. Additionally, the exact neurological bases for EC deficits in individuals with ASD remain unclear. Furthermore, managing EC deficits in autism using pharmacological, behavioral, and psychoeducational interventions does not enable recovering the underlying brain physiological mechanisms or producing optimal effects associated with neuromodulation,

which results in minimal efficacy (Francis, 2005; MacMaster, Sembo, Ma, & Croarkin, 2016). To overcome these limitations, transcranial electric stimulation has been used as an intervention medium for improving cognitive and underlying neurophysiological mechanisms in individuals with a wide range of disorders, including autism (Nitsche & Paulus, 2000). Therefore, the objectives of the thesis are to examine the neural substrates underlying temperamental EC deficits, explore EC and its relationship with prefrontal cortex (PFC) functioning in Chinese-Hong Kong participants with ASD, and study transcranial electric stimulation effects on EC and PFC functions in individuals with ASD. To broaden the understanding of objectives, the subsequent sections elaborate temperamental EC in terms of describing the concept and discussing the underlying neurogenic causative factors that contribute to EC deficits in ASD. It also further explains transcranial electric stimulation and its applicability in the autism context. Finally, it proposes the literature gaps with the aims and hypotheses of individual study to address corresponding research questions.

1.2. Introduction to Temperamental Effortful Control

Human beings perform a wide range of tasks in their daily lives, and a successful performance on any given task requires an innumerable number of cognitive functions. One such cognitive function is the ability to control oneself reacting to an irrelevant competing stimulus and focus attention solely on the relevant stimulus that originates from an assigned task. In other words, it is the ability to monitor one's own behavior while engaging in an activity and complete it without having deviated or distracted from an extraneous stimulus. The process of these abilities, such as inhibitory control over dominating stimuli, noticing deviations, bringing attention back to the task upon disruption, and correcting errors, are referred to as temperamental EC. Effortful control is formally defined as "the ability to inhibit a dominant response to perform a subdominant response, to detect errors and to

engage in planning" (Rothbart & Rueda, 2005). It is also defined as the "efficiency of executive attention-including the ability to inhibit a dominant response and/or to activate a subdominant response, to plan, and to detect errors" (Rothbart & Bates, 2006, p. 129). EC is conceptualized under the self-regulation component in the temperamental construct and is encompassed by both attentional and behavioral regulatory elements. The attentional element is primarily involved in focusing or shifting attention toward a needy task (*attentional control*), whereas the behavioral element is simultaneously involved in inhibiting existing behavior (*inhibitory control*) or generating new patterns of behavior in accordance with an emergence of favorable or unfavorable circumstances (Rothbart, 1989). In sum, EC is an inherent ability of one's executive attention, attentional control, cognitive flexibility, and inhibitory control, which help monitor or resolve conflicts among ideas, emotions, and reactions to regulate behavior associated with a proposed task.

1.3. Effortful Control Versus Executive Function

From a broader perspective, both EC and executive function (EF) help attain self-regulation of individuals. However, the core elements of these constructs vary in structural and conceptual underpinnings. EC is an inborn characteristic of temperament that relies on emotion to help suppress dominant and initiate subdominant responses by effective planning and noticing errors. EC is primarily regulated by four subcomponents: (a) inhibiting impulses, (b) switching and directing attention from undesirable to desirable tasks, (c) making decisions over conflicting stimuli, and (d) detecting and correcting errors by opting for the right course of action voluntarily (Rothbart & Bates, 2006, p. 129). These components of EC are predominantly volitional; for instance, a child can voluntarily suppress impulses toward watching television while writing, self-correcting errors that he/she has made in a

written assignment, and successfully completing the task in hand (Kim, Nordling, Yoon, Boldt, & Kochanska, 2013). Although EF and EC are highly related to each other, emotion-driven, self-controlled EC is a much more rudimentary component in self-regulation than purely cognitive-driven EF, especially in dealing with children who relate to their growth of conscience (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996). Moreover, adequate EC is an absolute prerequisite for the development of various socioemotional outcomes, such as negative emotionality (Fabes et al., 1999), prosocial behavior (Diener & Kim, 2004), social competence and adjustment (Eisenberg, Spinrad, & Eggum, 2010), and empathy-related response (Gurthrie et al., 1997). In contrast, children with low or deficient EC are prone to maladjustment (Caspi, Henry, McGee, Moffitt, & Silva, 1995; Henry, Caspi, Moffitt, Harrington, & Silva, 1999), behavioral issues (Kochanska & Knaack, 2003), and externalizing and internalizing problems (Lemery, Essex, & Smider, 2002; Murray & Kochanska, 2002), which lead to worsened social functioning (Posner & Rothbart, 2007). All this evidence suggests that EC is a crucial function for the self-regulation of children's behaviors and that a lack of such function results in poor socioemotional functioning.

In contrast to EC, EF is a top-down, goal-oriented cognitive process involved in supervising ongoing stimulus information and establishing control over the cognitive behavioral manifestation of individuals (Espy, 2004; Miller & Cohen, 2001). EF is primarily driven by three rudimentary concepts: a) inhibitory control, which involves restricting innate overdriven attention, the thinking process, emotion, and behavior on external alluring stimuli; b) working memory, which maintains verbal and visual-spatial information in the mind and manipulates them for ongoing tasks that are not perceptually obvious; and c) set-shifting, which involves switching attention back and forth over demanding stimuli based on priorities and requirements. The attainment of these three rudimentary concepts helps achieve a higher-order EF, namely, reasoning, problem-solving, and planning (Diamond, 2013). Therefore, the

EF-derived self-regulation is predominantly overt on using a set of cognitive functions rather than pure emotion-based exertion.

Although EC and EF components conceptually overlap with each other in the self-regulation construct, EC primarily differs from EF in five key areas, including emotion-dependent context, working memory involvement, developmental patterns, adaptive function relationships, and underlying neural substrates (Zhou, Chen, & Main, 2012). Thus, EC is investigated more on emotion-laden constructs with minimal involvement of working memory as opposed to EF, which is studied more on emotion-neutral constructs with the involvement of working memory as a prime component. EC components also develop much earlier in life, e.g., the executive attention system, including orientation and selective attention, develops first and second to third years of life, respectively. While the EF components, especially inhibitory control, set-shifting, and working memory, emerge after the third year and continue to develop until thirteen years old. Furthermore, EC is related to attaining a wide variety of adaptive functions, including socioemotion regulation (internalizing/externalizing issues, sympathy/empathy, conscience/moral development, prosocial behavior, and social competence) and academic achievements (math/phonemic awareness, school competence, and grade-point average). Whereas the EF is related to attaining narrow adaptive functions, including social competence, theory of mind, school readiness, and academic achievement. Finally, the neural correlates underlying EC components, especially executive attention, are confined to activating the lateral prefrontal cortex and anterior cingulate gyrus, whereas EF components, such as inhibitory control, set-shifting, and visual spatial working memory, recruit the orbitofrontal cortex and ventrolateral/dorsolateral prefrontal cortex (Zhou et al., 2012).

1.4. Development of Effortful Control

The development of EC relies heavily on the maturation of its subcomponents, including executive attention, attentional control, cognitive flexibility, and inhibitory control. Attention mechanisms appear to grow from infancy, such that an infant can orient to a novel sensory stimulus, maintain attention and implement earlier control over it (Posner & Rothbart, 1998; Rothbart & Bates, 2006). Executive attention begins in early infancy and continues to improve throughout toddlerhood and preschool years. More specifically, six- to seven-month-old infants develop anticipatory looking (look at the location well before the target is presented), and twelve-month-old infants demonstrate reaching a target away from the visual field and synchronizing reach with vision together (Sheese, Rothbart, Posner, White, & Fraundorf, 2008). At nine to eighteen months, infants can master conflict resolution while processing information, self-correcting errors and making a new plan of action (Posner & Rothbart, 1998), and thereby attention becomes more voluntary (Ruff & Rothbart, 2001). Between 30 and 38 months, toddlers learn switching attention (attention shifting) and concurrently deploying inhibitory action on overriding stimuli (Garon, Bryson, & Smith, 2008; Gerardi-Caulton, 2000; Posner & Rothbart, 1998). During preschool years, most toddlers inhibit behavior while receiving a command (Rothbart & Bates, 2006) and master new sets of EC skills, such as postponement, decelerating motor acts, suppressing or activating a response, and reducing vocalization and effortful attention (Kochanska, Murray, & Harlan, 2000). Consequently, children can inhibit behavior effortfully and attain stability in controlling extraneous behavior (Jones, Rothbart, & Posner, 2003), which leads to maximal EC stability, including attention focusing, attention shifting, and inhibitory control (Murphy, Eisenberg, Fabes, Shepard, & Guthrie, 1999; Valiente et al., 2006). By the end of early childhood, most children achieve superior EC indexed by heightened empathy, guilt/shame, and reduced displaying aggressiveness (Rothbart, Ahadi, & Hershey, 1994),

which potentially help achieve better socioemotional outcomes in the late childhood and adolescent years.

1.5. Effortful Control Measures

Traditionally, EC and its components, such as executive attention, attentional shifting (flexibility), inhibitory control and conflict resolution (Eisenberg et al., 2004; Rothbart, Sheese, & Posner, 2007; Rothbart & Bates, 2006), have been evaluated by means of observational, behavioral, and physiological measures. The Toddler Behavior Assessment Questionnaire (Goldsmith, 1996), Children's Behavior Questionnaire (Rothbart, Ahadi, Hershey, & Fisher, 2001), Early Adolescent Temperament Questionnaire (Capaldi & Rothbart, 1992), Effortful Control Scale (ECS; Lonigan & Phillips, 2001), and Adult Temperament Questionnaire (Evans & Rothbart, 2007) are commonly utilized to measure EC. The Toddler Behavior Assessment and Children's Behavior Questionnaires are parents or caregivers administered tools for toddlers and children aged between 1 and 3 years and 4 to 11 years, respectively. The Early Adolescent Temperament Questionnaire includes both self- and parent-caregiver versions and is administered to early adolescents aged between 5 and 15 years. The ECS is purely a self-administered tool and was designed to measure EC for early adolescents. Finally, the Adult Temperament Questionnaire (ATQ) is a self-reported tool to measure EC for adults.

In behavioral measures, the inhibitory control and conflict resolution components of EC are measured by Go/No Go (Kochanska & Knaack, 2003), Stroop task (González, Fuentes, Carranza, & Estévez, 2001), delay of gratification (Mischel, Shoda, & Rodriguez, 1989), and Head-Toes-Knees-Shoulders (Ponitz et al., 2008) tasks. The executive attention component is measured using the "Attention Network or Flanker's task (ANT or FT;

Rothbart, Sheese, & Posner, 2007)" and Spatial Conflict Task (Gerardi-Caulton, 2000) for children and adolescents of various age groups.

In physiological methods, cardiac vagal tone quantified by respiratory sinus arrhythmia is widely used to measure the self-regulatory component of EC (Calkins & Keane, 2004; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). In addition, a combination of behavioral and observational measures was also utilized to measure EC. For instance, Kochanska's multitask battery contains a series of tasks (Walking in a Line, Turtle's House, Telephone Poles, Circle, Star, and lowering voice) that are used to measure inhibition, error detection and cognitive flexibility components of EC in both children and adolescents. In summary, EC is an intertwined construct of attention, cognitive flexibility, and inhibition that is evaluated by means of observational, behavioral and physiological measures; however, utilization of a specific measure depends on the nature of a study characterizing the target population and age group.

1.6. Neural Substrates Underlying Effortful Control

As discussed above, the EC function comprises three subcomponents: attentional control, cognitive flexibility, and inhibitory control. Each component is regulated by specific neural substrates, and this section elaborates them in detail as follows:

The attentional control and cognitive flexibility subcomponents of EC play a major role in resolving conflicts among perception, thoughts, and action (Posner & Boies, 1971; Posner & Petersen, 1990). These are primarily regulated by the executive attention network, which is one of the central processing networks in Posner's initially proposed model of attention, in addition to alertness and orientation and is involved in monitoring conflict

resolution and responding to stimuli while controlling behavior (Posner & Fan, 2008). Typically, the behavioral elements of attentional control are measured using the stroop task (Stroop, 1992), simon task (Simon, 1990), spatial conflict task (Gerardi-Caulton, 2000), flanker task (Rothbart et al., 2007), and attention network test (Fan, McCandliss, Sommer, Raz, & Posner, 2002). The stroop task requires responding to ink color (e.g., green) and ignoring the word name printed in a specific color (e.g., red) simultaneously. During the task, participants read words automatically while the ink color interferes and produces conflicts between two competing responses. Similarly, the flanker task (a part of ANT) requires responding to a central stimulus pointing in the same direction (congruent) or in the opposite direction (incongruent) of other flankers surrounded by the central stimulus. Likewise, the spatial conflict task requires responding to the location of a target that appeared on the screen, such as the central position (neutral condition); the target is presented on the same side (congruent) or opposite side (incongruent) of the matching response stimulus. Studies with healthy individuals on these conflict tasks showed activation in the anterior cingulate and left ventral prefrontal cortices (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003). The involvement of these brain regions was also observed in other studies; for instance, trial-relevant activation in these regions was greater when responding to target, conflict and error stimuli than when responding to nontarget, nonconflict and correct stimuli, suggesting that executive attention is regulated by two distinguished top-down control networks (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). The first network is the frontoparietal network, which includes the dorsolateral prefrontal cortex and intraparietal sulcus and is involved in initiating, modulating, and switching responses based on each trial. The second network is the cingulo-opercular network, which includes the dorsal anterior cingulate, anterior insula, medial superior frontal, frontal operculum, and anterior prefrontal cortices. These networks are closely linked to the dorsolateral prefrontal network, which maintains task sets across

trials and regulates goal-oriented behavior (Dosenbach et al., 2007). Additionally, modulation of the prefrontal cortex to the anterior cingulate network potentially increased issues with attention, conflict resolution, inhibitory control, and flexibility functions (Posner, Rothbart, Sheese, & Voelker, 2012). These issues are primarily observed in children with autism, especially problems in attentional disengagement (Landry & Bryson, 2004) during infancy and the first year, which helps predict the diagnosis of autism at age 3 (Elsabbagh et al., 2013; Sacrey, Bryson, & Zwaigenbaum, 2013).

The third subcomponent of EC, "inhibitory control", plays an important role in activating or maintaining the self-regulation of individuals and is divided into two types: a) interference control and b) response inhibition. Interference control is further subdivided into cognitive inhibition and selective or focused attention. The cognitive inhibition of interference control diminishes dominant mental activity by opposing irrelevant memories or thought processes (Anderson & Levy, 2009). However, the "selective or focused attention" of interference control allows attending to relevant stimuli and ignoring irrelevant stimuli (Posner, & DiGirolamo, 1998) on the basis of an individual's priorities (Theeuwes, 2010). Interference control (cognitive inhibition and selective or focused attention) is measured behaviorally by the Go/No Go task (GNG), which requires responding to a target stimulus while ignoring a nontarget stimulus in the event of continuous stimulus presentation (Kochanska & Knaack, 2003; Lengua, Honorado, & Bush, 2007). According to signal detection theory (SDT), the responses of the GNG task are analyzed in four parameters: (a) correctly responding or hitting when a go stimulus is presented, (b) failing or missing to respond when a go stimulus is presented, and (c) false alarm, i.e., responding when a no-go stimulus is presented, (d) correctly ignores or rejects when a no-go stimulus is presented (Green & Swets, 1966; Macmillan, 2005; Swets, Dawes, & Monahan, 2000). Adhering to this theory, multiple neuroimaging studies have been conducted to explore the brain activation

patterns and circuitry in both normative and disordered populations. Particularly, a neuro-imaging study on the GNG task in healthy children and adults showed a parallel activation pattern in the prefrontal cortex; however, the total volume of brain activation was larger in children than adults while inhibiting stimuli. Furthermore, the inhibitory process was also observed establishing distributed activation phenomena among the anterior cingulate, dorsolateral, and orbitofrontal cortices, and these results were correlated with overall behavioral performance in terms of the number of false alarms (Casey et al., 1997).

The second type of inhibitory control, "response inhibition", involves withstanding against temptation and persisting in an activity (discipline) by refraining from impulsive behavior (self-control). Response inhibition was also measured using the GNG task, and greater activation in the ventral fronto-striatal circuitry was observed in children than adults. The activation in this region was highly correlated with the participants' age and their behavioral performance in the GNG task (Durston et al., 2002). Similar results were obtained in other neuroimaging studies; in particular, the "no-go" trials activated the anterior cingulate gyrus when processing information related to conflict response monitoring (Barch, Braver, Sabb, & Noll, 2000; Cameron et al., 2000; Matthew, Leigh, Kate, Cameron, & Jonathan, 1999) and detecting conflicts between two competing responses (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998). In contrast, studies in autism using similar GNG task paradigms showed abnormal activation patterns in the cingulate cortex; in particular, reduced left anterior cingulate activation was observed while detecting novel stimuli (Gomot et al., 2006). Similarly, individuals with autism performing inhibition tasks showed a reduction in activation in the anterior cingulate cortex and reduced connectivity in the anterior and middle cingulate gyri, insula, right middle frontal, inferior frontal, and inferior parietal cortices (Kana, Keller, Minshew, & Just, 2007). All these findings suggest that the

prefrontal cortices and anterior cingulate gyri play a significant role in regulating behavior associated with inhibitory control tasks.

Taken together, tracing the brain activation pattern and the accompanying network involvement during temperamental EC require individualized tasks that address attention control, inhibitory control, and cognitive flexibility subcomponents separately. During these tasks, healthy individuals were found to have common network involvement, including the frontoparietal and cingulo-opercular networks, which consist of brain regions involving the left frontal, bilateral parietal, cingulate, and insular cortices. Nevertheless, some of these brain regions were involved in individuals with autism, and it remains unclear whether the degree of activation and deactivation patterns among the brain sites and networks correspond to temperamental EC deficits in ASD. Therefore, further studies are warranted to dissociate the magnitude of neural underpinnings associated with each EC subcomponent in autism.

1.7. Effortful Control Deficit in Autism Spectrum Disorder

Temperamental EC was reported to be defective in individuals with numerous clinical conditions, including ASD, which constitutes autistic, Asperger, childhood disintegrative, and pervasive developmental disorders. Notably, Samyn, Roeyers, and Bijttebier (2011) claimed that dysfunctional EC measured using the EATQ and effortful control scale (ECS) in children with ASD hindered optimal performance in daily circumstances. Similarly, Konstantareas and Stewart (2006) reported that individuals with more ASD symptoms and less chronological age were found to have lower temperamental EC. Additionally, studies have also explored the relationship between EC deficits and socioemotional outcomes. For instance, lower attention and inhibitory control on the Children's Behavior Questionnaire (CBQ) were associated with worsened social affect (Faja & Dawson, 2015), heightened

aggression, self-injurious behavior and temper-tantrums (Adamek et al., 2011). Likewise, decreased EC from the Adult Temperament Questionnaire (ATQ) and EATQ was linked to provoking anxiety, internal issues, stereotypic behavioral frequencies (Uljarević, Richdale, Evans, Cai, & Leekam, 2017), and poor adaptive function with socioemotional incompetence (Schwartz et al., 2009). Although studies have revealed EC dysfunction and its association with socioemotional outcomes in ASD, larger findings have been derived from Western populations alone. Particularly, the Western samples were showed stronger negative association between EC and externalizing internalizing problems. Similarly, lower EC and higher anger irritability scores were associated with more externalizing problems among Western than Chinese individuals (Eisenberg et al., 2005; Kochanska & Knaack, 2003; Olson, Sameroff, Kerr, Lopez, & Wellman, 2005; Zhou, Lengua, & Wang, 2009). Furthermore, individuals of Chinese-Hong Kong descent appeared to outperform Westerners in inhibitory control, analogical reasoning, and solving complex issues (Richland, Chan, Morrison, & Au, 2010) implying generalization of EC function to Chinese-Hong Kong individuals based on Westerners' performance remain inconclusive. Theoretically, such cultural differences are attributed to three influential factors including the parenting model, parenting style, and school environment. In terms of parenting model, the Westerners adopt "individualistic approach" which perceives an individual as a separate and self-contained agent that supports self-independency and facilitates autonomy with separateness. Whereas the Chinese parenting adopts "relational allocentric approach" which perceives an individual within a family that supports inter-dependent self and develops acceptance of norms, values of family, obedience, and eventually self-regulation (Keller et al., 2007; MacDonald, 1992). Regarding the parenting style, the Westerners are liberal, and the Chinese are authoritative, which anticipates cultural emphasis on emotional maturation and rule conformation (Dornbusch, Ritter, Leiderman, Roberts, & Fraleigh, 1987; Wu et al., 2002). Finally,

regarding the schooling environment the Western schools are less structured which optimize individual-based learning style delivered through small classrooms. Whereas the Chinese schools are highly structured which optimize group-based learning style delivered through relatively larger classrooms. The Chinese school system also requires students to pay undivided attention to teacher with showing great respect them, respond queries, and complete seatwork in a timely and appropriate fashion. Therefore, the Chinese-Hong Kong participants may have presented with different temperamental EC profiles which require further study.

1.8. Neurogenic Factors Between Autistic Symptoms and Effortful Control Deficit

The stereotypic behavioral patterns associated with EC deficits in autism (Uljarević et al., 2017) are primarily concerned with abnormalities in sensorimotor gating (Perry, Minassian, Lopez, Maron, & Lincoln, 2007), intratelencephalic neuronal connectivity (Shepherd, 2013), and excitatory and inhibitory (E/I) homeostasis (Nelson & Valakh, 2015) mechanisms.

The sensorimotor gating mechanism is a volitional inhibitory process that filtrates extraneous sensory details entering the central nervous system and ensures that the brain perceives and responds back to relevant stimuli exclusively (Braff et al., 1978; Braff, Swerdlow, & Geyer, 1999). This mechanism was reported to be deficient in children and adolescents with high functioning ASD (Cheng, Chan, Hsu, & Liu, 2018). The sensorimotor gating impairment in autism also influenced cognitive gating function and thus an exacerbation of repetitive impulses associated with irrelevant ideas, behavior and speech. This accumulation of sensory information led to heightened executive dysfunction, including impairment in attention, inhibition, language, central coherence and theory of mind (Happe & Frith, 1996; S. Ozonoff, Pennington, & Rogers, 1991).

The second mechanism, “intratelencephalic neural connectivity”, is established by IT neurons, which essentially form connections between the cerebral cortex and striatum through the external capsule and corpus callosum. IT neurons are mainly found from the second to sixth layers of the cerebral cortex, and these layers formulate corticocortical (CCor) and corticostraital (CStr) projections (Shepherd, 2013). The CCor projection formulated by the second, third, fifth, and sixth layers of the cerebral cortex establishes connections within the cerebral cortex (Douglas & Martin, 2004; Weiler, Wood, Yu, Solla, & Shepherd, 2008), and it was observed to be hypoconnected or absent between the prefrontal cortex and posterior cingulate gyri during the resting state in individuals with ASD (Rane et al., 2015; Shepherd, 2013). In contrast, the corticostriatal projection establishes connections between the cerebral cortex and striatal subregions (pons, insula, pontine) and shows aberrantly increased connectivity, especially in the region between the right superior temporal gyrus and the insular cortex, during the resting state in autism (Di Martino et al., 2011).

The connectivity during task conditions is distinctive from resting conditions; for example, the inhibitory control task is regulated by five parallel circuits: a) the motor circuit, which helps initiate and control body movements; b) the oculomotor circuit, which assists in controlling eye movements; c) the dorsolateral prefrontal circuit; d) the lateral orbitofrontal circuit, which coordinates with the dorsolateral prefrontal circuit and is involved in planning, processing, and guiding actions or behavior; and e) the limbic circuit, which allows or avoids events related to emotion (Alexander, DeLong, & Strick, 1986). Among these circuits, the frontostriatal circuits (dorsolateral, lateral orbital, and limbic circuits) are mainly entitled for regulating three inhibitory control processes, such as stimulus selection, response selection, and response execution, through the influence of the basal ganglia using direct and indirect pathways. The direct pathway is an excitatory network, and it facilitates cortically orchestrated behavior by inhibiting striatal projections entering the internal structures of the

globus pallidus, substantia nigra and thalamus. However, the indirect pathway serves dual purposes, such that it inhibits corticostriatal projections to the thalamus and excites external structures of the globus pallidus and substantia nigra. These convolutional pathways in the brain structures functionally help regulate challenging behavior and its associated thinking patterns. Therefore, any disruption in these pathways leads to serious consequences; for example, disruption of the direct pathway causes persistent behavioral or thought interruptions, and disruption of the indirect pathway results in uncontrollable stereotypic behavioral and thinking patterns, as observed in individuals with ASD, attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and schizophrenia (Casey, Durston, & Fossella, 2001; Casey, Tottenham, & Fossella, 2002).

The intratelencephalic connectivity during the executive attention task recruits an attention network consisting of alertness, orientation, and execution. The first level, "alertness", consists of tonic and phasic elements. Tonic alertness (vigilance or sustained attention) helps maintain the general arousal or wakefulness state through an endogenous controlling mechanism. However, phasic alertness regulates the temporary alert state during experimental or behavioral stimulus presentation (Sturm & Willmes, 2001). These two phases are controlled independently with a separate alerting network; for example, the right dorsolateral prefrontal cortex (DLPFC) and ACC regulate tonic alertness with an influence of locus coeruleus-norepinephrine (LC-NE) nuclei and reticular formation (Robbins, 1997; Sturm et al., 1999). Concurrently, the right lateralized ventral frontoparietal network regulates phasic alertness during stimulus presentation (Corbetta, Patel, & Shulman, 2008; Posner & Petersen, 1990). These phases of the alerting network in individuals with ASD were observed to be hyperarousal (Hutt, Hutt, Lee, & Ounsted, 1964), hypoarousal (Rimland, 1964), and a deficit in arousal modulation (Ornitz & Ritvo, 1976), suggesting alerting network impairment. The second level attention network "orientation" perceives sensory

information from various sensory organs through the process of attentional disengagement, switching, and reengagement (Posner, Walker, Friedrich, & Rafal, 1984). The orientation process is typically regulated by the ventral frontoparietal network (also called the orientation network), which includes the superior parietal lobe, intraparietal sulcus, temporal-parietal junction, dorsofrontal (frontal eye fields; FEF) cortices, thalamus, and superior colliculus (Corbetta & Shulman, 2002; Mesulam, 1990). The orientation network is impaired in ASD while performing tasks related to visual attention (Townsend, Harris, & Courchesne, 1996), social and nonsocial stimuli (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998), and auditory stimuli to human voice (Maestro et al., 2002). In particular, individuals with ASD show intact responses to central cues (endogenous orientation driven by controlled processes) but fail to respond to peripheral cues (exogenous orientation driven by automatic processes), suggesting that individuals with autism experience atypical responses to orienting stimuli regulated by orientation networks (Casey, 2005; Renner, Grofer Klinger, & Klinger, 2006). The third level attention network "executive" is a multidimensional system that involves interrelated overlapping functions of working memory, attentional shifting (flexibility), inhibition, planning, and error monitoring (Huizinga, Dolan, & van der Molen, 2006; Miyake et al., 2000). The neural underpinnings of these executive functions predominantly underlie the executive control network consisting of multiple brain regions in which the activation typically differs based on a task condition; for instance, flexibility is mediated by the ACC, DLPFC, intraparietal sulci, and anterior insula (Wager, Jonides, & Reading, 2004). Similarly, the right ventral frontal regions are involved in manipulating information during a working memory task (Wager & Smith, 2003). In contrast to healthy individuals, the executive attention network in ASD is reported to be deficient, especially brain activation, and connectivity deficits are evident during cognitive flexibility (Ozonoff, South, & Provencal, 2013), working memory (Koshino et al., 2005), and other executive attention tasks (Just,

Cherkassky, Keller, Kana, & Minshew, 2007). This finding indicates that individuals with ASD show connectivity deficits in both CCor and CStr projections during the resting state and while performing various components of EC. It also implicates the necessity for an intervention to modulate CCor and CStr circuits to achieve optimal synchronization among cortical structures while processing information related to EC function in individuals with ASD.

The final mechanism of excitatory and inhibitory (E/I) homeostasis functions plays a mediatory role between sensorimotor gating and intratelencephalic connectivity through regulation of inhibitory and excitatory interneurons, which communicate together via chemical (GABA and glutamate) and electrical (by a gap between neuronal junctions) inputs. The chemical receptor "γ-aminobutyric acid (GABA)" is an inhibitory neurotransmitter in the cortex and hippocampus that executes inhibitory control function through GABAergic interneurons (Groves, 1983; McBain & Fisahn, 2001; Penney & Young, 1983). The activation of these GABAergic interneuron systems is regulated by three organizing principles, such as, synapse mapping, interaction principle, and synapse homogeneity (Gupta, Wang, & Markram, 2000), and five interneuron subtypes, including typical basket cells, small basket cells, Martinotti cells, bitufted cells, and nest basket cells (Figure 1.1).

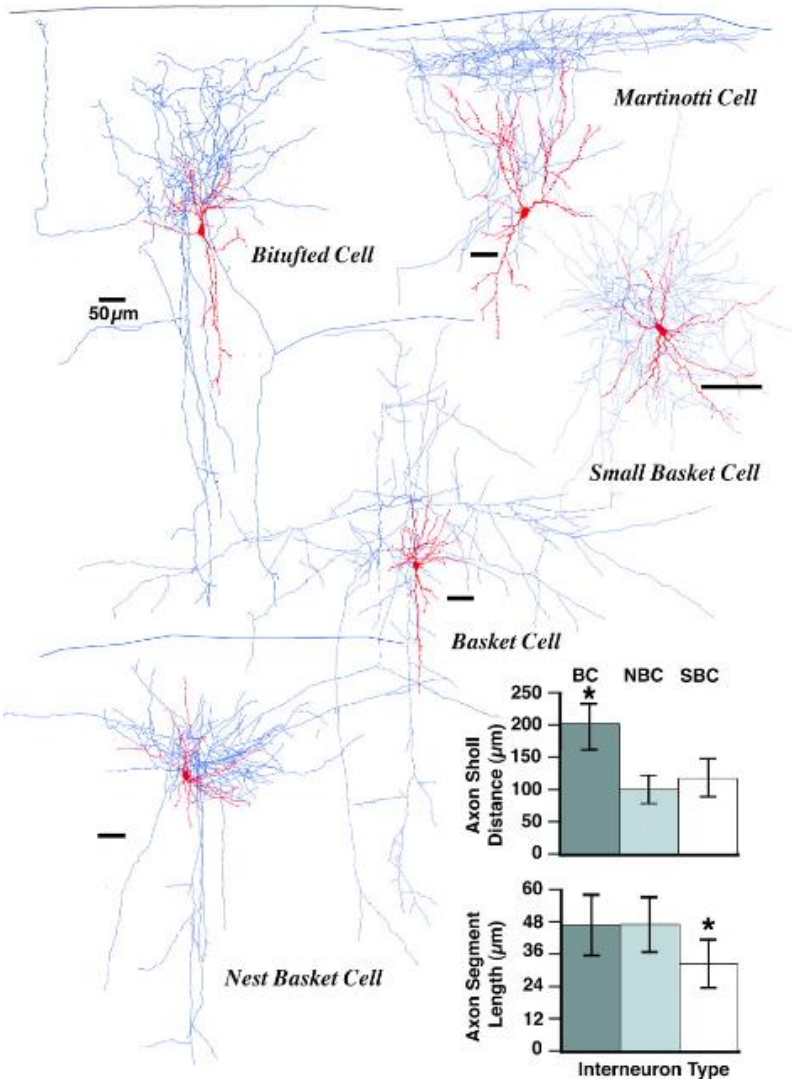

Figure 1.1: Five types of GABAergic interneurons (DeFelipe & Faire´n, 1982)

These GABAergic interneurons facilitate intercellular communication through the GABA receptor, which is classified into two major types, $GABA_A$ and $GABA_B$. The $GABA_A$ receptors are basically ligamentally gated (ionotropic); hence, the ions (Na^+, K^+, Ca^{2+}, and Cl) can enter through the membrane. The primary role of $GABA_A$ is to heighten membrane permeability and conductance (faster inhibitory action), especially to chloride and bicarbonate ions, which results in 'phasic' inhibition, meaning releasing of $GABA_A$ from the presynaptic vesicles followed by hyperpolarization of the $GABA_A$ in postsynaptic neurons.

The phasic inhibition induces a critical function of rhythmic oscillations in the neural network, during which the basket cells of the cortex and hippocampus innervate into pyramidal cells that facilitate connectivity among neurons. The GABA receptor also plays a significant role in tonic activation, especially when GABA is discharged from the synaptic cleft. There is an activation of receptors in the presynaptic terminals and a simultaneous reduction in GABA concentration in the extracellular space, which eventually leads to type A GABA tonic activation. The tonic activation of $GABA_A$ consistently heightens the input of cell conductance, which impacts the magnitude and duration of the response to the administering current (Farrant & Nusser, 2005).

In contrast to $GABA_A$, $GABA_B$ is a G protein-coupled (guanine nucleotide binding protein) receptor comprising a large protein cluster that causes cellular mechanisms by detecting extracellular molecules and facilitating inter signal transduction pathways, which in turn regularizes membrane excitability during synaptic transmission (Padgett & Slesinger, 2010). These $GABA_B$ receptors discharge several subunits, such as a) the Gβγ subunit, which is involved in activating K^+ (Gahwiler & Brown, 1985) and inhibiting Ca^{2+} channels (Mintz & Bean, 1993), and b) the $G\alpha_i/G\alpha_0$ subunit, which dampens the adenylyl cyclase component and thereby reduces cyclic adenosine monophosphate (cAMP) quantity and protein kinase A (PKA) function. All these factors contribute to the presynaptic release of neurotransmitters and postsynaptic conductance modulation (Figure 1.2).

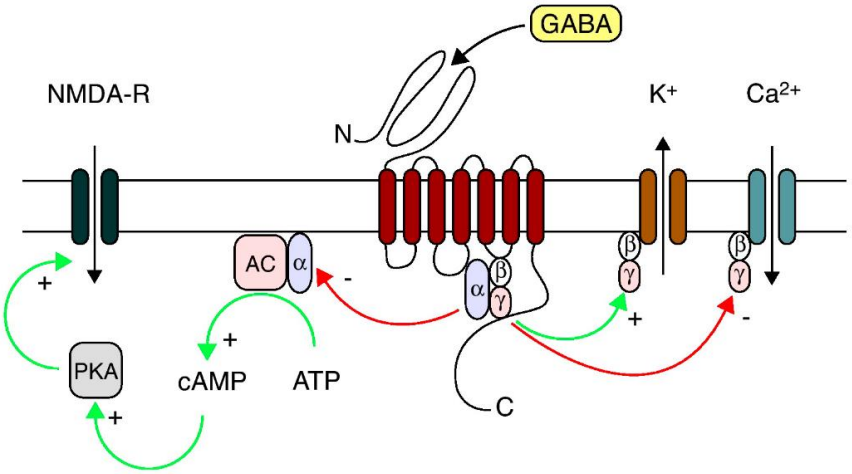

Figure 1.2: Postsynaptic intracellular $GABA_B$ receptor signalling (Xu & Wojcik, 1986)

During presynaptic release, the presynaptic action potential unlocks voltage-sensitive Ca^{2+} channels (VSCCs), which modulates fusion in vesicle molecular structures. At this stage, $GABA_B$ receptors inhibit the release of Ca^{2+} influx and activate K^+ channels, thereby limiting Ca^{2+} discharge and changing presynaptic action potentials. This mechanism causes a reduction in presynaptic release at both inhibitory and excitatory neuronal terminals (Dittman & Regehr, 1996; Thompson & Gahwiler, 1992). Additionally, the Gβγ subunit also dampens Ca^{2+} entry and modulates the release of neurotransmitters at presynaptic junctions (Blackmer et al., 2001). During postsynaptic conductance, the ionotropic receptors of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and n-methyl-d-aspartate (NMDA) at excitatory synapses are involved in posttranslational modifications (Dingledine, Borges, Bowie, & Traynelis, 1999). Such modifications alter the unlocking time of receptors, selection of ions in channels, and agonist attractions, e.g., Ca^{2+} permeability (NMDA receptor) upregulation. All these $GABA_B$ receptor functions potentially modify postsynaptic transmission permeability based on unique signaling outflow (Skeberdis et al., 2006).

Given that the GABAergic system is required for optimal cortical functions, prolonged impairment of this system causes behavioral and cognitive dysfunctions associated with ASD (DiCicco-Bloom et al., 2006; Polleux & Lauder, 2004). Individuals with ASD showed a reduced amount of GABA receptors and GABA-synthesizing enzymes in various regions of the brain, including the hippocampus, cerebrum, and cerebellum (Blatt et al., 2001; Casanova, Buxhoeveden, & Gomez, 2003; Hussman, 2001). More specifically, the postmortem analysis of an individual with an autistic brain showed that there was a significant reduction in $GABA_A$ receptors across several brain sites, primarily Brodmann's Area 40 in the parietal lobe, Broadmann's Area 9 in the frontal cortex, and in the cerebellum (Fatemi, Reutiman, Folsom, & Thuras, 2009). Similarly, deficits in the $GABA_A$ receptor in the cingulate cortex and fusiform gyrus result in disruptions of inhibitory control and emotional processing function in individuals with ASD (Oblak, Gibbs, & Blatt, 2011).

In contrast with the GABAergic system, the glutamatergic system is an excitatory neural system regulated by L-glutamate amino acids, which play a critical role in typical brain functions such as cognition, learning and memory (Collingridge & Lester, 1989; Headley & Grillner, 1990). Glutamate amino acids act on three different types of glutamate receptors (ionotropic, metabotrophic, and delta) to mediate synaptic function between neuronal cells.

The ionotropic receptors (NMDA, AMPA, and kainate) act quickly and are sensitive to voltage so that modulation of current occurs even when a small voltage difference exists across the membrane. During transmission, the ligands bind with these ionotropic receptors, which facilitate adaptive alteration of ions by allowing extracellular Na^+ influx and K^+ efflux concurrently. This mechanism induces depolarization of the postsynaptic cell membrane, which also triggers the transmission of signals to subsequent neuronal units (Figure 1.3) (Hollmann & Heinemann, 1994; Schoepfer et al., 1994).

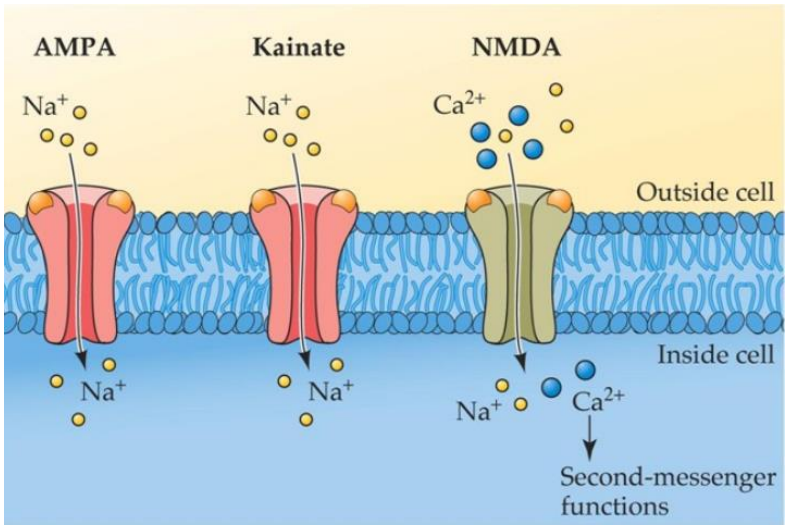

Figure 1.3: Ionotropic glutamate receptors (Hollmann & Heinemann, 1994; Schoepfer et al., 1994)

The metabotrophic glutamate receptors (Group 1, Group 2, and Group 3) act slowly and create an indirect effect through gene expression and protein formation processes. This indirect effect elevates the glutamate cell excitability rate and regularizes the magnitude of neurotransmission, which in turn impairs synaptic plasticity. During transmission, glutamate connects with metabotropic receptors and activates G-protein in the postsynaptic membrane, which results in stimulation of the second messenger unit and eventually unlocks a membrane channel for transmitting signals. This activation of G-protein also induces physiological changes in cytoplasmic metabolism, which leads to the termination of indirect processes such as the expression of genes and the synthesis of proteins (Lesage & Steckler, 2010).

The delta protein receptor in the nerve cell is relatively smaller than other receptors; however, it associates with other ionotropic receptors and takes part in carrying out cerebellar and high-frequency auditory functions through functional gating machineries and ionic permeation pathway mechanisms (Mayat, Petralia, Wang, & Wenthold, 1995; Orth, Tapken, & Hollmann, 2013).

Glutamate concentrations in the extracellular space, astrocytes (glial cells), and pre- and postsynaptic neurons are regulated by glutamate transporters (also called excitatory amino acid transporters (EAATs), which are essential for smooth synaptic transmission and prevent the hyperexcitability of neurons that leads to excitotoxicity (Kanai et al., 1994). The presence of EAATs in glial cells plays a significant role in maintaining the optimal level of glutamate in the extracellular space via the glutamate-glutamine cycle, during which glutamate is persistently recycled under typical circumstances, i.e., the glutaminase enzyme converts glutamine into glutamate (Danbolt, 2001). This glutamate-glutamine cycle is perpetuated by several phases: 1) presynaptic vesicles of axon discharge glutamate into the synaptic cleft, 2) amino acids in the synaptic cleft adhere to glutamate receptors (GLU-Rs), 3) the glutamate diffuses in the synapse as extrasynaptic GLU-Rs, glutamate reuptake into glial cells of astrocytes, and is converted back into glutamine through EAATs, 4) the glutamine synthetase (GS) enzyme converts glutamate in the astrocytes into glutamine, 5) the glutamine transporters transport glutamine from astrocytes back into neurons (presynaptic), 6) the glutaminase supplemented by mitochondria converts glutamine in the presynaptic neuron into glutamate again, 7) finally, new glutamate generated or the vesicular glutamate transporters transfer glutamine into the synaptic vesicles, and thereby the cycle is completed as shown in Figure 1.4 (Eid et al., 2016).

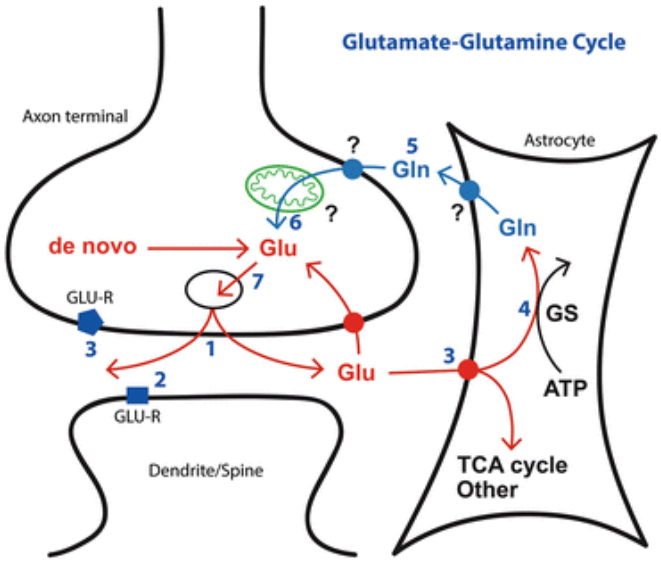

Figure 1.4: Glutamate-Glutamine Cycle (Eid et al., 2016)

Under abnormal circumstances, the glutamate-glutamine cycle and glutamine reuptake mechanisms do not function properly. In such occasions, failure of glutamine to convert to glutamate and glutamate reabsorption are more evident; consequently, rapid elevation of extracellular glutamate around the neurons occurs, which in turn excessive Ca^{+} ion influx into the nervous system and leads to glutamate toxicity (excitotoxicity) and neuronal destruction (Choi & Rothman, 1990; Olney, 1989). The findings from the neuroimaging, blood plasma serum, postmortem, and genetic analyses suggested that the individuals with ASD were reported to have altered glutamate mechanisms and their associated functions. In particular, neuroimaging studies have demonstrated heightened glutamate levels in the ACC (Bejjani et al., 2012; Joshi et al., 2013) and auditory cortex (Brown, Singel, Hepburn, & Rojas, 2013). Blood plasma serum studies also showed significantly increased serum glutamate levels in individuals with ASD compared with neurotypical controls (Hassan et al., 2013; Shinohe et al., 2006; Tirouvanziam et al., 2012). More specifically, a postmortem study utilizing a liquid chromatography technique to analyze

brain tissue also showed a dramatic increase in glutamate and glutamine components in ACC (Shimmura et al., 2013). Furthermore, genetic analyses of glutamatergic neurotransmission showed that there was an association between increased ionotropic glutamatergic subunits and genes causing autistic conditions (Jamain et al., 2002; Tarabeux et al., 2011; Yoo, Cho, Park, Yang, & Kim, 2012). In summary, glutamate is an excitatory neurotransmitter that is regulated by the glutamate-glutamine cycle and glutamate reuptake mechanisms. Excessive glutamate in the extracellular space increases neuronal activity aberrantly and can cause deleterious effects on the nervous system, leading to various neurological disorders. Autism is one such neurological disorder and was shown to have heightened glutamate receptors in the ACC that control various components of EC function via fronto-striatal circuitry.

To conclude, it is apparent that the individuals with ASD were shown to have deficits in GABA (inhibition) and excessive amounts of glutamate (excitation) receptors in the brain, implying that they tend to have excitatory and inhibitory imbalances. The imbalance was mainly observed in key neural regions responsible for performing EC tasks, which can lead to EC deficits. Thus, an intervention that can modulate E/I imbalance is implicated in addressing EC deficits in individuals with ASD. Given that, transcranial electrical stimulation (tES) appears to be a recommended intervention strategy.

1.9. Transcranial Electric Stimulation (tES)

The tES is a combination of noninvasive brain stimulation techniques that involves delivering low-intensity electric current (0.5 to 2 mA) to the brain through a power-controlled device attached to surface electrodes. The device enables modifying electrical stimulation parameters in terms of frequency, current density, amplitude, wavelength, and width. Simultaneously, the dual surface electrode systems (anode and cathode) referring to the

respective positive and negative voltage poles ensure electrical ions traversing either in unidirectional or bidirectional pathways (Peterchev et al., 2012). Consequently, alterations in neuronal excitability take place in the target brain site, which can potentiate behavioral changes (Reed & Cohen Kadosh, 2018). The tES comprises various techniques, notably transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), and transcranial random noise stimulation (tRNS; Peterchev et al., 2012). Although all these techniques are similar in procedural technicality, the stimulatory pattern and neuronal oscillations with connectivity vary from each other, thus exhibiting distinct cognitive and behavioral profiles. However, only tDCS functions in modulating neurotransmitters (GABA and glutamate) and the cortical excitability ratio, suggesting that tDCS appears to be a suitable technique for intervening in the imbalance of neurotransmitter and cortical excitability in brain regions.

1.10. Transcranial Direct Current Simulation (tDCS)

tDCS involves applying low-threshold direct electrical current constantly (Fig 1.5) to the brain via active (anode) and return (cathode) electrodes, which modulate the cortical excitability pattern by heightening it with anodal stimulation (Boros, Poreisz, Munchau, Paulus, & Nitsche, 2008) and dampening it with cathodal stimulation (Ardolino, Bossi, Barbieri, & Priori, 2005). The modulation of cortical excitability primarily occurs as a result of tDCS action on neurotransmitters, including brain-derived neurotrophic factor (BDNF), extrasynaptic GABA, and glutamate (Fritsch et al., 2010; Stagg et al., 2011). This modulatory effect was meant to be observed in altering neural oscillations across various neurological disorders (Buzsaki & Watson, 2012) and changing synchronization among brain regions during intrinsic (Bachtiar, Near, Johansen-Berg, & Stagg, 2015) and task (Weber, Messing,

Rao, Detre, & Thompson-Schill, 2014) conditions. Such observable effects of tDCS have been demonstrated to be safe in both ethical and legal aspects for individuals with various neuropsychiatric disorders, including ASD (Palm et al., 2016).

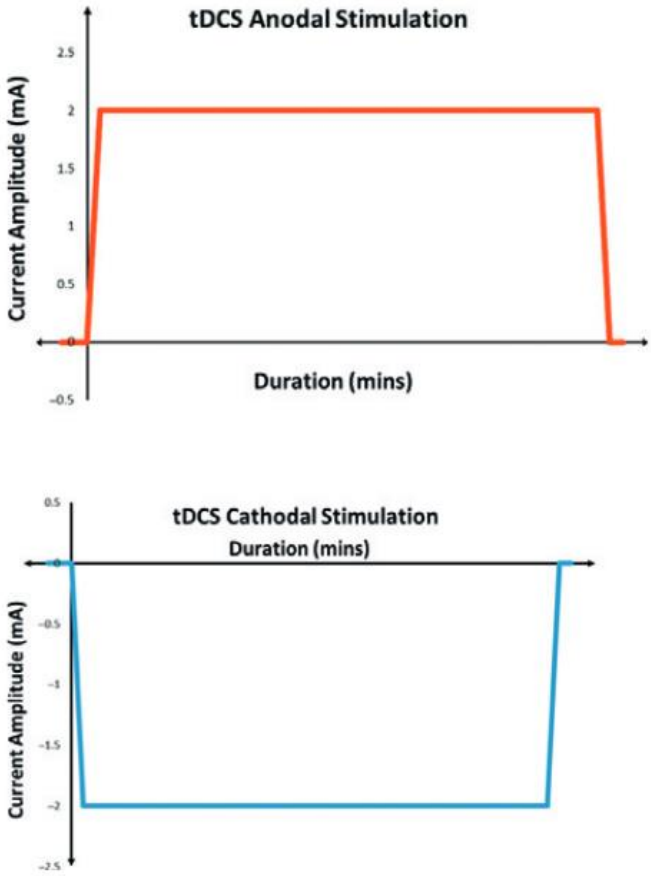

Figure 1.5: tDCS waveform (Moreno-Duarte et al., 2014)

1.11. tDCS and its Applicability in Autism

Although tDCS was declared to be a safe technique, its utilization was limited in the autism context until the last decade. However, it has recently gained popularity for studying stimulation-induced neurobehavioral effects in autism. Notably, Amatachaya et al. (2015) used anodal stimulation on the left DLPFC (F3) for a single session and observed positive

changes in social and health/behavior domains in the Autism Treatment Evaluation Checklist (ATEC). Likewise, Schneider and Hopp (2011) observed better language acquisition in children with autism when anodal stimulation was applied to the left DLPFC. In a subsequent replication of a previous study in children with autism, Amatachaya et al. (2014) found that stimulation of the F3 region led to significant improvement in behavior modulations measured by ATEC and the Childhood Autism Rating Scale (CARS). In addition, tDCS has also been shown to be effective for intervening in other clinical impairments in autism, including stereotypic behavioral patterns (Rothärmel et al., 2019), noncompliance and hyperactive behavior (D'Urso et al., 2015) and problems related to health, physical status, and sociability (Hadoush, Nazzal, Almasri, Khalil, & Alafeef, 2020). Above all, a recent systematic review and meta-analysis on the effect of tDCS in ASD has reported that it is a promising technique for addressing ASD symptomatology and improving various neuropsychological functions, e.g., socialization, behavioral, and health subscales measured by ATEC (García-González et al., 2021). It can therefore be concluded that stimulating different brain areas with tDCS potentially enhances functional and behavioral outcomes in children and adolescents with ASD without serious adverse effects.

1.12. Aims of the Thesis

The extensive body of literature supports that temperamental EC is linked to various academic, socioemotional, and adaptive functioning. Although EC deficits in autism have been arbitrated with parents' or caregivers' perception in Western populations, the exact neural underpinnings and the magnitude of EC impairment in the Chinese-Hong Kong population remain elusive. Additionally, individuals with ASD presented with abnormal structural and functional neural systems, including the prefrontal cortex (PFC), which

supervises attentional control, inhibitory control, and cognitive flexibility functions. Reversal of such abnormal brain functions requires intervention to modulate underlying neural activities, which can be accomplished using tDCS. Given that, the aims of this thesis are to study,

a) Neural substrates underlying temperamental EC deficits in individuals with ASD.
b) EC and its association with EF, socioemotional, and PFC functioning in Chinese-Hong Kong children, adolescents, and adults with ASD.
c) Effectiveness of tDCS on EC, EF, socioemotional and PFC activation and connectivity in ASD.

1.13. Hypotheses of the thesis

Having the central aims of this thesis, it includes a combination of four interlinked studies. Study One in "Chapter – 2" synthesizes available whole-brain fMRI studies on temperamental EC subcomponents, including attention control, inhibitory control, and cognitive flexibility. It also further compares the brain activation pattern between individuals with ASD and healthy controls. The study hypothesizes that the ASD group would show significantly reduced activation patterns in the frontoparietal and attention networks during attention control tasks, the default-mode network during inhibitory control tasks, and the frontoparietal and default mode networks during cognitive flexibility tasks.

Study Two in "Chapter 3" explores EC performance and examines the relationship between EC and its associated measures (EF and socioemotional function) with PFC functioning in Chinese-Hong Kong children with ASD. The study hypothesizes that children

with ASD would show significantly reduced EC and PFC functioning. The EC deficit would further be significantly associated with PFC functioning in children with autism.

Study Three in “Chapter 4” explores EC performance and examines the relationship between EC and its related measures (EF and socioemotional functions) with PFC functioning in Chinese-Hong Kong adolescents and adults with ASD. The study hypothesizes that adolescents and adults with ASD would show significantly reduced EC and PFC functioning. The EC deficit would further be significantly associated with PFC functioning in adolescents and adults with autism.

Study Four in “Chapter 5” compares the effect of tDCS and sham stimulations on temperamental EC, executive, socioemotional, and PFC functions in individuals with ASD across pre and post interventions. The study hypothesizes that tDCS stimulation would show significantly improved EC, executive, and socioemotional profiles. It would also show significantly decreased PFC cortex functioning than sham stimulation.

CHAPTER 2: STUDY ONE

Neural Substrates Underlying Temperamental Effortful Control Deficit in Individuals with Autism Spectrum Disorder - Meta-analysis of fMRI Studies.

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Neural substrates underlying effortful control deficit in autism spectrum disorder: a meta-analysis of fMRI studies

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2.1. Introduction

Autism spectrum disorder (ASD) is a highly prevalent psychiatric condition among children and adolescents that characterizes sociocommunicative dysfunction and exhibits restricted, repetitive and stereotypic behavior (American Psychiatric Association, 2013). The prevalence of ASD was estimated to be 1 out of 54 children (Maenner et al., 2020), of which impairment of temperamental effortful control (EC) function is broadly endorsed as underlying behavioral deficits of the disorder (Konstantareas & Stewart, 2006; Krishnamurthy, Yeung, Chan, & Han, 2020; Schwartz et al., 2009). Temperament refers to individual discordance in reactive and proactive aspects of self-regulation. The reactive aspect represents volitional defensive motivation that employs inflexible adaptation to external circumstances. Conversely, the proactive aspect is referred to as EC, which allows resolving conflicts between immediate and extended demands or tendencies (Rothbart, Ellis, & Posner, 2011). EC is formally defined as executive attention efficiency for subduing dominant or initiating a subdominant response to plan and detect errors (Rothbart & Bates, 2006). Since habitual and spontaneous actions of human beings underlie compulsion or overarching emotional response (Goldstein et al., 2007), EC is mandated for protecting cognitive mechanisms associated with engaging in such behavior (Claes, Vertommen, Smits, & Bijttebier, 2009).

EC comprises attention control, inhibitory control and cognitive flexibility subcomponents that aid alerting, orienting, withdrawing and modulating tendencies relevant to selective behavioral patterns (Eisenberg et al., 2010; Lengua, Bush, Long, Kovacs, & Trancik, 2008; Rothbart & Bates, 2006). Attention control involves both simple and executive attention (EA), which regulates one's response from numerous available options under conflicting circumstances. EA can be studied by administering a task that compares congruent (responding to a single stimulus pattern) and incongruent (responding to two

conflicting stimuli) conditions. Notably, the attention network task (ANT)/flanker task has been validated in children and adults for measuring the flanker conflict effect (EA index), which is the dissociation of reaction time between flanker incongruent and congruent conditions (Fan et al., 2009; Ishigami & Klein, 2011; Rueda et al., 2004). The ANT task elicits three attentional networks, including alerting – accomplishing and sustaining an alert state; orienting – opting information from sensory stimulus; and executive control – resolving conflicts while responding (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). Extensive neuroimaging studies in typical individuals showed that each of these networks recruits different brain regions such that the alerting component activates right frontoparietal regions (Coull, Frith, Frackowiak, & Grasby, 1996); the orienting component activates the superior parietal lobe, temporal parietal junction and frontal eye field (Corbetta & Shulman, 2002); and executive control activates the anterior cingulate and the lateral prefrontal cortex (MacDonald, 3rd, Cohen, Stenger, & Carter, 2000). However, studies with autism showed hypoactivation in the anterior cingulate cortex, midfrontal gyrus (predominantly right side), right inferior frontal gyrus and bilateral intraparietal sulcus during higher order incongruent compared to congruent conditions (Dichter & Belger, 2007, 2008), suggesting that attention control recruits dissociative brain activation patterns between individuals with ASD and typical controls.

Inhibitory control refers to the suppression of inappropriate or irrelevant impulses that exist in various dimensions, including a prepotent response or resistance to proactive and distractor interferences (Friedman & Miyake, 2004). Prepotent response inhibition suppresses preponderant motor action using a reactive stopping mechanism in which individuals cease responding immediately after a signal indication (Casey et al., 2001). Here, participants are required to respond swiftly to the majority of stimuli but withhold responding to minority stimuli indicated by a specific tone or letter signal. The stop-signal and Go/No-Go tasks are

classified by measuring prepotent response inhibition (Logan, Cowan, & Davis, 1984), during which the presupplementary motor area, left fusiform gyrus, right dorsolateral prefrontal, and inferior parietal circuits were hyperactivated in typical individuals (Simmonds, Pekar, & Mostofsky, 2008), whereas hyperactivation in the left inferior and orbito-frontal gyri (Schmitz et al., 2006) and hypoactivation in the ventral prefrontal cortex were observed in individuals with ASD (Shafritz, Bregman, Ikuta, & Szeszko, 2015). Proactive interference control prepares individuals to cease upcoming response stimuli more internally than external signals, i.e., inhibiting memory intrusion of previously related but currently unrelated information (Aron, 2011; Jonides & Nee, 2006). The warned reaction time task (Monsell, 1978), item-recognition task (Jonides & Nee, 2006), recent-probes task (Monsell, 1978), directed-forgetting task (Nee, Jonides, & Berman, 2007), and cued-recall task (Tolan & Tehan, 1999) are categorized as triggering proactive interference mechanisms during which typical individuals largely recruit the medial frontotemporal gyri, inferior parietal lobule, primary and supplementary motor cortices, posterior cingulate cortex with putamen, but individuals with ASD display hypo-activation in the left parietal cortex (Aron, 2011; Jaffard et al., 2008; Solomon et al., 2014). In contrast to other inhibitory dimensions, resistance to distractor interference requires ignoring irrelevant information while responding to relevant stimuli. The stroop, shape matching task, modified flanker and Simon tasks measure distractor interferences (Tiego, Testa, Bellgrove, Pantelis, & Whittle, 2018) in which the anterior cingulate and lateral prefrontal cortices, supplementary motor area, and precuneus are heavily activated in typical people (Liu, Banich, Jacobson, & Tanabe, 2004; MacDonald, 3rd et al., 2000), and the anterior cingulate, midfrontal (predominantly right side), right inferior frontal gyri and bilateral intraparietal sulcus are deactivated in ASD (Dichter & Belger, 2007, 2008).

Cognitive flexibility refers to switching behavioral response patterns back and forth on competing stimuli in accordance with contingency and rule-oriented feedback (Scott, 1962). Successful flexibility requires both attentive and inhibitory abilities, which together support acclimatizing ever-changing circumstances; however, flexibility deficits induce behavioral perseveration, which is frequently observed in the autism phenotype (Taylor, Donner, & Pang, 2012). Cognitive flexibility is measured using Wisconsin card sorting, set-shifting, intraextra dimensional set-shift (CANTAB), reversal learning and alphabet tasks (Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Stuss et al., 2000; Uddin, 2021) that predominantly activate the inferior frontal junction, posterior parietal, and frontopolar cortices in typical individuals (Kim, Cilles, Johnson, & Gold, 2012). In contrast, individuals with ASD showed mixed activation patterns, such that increased activation was found in the inferio-medial aspects of parietal cortices; superior, middle and inferior aspects of frontal gyri; and deactivation was observed in the DLPFC, ACC, intraparietal sulcus, basal ganglia, ventral striatum, posterior parietal, and premotor cortices (Uddin, 2021).

The distinct brain activation patterns between typical and ASD individuals during EC components might be impacted by developmental trajectories and the tasks that confounded with socioemotional components. From a developmental perspective, the attention network showed protracted growth in adults but an immature pattern in children while responding to conflicting stimuli in the adult ANT (Konrad et al., 2005). However, the network was stable and comparable with adults when children performed the child ANT version (R. Gupta & Kar, 2009; Rueda et al., 2004). Similarly, inhibitory control-elicited activation in the prefrontal cortex was greater in children than in young adults during the no-go condition, and such focused activation in the ventral prefrontal cortex was associated behaviorally with increasing age from 9 to 11 years (Casey et al., 1997; S. Durston et al., 2006). Likewise, cognitive flexibility indexed by speed-accuracy trade-off on switching cost (difference of

reaction time and accuracy between switching and nonswitching trials) indicated a gradual increase with age and reached a peak during the mid-adolescent phase (Huizinga et al., 2006). Specifically, behavioral trajectories of cognitive flexibility typically begin to appear in early childhood, develop primarily by 10 years, and reach a peak between 21 and 30 years old (Dajani & Uddin, 2015). Subsequent neuroimaging findings revealed that the cognitive shifting task elicited more activation in the anterior cingulate and interior frontoparietal regions and less activation in the DLPFC across adolescents (Rubia et al., 2006), suggesting that controlling age is necessary for reducing error variance in brain activation during EC tasks. In addition to developmental trajectories, embedding emotion stimuli in EC component tasks might influence brain activation patterns as an effect of emotion recognition difficulty in autism (Krishnamurthy et al., 2020), and the presence of affective stimuli and contextual relevant emotions interfered with the rapid processing of attention and response inhibition in typical individuals, respectively (Heim, Benasich, & Keil, 2013; Schel & Crone, 2013). Therefore, subgroup analysis without emotion components in EC tasks may provide a complete understanding of neural substrates underlying EC deficits in autism.

Summarizing the fMRI literature on EC components and their associated brain activations revealed that the frontoparietal regions during attention control, ACC during inhibitory control, and both brain regions during cognitive flexibility were engaged commonly in autism and control groups. Conversion of these brain sites into network parcellations revealed that the frontoparietal regions correspond to the frontoparietal network (FPN), dorsal attention and ventral attention networks (DAN and VAN), and the ACC corresponds to the default mode network (DMN) (Schaefer et al., 2018; Yeo et al., 2011). This suggests that alterations in neural activities in these brain regions and their corresponding networks during EC-related tasks may trigger EC deficits in autism. However, there is no compelling evidence to draw a conclusion, and therefore, this meta-analysis aimed

to examine neural correlates underlying temperamental EC deficits in autism. It also aimed to investigate predicting developmental patterns between ASD and control groups on altering brain activations that provoke EC deficits. We hypothesized that the autism group would demonstrate significantly reduced activation than the control group in the brain regions corresponding to FPN, DAN, and VAN in executive attention, DMN in inhibitory control, and FPN and DMN in cognitive flexibility components. Since EC deficits are evident in adults with autism (Schwartz et al., 2009; Uljarević et al., 2017), we also hypothesized that these networks would be deactivated with increasing age.

2.2. Methodology

2.2.1. Literature search

This meta-analysis was performed with guidelines proposed by Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, Altman, & The, 2009). Relevant studies were searched through electronic databases, including the Allied and complementary Medicine Database (AMED), Medline (EbscoHost), PsycINFO (ProQuest), PubMed, Scopus, and Web of Science, with a Boolean search using the following keyword combinations: “autism” OR “autism spectrum disorder” OR “asd” AND “effortful control” OR “temperament” OR “cognitive control” OR “hot executive function” AND “fMRI” OR “functional magnetic resonance imaging” AND “brain activation” OR “brain connectivity”. A literature search was also conducted in the NeuroSynth database by referring to the terms (asd, autism, autism spectrum, cognitive control, effortful, executive control, inhibitory control, and stop signal) and topic (number 062). The same terms were also typed in the search bar and searched for potential studies. Additionally, published meta-analyses in the brainmap database were searched, and the

reference sections of potential articles were further checked manually. The literature search was conducted twice, i.e., in October 2020 and May 2021, without specifying the publication timeline to confirm that the datasets included in this meta-analysis reflected the current literature.

2.2.2. Inclusion and exclusion of studies:

The retrieved articles were screened for duplicate removal, title screening, abstract screening, and full-text screening. Whole-brain fMRI studies on EC-related tasks compared in individuals with ASD and neurotypical controls were included in this meta-analysis. Studies without whole-brain fMRI activation during EC-related tasks, without ASD and control groups, without reporting brain activation in the standard spatial coordinates (MNI or Talairach), animal studies, reviews, meta-analyses, book chapters, commentaries, conference abstracts, resting-state brain activation, and region of interest-based activation were excluded. The rationale for including and excluding studies in each process is mentioned in Figure 2.1. The included studies were then screened for EC-related experiments addressing attention, inhibitory control, and cognitive flexibility subcomponents. Studies presented with more than one eligible experimental result in an EC subcomponent were pooled within the respective subcomponent. In this context, 19, 12, and 9 comparison results were pooled for attention, inhibitory control, and cognitive flexibility components, respectively. All screening processes were conducted by the first author (K.K), and the accompanying decisions were recorded in the endnote reference software and Excel spreadsheet. Discrepancies were resolved by consulting with the second (M. C) and third (Y. H) authors, and a consensus was reached before finalization.

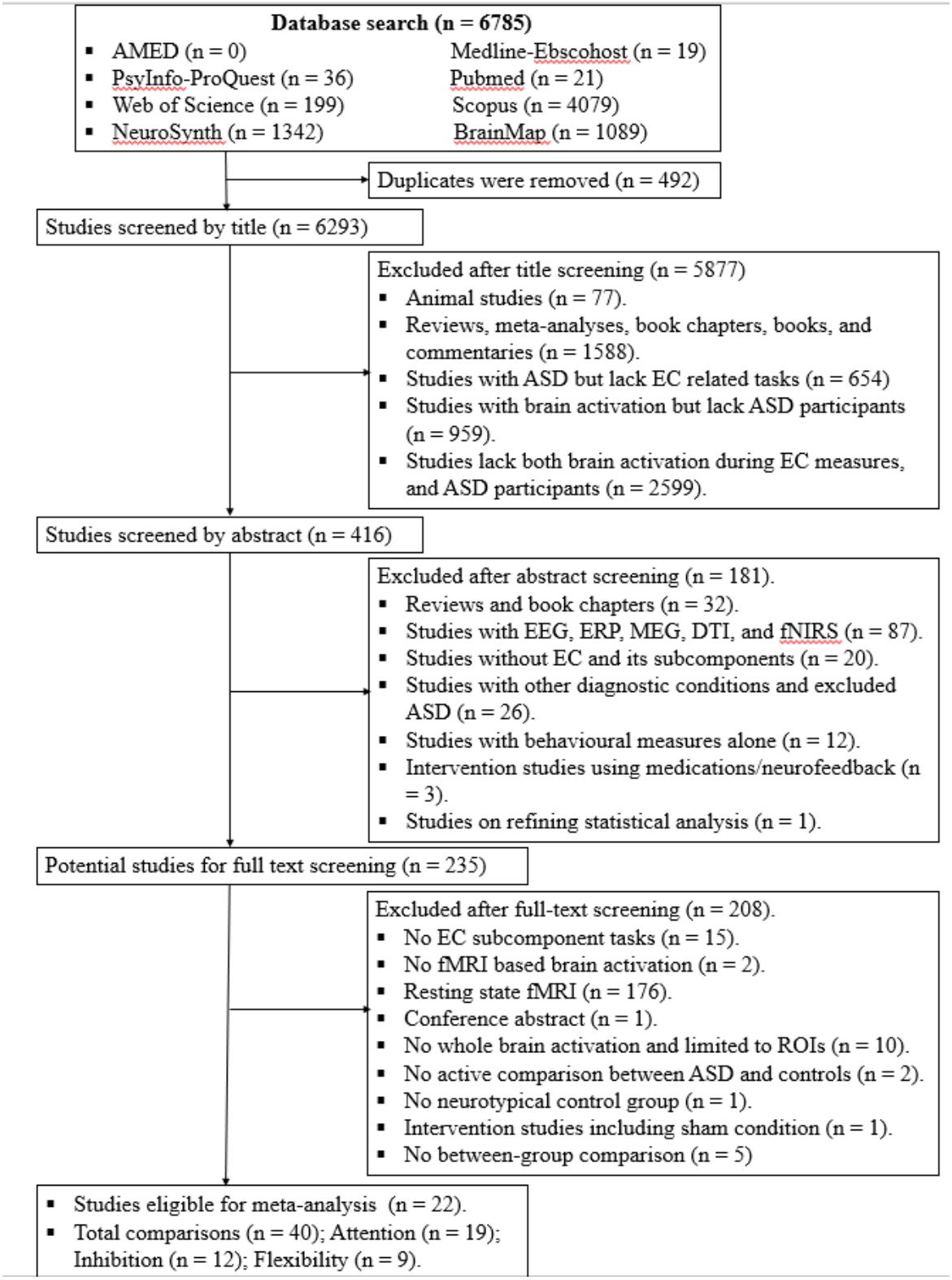


Figure 2.1: PRISMA flowchart of screening studies.

2.2.3. Data Extraction and Recoding

The first author (K. K) extracted demographics, experimental procedures, and fMRI details from the included papers and entered them into the database. The second author (M. C) validated the entries to maximize accuracy. Demographic data comprised the sample size, mean age, mean intelligence, gender ratio (female:male) of the two groups and their matching criteria. The mean age was further grouped into three categories: children (4 to 11.11 years), adolescents (12 to 17.11 years), and adults (above 18 years). The experimental procedures included information about the task with stimulus presentation, the existence of EC components, and the type of baseline comparison. The brain activation in the typical and ASD groups during EC-related tasks was categorized into neutral (presence of unanimated stimuli) and socioemotional (presence of animated stimuli) components (Table 2.1).

2.2.4. Data analysis

The meta-analysis between the two groups during EC components (attention, inhibitory control, and cognitive flexibility) was conducted separately using a random effect model at two levels, i.e., the main analysis was to combine both neutral and socioemotional stimuli, and a subgroup analysis included only neutral stimuli. The entire meta-analysis was conducted using seed-based d-mapping – permutation of subject images (SDM-PSI) software version 6.21, which allows estimating population effect size with minimal bias via a subject wise permutation test. The program also enhances true positive effects using the familywise error correction method derived from threshold-free cluster enhancement (TFCE) statistics. The algorithm also supports performing meta-regression using a studywise permutation test on given moderators (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019; Au - Albajes-Eizagirre et al., 2019). The analysis began with preprocessing of data on each EC component

separately with anisotropy = 1, isotropic full width at half maximum (FWHM) = 20 mm, voxel size = 2 mm on the gray matter mask and correlation template. Subsequently, the mean was estimated on each EC component by deducting the activation map of the ASD group from the control group, i.e., ASD-control contrast. Finally, to examine the influences of age on brain activation patterns during EC components, meta-regression was conducted using a simple linear regression model weighted as the square root of sample size and limited to predicting within the SDM cutoff values (-1 to 1) for the participants' age (Radua, Via, Catani, & Mataix-Cols, 2011). The output yielded a significant activation or deactivation pattern of brain sites between the two groups during each EC component while increasing age in years. As recommended, the significance for the main analysis was thresholded $p < 0.005$ for uncorrected estimates and $p < 0.05$ for TFCE corrected estimates. This necessitates the peak Z > 1 and cluster size of 10 voxels to control type I error and establish sensitivity. Similarly, the meta-regression significance was determined to be $p < 0.05$ to facilitate true-positive results (Radua et al., 2014; Radua et al., 2012). Additionally, the significant brain clusters obtained from the meta-analysis were further parcellated under corresponding brain networks using "freesurfer" software (Schaefer et al., 2018; Yeo et al., 2011). The heterogeneity of the included studies in the meta-analysis was assessed using I-squared (I^2) statistics, and low, medium, and high heterogeneity were determined with respective values of 25%, 50%, and 75% (Borenstein, Hedges, Higgins, & Rothstein, 2021; Higgins, Thompson, Deeks, & Altman, 2003). To assess the risk of publication bias, a funnel plot across studies was conducted to ascertain the linkage between the calculated and study effect sizes more than a chance (Higgins, Savović, Page, Elbers, & Sterne, 2019). In the case of publication bias, the funnel plot appears symmetrical at the top, and data points are missed in the middle and bottom sections of the plot. Subsequently, Egger's tests on the peak coordinates demonstrated dissociation between the ASD and control groups during EC

component tasks. A significant Egger's value denotes a small study effect. However, smaller studies may occasionally yield larger effects than studies with larger sample sizes, and this phenomenon occurs as the result of publication bias.

Table 2.1: Twenty-two fMRI studies on EC components (with 40 comparisons) included in the meta-analysis

Demographic Data										**Experimental Design**		
Study	**Subgroups**	**Sample size - ASD: HC**	**Age group**	**Mean IQ(SD)-ASD:HC**	**Sex ratio (F;M) ASD: HC**	**ASD severity measures**	**Symptom severity score: M(SD) - ASD:HC**	**Other measures & Brain activation pattern**	**Subject matching criteria**	**Task and stimuli presentation (with neutral or socioemotional component).**	**EC components - (Attention control, inhibitory control, and cognitive flexibility)**	**Baseline**
Dcruz, 2016	ASD-HC	17:23	Adults	103.90 (15.50): 110.90 (9.90)	5;12: 5;18	ADI-R	2.5(1.4): NA(NA)	RBS-R; whole brain activation.	Age, gender, IQ	Reversal learning task: 2 and 4 choice - (Neutral stimuli).	Within and between group contrasts: Cognitive flexibility (4-choice reversal). Within group contrast (2-choice reversal).	Blank screen.
Dirks, 2020	ASD-HC	24:33	Children	101.5 (18.25): 108.38 (11.92)	3;21: 11;22	ADOS-2nd edition	10.91 (3.23)	BRIEF-2; RBS-R; SCQ; Whole brain activation.	Age and IQ.	Set-shifting task - (Neutral stimuli).	Within and between group contrasts: Cognitive flexibility (mixed > color+shape; mixed > color blocks).	Blocks of low-level fixation.
Duerden, 2013	ASD-HC	16:17	Adults	111.89 (13.71): 114.32 (14.8)	5;11: 5;12	ADI-R; ADOS-G	No total score	NA; whole brain activation.	IQ	Emotional Go/NoGo task - (Socioemotional stimuli).	Within group contrasts: Inhibitory control (NoGo > Go; NoGo < go). Between group contrast (NoGo > go).	Cue fixation.

Fan, 2012	ASD-HC	12:12	Adults	115(14): 120(15)	3;9: 2;10	ADI-R; ADOS-G	ADI-R - 38.4(13.4); ADOS-G - 12.2(4.1)	NA; whole brain activation.	Age, IQ, gender, and handedness score.	Attention Network Test - (Neutral stimuli).	Between group contrasts: Attention control (flanker conflict; alert by conflict; and no cue > double cue). Inhibitory control (disengaging).	Cue fixation cross.
Gilbert, 2008	ASD-HC (only right handers)	15:18	Adults	119(14): 119(11)	3;12: 5;13	ADI-R; ADOS-G	No total score	NA; whole brain activation.	Age, and IQ.	Alphabet task - (Neutral stimuli).	Within and between group contrasts: Cognitive flexibility (stimulus orientation > stimulus independent; and vice versa).	Classify straight or curved pattern from nonalphanumeric nonmeaningful stimuli.
Gilbert, 2009	ASD-HC (only right handers)	16:16	Adults	Full scale IQ - NA	2;14: 4;12	ADOS-G	No total score	NA; whole brain activation.	Age, IQ (verbal and performance).	Alphabet task - (Neutral stimuli).	Within and between group contrasts: Cognitive flexibility (mentalizing > nonmetalizing). Within group contrast: Cognitive flexibility (stimulus orientation > stimulus independent).	Nonmentalizing and stimulus orientation stimuli.
Gordon, 2020	ASD-HC	64:77	Adolescents	103.72 (12.88): 110.05 (11.23)	11;53: 16;61	ADOS	No total score.	NA; whole brain activation.	Age, and gender.	Rapid Preparing to Overcome Prepotency Task - (Neutral	Between group contrasts: Attention control (red, and green cues) Inhibitory control (red probe).	Fixation cross.

									Stimuli).			
Hames, 2016	ASD-HC	6:6	Adolescents	NA	2;4: 2;4	ADOS	NA	NA; whole brain activation.	NA	The modified child ANT task - (Neutral stimuli).	Between group contrasts: Attention control (incongruent > congruent; no cue > double cue).	Fixation cross.
Kana, 2007	ASD-HC	12:12	Adults	110.1 (12.6): 117.0 (8.7)	1;11: 1;11	ADI-R; ADOS	NA	NA; whole brain activation.	Age, and IQ.	The response inhibition task - (Neutral stimuli).	Between group contrast: Attention control (simple inhibition); Inhibitory control (1-back inhibition)	Press every letter except 'A'.
Kathleen, 2012	ASD-HC	14:14	Children	113.21 (NA): 116.64 (NA)	2;12: 3;11	ADI-R; ADOS-G	NA	BRIEF-2; RBS-R; ASI (NEPSY-II); TEA-Ch; TMT; Whole brain activation.	Age, gender, and IQ.	Set-shifting task - (Neutral stimuli).	Between group contrast: Cognitive flexibility (extra > intra dimension). Attention control (extra dimension > fixation).	Fixation cross.

Keehn, 2016	ASD-HC	16:21	Adolescents	Verbal= 112(17): 106(10); Nonverbal=112(14):107(11).	2;14: 5;16	ADI-R; ADOS	No total score.	NA; whole brain activation.	Age, nonverbal IQ, and motion during MRI scanning.	Rapid serial visual presentation - (Neutral stimuli).	Between group contrasts: Inhibitory control (target color > nontarget color). Attention control (target present neutral). Within group contrast: Attention control (target present).	Baseline number task
Murphy, 2017	ASD-HC	23:35	Children	114.90 (16.30): 121.97 (10.63)	6;17: 18;17	ADI-R; ADOS-G	ADOS (overall severity): 6.61(2.28)	NA; whole brain activation.	Age, and IQ.	Nonsocial dot probe task - (Neutral stimuli).	Within and between group contrasts: Attention control (neutral 18 < > bias 18; neutral 18 < > bias 72).	Fixation cross.
Ohta, 2012	ASD-HC	24:25	Adults	112.80 (6.40): 109.20 (7.70)	3;21: 3;22	AQ	AQ = 36.1(5.9): 15.6(7.4)	HADS; whole brain activation	Age, and IQ.	Rapid serial visual presentation - (Neutral stimuli).	Within and between group contrasts: Attention control (distractor present vs absent).	Fixation cross.
Sabatino, 2013	ASD-HC	15:17	Adults.	109.9 (20.3): 127.0 (8.1)	2;13: 5;12	ADOS; AQ	AQ = 24.7(13.1): 12.4(5.3)	RBS-R; SRS-SR; whole brain activation.	Age, and gender.	Visual oddball target detection task - (Neutral, and socioemotional stimuli).	Between group contrasts: Attention control (face, and nonface stimuli).	Central fixation cross.
Schmitz, 2006	ASD-HC	10:12	Adults	105(14): 106(13)	0;10: 0;12	ADI-R	No total score	NA; whole brain activation.	Age, and IQ.	Three tasks, a) Go/NoGo task, b) stroop task, c) switch task - (Neutral stimuli).	Within and between group contrasts: Inhibitory control (correct NoGo; and correct stroop). Cognitive flexibility (correct	Central fixation cross.

										switch).		
Shafritz, 2015	ASD-HC	15:15	Adults.	101.5 (18.6): 115.2 (9.3)	3;12: 3;12	ADI-R; ADOS-G.	NA	NA; whole brain activation.	NA	Block design Go/NoGo task - (Neutral and socioemotional stimuli).	Within and between group contrasts: Inhibitory control (xNoGo > letter NoGo). Attention control (emotion NoGo > letter NoGo).	Central fixation cross.
Solomon, 2009	ASD-HC (only right handers)	22:23	Adolescents	107(14): 113(11)	5;17: 5;18	ADOS-G	No total score	SCQ; whole brain activation.	NA	Preparing to Overcome Prepotency (POP) task - (Neutral stimuli).	Within and between group contrasts: Cognitive flexibility (red > green). Between group contrast: Attention control (red > baseline).	Central fixation cross.
Takarae, 2007	ASD-HC	13:14	Adults	105.90 (12.30): 110.30 (13.70)	NA	ADOS-G	NA	NA; whole brain activation.	Age, and IQ.	Visually guided saccade task - (Neutral stimuli).	Between group contrast: Attention control (saccadic target movement right or left).	Central fixation.

Thakkar, 2008	ASD-HC	12:14	Adults	No full scale IQ.	2;10: 6;8	ADI-R; ADOS	NA	NA; whole brain activation.	Age, sex, and handedness.	Saccadic paradigm - (Neutral stimuli).	Between group contrast: Inhibitory control (correct prosaccade + antisaccade vs fixation).	Fixation.
Vaidya, 2011	ASD-HC	11:14	Children	113.85 (15.40): 119.17 (14.19)	3;8: 3:11	ADI-R; ADOS.	NA	NA; whole brain activation.	Age, and IQ.	Arrow and Gaze tasks - (Stroop like task; neutral, and socioemotional stimuli).	Between group contrasts: Attention control (congruent > neutral). Inhibitory control (incongruent > congruent).	Fixation trials.
Velasquez, 2017	ASD-HC	19:22	Adults	115.53 (12.82): 112.27 (11.84)	6;13: 6;16	ADI-R; ADOS.	ADI-R=No total score. ADOS=3.77(2.21)	SADS; whole brain activation.	Age, IQ, and gender.	Go/NoGo task - (Neutral and socioemotional stimuli).	Between group contrasts: Inhibitory control (letter, and face NoGo > Go). Attention control (face NoGo > letter NoGo).	Fixation cross.
Yerys, 2015	ASD-HC	20:19	Children	114.70 (14.50): 119.58 (13.25)	4;16: 6;13	ADI-R; ADOS	ADI-R=No total score. ADOS=11.15(2.92)	NA; whole brain activation.	Age, IQ, and gender.	The set-shifting task - (Neutral stimuli)	Within and between group contrasts: Cognitive flexibility (switch > stay).	STAY and SWITCH instructions in the center of the screen.

Note: ASI (NEPSY-II) = Animal Sorting and Inhibition subtests from NEPSY-II; BRIEF = Behavior Rating Inventory of Executive Function; SCQ = Social Communication Questionnaire; DISC-IV = Diagnostic Interview Schedule for Children; DAWBA = Development and Well-being Assessment; RBS-R = Repetitive Behavior Scale - Revised Questionnaire); DISCO - Diagnostic Interview for Social and Communication Disorders; HADS = Hamilton Anxiety and Depression Scale; SADS = Social Avoidance and Distress Scale; TEA-Ch = Test of Everyday Attention for Children; TMT = Trail Making Test.

Table 2.2: Between-group fMRI meta-analysis and meta-regression on EC components (attention, inhibitory control, and flexibility) with age as a covariate and regressor, respectively: Emotional components included.

Brain regions with significant peak activation							Cluster breakdown	
Anatomical region	ASD > TD/ASD < TD	Total voxels	MNI coordinates	SDM-Z	*p* (uncorrected)	*p* - TFCE corrected	Anatomical regions (Broadmann areas)	Network parcellation
Meta-analysis of attention with age as a covariate (studies n = 14)								
Left inferior frontal gyrus, triangular part	ASD > TD	47	-42,34,26	3.580	<.0005	n.s.	Left middle frontal gyrus (BA46) Left inferior frontal gyrus, triangular part (BA45) Left middle frontal gyrus (BA45) Left inferior frontal gyrus, triangular part (BA46) Corpus callosum	FPN
Right precentral gyrus	ASD > TD	10	40, 16,56	2.977	<.005	n.s.	Right precentral gyrus (BA4 and BA6)	SMN
Right thalamus	ASD > TD	10	4, 18,2	2.775	<.005	n.s.	Right thalamus (NA) Right anterior thalamic projections (undefined)	
Left superior occipital gyrus	ASD > TD	1	-24, 78,40	2.652	<.005	n.s.	Left superior occipital gyrus (BA7)	VN
Right cerebellum, crus II	ASD < TD	167	26, 78, 36	-3.465	<.0005	n.s.	Right cerebellum, crus I and II Right cerebellum, hemispheric lobule VI (BA19) Right cerebellum, hemispheric lobule VI (BA37)	FPN

Right superior occipital gyrus	ASD < TD	135	26, 74,42	-3.253	<.0005	n.s.	Right superior occipital gyrus (BA7, BA18, BA19) Corpus callosum Right cuneus cortex (BA7, BA18, BA19)	VN
Left inferior occipital gyrus	ASD < TD	51	-40, 74, 10	-2.967	<.005	n.s.	Left inferior occipital gyrus (BA19, BA37) Left inferior temporal gyrus (BA37) Left fusiform gyrus (BA19) Left middle temporal gyrus (BA37) Left inferior network, inferior longitudinal fasciculus (NA)	VN
Left precentral gyrus	ASD < TD	41	-32, 18,56	-3.169	<.005	n.s.	Left precentral gyrus (BA6, BA4) Corpus callosum	SMN
Left middle occipital gyrus	ASD < TD	31	-32, 72,24	-3.151	<.005	n.s.	Left middle occipital gyrus (BA19, BA39) Left inferior network, inferior longitudinal fasciculus (NA)	VN
Corpus Callosum	ASD < TD	13	30, 34, 10	-2.863	<.005	n.s.	Left superior longitudinal fasciculus I Corpus callosum Right hippocampus (BA20, BA37) Right parahippocampal gyrus (BA37)	
Left fusiform gyrus	ASD < TD	6	-42, 62, 16	-2.792	<.005	n.s.	Left inferior frontal gyrus, opercular part (BA44) Corpus callosum	DAN (Top-down)

Left inferior frontal gyrus, opercular part	ASD < TD	5	-58,12,16	-2.886	<.005	n.s.	Left inferior frontal gyrus, opercular part (BA44, BA6)	VAN (Bottom-up)
Corpus Callosum	ASD < TD	1	-18, 58,52	-2.62	<.005	n.s.	Corpus callosum	
Meta-regression of attention with age as a regressor ($p < 0.05$)								
Right precentral gyrus	Decreasing activation with increasing age	77	24, 22,64	-2.199	0.013	n.s.	Right precentral gyrus (BA6, BA4)	SMN
Left inferior frontal gyrus, triangular part	Decreasing activation with increasing age	10	-38,40,8	-2.128	0.017	n.s.	Left inferior frontal gyrus, triangular part (BA45) Left anterior thalamic projections Corpus callosum Left superior longitudinal fasciculus III	FPN
Right precentral gyrus	Decreasing activation with increasing age	2	40, 18,58	-1.779	0.038	n.s.	Right precentral gyrus (BA4)	SMN
Meta-analysis of inhibitory control with age as a covariate (studies n = 10)								
Left anterior cingulate/paracingulate gyri	ASD < TD	773	-4,26,18	-4.240	<.0001	<.001	Left and right anterior cingulate/paracingulate gyri (BA24, BA32) Left median network Left superior frontal gyrus, medial (BA32)	DMN

							Right, and left median cingulate/paracingulate gyri (BA24, BA32) Corpus callosum Right angular gyrus (BA39, BA19)	
Right angular gyrus (BA39)	ASD < TD	196	48, 72,30	-3.162	<.005	n.s.	Right middle occipital gyrus (BA19, BA39) Right middle temporal gyrus (BA39) Right angular gyrus (BA19)	DAN (Top-down)
Meta-analysis of flexibility with age as a covariate (n = 8)								
Left anterior cingulate/paracingulate gyri	ASD < TD	388	0,40,16	-3.148	<.005	n.s.	Right and left anterior cingulate/paracingulate gyri (BA24,32) Left superior frontal gyrus, medial (BA32) Right median cingulate/paracingulate gyri (BA32)	DMN
Corpus callosum	ASD < TD	8	-18,46,28	-3.021	<.005	n.s.	Corpus callosum Left middle frontal gyrus (BA9)	
Left inferior frontal gyrus, triangular part	ASD < TD	7	-42,30,26	-2.888	<.005	n.s.	Left inferior frontal gyrus, triangular part (BA45, BA46, BA48) Left middle frontal gyrus (BA45, BA46)	FPN
Left precuneus	ASD < TD	3	-8, 70,48	-2.664	<.005	n.s.	Left precuneus (BA7)	DAN (Top-down)
Left inferior frontal gyrus, triangular part	ASD < TD	2	-44,28,20	-2.623	<.005	n.s.	Left inferior frontal gyrus, triangular part (BA48)	FPN

Meta-regression of flexibility with age as a regressor ($p < 0.05$)								
Left anterior cingulate/paracingulate gyri	Decreasing activation with increasing age	93	0,44,4	-2.064	0.019	n.s.	Left anterior cingulate/paracingulate gyri (BA10, BA32) Right anterior cingulate/paracingulate gyri, BA(10) Right superior frontal gyrus, medial (BA10)	DMN

Note: FPN = Fronto-Parietal Network; SMN = Somato-Motor Network; VN = Visual Network; DAN = Dorsal Attention Network; VAN = Ventral Attention Network; DMN = Default Mode Network.

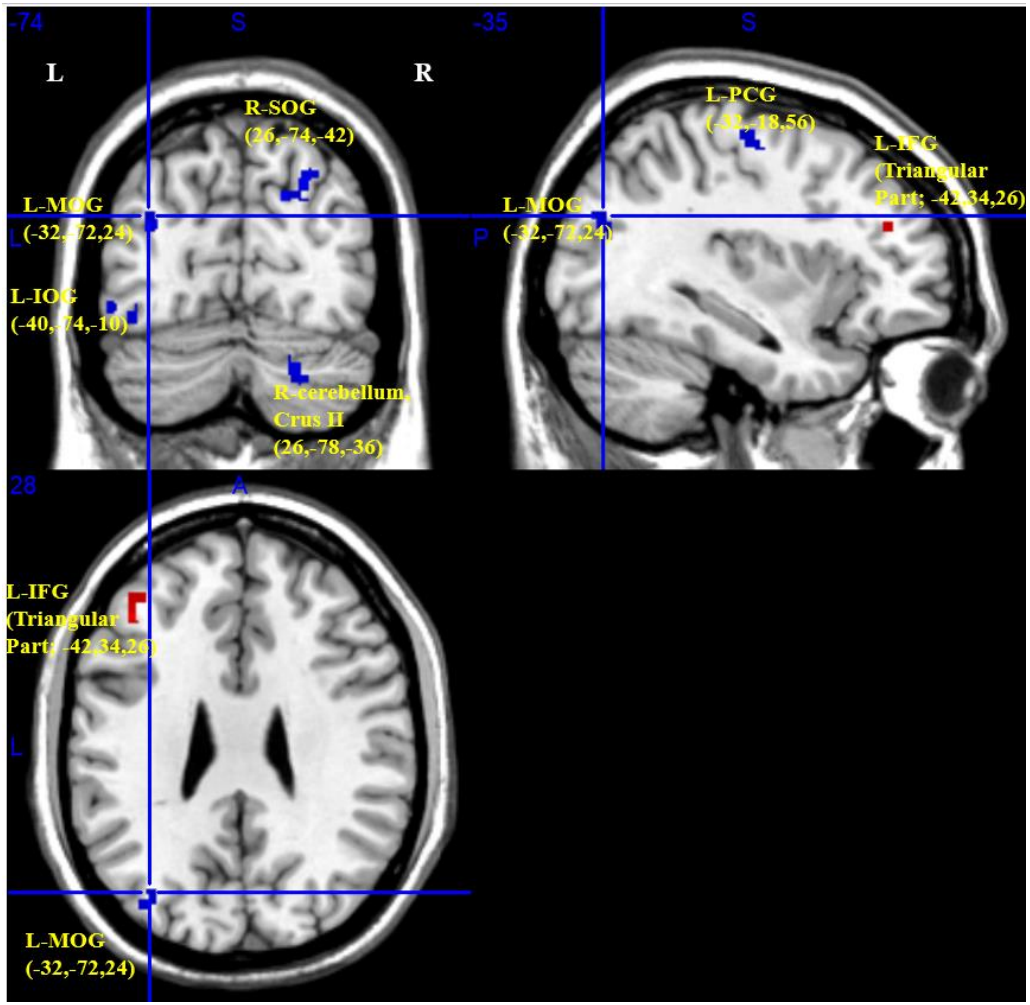


Figure 2.2: Differences of brain activation between ASD and HC groups during attentional control. Cluster with red and blue colors indicates hyperactivation and hypoactivation when compared with HC ($p < 0.005$, uncorrected; Note: L = left, R = right, SOG = superior occipital gyrus, MOG = middle occipital gyrus; IOG = inferior occipital gyrus; IFG = inferior frontal gyrus; PCG = precentral gyrus)

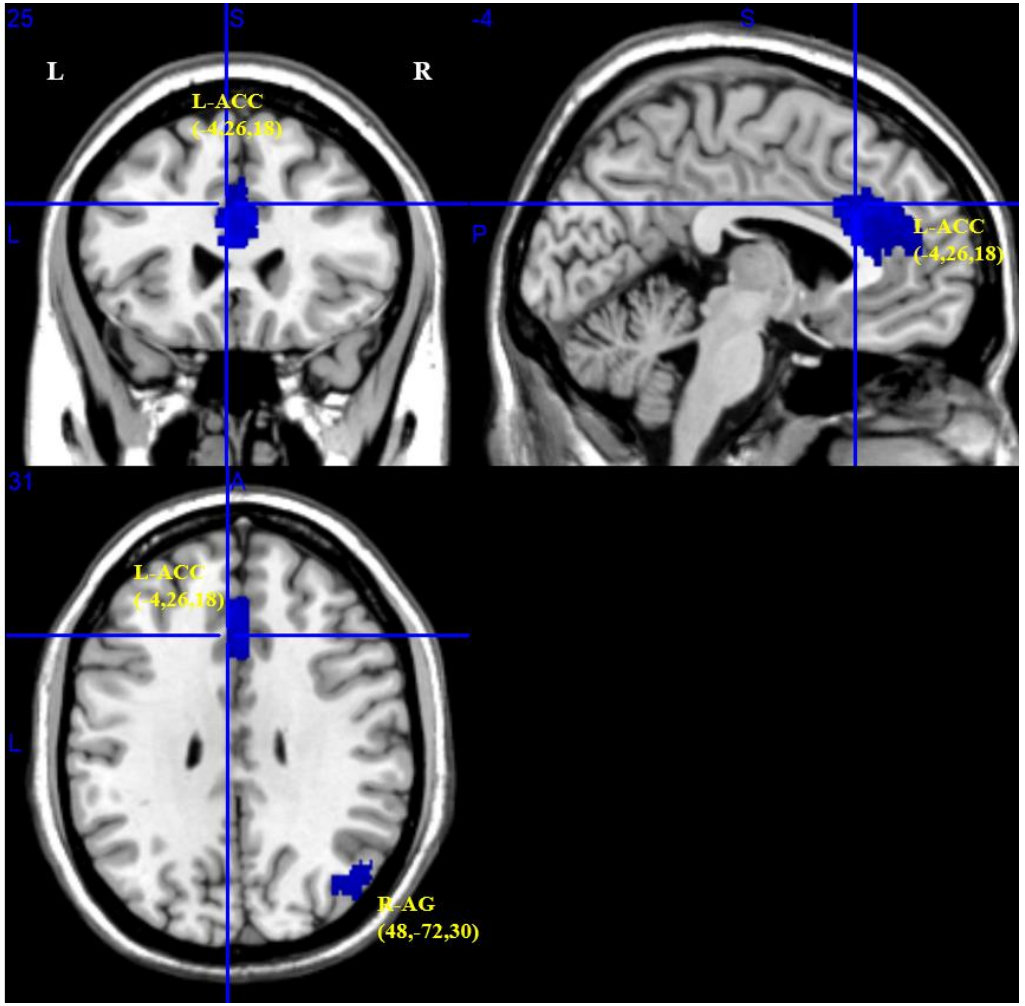


Figure 2.3: Differences of brain activation between ASD and HC groups during inhibitory control. Cluster with blue color indicates hypoactivation when compared with HC ($p < 0.005$, uncorrected; Note: L = left, R = right, ACC = anterior cingulate cortex, AG = angular gyrus)

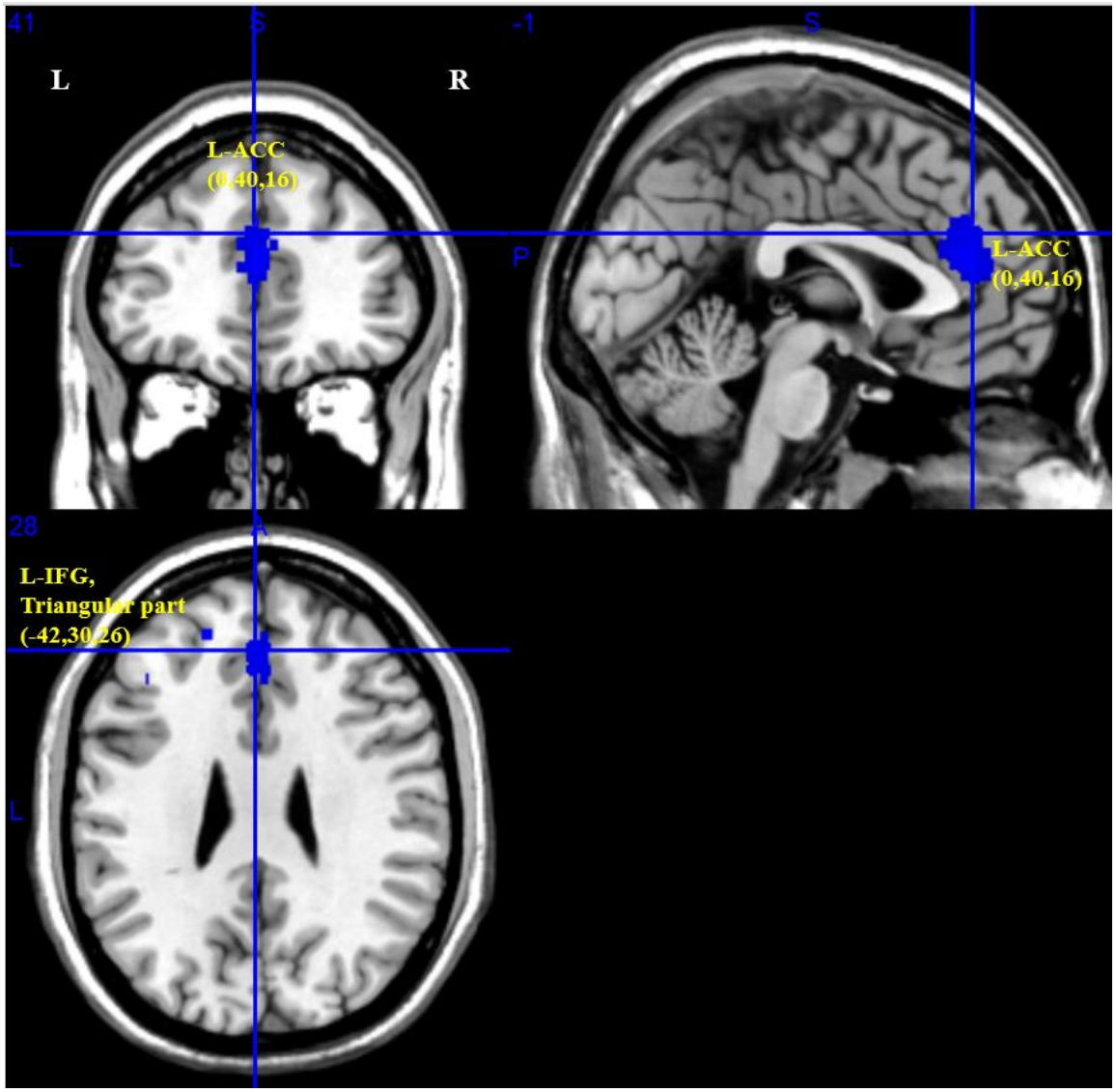


Figure 2.4: Differences of brain activation between ASD and HC groups during cognitive flexibility. Cluster with blue color indicates hypoactivation when compared with HC ($p < 0.005$, uncorrected; Note: L = left, R = right, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus)

2.3. Results

2.3.1. Attentional Control Tasks with Combined Stimuli

Study characteristics

Fourteen studies containing 19 comparisons were included in the meta-analysis, which compared 266 individuals with ASD (48 children, 108 adolescents, and 110 adults)

with 297 healthy controls (53 children, 127 adolescents, and 117 adults). The demographic and experimental details of the included studies are summarized in Table 2.1.

Brain activation

As shown in Table 2.2 and Figure 2.2, attention tasks induced significantly greater activation in the frontoparietal network (FPN) and somato-motor network (SMN; right precentral gyrus). Simultaneously, there were also significant deactivations in the visual network (VN), FPN, SMN, dorsal attention network (DAN), and ventral attention network (VAN) with mean age as a covariate (uncorrected *ps* < 0.005; Figure 2.2). For the FPN, an activation peak was observed in the left frontal region (triangular part) where the cluster extended from the mid to the inferior frontal region. In contrast, the deactivation peak of FPN was observed in the right cerebellum crus II, where the cluster extended from the right cerebellum crus I and II to its hemispheric lobule VI. Likewise, in the SMN, the activation peak was observed in the right precentral gyrus, and the deactivation peak was observed in the left precentral gyrus. The clusters of these peaks were restricted to the corresponding brain regions alone. For the VN, the peak was observed in the left inferior occipital gyrus, and the cluster extended from the peak site to the left fusiform gyrus and fasciculus. For the VAN and DAN, peaks were observed in the left fusiform and left inferior frontal gyrus (opercular part), respectively, and the corresponding clusters extended from the left inferior frontal gyrus (opercular part) to the corpus callosum. Meta-regression between the mean age and FPN and SMN during attention tasks revealed significant negative relationships, indicating increasing age with decreasing FPN and SMN activation (Table 2.2). The I^2 statistic for the left inferior frontal gyrus (6.14%), right precentral gyrus (4.73%), right cerebellum crus II (7.59%), right superior occipital gyrus (18.12%), left fusiform gyrus (10.22%), and left inferior frontal gyrus (opercular part; 6.98%) indicated low heterogeneities.

2.3.2. Inhibitory Control Tasks with Combined Stimuli

Study characteristics

Ten studies containing 12 comparisons were included in the meta-analysis, which compared 187 individuals with ASD (11 children, 80 adolescents, and 96 adults) with 216 healthy controls (14 children, 98 adolescents, and 104 adults). The demographic and experimental details of the included studies are summarized in Table 2.1.

Brain activation

As shown in Table 2.2 and Figure 2.3, inhibitory control tasks induced significantly reduced activation in the default mode network (DMN), and DAN with mean age was a covariate (uncorrected *ps* < 0.005; Figure 2.3). For the DMN, a deactivation peak was observed in the left anterior cingulate/paracingulate gyri region, where the cluster extended from the bilateral anterior cingulate to the bilateral median cingulate gyri. For the DAN, a deactivation peak was observed in the right angular gyrus, where the cluster extended from the right angular gyrus to the right middle occipital and temporal gyri regions. Notably, the DMN cluster survived familywise error correction (773 voxels; SDM-Z = -4.24; TFCE-corrected $p < 0.001$). However, the peaks did not yield significant results in the meta-regression analysis (Table 2.2). The I^2 statistic for the left anterior cingulate/paracingulate gyri (4.65%) and right angular gyrus (12.26%) indicated low heterogeneities.

2.3.3. Cognitive Flexibility Tasks with Combined Stimuli

Study characteristics

Eight studies containing 9 comparisons were included in the meta-analysis, which compared 138 individuals with ASD (58 children, 22 adolescents, and 58 adults) with 158 healthy controls (66 children, 23 adolescents, and 69 adults). The demographic and experimental details of the included studies are summarized in Table 2.1.

Brain activation

As shown in Table 2.2 and Figure 2.4, cognitive flexibility tasks induced significantly reduced activation in the default mode network (DMN), FPN and DAN with mean age as a covariate (uncorrected *ps* < 0.005; Figure 2.4). For the DMN, a deactivation peak was observed in the left anterior cingulate/paracingulate gyri region, where the cluster extended from the bilateral anterior cingulate to the right median cingulate gyri. For the FPN, the deactivation peak was observed in the left inferior frontal gyrus (triangular part), where the cluster extended from the left inferior frontal to the left middle frontal gyrus. For the DAN, a deactivation peak was observed in the left precuneus, and the cluster was restricted to this brain region alone. Meta-regression between the mean age and DMN during cognitive flexibility tasks revealed significant negative relationships, indicating increasing age with decreasing DMN activation (Table 2.2). The I^2 statistic for the left anterior cingulate/paracingulate gyri (6.23%), left inferior frontal gyrus (8.73%), and left precuneus (1.51%) indicated low heterogeneities.

2.3.4. Subgroup Analysis of EC Components with Neutral Stimuli Alone

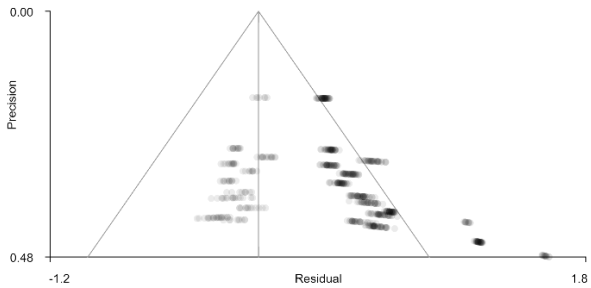
Similar results were obtained for combined stimuli (neutral and socioemotional) in all EC components (attention, inhibitory control, and cognitive flexibility) when the analysis was included with the neutral stimuli alone (Appendix: Supplementary table 1).

2.3.5. Risk of publication bias:

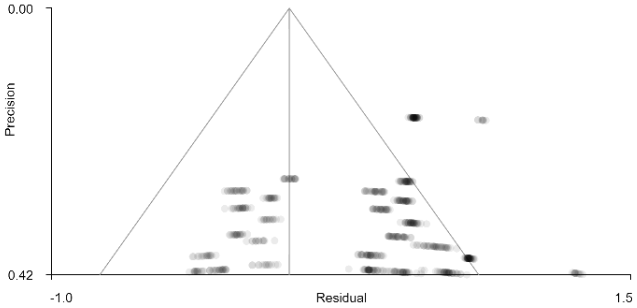
2.3.5.1. Attentional control tasks

The funnel plots were generated for the significant peak coordinates of estimated effect size during attention tasks between ASD and healthy control groups (listed in table 2.2). Visual inspection of the funnel plots did not show obvious asymmetries in the left inferior frontal gyrus (triangular part; Fig. 2.5a), right cerebellum crus II (Fig. 2.5c), right superior occipital gyrus (Fig. 2.5d), left fusiform gyrus (Fig. 2.5e), left inferior frontal gyrus (opercular part; Fig. 2.5f), or left precentral gyrus (Fig. 2.5 g), and Egger's test of these brain regions was nonsignificant (*ps* > 0.856), indicating no publication bias and no prominent small-study effects. However, the funnel plot of the right precentral gyrus (Fig. 2.5b) showed asymmetry, with the corresponding Egger's test being significant ($p > 0.000$), indicating publication bias with small study effects presented with this cluster. Nevertheless, the overall result showed larger study effects among the included studies in the meta-analysis, and the result was not confounded with publication bias.

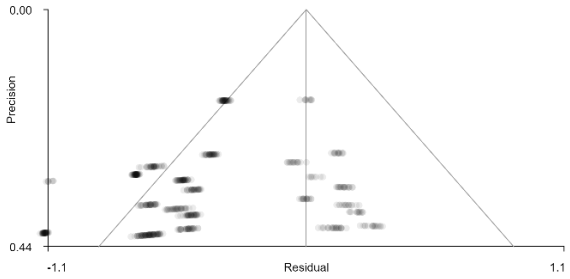
a) Left inferior frontal gyrus (Triangular part; -42,34,26);
Egger's test $p = 1.000$



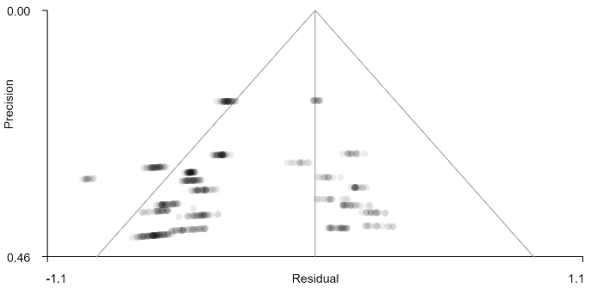
b) Right precentral gyrus (40, 16,56)
Egger's test $p = 0.000$



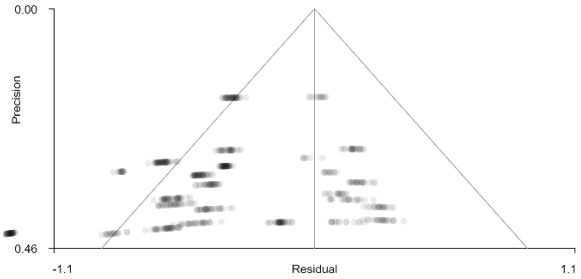
c) Right cerebellum, crus II (26, 78, 36);
Egger's test $p = 0.856$



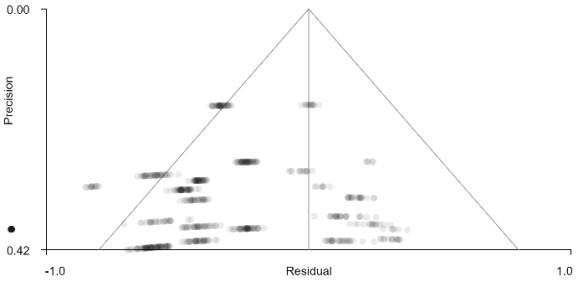
d) Right superior occipital gyrus (26, 74, 42);
Egger's test $p = 0.995$



e) Left fusiform gyrus (-42, 62, 16);
Egger's test $p = 0.996$



f) Left inferior frontal gyrus (opercular part; -58,12,16);
Egger's test $p = 0.979$



g) Left precentral gyrus (-32, 18,56);
Egger's test $p = 0.905$

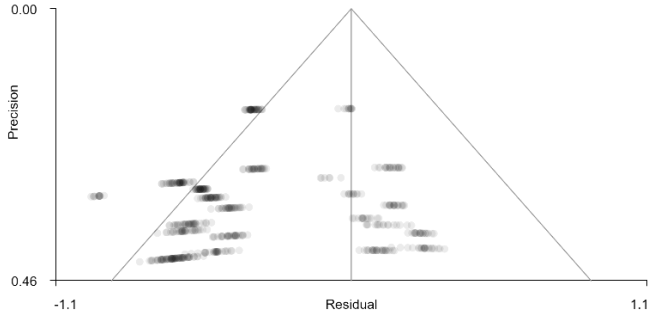


Figure 2.5: Funnel plots of the significant peak coordinates during attention tasks with combined stimuli. The x-axis denotes the effect size (Hedges's g) between two groups, and the y-axis is the precision (1/SE) with random effects model.

2.3.5.2. Inhibitory control tasks

The funnel plots were generated for the significant peak coordinates of estimated effect size during inhibitory control tasks between ASD and control groups (listed in table 2.2). Visual inspection of the funnel plots did not show obvious asymmetries in the left anterior cingulate/paracingulate gyri (Fig. 2.6a) or right angular gyrus (Fig. 2.6b). Egger's tests of these brain regions were nonsignificant (*ps* > 0.246), indicating no publication bias or prominent small-study effects of the included studies in the meta-analysis.

a) Left anterior cingulate/paracingulate gyri (-4,26,18); Egger's test $p = 0.246$

b) Right angular gyrus (48, 72,30); Egger's test $p = 0.942$

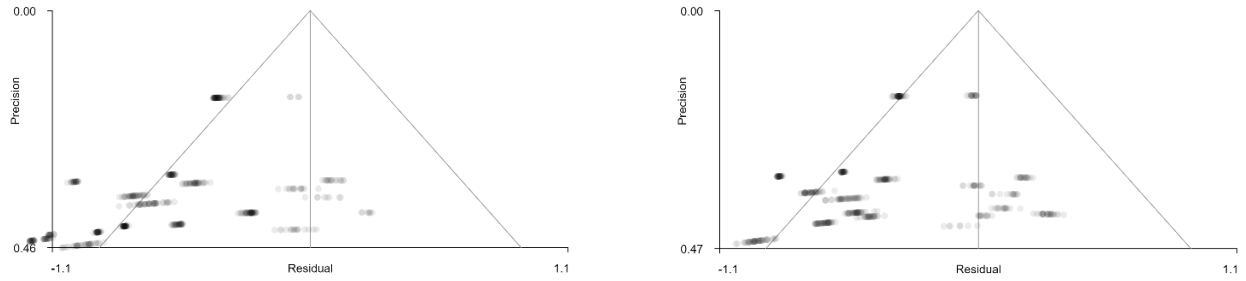


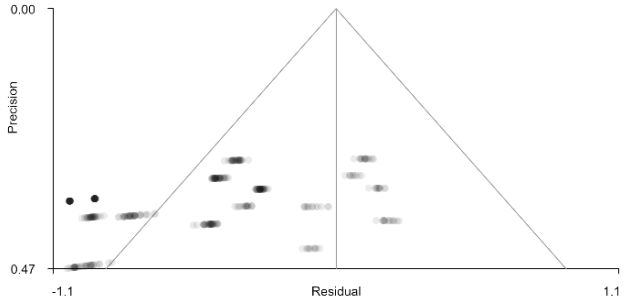
Figure 2.6: Funnel plots of the significant peak coordinates during inhibitory control tasks with combined stimuli. The x-axis denotes the effect size (Hedges's g) between two groups, and the y-axis is the precision (1/SE) with random effects model.

2.3.5.3. Cognitive flexibility tasks

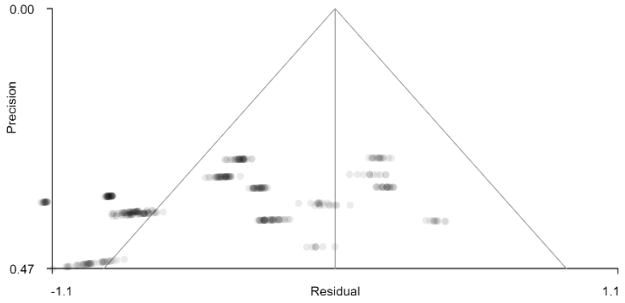
The funnel plots were generated for the significant peak coordinates of estimated effect size during cognitive flexibility tasks between ASD and control groups (listed in table 2.2). Visual inspection of the funnel plots did not show obvious asymmetries in the left anterior cingulate/paracingulate gyri (Fig. 2.7a), left inferior frontal gyrus (triangular part;

Fig. 2.7b), or left precuneus (Fig. 2.7c). Egger's tests of these brain regions were nonsignificant (*ps* > 0.994), indicating no publication bias or prominent small-study effects of the included studies in the meta-analysis.

a) Left anterior cingulate/paracingulate gyri (0,40,16); Egger's test $p = 1.000$



b) Left inferior frontal gyrus (triangular part; -42,30,26); Egger's test $p = 0.999$



c) Left precuneus (-8, 70,48);
Egger's test $p = 0.994$

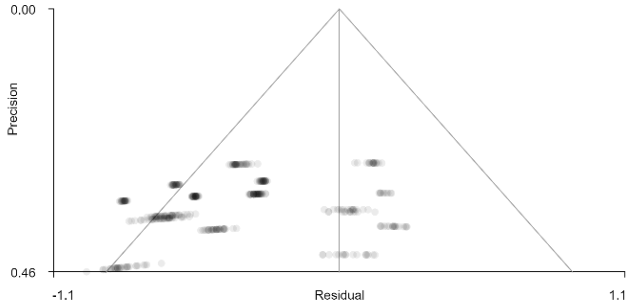


Figure 2.7: Funnel plots of the significant peak coordinates during cognitive flexibility tasks with combined stimuli. The x-axis denotes the effect size (Hedges's g) between two groups, and the y-axis is the precision (1/SE) with random effects model.

2.4. Discussion

This coordinate-based meta-analysis aimed to investigate the neural basis of temperamental EC deficits and predict the developmental pattern of brain activations associated with EC components between individuals with autism and healthy controls. The literature search yielded 22 whole-brain fMRI studies, of which 14 studies addressed

attention control with 19 comparisons, 10 studies addressed inhibitory control with 12 comparisons, and 8 studies addressed cognitive flexibility with 9 comparisons. This meta-analysis highlighted two important findings: a) the neural substrates underlying temperamental EC are impaired in individuals with autism indexed by attention control, inhibitory control, and cognitive flexibility tasks; b) age subserves a significant predictor of EC function in autism.

The findings of this meta-analysis favored our hypothesis. First, the ASD group elicited significantly less activation than their healthy counterparts in DAN in the left inferior frontal gyrus cluster (opercular part) and VAN in the left fusiform cluster. The DAN modulates intentional, target-oriented, top-down endogenous attention, which is activated while presenting cues to indicate arrow appearance (Corbetta & Shulman, 2002). In contrast, the VAN modulates involuntary, autonomous, bottom-up exogenous attention, which is activated while responding to unpredictable targets. Therefore, VAN assumes a "circuit breaker" role for DAN while shifting attention to objects from one place to another (Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005). These inherent mechanisms in the VAN and DAN during attention orienting tasks were found to be defective in autism; notably, the autism group exhibited weaker recruitment of DAN during cue-only, target-driven, endogenous attention control tasks and the VAN during valid trials of attention orienting tasks (Fitzgerald et al., 2015). The diverging pattern of top-down and bottom-up network recruitment resulted from developmental processes, explaining why the age-increased deactivations of networks were evident in adults compared with children with autism (Farrant & Uddin, 2016). In addition to the VAN and DAN, the FPN of this study showed mixed activation patterns in autism, such that the cerebellum crus II cluster was hypoactivated, and the left inferior frontal (triangular part) cluster was hyperactivated during attention control tasks. Although cerebellar involvement is primarily confined to motor behavior/learning and

coordination deficits in autism (Bruchhage, Bucci, & Becker, 2018), the cerebellar recruitment of this meta-analysis suggests its integral role in attentional control. Specifically, the current finding corroborated a previous study on attention tasks that induced more activation in the left posterior quadrangular lobule and the left superior semilunar lobule of the cerebellum in healthy adults. This implies that the healthy participants presented with intact cerebellar functions that optimized better oculomotor control, gaze fixation, and rapid saccadic eye movements while attending visual stimuli alone in the attention task, and such cerebellar-controlled optimization was found to be defective in autism (Allen, Buxton, Wong, & Courchesne, 1997; Mosconi, Wang, Schmitt, Tsai, & Sweeney, 2015).

The concurrent involvement of another FPN cluster, the "left inferior frontal gyrus (L-IFG; triangular part), is activated while inhibiting responses over competing stimuli (Swick, Ashley, & Turken, 2008) and reorientating responses, i.e., while adapting to prominent unpredictable stimuli in given circumstances (Corbetta et al., 2008). Notably, the activation of the L-IFG is more evident in attention constructs, while low-contrast targets coexist with high-contrast nontargets, which have similar perceptual or better salient characteristics (DiQuattro & Geng, 2011). Similarly, the L-IFG becomes heavily activated when stimulus-driven attention is confined to more observable behavioral events, such as orienting unpredictable exogenous cues or responding to contextual knowledge cues (Vossel, Geng, & Fink, 2014). Given that, the hyperactivation of the L-IFG in the ASD group of this meta-analysis implies that they might recognize high-contrast nontarget stimuli or orient external cues using contextual information while responding to attention control tasks, and this warrants further research. Unexpectedly, the ASD group also showed decreased activation in the VN involving the left inferior occipital gyrus cluster and SMN in the left precentral gyrus cluster. The deactivation of the VN during the attention task was consistent with previous results claiming that individuals with autism demonstrated decreased activation patterns in

various occipital regions while detecting visual information, perceiving movements, and processing facial expressions. The deactivation and poor network integration in VN regions while relaying visual information led to disrupted visual perceptual abilities and social brain circuits in autism (Chung & Son, 2020). The simultaneous involvement of the precentral gyrus (PCG) belonging to SMN primarily regulates voluntary motor actions of contralateral limbs and planning intentional movements of extremities (Banker & Tadi, 2021). Although the causal relationship between PCG activation and motor behavior in autism is not exclusively available, evidence supports that individuals with autism experience motor impairments, and the associated symptoms worsen with altered synchronization of PCG (Nebel, Eloyan, Barber, & Mostofsky, 2014). With this notion, the findings of increased activation in the right precentral gyrus and decreased activation of the left precentral gyrus in autism implies that right-handed individuals might demonstrate more motor behavioral and execution deficits than left-handed individuals while responding to attention tasks prompted by pressing keys or clicking the mouse.

Second, as expected, the DMN, including the left anterior cingulate/paracingulate gyri cluster, was deactivated in autism during inhibitory control and cognitive flexibility tasks. The anterior cingulate cortex (ACC) has long been implicated as the primary node for monitoring conflicts, errors, and shifting response patterns during inhibitory control and cognitive flexibility functions. Specifically, paradigms assessed inhibitory skills across 173 experiments while refraining prepotent action with or without motor responses, and interference control in healthy adults activated the anterior midcingulate cortex (Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015). Additionally, the role of ACC was studied on conflict hypothesis mechanism supporting that better control over intensive conflicting and error trials during inhibition were associated with greater ACC recruitment (Kerns et al., 2004). These conflict monitoring and modulating response mechanisms of the ACC aid in

successful cognitive flexibility during switching trials despite momentary fluctuations being evident in healthy individuals (Leber, Turk-Browne, & Chun, 2008). In this context, decruitment of the ACC in autism in this meta-analysis was consistent with previous studies showing a significant deactivation and underconnectivity of the ACC during inhibitory control (Kana et al., 2007) and cognitive flexibility (Uddin, 2021) subcomponents, which implies that the individuals with autism employed defective mechanisms during inhibition and flexibility. Together with the DMN, DAN, including the right angular gyrus, was deactivated during inhibitory control. Activation of the angular gyrus was more pronounced in a healthy population when interference resolution, action withholding, and action cancellation were combined as response inhibition constructs (Zhang, Geng, & Lee, 2017). Notably, the right angular gyrus (R-AG) typically involves inhibiting irrelevant stimuli across various go/no-go tasks, which require resolving conflicts during the selection and execution of appropriate responses through distinct processing stages (Nee, Wager, & Jonides, 2007). Therefore, the deactivation of R-AG in individuals with autism might be explained as a consequence of difficulty in overcoming prepotent response tendencies either to opt for appropriate response patterns or withhold executing inappropriate responses during task performance. Similarly, the ASD group also showed deactivation in another DAN cluster (left precuneus) and the FPN cluster (left inferior frontal gyrus; triangular part) during cognitive flexibility tasks. In terms of the left precuneus and left inferior frontal gyrus involvement, healthy individuals were found to have greater activation in these brain regions during stimulus-switch, response-switch, and cognitive-switch conditions than during nonswitch conditions in both condition wise contrast and group-level conjunction (all three-switching vs non switching conditions) analyses (Kim, Johnson, Cilles, & Gold, 2011). However, a subsequent meta-analysis revealed that the left inferior frontal gyrus was activated during response, context, and perceptual switching contrasts, and the left precuneus

activity was observed during response and context switching contrasts alone. Response switching involves shifting between two or more contrasting stimulus-response (S-R) mappings (e.g., S-R reversal paradigms), which require participants to hold and shift S-R contingencies with reference to cues. Context switching refers to endogenous cognitive set-shifting processes, e.g., WCST, which mandates that individuals employ internal control mechanisms while holding or switching among numerous cognitive sets. Perceptual switching involves shifting attention between perceptual characteristics of stimuli (direction/shape) or preference rules that necessitate active attentional shift while making task-relevant decisions about stimulus characteristics (Kim et al., 2012). Given this plausibility, deactivation of the left precuneus and left inferior frontal gyrus during cognitive flexibility tasks in autism suggests dysfunctional response, contextual, and perceptual switching mechanisms while encountering set-shifting trials.

Finally, in line with our expectation, the meta-regression analysis showed a negative correlation between age and FPN (L-IFG; triangular part) and SMN (right precentral gyrus) in the autism group during attention control tasks. IFG activity was found to increase activation with age while attending salient stimuli and suppressing prepotent responses in typical individuals (Rubia et al., 2000). Specifically, healthy children exhibited more L-IFG activation, and healthy adults activated more right IFG during interference suppression, i.e., incongruent > neutral contrast in Ericksen's flanker task, explaining that the children utilized more verbal strategies by labeling the central arrow pointing direction as "left or right" to minimize the effects of distractors (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). This suggests that the lack of such verbal strategies in autism while responding to task conditions might be an underlying reason for the age-increased L-IFG deactivation found in this meta-analysis. Concomitantly, the right precentral gyrus cluster in SMN deactivation with increasing age in autism during attentional control was concordant with a study on

healthy individuals showing that the brain region was activated in children and deactivated in adults, while nonsymbolic numerical trials were subtracted with spatial processing stimuli. Subtraction of numerical stimuli left with spatial orientation of the limb without a general attention component implies that the right precentral gyrus would be associated with controlling limb movement or recognizing limb position (Kaufmann et al., 2008). Given that, individuals with autism may experience worsened motor acts as they grow older while responding to tasks addressing cognitive functions. In addition to the FPN and SMN, the DMN (left anterior cingulate/paracingulate gyri) was negatively associated with age in autism during cognitive flexibility tasks. The involvement of the ACC in healthy individuals was reported consistently across studies (Dajani & Uddin, 2015); notably, the magnitude of ACC recruitment showed more synchronized patterns in childhood, intermediate trends in adolescents, and converging patterns in adults while monitoring conflicts (Kelly et al., 2009). This inverse linear progression of ACC involvement during cognitive flexibility suggests that activation is more evident in early life and becomes less evident with increasing age in typical individuals. Such developmental patterns were consistent with ACC in terms of deactivation in autism, which could result from cognitive flexibility deficits across age groups.

The meta-analysis has several limitations. First, it included a limited number of studies despite extensive literature searches conducted using various electronic databases and manual search methods. The meta-analysis was performed on whole-brain data, with 14 studies comprising 19 comparisons in attention control, 10 studies with 12 comparisons in inhibitory control, and 8 studies with 9 comparisons in cognitive flexibility components. There were an additional 10 potential studies for inclusion; however, they either lacked whole-brain analyses or the analyses were limited to specific regions of interest. Subject to the availability of additional whole-brain studies, the meta-analysis power would have been

higher and might yield a comprehensive understanding of EC functions in autism. Nonetheless, our meta-analysis supports existing findings that attention control elicits DAN, VAN, FPN; inhibitory control recruits DMN; and cognitive flexibility employs DMN and FPN as the influential networks. Second, the age range (in years) of our meta-analysis was limited to 10.78-30.20 for ASD and 10.42-32.40 for TD group in attention control; 10.78-38.00 for ASD and 10.96-39.00 for TD group in inhibitory control; 9.99-38.00 for ASD and 9.58-39.00 for TD group in cognitive flexibility subcomponents. Therefore, this meta-analysis examined the influence of age on EC components within given ranges, and the degree of brain region and accompanying neural network involvement outside this range is still undisclosed. Hence, it is recommended that the forthcoming fMRI studies on EC components be confined to this age range to ascertain developmental trajectories of EC functions more comprehensively. Third, heterogeneity of sex ratio and IQ evidenced that the deactivation patterns in attentional control, inhibitory control, and cognitive flexibility were lost when analyses treated these variables as covariates. Therefore, future studies with more homogeneous samples may aid in validating the current meta-analytical findings. Additionally, the meta-analysis included a disproportionately small number of children in the attention and inhibitory control components and adolescents in the cognitive flexibility component. Therefore, the overall result cannot be generalized to children and adolescents with ASD in the respective EC components. Hence, prospective studies incorporating the ASD group with a wider age range would be beneficial to examine the dynamic relationship with age and IQ. Furthermore, the sample size of the cognitive flexibility component ranged from 10-24 in the ASD group and 12-33 in the control group. Since the small sample size in a study appears to inflate the study effect size (Sterne et al., 2011), deactivation of the brain regions in the autism group during the cognitive flexibility task could have been inflated.

Consequently, caution is exercised in interpreting the cognitive flexibility results of this meta-analysis, which should be limited to studies with small sample sizes.

2.5. Conclusion

This coordinate-based fMRI meta-analysis aimed to investigate brain activation patterns between individuals with autism and healthy controls during EC subcomponents, including attention control, inhibitory control, and cognitive flexibility. The available whole-brain fMRI data in each EC subcomponent were synthesized independently using the SDM-PSI meta-analytic algorithm. To conclude, the meta-analysis indicated that the attentional control, inhibitory control, and cognitive flexibility systems were predominantly hypoactivated in autism, and the dysfunctional pattern was further moderated by age, which together may serve as an underlying causative factor for EC deficits in these individuals.

CHAPTER 3: STUDY TWO

Effortful Control and Prefrontal Cortex Functioning in Children with Autism Spectrum Disorder – An fNIRS Study

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Article

Effortful Control and Prefrontal Cortex Functioning in Children with Autism Spectrum Disorder: An fNIRS Study

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3.1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by sociocommunicative dysfunction with the presence of repetitive or stereotypic behavioral patterns and interests (American Psychiatric Association, 2013). These features are escalated in individuals with ASD as a result of impaired temperamental effortful control (EC; Eisenberg et al., 2004; Konstantareas & Stewart, 2006; Schwartz et al., 2009). EC is defined as "the efficiency of executive attention including the ability to inhibit a dominant response and/or to activate a subdominant response, to plan, and to detect errors" (Rothbart & Bates, 2006). As human behavior comprises habitual or spontaneous actions, EC is mandatory to inhibit a dominant response and initiate a subdominant response (Goldstein et al., 2007). Therefore, EC becomes a major component in controlling cognitive processes with their associated behavior (Rothbart & Bates, 2006) and serves as a defensive mechanism against compulsive thoughts while regulating overarching emotions (Claes et al., 2009).

EC encompasses executive attention, flexibility, and inhibitory control components, which help activate, modulate, or withdraw tendencies pertinent to chosen behavior (Eisenberg et al., 2010; Lengua et al., 2008; Rothbart & Bates, 2006). In contrast to EC, executive function (EF) consists of a set of higher-order cognitive processes, including updating (or working memory), inhibitory control, and set-shifting, which support goal-oriented actions (Miyake et al., 2000). Although EC and EF components conceptually overlap with each other in the self-regulation construct, EC differs from EF primarily in five key areas, including engagement in emotion-dependent contexts, working memory involvement, developmental patterns, adaptive function relationships, and underlying neural substrates (Zhou et al., 2012).

The prefrontal cortex (PFC) has long been implicated in the top-down control of behavior (Miller & Cohen, 2001). In healthy children, tasks that engage the core EC

components, such as flexibility and inhibitory control, typically activate parts of the PFC, anterior cingulate cortex, and parietal regions (Kelley, Wagner, & Heatherton, 2015; Miller & Cohen, 2001; Quinones-Camacho, Fishburn, Camacho, Wakschlag, & Perlman, 2019). Additionally, the PFC synchronizes with neighboring regions while regulating behavior associated with attention and inhibitory control in healthy individuals (Dosenbach et al., 2007; Seeley et al., 2007). In the context of EC, one functional near-infrared spectroscopy (fNIRS) study found that parent-reported temperamental EC was associated with better performance on a child version of the Stroop task and with less activation in the dorsolateral PFC during task performance in healthy young children (Quinones-Camacho et al., 2019). In another fNIRS study, Fekete, Beacher, Cha, Rubin, and Mujica-Parodi (2014) found that a lower level of EC reported by parents was associated with a decrease in frontal network segregation during movie viewing. Altogether, the literature suggests a link between PFC functioning and EC in healthy children.

Extensive structural and functional imaging studies have implicated abnormalities in the brain, especially the PFC, in ASD (Courchesne & Pierce, 2005; Ecker, Bookheimer, & Murphy, 2015; Philip et al., 2012). Functional magnetic resonance imaging (fMRI) studies have found that, compared to typically developing (TD) individuals, individuals with ASD demonstrated altered activation in the PFC and other parietal regions during a variety of EF tasks (Philip et al., 2012; Zhang, Peng, & Zhang, 2020). These individuals also displayed altered connectivity within the frontal lobe and between the PFC and parietal regions. For example, some studies have found that individuals with ASD showed weaker functional synchronization between the cingulo-insular regions and the right lateral frontal and inferior parietal areas (Kana et al., 2007), between the frontal eye field and intraparietal sulcus (Fitzgerald et al., 2015), and between the right anterior PFC and left visual cortex (Solomon et al., 2009) during inhibitory control and attention-orienting tasks. Notwithstanding the

evidence that ASD can be conceived as a disorder of frontal lobe function or connection (Courchesne & Pierce, 2005; O'Reilly, Lewis, & Elsabbagh, 2017), the relationship between PFC functioning and EC in children with ASD is still not clear.

Convergent evidence from human lesion, fMRI, and fNIRS studies has shown that the *n*-back task, which requires participants to judge whether the stimulus they are currently seeing is identical to that presented *n* trials prior, relies critically on the PFC (Owen, McMillan, Laird, & Bullmore, 2005; Tsuchida & Fellows, 2008; Yeung et al., 2016). Although the *n*-back task is often considered a task for working memory, other cognitive processes, including executive attention and inhibitory control, are subsumed while responding to relevant stimuli and ignoring irrelevant stimuli, respectively (Di Martino et al., 2011; Gajewski, Hanisch, Falkenstein, Thönes, & Wascher, 2018). The *n*-back task has been utilized to study a wide range of populations, including ASD (Barendse et al., 2018). Whereas the literature has reported inconsistent task performance results in individuals with ASD (Lever, Werkle-Bergner, Brandmaier, Richard Ridderinkhof, & Geurts, 2015; Williams, Goldstein, Carpenter, & Minshew, 2005), almost all fMRI and fNIRS studies have found altered patterns of PFC activation and/or connectivity during the *n*-back task in adolescents and adults with ASD (Koshino et al., 2005; Yeung, Lee, & Chan, 2019), suggesting that the *n*-back task is sensitive in revealing altered PFC functioning in ASD. Thus, we used the *n*-back task as a probe for PFC functioning in this study to clarify whether impaired EC is related to altered PFC functioning in children with ASD.

As an optical neuroimaging tool, fNIRS uses lights in the near-infrared spectrum (700–1000 nm) to measure changes in the concentration of oxygenated (HbO) and deoxygenated (HbR) hemoglobin that take place at the cortical surface (Boas, Elwell, Ferrari, & Taga, 2014; Ferrari & Quaresima, 2012). This method has been validated against fMRI (Cui, Bray, Bryant, Glover, & Reiss, 2011). Over the past 10 years, this technique has been widely

utilized in ASD research and has shown promise in understanding ASD (F. Zhang & Roeyers, 2019). As fNIRS is a relatively nondemanding neuroimaging modality for children, we used it to measure PFC activation and connectivity in this study. We hypothesized that, compared to TD children, children with ASD would demonstrate deficits in EC and its related functions (i.e., EF and socioemotional function). We predicted that these children would also exhibit altered PFC activation and connectivity during the *n*-back task (i.e., a frontal-sensitive task). Furthermore, we expected EC deficits to be associated with altered patterns of PFC activation and connectivity during the *n*-back task in children with ASD.

3.2. Materials and Methods

3.2.1. Participants

Participants were recruited from primary schools through an advertisement placed on campus and social media and sent to schools by post. Consequently, 39 right-handed Chinese children, aged between 8 and 12 years, were recruited, with written informed consent obtained from children and their parents. Twenty children diagnosed with ASD by a psychiatrist and clinical psychologist using the Diagnostic and Statistical Manual of Mental Disorders—5th Edition (DSM-5; American Psychiatric Association, 2013) were included in the ASD group. Children with ASD receiving medications were excluded. In addition, 19 age-, handedness-, and IQ-matched children were recruited in the TD group. No children in the TD group had episodes of epilepsy, head trauma, developmental delay, or other neuropsychiatric disorders.

3.2.2. Procedure

The study was conducted in accordance with the ethical principles for medical research involving human subjects declared by Helsinki. The experimental protocol was approved by

the Human Subjects Ethics Sub-Committee of the Hong Kong Polytechnic University (ethics approval code: HSEARS20170203004). All children were evaluated independently in two sessions (neuropsychological evaluation and fNIRS data acquisition), which lasted approximately 2 h in total, including breaks. Simultaneously, the parents or caregivers of children were interviewed with standardized interviewing protocols, which included the short form of the Early Adolescent Temperament Questionnaire–Revised (EATQ-R), Social Responsiveness Scale–Second Edition (SRS-2), and Autism Diagnostic Interview–Revised (ADI-R). The assessments and interviews were conducted by a clinical psychologist, skilled research assistants, and graduate students.

3.2.3. Measures

3.2.3.1. Short Form of the Early Adolescent Temperament Questionnaire: Revised (EATQ-R)

The level of EC was measured using the short form of the EATQ-R, which is a standardized parent-rated instrument containing 16 items in three subscales (i.e., activation control, attention, and inhibitory control). The items are rated on a 5-point Likert scale, ranging from 1 (almost always untrue of you) to 5 (almost always true of you) for the direct items and vice versa for the reversed items. A higher score in each domain indicates a greater ability in EC (Muris & Meesters, 2009).

3.2.3.2. d2 Attention Test

The d2 Test of Attention is a standardized paper-and-pencil test for attention, which involves cancelling out all target letters (i.e., the letter “d” with two dashes positioned above or below) interspersed with nontarget letters i.e., the letter “d” without two dashes and the letter “p” with any quantifiable dashes (Bates & Lemay, 2004). The concentration performance index obtained by subtracting the sum of correct responses from the sum of

commission errors was adopted as the primary measure (José, Elena, & María, 2014). The task takes 4.7 min to complete.

3.2.3.3. Cambridge Neuropsychological Test Automated Battery (CANTAB)

Three subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered via a 10.5-inch Apple iPad. The reaction time (RTI) task assesses attention in terms of processing speed (motor and mental) and impulsivity. The task involves holding the response button at the bottom of the screen initially, and as one of the five circles positioned at the top of the screen flashes yellow, participants are required to tap the highlighted circle (target button) as quickly as possible. The mean reaction times (i.e., mean duration of releasing the response button after stimulus presentation) of five-choice variants were calculated (Syvaoja et al., 2015).

The multitasking test (MTT) measured selective attention (responding to task-relevant stimuli) and inhibition (ignoring task-irrelevant stimuli). In each trial, a leftward- or rightward-facing arrow was presented on either the right or left side of the screen. Meanwhile, a cue is presented at the top of the screen, specifying the arrow's direction or location. Participants must press the right or left button at the bottom of the screen, in accordance with the arrow's location or direction, depending on the task cue. The switching block error, denoting the sum of incorrect responses during the block with intermixing task cues, i.e., the mean duration of stimuli appearance to pressing the button between congruent to incongruent stimuli and vice versa, was adopted as a prime measure in this study. The task included 40 practice and 120 test trials, lasting 8 min (Wild & Musser, 2014).

The emotion recognition task (ERT) evaluates the ability to distinguish basic facial expressions. The test requires participants to label photographs of male or female facial expressions presented for 200 ms each using one of six labels (i.e., sadness, happiness, fear, anger, disgust, and surprise) shown on the screen. There is no time limit for responding. The

total number of correct responses was adopted as the primary measure. This task included 5 practice and 90 test trials, lasting 9 min.

3.2.3.4. *n*-back Task

An *n*-back paradigm adopted from previous studies was employed as the activation task to probe PFC functioning (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008; Yeung et al., 2016). It involved two loading conditions (low and high; 0- and 1-back). Trials were presented in 45 s blocks, interleaved with 30 s of rest, for a total duration of 330 s. Each condition was presented twice, and the two conditions were administered in alternating order (i.e., low–high–low–high; or high–low–high–low). The order was counterbalanced across participants to eliminate order effects. Each task block started with 5 s of a visual cue for a condition, followed by 20 (5 target and 15 nontarget) trials presented pseudorandomly. Each trial included a digit that appeared at the center of the screen for 500 ms, followed by an interstimulus interval of 1500 ms (Figure 3.1). The low-loading (0-back) condition required participants to left click the mouse with their right index finger when the number "0" (target) was shown but to right click the mouse with their right middle finger when other numbers (nontargets) were shown. The high-loading (1-back) condition required participants to left-click the mouse when the number that appeared was the same as the number shown one trial before (i.e., target) but to right-click the mouse for other numbers (i.e., nontargets). E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA) was utilized to present all stimuli. During task performance, frontal brain activities were captured using a fNIRS machine.

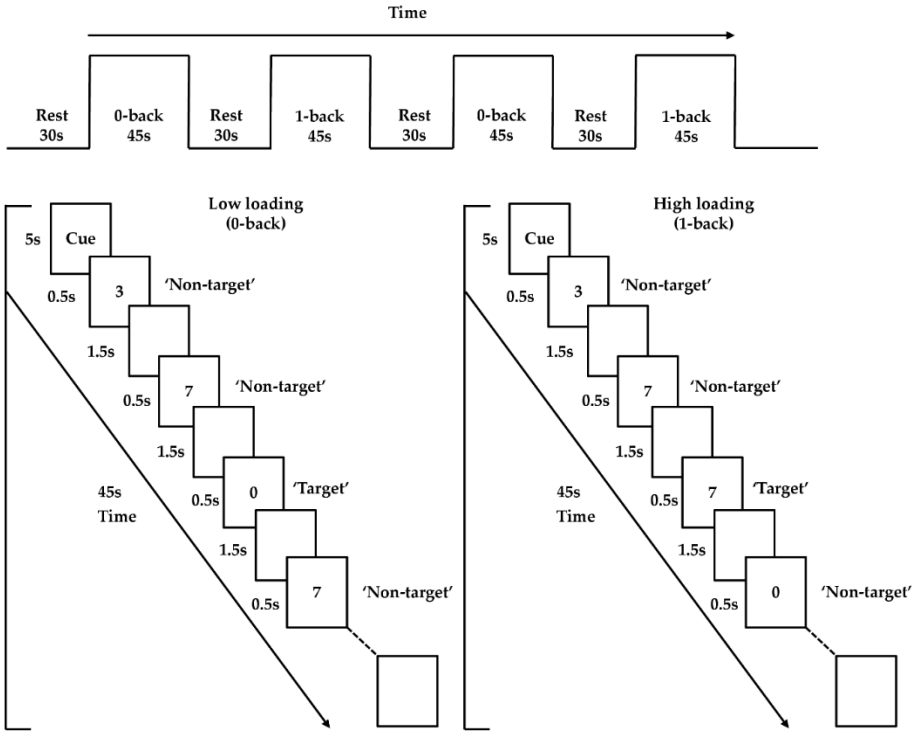
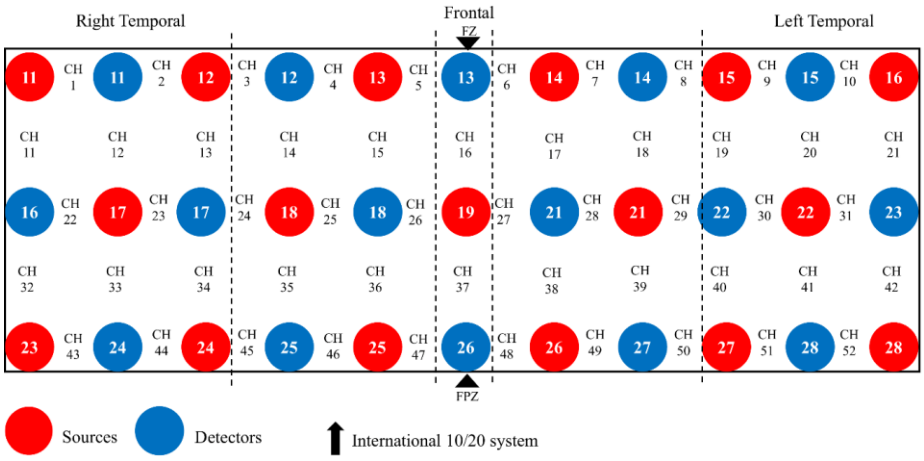


Figure 3.1. *n*-back task paradigm.

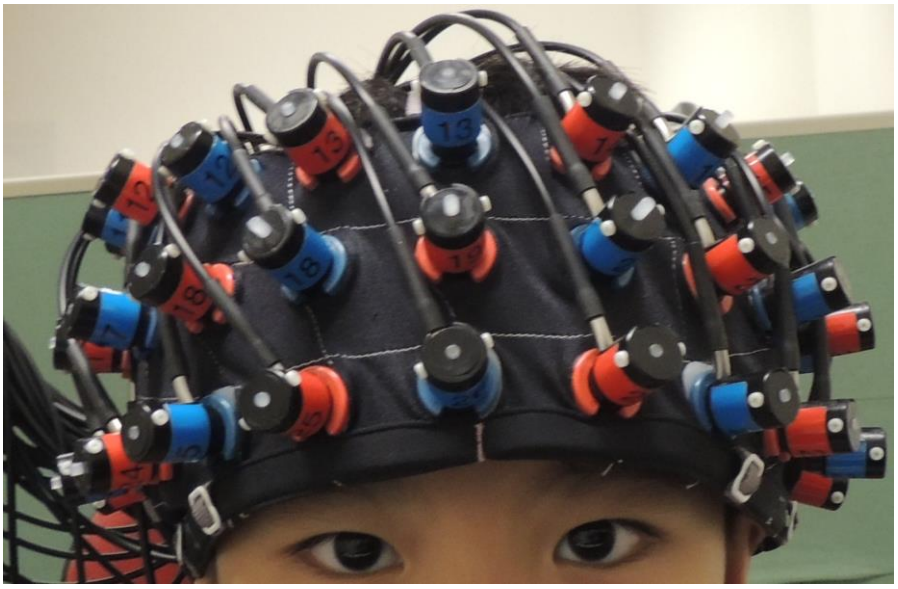
3.2.4. fNIRS recording

During the *n*-back task, fNIRS data acquisition was performed using the Hitachi ETG-4000 machine, which used two wavelengths (695 nm and 830 nm) and sampled data at a rate of 10 Hz. The machine included 33 optodes, including 17 sources and 16 detectors (52 channels), aligned in a 3 × 11 montage with a 3 cm source-detector separation (Figure 3.2). During recording, participants sat on a chair 60 cm away from a 15′’ LCD monitor in a quiet dimly lit room. Participants’ head dimensions (nasion-inion, left-right ear, and head circumference) were measured to facilitate offline spatial registration of NIRS channels (Singh, Okamoto, Dan, Jurcak, & Dan, 2005), in which the channel positions were transformed into the Montreal Neurological Institute (MNI) space and then projected onto the surface of a volume-rendered children brain template (Sanchez, Richards, & Almli, 2012; Xie et al., 2015). The probe placement regions (forehead) were disinfected with an alcohol pad for better signal quality. A custom-built headband mounted with probes was then placed on the participant’s forehead (covering the PFC). As guided by the standardized reference point

on the headband, the center of the bottom optode was anchored at Fpz according to the international 10–20 system. The spatial coordinates of 5 anatomical landmark points (nasion, inion, vertex, and left and right auricular points) and 33 optodes were digitized using a 3D digitizer. Based on the calibration procedure implemented in the acquisition software, good signal quality was ensured before the *n*-back task began.



(**a**)



(**b**)

Figure 3.2. The 3 × 11 montage of the functional near-infrared spectroscopy (fNIRS) system: (**a**) 33 optodes and 52 channels (CH) arrangement; (**b**) placement on head.

3.2.5. Data Analysis

Before analyzing the data, normality was checked through Shapiro–Wilk tests. Subsequently, any nonnormal data were log-transformed for suitability for parametric testing. If the log-transformed variables still violated the normality assumption, then nonparametric tests were conducted. The data screening and analysis were performed using IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA).

3.2.5.1. Questionnaires and neuropsychological measures

The SRS-2 total *T*-score, EATQ-R total score, and other behavioral measures fulfilled the normality assumption. Thus, independent-sample *t* tests were used for group comparisons. However, the behavioral measures of the *n*-back task did not meet the normality assumption even after log transformation. Hence, Mann–Whitney U tests were used to explore the group differences for these variables.

3.2.5.2. Preprocessing for fNIRS Data

Data preprocessing and analysis were performed using the AnalyzIR Toolbox (Santosa, Zhai, Fishburn, & Huppert, 2018) and MATLAB 2019a (The Mathworks, Natick, MA, USA). First, the raw fNIRS data of the *n*-back task were derived in integral mode after preprocessing with a 0.1 Hz low-pass and a 5 s moving average filter using the inbuilt Hitachi machine software. The data were then input into the AnalyzIR Toolbox, in which the data were corrected for missing, flat, or saturated channel issues using default functions. Next, the signals were resampled at 1 Hz, and a 0.1 partial pathlength factor was applied while converting optical density changes into HbO and HbR via the modified Beer–Lambert law (Delpy et al., 1988). Subsequently, first-level statistical analysis was conducted using the autoregressive iterative reweighted least-squares (AR-IRLS) approach to estimate activation during task performance (Barker, Aarabi, & Huppert, 2013). The robust autoregressive

whitened correlation method in the advanced general linear model was also used to estimate connectivity between possible channel pairs. The activation (beta value) and connectivity (*Z* score) variables were then utilized for group analysis (second-level analysis). We focused on HbO because, relative to HbR, it has been shown to have a higher signal-to-noise ratio and to correlate more strongly with the blood oxygenation level-dependent (BOLD) signals measured by fMRI (Cui et al., 2011).

Spatial registration of channels based on the digitized spatial coordinates (5 reference points and 33 optodes) was performed using near infrared spectroscopy-statistical parameter mapping (NIRS-SPM; Ye, Tak, Jang, Jung, & Jang, 2009). The output of individual MNI coordinates was further grouped together using BrainNet Viewer (Xia, Wang, & He, 2013), and the mean composite estimation was obtained. Using an 80% registration probability, channels that fell in the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and superior frontal gyrus (SFG) on each side were determined, and the 6 anatomically defined PFC regions were defined as regions of interest (ROIs; Figure 3; Zhu et al., 2017). Note that some PFC channels were not classified into any ROI because none of them fell into any ROI with an 80% registration probability and that temporal lobe channels were not analyzed because most of them yielded poor signal quality due to poor optode–scalp contact. The detailed explanation for deriving a subject-wise ROI connectivity patterns with their MATLAB scripts provided in the Appendices supplementary 2 and 3.

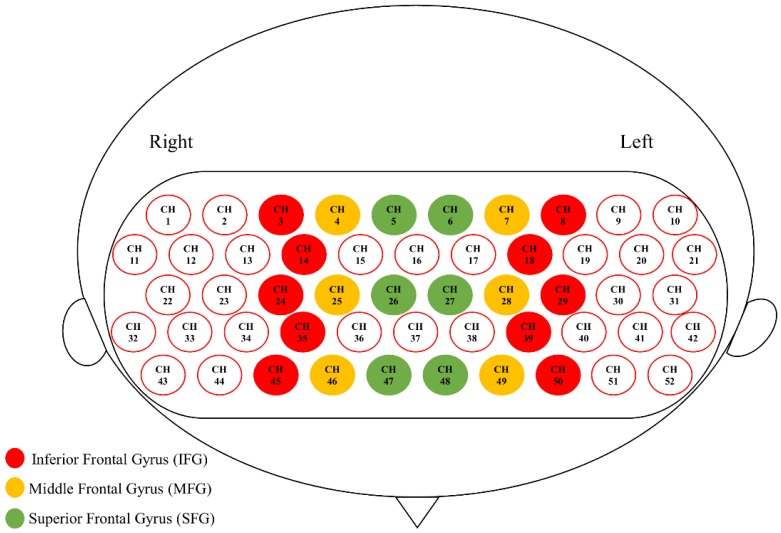


Figure 3.3. Six anatomically defined ROIs in the prefrontal cortex (PFC).

3.2.5.3. fNIRS Data Analysis

For activation, the beta values fulfilled the normality assumption. Hence, a 2 × 2 × 2 mixed multifactorial analysis of variance (ANOVA) was utilized to analyze changes in HbO in terms of beta values. The statistical model included two within-group factors, loading (low and high) and frontal side (left and right), and one between-group factor (TD and ASD).

For connectivity, 6 connectivity patterns were extracted based on the specified ROIs (Figure 3.4; Zhu et al., 2017). Channel pairs were averaged for each connectivity pattern. All connectivity variables (i.e., mean *Z* scores) fulfilled the normality assumption; hence, intrahemispheric connectivity was analyzed with a 2 × 2 × 2 × 2 mixed ANOVA, which included connectivity pattern (within and between ROI), loading (low and high), and frontal side (left and right) as within-subjects factors and group (TD and ASD) as the between-subjects factor. Additionally, interhemispheric connectivity was analyzed with a 2 × 2 × 2 mixed ANOVA, which included connectivity pattern (within and between ROI) and loading (low and high) as within-subjects factors and group (TD and ASD) as the between-subjects factor.

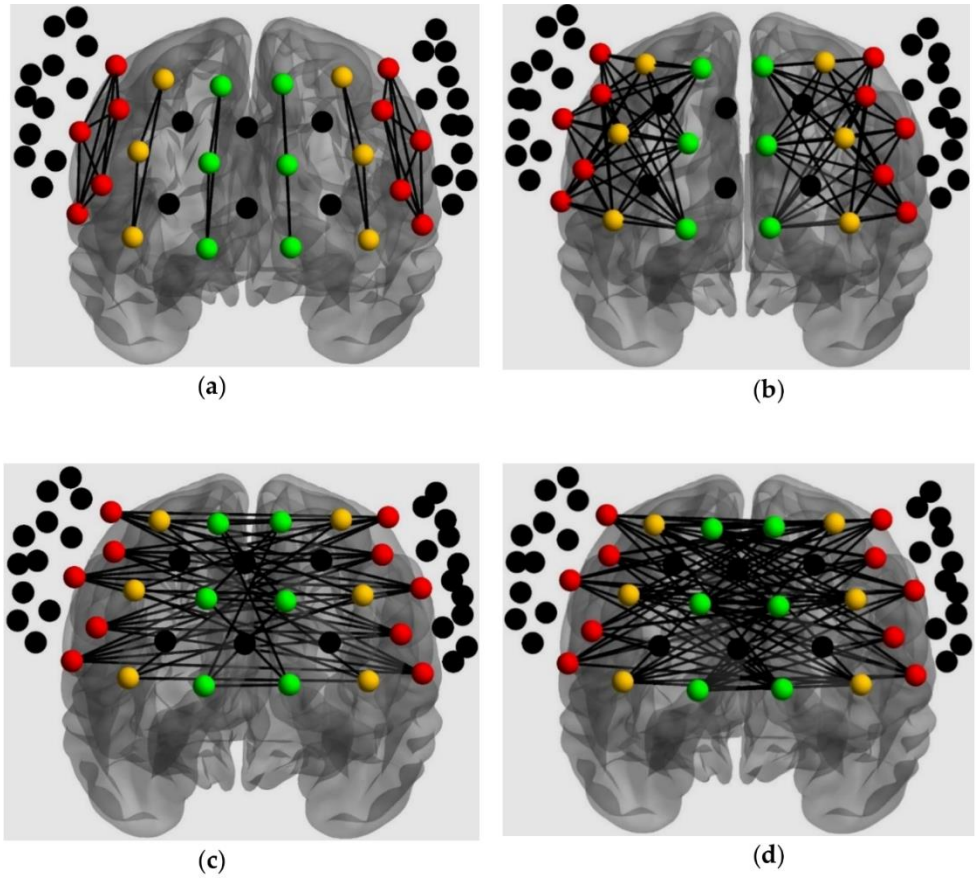


Figure 3.4. ROIs analysis for connectivity: (**a**) Intrahemispheric connectivity within ROI; (**b**) Intrahemispheric connectivity between ROIs; (**c**) Interhemispheric connectivity within ROIs; (**d**) Interhemispheric connectivity between ROIs.

3.2.5.4. Brain–Behavior Relationship

To explain individual differences in EC among children with ASD, we specifically examined the relationship between measures of EC and measures of PFC functioning and EC-related constructs (i.e., EF and socioemotional measures) for the ASD group. Variables that met and did not meet the normality assumption were analyzed using Pearson's correlations (r) and Spearman's correlation (r_s), respectively. To reduce the number of comparisons, only variables in which the two groups differed significantly were analyzed.

3.3. Results

3.3.1. Demographic, Intellectual, and Clinical Characteristics

Table 3.1 shows the demographic, intellectual, and clinical information of the TD and ASD groups. The two groups were matched for age and IQ, *t*s < 0.42, *p*s > 0.11. Although gender was not matched between groups, $\chi^2(1) = 6.65$, $p = 0.01$, independent-sample *t* tests revealed no significant differences between male and female TD children in any variable (*p*s > 0.05). As gender was not a confounding factor, it was not controlled for in any subsequent analyses.

Table 3.1. Demographic, intellectual, and clinical characteristics of the TD and ASD groups.

	TD (*n* = *19)*	**ASD (*n* = 20)**		
	Mean (*SD*)	**Mean (*SD*)**	***t*/χ^2/*r***	***p***
Age (years)	10.28 (0.67)	10.16 (1.04)	0.42	0.68
IQ	108.79 (9.47)	101.65 (16.96)	1.63	0.11
Gender (Males:Females) [#]	12:07	20:00	6.65	0.010**
ADI-R Social Interaction [##]	-	14.20 (7.41)	0.052	0.83
ADI-R Communication [##]	-	10.75 (5.70)	−0.32	0.18
ADI-R Restricted and Stereotyped Behavior [##]	-	5.35 (2.70)	−0.30	0.21

Note: *SD*: Standard deviation; ADI-R: Autism Diagnostic Interview—Revised; [#] Groups were compared using the chi-squared test with Yates' correction of the likelihood ratio; [##] Correlation with Early Adolescent Temperament Questionnaire—Revised (EATQ-R) (total score). ** $p < 0.01$.

3.3.2. EC, executive, and socioemotional measures

The two groups differed significantly in all EC, executive, and socioemotional measures (Table 3.2), in which the ASD group showed more deficits than TD controls with a large effect size on the EATQ-R total score, t (36) = 2.83, $p = 0.007$, the concentration performance index on the d2 Test of Attention, t (37) = 2.69, $p = 0.011$, the mean score on

the CANTAB reaction time, t (36) = 2.67, p = 0.011, the switch block error score on the CANTAB multitasking test, t (30.37) = 2.46, p = 0.019, the total score on the CANTAB emotion recognition task, t (35) = 3.48, p = 0.001, and the SRS-2 total T-score, t (35) = 6.22, p < 0.001. As the EATQ-R consisted of three discrete constructs, we performed independent-sample t tests to compare the groups on each subscale after adjusting the p value threshold to 0.017. The results showed that the ASD group had more deficits on the attention, t (36) = 2.79, p = 0.008, and inhibitory control subscales, t (36) = 3.05, p = 0.005, but not on the activation control subscale, t (36) = 1.39, p = 0.17, than the TD group.

Table 3.2. Effortful control, executive and socioemotional functions in the TD and ASD groups.

Variables	TD (*n* = 19)	ASD (*n* = 20)			
	Mean (*SD*)	Mean (*SD*)	*t*	*p*	*d*
EATQ-R [#]					
Total	3.18 (0.50)	2.67 (0.61)	2.83	0.007 **	0.91
Attention	3.16 (0.68)	2.54 (0.67)	2.79	0.008 **	0.92
Inhibitory control	3.42 (0.48)	2.79 (0.76)	3.05	0.005 **	0.99
Activation control	2.97 (0.57)	2.68 (0.69)	1.39	0.17	0.46
D_2 Test of Attention					
Concentration performance index	141.2 (20.2)	121.5 (25.0)	2.69	0.011*	0.86
CANTAB Reaction Time Task [#]					
Mean reaction time (ms)	421.8 (51.2)	468.0 (117.3)	2.67	0.011 *	0.51
CANTAB Multitasking Test [#]					
Switch block error	7.28 (4.39)	12.45 (7.86)	2.46	0.019 *	0.81
CANTAB Emotion Recognition Task [#]					
Total hit rate	23.72 (3.89)	19.00 (4.33)	3.48	0.001 **	1.15
SRS-2 [#]					
Total *T*-score	40.3 (17.4)	87.4 (26.8)	6.22	<0.001 ***	2.09

Note: SRS-2: Social Responsiveness Scale—Second Edition; * p < 0.05; ** p < 0.01; *** p < 0.001; [#] Missing data: The EATQ-R was incomplete for 1 child with ASD; The Cambridge Neuropsychological Test Automated Battery (CANTAB) was not administered to 1 TD child; 1 ASD child did not complete the Emotion Recognition Task; The SRS-2 was incomplete in 2 TD children.

Additionally, children with ASD were slower to respond than TD controls in the low loading condition of the *n*-back task (U = 78.00, p = 0.001; Table 3.3), despite comparable accuracy, p = 0.79. There was no significant difference in accuracy or mean reaction time between the two groups in the high loading condition, ps > 0.074. However, we noted a significant large correlation between accuracy and mean reaction time in the high loading condition among children with ASD (r = −0.58, p < 0.01), suggesting a speed–accuracy tradeoff. To control for this, the inverse efficiency score (IES) was calculated by dividing the mean reaction time by the accuracy for each condition (James Townsend & Ashby, 1978, 1983). The IES score was also calculated for the low loading condition to facilitate comparison between conditions. The results indicated that the ASD group had significantly poorer performance in terms of the IES than the TD group in both loading conditions.

Table 3.3. *n*-back task performance in the TD and ASD groups.

Variables	TD (*n* = 19)	ASD (*n* = 20)			
	Median (95% CI)	Median (95% CI)	*Z*	*p*	*r*
Mean reaction time (ms)					
Low load	445.1 (423.8–538.7)	502.1 (517.1–687.1)	3.15	0.001 **	0.50
High load	536.0 (505.0–644.4)	636.3 (603.9–811.6)	1.80	0.074	0.29
Accuracy					
Low load	0.97 (0.93–0.97)	0.95 (0.92–0.97)	0.27	0.79	0.043
High load	0.94 (0.87–0.95)	0.89 (0.83–0.93)	0.64	0.53	0.10
Inverse efficiency score					
Low load	496.1 (494.7–518.4)	633.8 (621.2–653.9)	5.36	<0.001 ***	0.86
High load	611.3 (608.8–664.8)	794.8 (761.2–875.0)	4.72	<0.001 ***	0.76

Note: ** p < 0.01; *** p < 0.001

3.3.3. PFC Activation During the N-Back Task

The 2 × 2 × 2 (group × frontal side × condition) mixed ANOVA showed a significant main effect of group, $F(1,36)$ = 4.12, p = 0.050, η_p^2 = 0.10, in which the ASD group exhibited

more PFC activation (M = 0.071, SE = 0.018) than the TD group (M = 0.019, SE = 0.018). No other effects were significant (ps > 0.05).

3.3.4. PFC Connectivity during the n-Back Task

3.3.4.1. Intrahemispheric Connectivity

The results of the 2 × 2 × 2 × 2 (group × connectivity pattern × loading × frontal side) mixed ANOVA conducted for intrahemispheric connectivity (i.e., mean Z scores) are presented in Table 3.4. ANOVA demonstrated significant main effects of connectivity pattern, $p < 0.001$, loading, $p = 0.041$, and frontal side, $p = 0.037$. Whereas the main effect of group was not significant, $p = 0.26$, there was a significant interaction between frontal side and group, $p = 0.005$. Independent-sample t tests showed a significant group difference in right intrahemispheric connectivity, $t(35) = 2.55$, $p = 0.015$, in which the TD group exhibited greater right frontal connectivity (M = 0.22, SD = 0.083) than the ASD group (M = 0.15, SD = 0.088). There was no significant group difference in left intrahemispheric connectivity, p = 0.38.

There was also a significant three-way interaction between connectivity pattern, loading, and group, $p = 0.024$. Follow-up independent-sample t tests, exploring differences between the TD and ASD groups in within- and between-ROI connectivity in the two loading conditions, separately showed a significant difference between the two groups on between-ROI connectivity in the high-loading condition, $t(35) = 2.17$, $p = 0.037$, in which the TD group exhibited greater frontal connectivity (M = 0.24, SD = 0.037) than the ASD group (M = 0.19, SD = 0.082). The two groups did not differ significantly in between-ROI connectivity in the low-load condition or in within-ROI connectivity in either load condition (ps > 0.05).

Table 3.4. Mixed ANOVA (group × loading × frontal side × connectivity pattern) results for intrahemispheric connectivity (i.e., mean Z scores).

Main/Interaction Effects	Mean (*SE*)	*F*(1,35)	*p*	η_p^2
Connectivity pattern (within and between ROI)	Within: 0.18 (0.011) Between: 0.22 (0.012)	48.28	<0.001 ***	0.58
Loading (low and high)	Low: 0.21 (0.013) High: 0.19 (0.010)	4.50	0.041 *	0.11
Frontal side (left and right)	Right: 0.18 (0.014) Left: 0.22 (0.013)	4.68	0.037 *	0.12
Group (TD and ASD)	TD: 0.21 (0.015) ASD: 0.19 (0.015)	1.29	0.26	0.036
Two-way interaction				
Connectivity pattern × loading		3.09	0.088	0.081
Connectivity pattern × frontal side		0.037	0.85	0.001
Loading × frontal side		2.42	0.13	0.065
Loading × group		0.61	0.44	0.017
Connectivity pattern × group		0.23	0.63	0.007
Frontal side × group		8.98	0.005 **	0.20
Three-way interaction				
Connectivity pattern × loading × frontal side		5.71	0.022 *	0.14
Connectivity pattern × loading × group		5.61	0.024 *	0.14
Connectivity pattern × frontal side × group		0.010	0.92	0.000
Loading × frontal side × group		2.99	0.092	0.079
Four-way interaction				
Connectivity pattern × frontal side × loading × group		0.006	0.94	0.000

Note: *SE: Standard error;* * $p < 0.05$; * *$p < 0.01$; *** $p < 0.001$.

3.3.4.2. Interhemispheric Connectivity

The results of the 2 × 2 × 2 (groups × connectivity pattern × loading) mixed ANOVA conducted for interhemispheric connectivity (i.e., mean *Z* scores) are presented in Table 3.5. The ANOVA demonstrated significant main effects of connectivity pattern, $p = 0.003$, and loading, $p = 0.026$. The main effect of group was not significant, $p = 0.15$, but there was a significant interaction effect between connectivity pattern and group, $p = 0.043$. Nevertheless, independent-sample *t* tests revealed no significant difference in either within- or between-ROI connectivity between the two groups (*p*s > 0.05). This interaction effect was driven by the presence of higher between-ROI than within-ROI connectivity in the TD group but not in the ASD group.

Table 3.5. Mixed ANOVA (group × loading × connectivity pattern) results for interhemispheric connectivity (i.e., mean Z scores).

Main/Interaction Effects	**Mean (*SE*)**	***F*(1,34)**	***p***	η_p^2
Connectivity pattern (within and between ROI)	Within ROI: 0.19 (0.014) Between ROI: 0.20 (0.013)	10.06	0.003 **	0.23
Loading (low and high)	Low: 0.21 (0.015) High: 0.18 (0.014)	5.43	0.026 *	0.14
Group (TD and ASD)	TD: 0.21 (0.019) ASD: 0.17 (0.018)	2.14	0.15	0.059
Two-way interaction				
Connectivity pattern × loading		0.75	0.39	0.021
Loading × group		1.44	0.24	0.041
Connectivity pattern × group		4.41	0.043 *	0.12
Three-way interaction				
Connectivity pattern × loading × group		0.14	0.71	0.004

Note: * $p < 0.05$; ** $p < 0.01$.

3.3.5. Individual Differences in EC in the ASD Group

We conducted correlation analyses to elucidate the basis of individual differences in EC among children with ASD. These children were found to have poorer performance in all EF and socioemotional measures, increased PFC activation across regions and conditions, and reduced right intrahemispheric connectivity across connection patterns and conditions compared to TD children. Thus, we examined the correlation between the EATQ-R total score and each EF and socioemotional measure, overall PFC activation, and overall right intrahemispheric connectivity. The EATQ-R total score correlated significantly with the SRS-2 total *T*-score only, $r = -0.69$, $p = 0.001$. No other correlations were significant, ps > 0.05.

3.4. Discussion

The primary objective of this study was to elucidate the relationship between EC and PFC functioning in terms of activation and connectivity during a frontal-sensitive (*n*-back) task in children with ASD. We found that the ASD group demonstrated significantly lower levels of EC and its relevant EF and socioemotional measures than TD controls. Children with ASD also exhibited altered PFC functioning, indicated by PFC hyperactivation and reduced right frontal connectivity across *n*-back conditions. We further showed that EC was associated with social skills but not with PFC processing or EF in the ASD group, suggesting that individual differences in EC among children with ASD may be explained by individual differences in social functioning only.

The current findings support our hypotheses. First, the children with ASD presented with more EC deficits than the TD group, such that the EATQ-R differentiated the two groups of children on the attentional and inhibitory control components. This result is consistent with

previous findings, in which the parents of adolescents with ASD perceived lower attentional and inhibitory control abilities over a dominating response (Adamek et al., 2011; Konstantareas & Stewart, 2006; Samyn et al., 2011). However, in contrast to Samyn et al. (2011) report of an activation control deficit in ASD, the current finding showed a comparable effect of ASD on activation control, suggesting that the children from the TD and ASD groups had a similar ability to generate and persist with a novel action even when there is an urgency to terminate. The inconsistency may be due to age differences, as they (Samyn et al., 2011) focused on adolescents with ASD, and activation control deficits may become more pronounced with age due to underdevelopment in ASD.

Our fNIRS findings of reduced right PFC connectivity during the *n*-back task in the ASD group corroborate the "frontal disconnection syndrome" theory of autism, which postulates that frontal disconnection negatively influences the performance of higher-order cognitive tasks (Geschwind & Levitt, 2007; Zeestraten et al., 2017). Our findings specifically support the underconnectivity theory of ASD, which bridges the neurophysiological basis of complex information processing impairment to its associated frontal lobe dysfunction in individuals with autism (Frith, 2004; Just, Keller, Malave, Kana, & Varma, 2012). The *n*-back task used in our study required participants to monitor and hold onto a piece of information briefly, in accordance with specific loading conditions. It also requires participants to respond to interchanging stimuli involving activating, inhibiting, and switching elements, which necessitates a complex information processing system found to be defective in ASD (Minshew, Goldstein, & Siegel, 1997). As the right lateral frontal lobe has been shown to play an essential role in monitoring (Stuss & Alexander, 2007), hypoconnectivity in the right frontal lobe revealed that children with ASD had difficulty monitoring and processing complex information.

Our findings of a link between EC deficits and social impairment in ASD corroborate the hypothesized role of EC in social affect, empathy, and prosocial behavior, which together assist children in gaining adaptive function (Faja & Dawson, 2015; Schwartz et al., 2009). However, the present study did not yield significant relationships between EC and task measures of other related constructs (i.e., EF tests, ERT, and *n*-back behavioral measures) or between EC and PFC activation or connectivity. These findings suggest that EC may be a different construct from EF. In addition, questionnaires and behavioral measures may tap distinct response processes. That is, questionnaires include items on real-life behavior that require individuals to respond using subjective perception or judgment in an open-ended environment and under noncompetitive circumstances, whereas the behavioral measures require individuals to respond on the basis of task performance in a structured setting and under competitive circumstances (Hedge, Powell, & Sumner, 2018).

Notably, the absence of significant correlations between questionnaires and behavioral measures may be due to the methodological constraints of behavioral measures, which have poor reliability in general (Dang, King, & Inzlicht, 2020). However, the test–retest reliability of the parent-report and behavioral measures used in the present study has been shown to be at least moderate-to-high and comparable with each other (e.g., CANTAB RTI five-choice reaction time in children: $r = 0.63$ (Syvaoja et al., 2015); d2 Concentration Performance in adolescents: $r = 0.74$ (Brickenkamp & Rump, 1966); EATQ-R score in Chinese adolescents: *r*s from 0.62 to 0.72 (Zhang, Shen, Gao, & Yan, 2008); SRS-2 total score in TD and ASD children/adolescents: *r*s from 0.72 to 0.95 (Bolte, Poustka, & Constantino, 2008). Thus, poor reliability of behavioral measures is not a plausible explanation for the lack of correlations.

Although we found EC deficits and altered PFC functioning in the ASD group, there was a lack of a monolithic relationship between the two, suggesting that individual differences in EC deficits cannot be explained by the degree of overall PFC activation or right frontal

underconnectivity among children with ASD. Temperamental EC refers to the ability to inhibit a dominant response to perform a subdominant response in emotionally salient settings (Rothbart & Bates, 2006). In addition, emotion perception and behavior have been shown to heavily engage the amygdala and anterior cingulate cortex, as well as their interactions with the medial frontal cortex (Etkin, Egner, & Kalisch, 2011; Phelps & LeDoux, 2005). It has long been known that these regions exhibit structural and functional abnormalities in ASD (Baron-Cohen et al., 2000). Thus, it is possible that the EC deficits in ASD are better explained by disturbances in these brain regions and circuits, which remains to be determined.

This study is one of the first to explore EC and its relationship with brain theories and EF in children with ASD. The findings yield valuable evidence that EC deficits and altered PFC functioning are present in these children, but there is no evidence that individual differences in EC can be explained by the extent of altered PFC functioning among children with ASD. In addition, the current study demonstrates temperamental EC deficit and its strong link with social dysfunction in children with ASD, suggesting that EC intervention may be clinically useful to improve real-world social skills in these children. Furthermore, this study generates support for the application of fNIRS to understand ASD (Zhang & Roeyers, 2019) and as a cost-effective and user-friendly tool to probe the functional coupling of cortical (but not subcortical) regions during cognitive tasks.

The study has several limitations. First, the small sample size and inclusion of only boys with high-functioning ASD means that the findings may not be generalized to girls with ASD, low-functioning ASD, or other age groups. Nevertheless, we found that sex was not a confounding factor in any variables among TD children. Second, EC was measured using a parent-report questionnaire alone, and the possibility of parental bias that affects the estimation of the true EC status cannot be ruled out. Third, the *n*-back task had limited

difficulty levels in terms of working memory loading and interference (Szmalec, Verbruggen, Vandierendonck, & Kemps, 2011), which is necessary to make it understandable to most, if not all, children. Thus, this task may lack optimal sensitivity to assess the level of PFC functioning to be correlated with the EC measure.

3.5. Conclusions

This study showed general deficits in EC and its related constructs (i.e., executive and socioemotional function), as well as altered PFC functioning in children with ASD. It also expands on the previous knowledge of PFC processing during working memory processing among these children and adds converging support for the model of frontal disconnection syndrome and information processing disorder as a neuropathological biomarker of ASD. The relationship between the EC deficit and social dysfunction observed in children with ASD implies that EC may be central to enhancing the social functioning of these children. The lack of a significant monolithic relationship between EC and PFC activation/connectivity among children with ASD warrants further research with the inclusion of a larger sample size and individuals with diverse autistic symptoms, examining the contribution of dysfunction in non-PFC (e.g., limbic) regions or circuits to EC deficits in ASD.

CHAPTER 4: STUDY THREE

Effortful Control and Prefrontal Cortex Functioning in Adolescents and Adults with Autism Spectrum Disorder – An fNIRS Study

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Article

Abnormal Prefrontal Functional Connectivity Is Associated with Inflexible Information Processing in Patients with Autism Spectrum Disorder (ASD): An fNIRS Study

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4.1. Introduction

Chapter 3 of this thesis examined the statistical correlation between EC and prefrontal functioning in children with high-functioning ASD. The findings revealed that children with ASD significantly differed from healthy controls in EC and its associated constructs, including executive and socioemotional abilities. The study also demonstrated significantly increased PFC activation and decreased right frontal synchronization in autism while performing the n-back task. However, there was no significant correlation between EC deficits and altered PFC functioning, explaining why the frontal sensitive n-back task used in this study was sensitive to measuring working memory and might not tap into the EC subcomponents, including attention control, inhibitory control, and cognitive flexibility. Therefore, the frontal-sensitive task, which measures an underlying EC subcomponent, is recommended to examine the causal link between EC and PFC functioning. Similarly, such a relationship was attempted to demonstrate in children, and it is poorly studied in adolescents and adults with autism, which results in incomplete understanding of behavioral issues, adaptability, and socioemotional compatibility.

In the evolutionary context, the adolescence phase is linked to taking risks, heightening creativity, and exhibiting impulsive behavior, which necessitate acquiring motivation and impudence to explore new possibilities for establishing independent living skills (Spear, 2004). Successful adolescence lies in shaping or altering earlier temperamental tendencies, thereby laying a foundation for meeting specific cultural expectations and demands in adulthood. With this notion, EC function in adolescence is viewed as a modulator of behavioral specificity and complexity that facilitates adaptive functioning and socializing oneself within given cultural expectations (Perez-Edgar, 2015). Continuation of development and optimal EC functioning relates to better socioemotional functioning and educational attainment, including interpersonal warmth and externalizing behavior, resilience to stress,

academic competence, and protection against problematic behavior in adolescents and adulthood (Cain, Meehan, Roche, Clarkin, & De Panfilis, 2019; Ruof, Elam, & Chassin, 2020; Véronneau, Racer, Fosco, & Dishion, 2014). Conversely, defective EC in adolescents and young adults results in behavioral problems at school, including poor conduct, skip classes, early sexual activities, and school dropouts (Atherton, Zheng, Bleidorn, & Robins, 2019). Similar to EC functioning in a healthy population, Uljarević et al. (2017) asserted that the EC deficit in adolescents and adults with autism was associated with the persistence of rigid, repetitive, stereotypic behavioral patterns and anxiety. Likewise, Schwartz et al. (2009) demonstrated that adaptive functioning in socioemotional outcomes was influenced by temperament in adolescents with high-functioning autism. However, such deficits and their relatedness to PFC functioning remain undisclosed in adolescents and adults with ASD.

The prefrontal cortex (PFC) controls top-down behavior; notably, it regulates task sets that require switching between two competing stimuli in accordance with stimulus choice or perceptual-stimulus relationships (Sakai, 2008). Additionally, meta-analyses on neurotypical adults during cognitive flexibility tasks showed that the PFC synchronized with neighboring brain regions such as the ACC, premotor cortex, superior and inferior parietal cortices, inferior temporal cortex, caudate and thalamus while updating task guidelines or directions, resolving interferences, integrating visuomotor components and executing visual attentional processes (Kim et al., 2012; Niendam et al., 2012). From an EC perspective, a functional near-infrared spectroscopy (fNIRS) study found that more efficient dorsolateral prefrontal cortex activation during a cognitive flexibility task was associated with better temperamental EC. Although the study was conducted in healthy children, the finding suggests a causal link between EC and prefrontal cortex activity observed using a cognitive flexibility task (Quinones-Camacho et al., 2019).

Individuals with autism have been found to have atypical brain structures and functions, including the PFC (Courchesne & Pierce, 2005; Ecker et al., 2015; Philip et al., 2012). Extensive functional magnetic resonance imaging (fMRI) studies revealed abnormal prefrontal and parietal cortex activation in autism compared with neurotypical controls during numerous executive function (EF) tasks (Philip et al., 2012; Zhang et al., 2020). Specifically, adults with autism demonstrated hypoactivation in the frontal cortex and striatum during reversal learning tasks that measured behavioral flexibility (D'Cruz, Mosconi, Ragozzino, Cook, & Sweeney, 2016). Similarly, young adults with autism deactivated frontal, parietal, and striatal regions during set-shifting tasks, and such hypoactivation was negatively correlated with activation of the anterior cingulate and posterior parietal cortices along with autistic symptom severity, suggesting that decreased activation of the frontal cortex elicits poorer networks among adjacent brain regions (Shafritz, Dichter, Baranek, & Belger, 2008). Nevertheless, evidence supports frontal lobe abnormalities in terms of activation or synchronization in autism, and the interdependency between EC and PFC functions in adolescents and adults with ASD remains elusive.

Traditionally, the Wisconsin Card Sorting Test (WCST), which mandates individuals to categorize cards sequentially into four piles based on mastering rules from experience, has been utilized as a measure of cognitive flexibility, particularly in the autism context (Ozonoff, 1995; Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). A substantial proportion of neuroimaging studies also supported that the WCST probed prefrontal cortex function, especially task-induced activations that were much observed in the DLPFC during set-shifting and ACC while detecting errors (Lie, Specht, Marshall, & Fink, 2006; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). Notably, fractionation of neural processes underlying WCST in healthy adults revealed left prefrontal activation when card sorting instruction was provided prior to each trial; right prefrontal cortex activation while card

sorting instruction was given at the time of changing trials; and right prefrontal with frontoparietal network activations when no instruction about the sorting dimension was provided (Lie et al., 2006). This finding suggests that involvement of the PFC is more apparent regardless of task complexity in WCST increases; therefore, this study utilized WCST for probing altered PFC functioning and further examined its relatedness with EC performance in adults and adolescents with ASD.

Functional near-infrared spectroscopy (fNIRS) is an optical neuroimaging modality that uses the infrared light spectrum between 700 and 1000 nm to measure changes in oxygenated and deoxygenated hemoglobin concentrations in the cerebral cortex (Boas et al., 2014; Ferrari & Quaresima, 2012). The oxygenated hemoglobin of the fNIRS signal was highly correlated with the blood oxygenation level-dependent (BOLD) fMRI measure during various cognitive tasks (Cui et al., 2011); therefore, it has been used for studying task-related cortical activities in numerous disorders, including individuals with autism (Zhang & Roeyers, 2019). Since fNIRS is a user-friendly and nondemanding neuroimaging instrument, this study utilized it to record PFC functioning in adolescents and adults with ASD. We expected that the ASD group would show significantly reduced EC, EF, and socioemotional functions compared with the healthy control group. We also hypothesized that the ASD group would demonstrate altered PFC functioning in terms of activation and connectivity during the WCST, and such altered PFC functions would be associated with EC deficits.

4.2.Methods

4.2.1. Participants

Participants were recruited via advertisements featured in social media, university campuses, and autism intervention centers in Hong Kong. The inclusion criteria for the experimental group encompassed ASD participants whose diagnosis was confirmed by a

psychiatrist or clinical psychologist using the Diagnostic and Statistical Manual of Mental Disorders–5th Edition (American Psychiatric Association, 2013). In contrast, the inclusion criteria for the healthy control group (HC) comprised participants without autistic features or other neurological disorders. Participants with a history of comorbid conditions, including seizures, head injury, delayed development, and episodes of neuropsychiatric disorders, were excluded from the study. The final sample included 27 right-handed Chinese adolescents and adults (ASD n = 14; Control n = 13) aged between 15 and 22 years who participated in the study with informed consent.

4.2.2. Procedure

The study was undertaken with the proposed guidelines of Helsinki on ethical principles for medical research comprising human subjects. The experimental protocol was endorsed by the Ethics Sub-Committee for Human Subjects at Hong Kong Polytechnic University. All participants were assessed individually in two sessions, i.e., neuropsychological and fNIRS data recording, which extended approximately two hours in total, with a 10-min interval between them. Concurrently, structured interviews were conducted with parents/caregivers of the participants using standardized protocols, including the Adult Temperament Questionnaire (ATQ; for adults), Early Adolescent Temperament Questionnaire-Revised (EATQ-R; for adolescents), Autism Diagnostic Interview-Revised (ADI-R), and Social Responsiveness Scale-Second Edition (SRS-2). Skilled research assistants, graduate students, and a clinical psychologist conducted the assessment and interview sessions.

4.3. Measures

4.3.1. Short Forms of the Early Adolescent Temperament Questionnaire-Revised (EATQ-R) and Adult Temperament Questionnaire (ATQ)

In addition to the short form of the revised EATQ-R, which was described in chapter 3 (section 3.3.1) of this thesis, the EC domain of adults was measured using ATQ short form. It is a standardized self-reported instrument consisting of 19 items categorized under activation control, attention control, and inhibitory control components. The items are rated with a 7-point Likert scale, with a score of 1 constituting "extremely untrue of you" and a score of 7 constituting "extremely true of you" for the direct items and inversely coded for the reversed items. A higher score on each component indicates better control over attention, activation, and inhibition (Evans & Rothbart, 2007). Since both the EATQ-R and ATQ share the same subcomponents, this study combined respective subcomponent scores from these measures as the EC index, and the total score was an average of attention control, inhibitory control, and activation control in the EC index. Therefore, the EC index used in the study denoted EC performance for both adolescents and adults.

4.3.2. d2 Attention Test

It is a standardized paper-and-pencil measure for attention, which requires striking down the letter "d" with two dashes presented above or below while ignoring interspersed letters of "d" without two dashes and the letter "p" with any number of dashes (Bates & Lemay, 2004). The concentration performance was used as the primary metric, which denotes deducting the total correct responses from the total commission errors. The duration of task completion is 4.7 min (José et al., 2014).

4.3.3. Cambridge Neuropsychological Test Automated Battery (CANTAB)

Three standardized tests from the CANTAB were administered using a 10.5-inch Apple iPad. The reaction time (RTI) test evaluates impulsivity and attention by means of

motor and mental processing speed. The task requires participants to tap one of the five circles highlighted in yellow at the top of the screen by releasing the hold of the response button at the bottom. The mean reaction time indicating the average latency of response button release from five-choice variants was estimated (Syvaoja et al., 2015).

The multitasking test (MTT) assesses selective attention and inhibition while responding to task-related and disregarding task-unrelated stimuli, respectively. The task involves presenting the right or left directing arrows located on the right or left side of the screen (cues), and participants were required to respond based on direction or location arrow cues. The switching block error was used as the prime measure indicating the total incorrect response in the block with mixed cues, i.e., the average latency of appearing stimuli to making responses between congruent and incongruent arrows and vice versa. The task encompassed 40 rehearsal and 120 test trials, prolonging 8 min (Wild & Musser, 2014).

The emotion recognition task (ERT) involves labeling images of male and female facial expressions in one of six categories, i.e., sadness, happiness, fear, anger, disgust, and surprise, which appeared for 200 ms each. The measure contained 5 rehearsal and 90 test trials, prolonging 9 min, and the sum of correct responses was used for reporting results. Additionally, six categories of emotions were also investigated separately as a subgroup analysis.

4.3.4. Wisconsin Card Sorting Test (WCST)

The WCST is a validated computerized task that primarily evaluates attentional shifting (cognitive flexibility) and secondarily measures working memory and visual processing functions. During the task, participants are required to match a target card with one of four samples presented with different shapes, colors, and numbers. Each trial offers feedback that demonstrates the participants mastering the rule on sorting through a trial-and-

error strategy. The task includes 30 trials in each category, i.e., numbers, colors, and shapes, and the sorting rule changes in every 10 responses (Grant & Berg, 1948; Teubner-Rhodes, Vaden, Dubno, & Eckert, 2017). The task was publicly made available at https://support.pstnet.com/hc/en-us/articles/360007751894-Wisconsin-Card-Sorting-Test-WCST-30115 and administered via E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA), which records the total number of trials, correct response, and error rates for interpretation. During the task, four stimulus cards in a row at the top and a response card at the bottom of the 15" LCD screen appeared without revealing the trial category. Participants were instructed to press z, x, c, and v letters with their index, middle, ring, and little fingers to indicate color, shape, number, and reference trials, respectively. The task included 90 trials in total without a response time limit. Frontal lobe function was recorded using fNIRS during the WCST.

4.4. fNIRS Data Acquisition

The fNIRS data were recorded during WCST using a Hitachi ETG-4000 machine, which uses dual wavelengths (695 and 830 nm) and works at a sampling rate of 10 Hz. The machine includes 33 optodes with 17 emitters and 16 detectors constituting 52 channels that are distanced at 3 cm and arranged in a 3 x 11 probe set (Figure 3.2 a and b). Data acquisition was taken place in a silent dimly lit room, where participants positioned on a chair approximately 60 cm away from the 15'' LCD monitor. Subsequently, participants' heads were measured across nasion-inion, right-left ear, and head circumference to register channel positions spatially offline, which were further converted into Montreal Neurological Institute (MNI) space and then laid over the volume-rendered adolescent and adult brain templates (Singh et al., 2005). Before placing the customized headband attached to the probe set on the participants' forehead in accordance with the international 10-20 system, the region was

disinfected with an alcohol pad to maximize signal receptance. Next, 3D digitization was performed on 5 anatomical (nasion, inion, right and left auricular, and vertex) and 33 optode sites.

4.5. Data Screening and Analysis

The data screening began with checking parametric test assumptions using Shapiro–Wilk tests for normality. Any nonnormality data were then log-transformed for parametric tests; however, if the transformed data were found to violate normality again, nonparametric tests were eventually adopted. IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) was used to conduct data screening and analysis.

4.5.1. Questionnaires and neuropsychological measures

The normality assumption was met with all EC indices (total, and inhibitory control scores were log transformed), d2 test of attention, MTT, ERT in total, anger, disgust, fear, sadness and surprise, and SRS-2 total scores. Therefore, independent t tests were utilized to compare differences between two groups. However, the RTI and happiness component of ERT in the CANTAB measure did not meet the normality assumption even though log transformations were instituted. Thus, group differences in these variables were explored using Mann–Whitney U tests.

4.5.2. Preprocessing of fNIRS Data

This study used the AnalyzIR toolbox run in MATLAB 2019a (The Mathworks, Natick, MA, USA) for preprocessing and analyzing the fNIRS data (Santosa et al., 2018). The raw data of the WCST task were derived in the continuous mode from the Hitachi ETG-4000 machine and subsequently entered into the AnalyzIR toolbox. Preprocessing was then initiated with default functions that resolve flat, missing, and saturated channel issues. Next, the raw optical density was converted into oxygenated (HbO) and deoxygenated (HbR)

hemoglobin using the modified Beer–Lambert law after resampling the signal at 1 Hz with a 0.1 partial pathlength factor (Delpy et al., 1988). First-level statistical estimation of task-induced activation was further conducted using the autoregressive iterative reweighted least-squares (AR-IRLS) method. Concurrently, connectivity among possible channel pairs was estimated using the sophisticated autoregressive whitened correlation technique in a general linear model. The variables of activation (t-statistics) and connectivity (Z scores) were then used for second-level group analysis. Since HbO was found to have a higher signal-to-noise ratio than HbR and is highly correlated with the BOLD signal of fMRI, this study interpreted the results based on HbO only (Cui et al., 2011).

Furthermore, channel wise spatial registration in accordance with digitized coordinates (33 optodes and 5 reference points) was conducted using near infrared spectroscopy-statistical parameter mapping (NIRS-SPM; Ye et al., 2009). The resulting outputs of MNI coordinates for each participant were pooled in BrainNet viewer, and the mean composite scores were estimated (Xia et al., 2013). Then, with 80% probability registration, channels corresponding to inferior, middle, and superior frontal gyri (IFG, MFG, and SFG) on both sides were ensured, and these 6 PFC sites were defined as regions of interest (ROIs; Figure 3.3; Zhu et al., 2017). The channels that did not withstand the 80% threshold of probability registration or exhibited insufficient signal quality due to inadequate optodes-scalp contingence were excluded from the analysis. Thus, some channels in the PFC and temporal lobe were not analyzed in this study.

4.5.3. fNIRS Data Analysis

The right and left PFC activation scores (HbO; t-statistics) during the WCST task met the normality assumption. Hence, a 2 x 2 mixed ANOVA denoting group (TD and ASD) as the between-subject factor and frontal sides (right and left) as the within-subject factor were

used to explore PFC activation between the two groups.

In terms of PFC synchronization, 6 patterns of connectivity were derived from the defined ROIs, and the respective channel pairs were averaged across each pattern (Figure 3.4). The mean Z scores of all connectivity patterns assumed normality; therefore, a 2 x 2 x 2 mixed ANOVA indicating groups (TD and ASD) as the between-subject factor and connectivity patterns (within and between ROI) and frontal sides (left and right) as within-subject factors were included for intrahemispheric connectivity analysis. Similarly, a 2 x 2 mixed ANOVA specifying groups (TD and ASD) as the between-subject factor and connectivity patterns (within and between ROI) as the within-subject factor were used for interhemispheric connectivity analysis.

4.5.4. Brain-behavior relationship

To describe individual variations in EC among adolescents and adults with ASD, the link between EC measures and other variables, including PFC, EF, and socioemotional measures, was examined in the ASD group. Variables assumed or not assumed to be normal were analyzed using Pearson's (r) and Spearman's (r_s) correlations, respectively. To minimize multiple comparisons, only variables that differed significantly between the two groups were examined.

4.6. Results

4.6.1. Demographic, clinical, and intellectual profiles

Table 4.1 shows the demographic, clinical, and intellectual information of the two groups, which were matched by age, $Z(25) = 1.80$, $p > 0.05$. Although IQ was not matched between groups, $Z(25) = 2.48$, $p = 0.012$, subsequent correlation analysis between IQ and EC, EF, socioemotional, and PFC activations during WCST was not significant ($p > 0.05$). This

suggests IQ did not influence EC, EF, socioemotional, or PFC activation, and therefore, it was not controlled while executing between-group analyses on these variables. However, IQ was significantly correlated with both intra- and interhemispheric connectivity scores during the WCST task, and therefore, it was considered a covariate in the subsequent between-group analyses.

Table 4.1. Demographic, intellectual, and clinical characteristics of the healthy control (HC) and autism spectrum disorder (ASD) groups.

	HC (*n* = 13)	**ASD (*n* = 14)**			
	Median (95% CI)	**Median (95% CI)/Mean (*SD*)**	***Z***	***p***	***r***
Age (years)	20.68 (18.76-21.26)	18.58 (17.15-19.80)	1.80	0.076	0.35
IQ	104.00 (97.68-106.94)	89.50 (82.98-100.31)	2.48	0.012*	0.48
ADI-R Social Interaction[#]	-	22.33 (8.37)	-	-	-
ADI-R Communication[#]	-	17.25 (8.08)	-	-	-
ADI-R Restricted and Stereotyped Behavior[#]	-	5.17 (2.79)	-	-	-

Note: ADI-R = Autism Diagnostic Interview–Revised; [#] Mean (SD); *$p < .05$

4.6.2. EC, EF, and socioemotional functions

There were significant differences between the two groups in all EC, EF, and socioemotional functions (Table 4.2), in which the ASD group displayed a greater deficit than TD controls with a larger effect size on the EC index, including total score, t (23) = 5.55, p = 0.000; attention, t (23) = 5.45, p = 0.000; inhibitory control, t (23) = 5.62, p = 0.000; activation control, t (23) = 3.53, p = 0.002; the concentration performance index of the d2 test of attention, t (25) = 3.86, p = 0.001; the mean reaction time of the CANTAB, Z (25) = 2.07, p = 0.039; switch block error of the CANTAB multitasking test, t (25) = 3.61, p = 0.003; total hit rate of the CANTAB emotion recognition task, t (25) = 3.92, p = 0.001; and SRS-2 total score, t (20) = 6.04, p = 0.000.

The subgroup analyses of the CANTAB emotion recognition task on anger, disgust, fear, sadness, and surprise emotions with an adjusted p value cutoff of 0.010 revealed that

there was a significant difference between the two groups in recognizing disgust emotions, in which the ASD group showed more deficits than the TD group, with a larger effect size, t (23) = 5.67, p = 0.000.

Table 4.2. Effortful control, executive and socioemotional functions in the healthy control (HC) and autism spectrum disorder (ASD) groups.

Variables	HC (n = 13)	ASD (n = 14)	*t/Z*	*p*	*d/r*
	Mean (*SD*)/Median (95% CI)	**Mean (*SD*)/Median (95% CI)**			
EC [EATQ-R and ATQ-R[###] (TD n = 13; ASD n = 12)]					
Total[#]	1.44 (0.06)	1.22 (0.13)	5.55	0.000***	2.17
Attention	20.92 (3.12)	13.42 (3.75)	5.45	0.000***	2.17
Inhibitory control[#]	1.51 (0.06)	1.24 (0.15)	5.62	0.000***	2.36
Activation control	31.08 (5.96)	20.42 (8.94)	3.53	0.002**	1.40
D_2 Test of Attention					
Concentration performance index	229.07 (31.90)	158.79 (60.30)	3.86	0.001**	1.46
CANTAB Reaction Time Task					
Mean reaction time (ms)[##]	363.17 (351.48-383.55)	395.77(330.51-581.87)	2.07	0.039*	0.39
CANTAB Multitasking Test					
Switch block error	3.0 (.96)	10.36 (7.56)	3.61	0.003**	1.37
CANTAB Emotion Recognition Task					
Total hit rate	29.64 (4.03)	21.86 (6.24)	3.92	0.001**	1.48
Anger	3.14 (1.41)	2.86 (1.79)	0.47	0.64	0.17
Disgust	6.14 (1.41)	2.71 (1.77)	5.67	0.000***	2.14
Fear	2.57 (1.65)	1.93 (1.82)	0.98	0.34	0.37
Sadness	5.64 (1.34)	4.36 (1.78)	2.16	0.040*	0.81
Surprise	5.57 (0.94)	3.93 (2.13)	2.642	0.017*	1.00
Happiness[##]	7.0 (6.03-7.11)	6.50 (5.24-6.90)	0.81	.45	0.15
SRS-2[###] (TD n = 9; ASD n = 13)					
Total *T*-score	48.22 (19.68)	102.92 (21.66)	6.04	0.000***	2.64
Awareness	6.78 (3.19)	12.77 (2.46)	4.98	0.000***	2.10
Communication	16.00 (7.33)	35.77 (8.67)	5.59	0.000***	2.46
Cognition	10.78 (2.95)	21.46 (4.20)	6.58	0.000***	2.94
Motivation	8.44 (4.25)	15.08 (4.63)	3.42	0.003**	1.49
Repetitive restrictive behavior	6.22 (5.31)	17.85 (9.02)	3.79	0.001**	1.57

Note. SRS-2 = Social Responsiveness Scale-Second Edition. *p < 0.05; **p < 0.01; ***p < 0.001. [#] Log transformed; [##] Mann and Whitney U test; [###]Missing data: The EATQ-R/ATQ-R was uncompleted for 1 participant with TD and 2 participants with ASD; The SRS-2 was not uncompleted for 5 TD and 1 ASD participants.

4.6.3. PFC Activation during WCST Task

The 2 x 2 (groups x frontal sides) mixed ANOVA revealed that there were no significant main effects on groups, frontal sides, and the interaction effect between group and frontal sides (*p*s > 0.05).

4.6.4. PFC Connectivity during WCST Task

4.6.4.1. Intrahemispheric Connectivity

The 2 x 2 x 2 (groups x frontal sides x connectivity patterns) mixed ANOVA with controlling IQ revealed that there was a significant main effect on groups, $F(1,22) = 7.48$, $p = 0.012$, $\eta_p^2 = 0.25$, in which the ASD group elicited decreased connectivity ($M = 0.22$, $SE = 0.034$) compared with the TD group ($M = 0.37$, $SE = 0.036$). No significant results were obtained for other effects (*p*s > 0.05; Table 4.3).

Table 4.3. Mixed ANOVA (groups × frontal sides × connectivity patterns) with IQ as a covariate results for intrahemispheric connectivity (i.e., mean Z scores) during WCST condition.

Main/Interaction Effects	Mean (*SE*)	df	*F*	*p*	η_p^2
Connectivity pattern (within and between ROI)	Within: 0.27 (0.024) Between: 0.31 (0.024)	1,22	0.043	0.84	0.002
Frontal side (left and right)	Right: 0.25 (0.023) Left: 0.34 (0.031)	1,22	0.13	0.72	0.006
Group (TD and ASD)	TD: 0.37 (0.036) ASD: 0.22 (0.034)	1,22	7.48	0.012*	0.25
Two-way interaction					
Connectivity pattern × frontal side		1,22	0.69	0.42	0.030
Connectivity pattern x group		1,22	1.61	0.22	0.068
Connectivity pattern x IQ		1,22	0.39	0.54	0.017
Frontal side × group		1,22	0.43	0.52	0.019
Frontal side × IQ		1,22	0.54	0.47	0.024
Three-way interaction					
Connectivity pattern × frontal side × group		1,22	0.72	0.41	0.031
Connectivity pattern × frontal side × IQ		1,22	0.81	0.38	0.035

Note: *$p < 0.05$

4.6.4.2. Interhemispheric Connectivity

The 2 x 2 (groups x connectivity patterns) mixed ANOVA with controlling IQ revealed that there was a significant main effect on groups, $F(1,22) = 9.98$, $p = 0.005$, $\eta_p^2 = 0.31$, in which the ASD group showed reduced connectivity ($M = 0.19$, $SE = 0.033$) compared with the TD group ($M = 0.35$, $SE = 0.034$). No significant results were found for other effects ($ps > 0.05$; Table 4.4).

Table 4.4. Mixed ANOVA (groups × connectivity patterns) with IQ as a covariate results for interhemispheric connectivity (i.e., mean Z scores) during WCST condition.

Main/Interaction Effects	Mean (*SE*)	df	*F*	*p*	η_p^2
Connectivity pattern (within and between ROI)	Within ROI: 0.27 (0.022) Between ROI: 0.26 (0.024)	1,22	0.14	0.71	0.006
Group (TD and ASD)	TD: 0.35 (0.034) ASD: 0.19 (0.033)	1,22	9.98	0.005**	0.31
Two-way interaction					
Connectivity pattern × IQ		1,22	0.11	0.75	0.005
Connectivity pattern × group		1,22	2.90	0.10	0.12

Note: *$p < .05$; **$p < .01$

4.6.5. Individual Differences in EC in the ASD Group

The adolescents and adults with ASD showed defective executive and socioemotional functions and reduced intra- and interhemispheric connectivity patterns during the WCST task relative to healthy controls. Therefore, correlation analyses were conducted between the total score of the EC index and EF, socioemotional, and both intra- and interhemispheric connectivity measures to elucidate underlying differences in EC among adolescents and adults with ASD. The total score of the EC index was significantly associated with the SRS-2 total T-score, $r = -0.65$, $p = 0.023$, and the RTI of the CANTAB task, $r_s = -0.64$, $p = 0.026$. No significant correlations were found between the total score of the EC index and other variables, $ps > 0.05$.

4.7. DISCUSSION

This study aimed to examine the association between EC and PFC functioning with regard to activation and connectivity during the WCST task in adolescents and adults with ASD. The current study indicated that the ASD group elicited significantly lower levels of EC, executive, and socioemotional functions than typical controls. The ASD group also showed altered PFC functions such that their PFC connectivity was lower while performing the WCST task. The study further demonstrated that the total score of the EC index was interlinked with social and executive functioning in terms of attention but not with other executive, emotional, or PFC processing in the ASD group. This implies that the individual differences in EC among adolescents and adults with ASD could be explained by social and attention functioning alone.

The present study supported our hypotheses. First, adolescents and adults with ASD showed more EC deficits than typical controls, such that the combined EATQ and ATQ measures differentiated two groups of individuals across all EC subscales, including attention, inhibitory, and activation control, along with overall total scores. The results produced novel insights about EC deficits in adolescents and adults with ASD, although previous studies have attempted to study EC function in these individuals. For instance, Uljarević et al. (2017) examined EC using ATQ (adolescent/adult versions) measures in ASD; however, the study did not compare EC performance with healthy controls; consequently, the EC deficit in adolescents and adults with ASD could not be ascertained. Likewise, Schwartz et al. (2009) reported temperament deficits in other constructs, i.e., excluding the EC construct in adolescents with high-functioning ASD. Extending from the EC deficit, the current finding also differentiated two groups on executive function measures, including the d2 test of attention and the CANTAB tests (RTT and MTT), suggesting that adolescents and adults with ASD presented with poorer attention, inhibition, and cognitive

flexibility components of EC. This finding was corroborated by earlier studies claiming that greater autistic trait was associated with worsened attention, inhibition, and flexibility components of EC (Han & Chan, 2017; Leung & Zakzanis, 2014; Rana, Laila, & Shahid, 2014).

Second, as hypothesized, the current study distinguished adolescents and adults with ASD from their typical counterparts in socioemotional functions indexed by SRS-2 and ERT measures. In terms of social dysfunction, the present study is consistent with previous studies that predicted autistic symptoms through social impairment, linked behavioral outcomes with social skills (Chan, Smith, Hong, Greenberg, & Mailick, 2017), and examined social deficit inheritance from parents of ASD to children (Lyall et al., 2014). The result also favors that individuals with ASD tend to have worse social function than typical controls while growing older (Wallace et al., 2017). Notably, the age-related adaptive social function indexed by the Vineland Adaptive Behavior Scale was also impaired in autism (Pugliese et al., 2015), which together supports that individuals with autistic traits undergo substantial social dysfunction regardless of developmental phase. In terms of emotional dysfunction, the current finding is consistent with a recent meta-analysis that concluded that adults with ASD showed greater difficulty in perceiving and processing emotion-related information (Velikonja, Fett, & Velthorst, 2019). The emotion recognition deficit in autistic individuals is explained as a result of abnormal social motivation and social cognitive functions (Gaigg, 2012). Social motivation typically perceives odd facial expressions (Weigelt, Koldewyn, & Kanwisher, 2012), and the social cognitive function simultaneously processes social information while detecting people's emotions and responding back to such emotions precisely (Henry, von Hippel, Molenberghs, Lee, & Sachdev, 2015). Under typical circumstances, these functions were integrated together to attain higher-order social skills such as theory of mind, affective empathy, social perception, and social behavior. However, individuals with ASD encounter

difficulties in synchronizing those functions, such as exhibiting unfamiliar processes while recognizing emotion (Weigelt et al., 2012) or displaying maladaptive emotional reactions that lead to disruptive interpersonal behavior (Peterson, 2014).

Third, as expected, adolescents and adults with ASD demonstrated weaker frontal cortical synchronization than typical controls during the WCST. Although brain connectivity during WCST has not been explored much in autism, findings from similar tasks revealed profound disconnection across brain regions. For example, poor neural circuity in the frontal lobe was reported in adults with ASD during the target detection task, which required individuals to shift targets within a cognitive set (Shafritz et al., 2008). Similarly, diminution of frontal synchronization was also evident in ASD during extradimensional set-shifting of the CANTAB task, which involved alternating rules for matching dimensions either from color to shape or shape to color patterns (Doesburg, Vidal, & Taylor, 2013). In line with these studies, the set-shifting and task switching paradigms in cognitive flexibility tasks widely induced disconnection of lateral frontoparietal and midcingulo-insular networks in autism (Uddin, 2021). Altogether, the weaker frontal connectome during the WCST task in ASD has been concordant with the postulates of "frontal disconnection syndrome", which negatively impacts the cognitive performance of tasks (Geschwind & Levitt, 2007; Zeestraten et al., 2017), and "underconnectivity theory", which unifies neurophysiological understandings of processing multifarious information difficulties related to frontal lobe deficits in autism (Just et al., 2012).

Finally, the relationship between EC deficits and social dysfunction in autism is consistent with the predictable EC outcome in social skills, adaptive functions, and empathy, which together aid in the maturation of adaptive skills in adolescents with autism (Schwartz et al., 2009). Likewise, the correlation between EC deficits and RTI impairment in CANTAB suggests that the dependency of attention skills on EC function is more pronounced in

adolescents than in children with autism (Krishnamurthy et al., 2020). The plausibility of such EC and attentional maturation could be the result of neuronal myelination, network pruning, and modulation of blood circulation in the brain regions associated with the executive attention network, including the PFC, which has yet to be clarified (Casey, Giedd, & Thomas, 2000). However, the current study did not find significant relationships between EC and MTT and ERT or PFC activation and connectivity during the WCST task. The absence of relationships implies that the EC and EF constructs are different from each other, and further, the characteristics of behavioral measures employed in EF constructs and questionnaires for EC function (EATQ/ATQ) might yield differential response patterns that could eventually lead to nonsignificant correlations (Hedge et al., 2018). Although such a nonsignificant relationship between behavioral measures and questionnaires might be attributed to the poor reliability of behavioral measures (Dang et al., 2020), the test-retest reliability scores of the included measures were above the moderate level. For instance, the d2 (concentration performance) in adolescents was $r = 0.74$ (Brickenkamp & Rump, 1966), and the EATQ-R in Chinese adolescents was rs = 0.62 to 0.72 (Zhang et al., 2008), suggesting that poor reliability is not a probable explanation for the absence of relationships. The absence of correlation also exists between EC and PFC functioning and ERT, suggesting that the individual variations in EC performance might not be limited to PFC activation or hypoconnectivity in adolescents and adults with ASD. For example, perception of emotion highly depends on anterior cingulate cortex and amygdala activations with medial frontal cortex connection (Etkin et al., 2011; Phelps & LeDoux, 2005). Since autism individuals showed anatomical and functional abnormalities in these emotion-controlled brain regions (Baron-Cohen et al., 2000), the EC deficit related to emotion impairment is better explained when studying these brain sites and their associated connectomes during emotion recognition.

Our findings are the foremost to examine EC and its link with frontal lobe theory, executive, and socioemotional functions in adolescents and adults with ASD. The findings reveal EC deficits and decreased PFC connectivity in adolescents and adults with autism; however, they do not demonstrate individual differences in EC that are explained by the degree of PFC connectivity among these individuals. Furthermore, the study shows temperamental EC impairment and its inextricable link with social dysfunction in adolescents and adults with autism, implying that clinical interventions on social skill development might be beneficial to enhance its functionality in the real-world context.

This study has some limitations. First, the sampling size was small, such that it included only high-functioning males with ASD; hence, the result cannot be generalized to females and low-functioning adolescents or adults with ASD. Second, the EC index was measured using parent reports of ATQ and EATQ measures, which might be attributed to potential bias while interpreting the questionnaires and scoring items accordingly. Third, age-related WCST task performance varies among young and older participants (Rhodes, 2004); thus, using WCST as a probe to study PFC functioning in the combined samples of adolescents and adults might be influenced by the nature of performance variations.

4.8. CONCLUSION

This study demonstrated deficits in EC, executive, and socioemotional functions along with altered PFC connectivity in adolescents and adults with ASD. It also supports the existing knowledge of PFC processing deficits during cognitive flexibility tasks in autism and further augments the notion of information processing difficulty and frontal disconnection syndrome, which together serve as neuropathological biomarkers in autism. The link between impaired EC and social deficit observed in the ASD group suggests that EC plays a vital role in improving the social skills of these individuals. However, the lack of an association

between EC and PFC functioning among adolescents and adults with ASD warrants future research that includes more diverse autistic samples and expands the role of other brain regions or circuity to EC dysfunction in autism.

CHAPTER 5: STUDY FOUR

Effectiveness of Transcranial Direct Current Stimulation on Effortful Control and Functional Connectivity in Autism Spectrum Disorder – An fNIRS Pilot Study

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Neurophysiological and behavioral effects of multisession prefrontal tDCS and concurrent cognitive remediation training in patients with autism spectrum disorder (ASD): A double-blind, randomized controlled fNIRS study

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5.1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition that typifies socio communicative impairment and exhibits recurrent, restrictive behavioral manifestations or interests (American Psychiatric Association, 2013). ASD prevalence reaches nearly 1 out of 54 children (Maenner et al., 2020); consequently, the affected individuals, families, and societies experience appalling economic hardship associated with continuing care. For example, the lifespan expenditure for manging a single ASD person incurs US$ 1.78 to 2.4 million in the USA and UK, highlighting the necessity for intervention to enhance an individual's overall functioning and minimize long-term care expenses (Buescher, Cidav, Knapp, & Mandell, 2014). Conventional treatments, including pharmacological, psychoeducational, and behavioral methods, have been proposed for ASD; however, they lack addressing the underlying brain pathophysiology, which in turn results in minimal efficacy (Francis, 2005; MacMaster et al., 2016). Given the abnormal structural and functional aspects of the ASD brain (Cardinale, Shih, Fishman, Ford, & Müller, 2013; Verhoeven, De Cock, Lagae, & Sunaert, 2010), noninvasive brain stimulation techniques such as transcranial magnetic and transcranial electric stimulations may yield beneficial effects on intervening autism deficits. Transcranial magnetic stimulation (TMS) is useful for neuromodulation; however, a poorer intervention schedule and possibilities of placebo effects in the reported findings may interfere with overall treatment effectiveness (Barahona-Corrêa, Velosa, Chainho, Lopes, & Oliveira-Maia, 2018).

Transcranial electric stimulation (TES) is an alternative technique that passes a low threshold electrical current between 1 and 2 mA through the scalp to modulate underlying neuronal activities. Transcranial direct current stimulation (tDCS) is a kind of TES that applies positive or negative current via anodal or cathodal electrodes to enhance or dampen the neural excitability rate, respectively (Nitsche & Paulus, 2000). These electrical inputs

alter neuronal transmembrane potentiation, thereby influencing its firing rate while providing additional inputs (Wagner et al., 2007). The tDCS effects are interlinked with numerous mechanisms, particularly alteration of local hydrogen and calcium ion concentrations, modulation of protein formation, cyclic adenosine monophosphate status, and N-methyl-D aspartate efficacy (Islam, Aftabuddin, Moriwaki, Hattori, & Hori, 1995; Nitsche et al., 2004). Additionally, tDCS has a potential impact on glutamate and gamma aminobutyric acid (GABA) neurotransmitter secretion, such that anodal stimulation increases the excitatory glutamate receptor concentration, whereas cathodal stimulation increases the inhibitory GABA receptor concentration locally (Bachtiar et al., 2015; Clark, Coffman, Trumbo, & Gasparovic, 2011). These molecular and neurotransmitter modulations at stimulated sites promote neural plasticity and connectivity changes in both local and distributed brain regions (Polanía, Paulus, Antal, & Nitsche, 2011; Sehm et al., 2012). tDCS has been demonstrated to be safe for human beings with a power intensity of 1 – 2 mA for 20 minutes per session (Woods et al., 2016), and with this parameter, it has been applied in individuals with various neurodevelopmental disorders, including autism (García-González et al., 2021). However, the widespread utility of examining tDCS effects in various neuropsychological functions, including temperamental effortful control, remains elusive in individuals with ASD.

Effortful control (EC) refers to the efficient deployment of executive attention ability to suppress a dominant or activate a subdominant response (Rothbart & Bates, 2006). EC consists of executive attention, inhibitory control, and cognitive flexibility subcomponents, which together assist orienting, retracting, and alternating behavioral tendencies associated with relevant circumstances (Eisenberg et al., 2010; Lengua et al., 2008; Rothbart & Bates, 2006). EC is dysfunctional in children and adolescents with ASD; for instance, children with ASD are reported to have less efficient attention, inhibitory control, and cognitive flexibility skills than their typical counterparts (De Pauw, Mervielde, Van Leeuwen, & De Clercq,

2011; Konstantareas & Stewart, 2006). Individual differences in EC among the ASD population are also associated with social interaction abilities and everyday functioning (Krishnamurthy et al., 2020). Notably, Poole, Gowen, Warren, and Poliakoff (2018) reported that individuals with ASD encountered difficulty in suppressing visual distractors coming from the external environment while attending to tactile stimuli, and such attention to targets was comparatively slower than neurotypical controls. Extended with the findings, Hogeveen, Krug, Elliott, Carter, and Solomon (2018) reported that individuals with ASD were relatively slower to process context-relevant targeting information (AY targets) than context-irrelevant nontargets (B-cue trials) during continuous performance tasks that tap inhibitory control, and the observed response pattern was significantly associated with increased stereotypic behavior in real life. Additionally, slower switching performance on the Trail Making Test and its association with behavior inflexibility (Strang et al., 2017), committing more errors after changing the rule in the multitasking test (Krishnamurthy et al., 2020) support the notion that EC underlies the ASD phenotype and is mediated by the processing speed of individuals with ASD while performing these tasks.

Although the precise neurophysiological mechanism of ASD underlying EC deficits and the concomitant social dysfunctions have yet to be examined, an excitatory-inhibitory (E:I) imbalance in the local neural networks involving cognitive and affective functions hinders global brain signaling; therefore, individuals with ASD may experience difficulties in executing EC components and goal-oriented behavior (Rubenstein & Merzenich, 2003; Sohal & Rubenstein, 2019). Notably, individuals with ASD show a heightened E:I ratio in the prefrontal cortex due to increased excitability of excitatory neuronal activities (Trakoshis et al., 2020) but not a deficit in inhibitory neurons (Coghlan et al., 2012). The regional E:I ratio also plays a significant role in organizing resting-state functional connectivity (Zhou et al., 2021); specifically, a greater local E:I ratio is linked with reduced functional connectivity in

the default mode network (Gu, Hu, Chen, He, & Yang, 2019), which supports performing EC components and socio cognitive functions (Smallwood et al., 2021; Vatansever, Menon, & Stamatakis, 2017). The structural and functional aspects of the default mode network have been found to be altered in individuals with ASD and further demonstrated to be linked with socio cognitive dysfunctions in these individuals (Padmanabhan, Lynch, Schaer, & Menon, 2017).

Therefore, a therapeutic intervention that can reduce neuronal excitability may be beneficial for enhancing EC and sociocommunicative functions in individuals with ASD. Consistent with this, cathodal tDCS stimulation has been a promising method and has been shown to dampen neuronal excitability through a reduction in excitatory glutamate secretion (Zhao et al., 2020). Among the numerous tDCS protocols, stimulating the dorsolateral prefrontal cortex (dlPFC) is the most common montage selection and has been demonstrated to enhance the EC component with emotion-related information processing in patients with various neuropsychiatric disorders (Nitsche et al., 2012; Soyata et al., 2019). In fact, some preliminary findings have demonstrated that cathodal stimulation could improve cognitive functioning and social behavior in individuals with ASD. For example, cathodal stimulation over the left dlPFC in adults with ASD led to decreased irritability, social withdrawal, and hyperactivity and enhanced processing speed with cognitive flexibility (D'Urso et al., 2015; Rothärmel et al., 2019). However, the outcomes of these findings were compromised by limitations in the sample size and study design. Therefore, the clinical, neurobehavioral, and neurophysiological effects of cathodal stimulation in individuals with ASD have remained equivocal. Hence, this study aimed to examine the potential effects of cathodal tDCS in individuals with ASD and hypothesized that the cathodal group would demonstrate better EC, social function, and increased resting-state functional connectivity over the left dlPFC.

5.2. Materials and Methods

5.2.1. Study Design and Participants

This study was a two-armed randomized controlled trial (RCT) conducted with the proposed guidelines issued by the Declaration of Helsinki. The trial was registered in the ClinicalTrials.gov Protocol Registration and Results System (ID: NCT03814083), and the Human Subjects Ethics Sub-Committee of Hong Kong Polytechnic University approved the study protocol (HSEARS20171230001). Participants were recruited from hospitals, special schools, and nongovernmental organizations through psychiatrists' referrals and advertisements. Subsequently, 30 right-handed Chinese adolescents and adults (25 males and 5 females) aged 14 - 21 years were recruited with the parents and self-informed consent. The diagnosis of ASD was confirmed by a psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5; (American Psychiatric Association, 2013). The intelligence quotient (IQ $\geq$ 60) was measured by clinical/educational psychologists using the Wechsler Intelligence Scale (4th edition) in adult/child versions. Participants receiving medication and those who presented with a history of epilepsy, comorbid neuropsychiatric conditions, developmental delay, traumatic head, and open bruising or infection on the scalp were excluded.

5.2.2. Procedures

The participants were assessed independently at two timepoints (before brain stimulation and immediately after completing ten sessions of intervention) with two sessions, neuropsychological evaluation and fNIRS data acquisition, which lasted approximately 2 hours in total with a ten-minute interval. Concurrently, interviews with parents or caregivers of participants were conducted with validated protocols, including Autism Diagnostic Interview-Revised (ADI-R), Social Responsiveness Scale-Second Edition (SRS-2), and Adult

Temperament Questionnaire – Short form (ATQ–SF) or Early Adolescent Temperament Questionnaire-Revised (EATQ-R). The clinical psychologist and trained research assistants conducted evaluations and interviews.

5.3. Measures

5.3.1. Short Forms of the Early Adolescent Temperament Questionnaire-Revised (EATQ-R) and Adult Temperament Questionnaire (ATQ)

The description of the EATQ-R and ATQ were presented in the section 4.3.1.

5.3.2. Cambridge Neuropsychological Test Automated Battery (CANTAB)

This study used reaction time (RTI) and multitasking test (MTT). The description of these measures was presented in the section 4.3.3.

5.3.3. Wisconsin Card Sorting Test (WCST)

The description of this measure was presented in the section 4.3.4.

5.3.4. Children's Color Trial Test

It was a standardized paper-based test consisting of two trials (CCTT1 and CCTT2). Both trials measured perceptual tracking, graphomotor abilities, and sustained attention, and the CCTT2 measured cognitive flexibility (Llorente, 2003). The test required conjoining pink and yellow circles of numbers from 1 to 15 alternatively in an ascending order. The task duration calculated in seconds with errors, prompts, and near-miss scores were variables. The test-completion time on the first and second trials (recruit frontal functions) was recorded, and the shorter duration implied better attention (information processing) and attentional switching, respectively (Williams et al., 1995).

5.3.5. Resting State Frontal Lobe Functioning

It was a customized measure that required the participants to look at a picture on the computer screen for three minutes. During rest, a functional near infrared spectroscopy (fNIRS) machine was utilized to capture frontal lobe connectivity.

5.3.6. Outcome Measures Interpretation

Given the wider interpersonal differences in executive function profiles among individuals with autism and limitations in interpreting a complex cognitive domain, i.e., cognitive flexibility (Fabio, Esposito, Carrozza, Pino, & Caprì, 2020), using a single measure, cognitive flexibility (CF) was measured by combining CCTT2 (total time), CANTAB MTT (switch cost), and WCST (mean reaction time during switching block). Initially, the raw scores of these measures were converted into Z scores using the normative data, which were then averaged to obtain a mean composite CF score. Similarly, the raw scores of the total time taken to complete the CCT1 and RTI mean reaction time were converted into Z scores, which were then averaged to obtain the "information processing efficiency (IPE) composite" score. Higher CF and IPE composite scores indicated better performance.

5.4. fNIRS Data Acquisition

The fNIRS data were recorded at rest using a Hitachi ETG-4000 machine, which works at a sampling rate of 10 Hz and wavelengths between 695 and 830 nm. The machine included 33 optodes with 17 emitters and 16 detectors constituting 52 channels that were distanced at 3 cm and arranged in a 3 x 11 probe set (Figure 3.2 a and b). Data acquisition was taken place in a silent dimly lit room, where participants positioned on a chair approximately 60 cm away from the 15'' LCD monitor. Subsequently, participants' heads were measured across nasion-inion, right-left ear, and head circumference to register channel

positions spatially offline, which were further converted into Montreal Neurological Institute (MNI) space and then laid over the volume-rendered adolescent and adult brain templates (Singh et al., 2005). Before placing the customized headband attached to the probe set on the participants' forehead in accordance with the international 10-20 system, the regions were disinfected with an alcohol pad to maximize signal receptance. Next, 3D digitization was performed on 5 anatomical (nasion, inion, right and left auricular, and vertex) and 33 optode sites.

5.5. tDCS Intervention Protocol

The experiment was a double-blind randomized controlled trial that included cathodal (n = 15) and sham (n = 15) conditions. Both conditions received stimulations over the left dorsolateral prefrontal cortex (DLPFC; F3; Figure 5.1a) with return electrical current applied simultaneously over the right rostro-lateral prefrontal cortex (FP2; Figure 5.1a). The cathodal group received electrical stimulation of 1.5 mA constantly for 20 minutes per session with 30 s ramp-up/ramp-down of power before and after the stimulation. The sham group received only 30 s ramp-up/ramp-down sequences without 20 minutes of stimulation, although the tDCS machine was on. The electrical current was applied using a battery-powered tDCS machine "Starstim-8 (Neuroelectrics, Barcelona, Spain)" with 25 cm^2 sponstim electrodes soaked with saline solution (Figure 5.1b-g). During the stimulation, both groups of participants played 10 brain training games targeting attention, attentional shifting and working memory domains from the lumosity app delivered via a 10-inch apple i-pad. The total duration of intervention included 10 sessions of 5 days a week for 2 weeks. After completing the experimental protocol, each participant responded to a questionnaire for evaluating potential discomforts associated with cathodal or sham stimulation (Fertonani, Ferrari, & Miniussi, 2015).

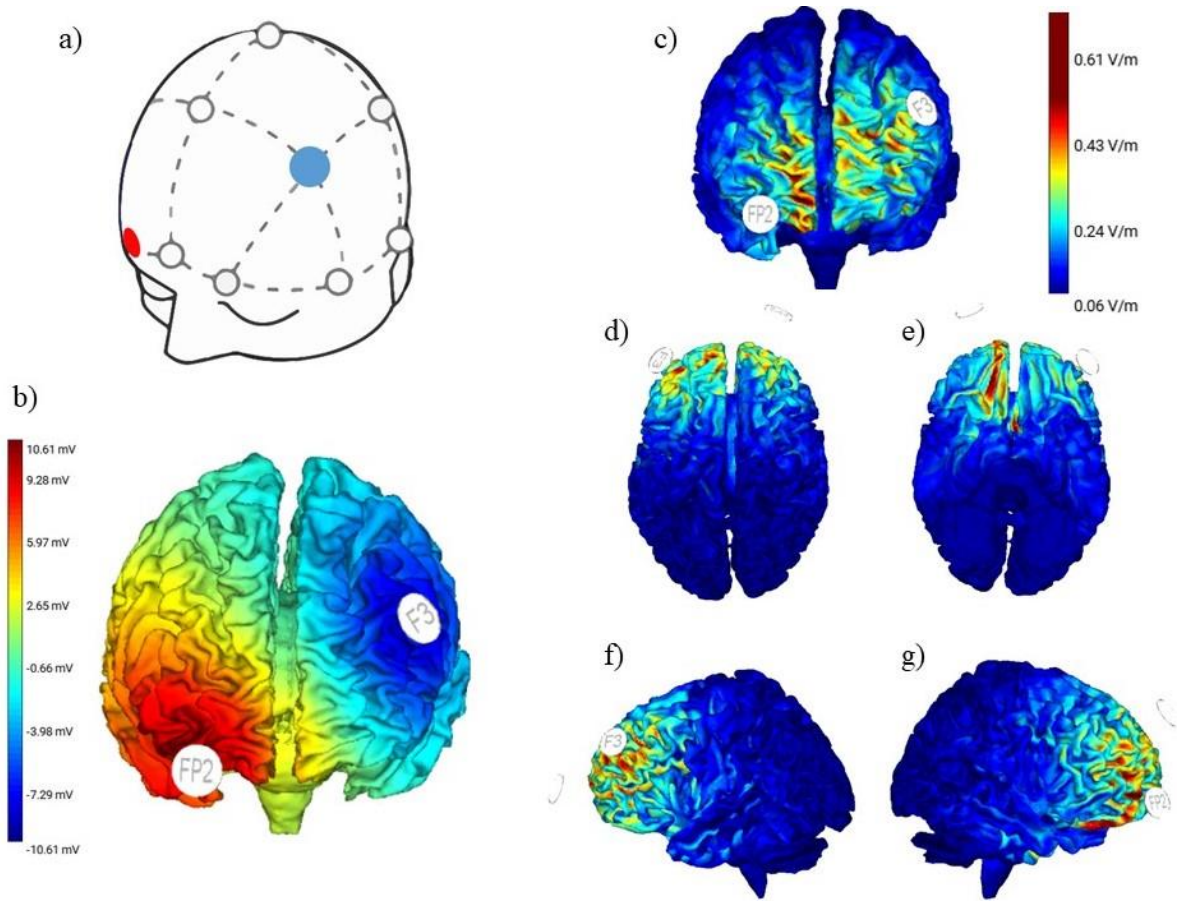

Figure 5.1. Electrode placement, voltage and electric field distribution of the tDCS protocol used in this study. (a) A circular cathode electrode (25 cm^2) was placed at the F3 region of the 10-20 electroencephalogram (EEG) system, which corresponds to the left dlPFC. A circular return electrode (25 cm^2) was placed at the Fp2 region of the 10-20 EEG system, which corresponds to the right orbitofrontal area. (b) Voltage generated by 1.5 mA, left dlPFC (cathode) – right supraorbital region (anode) montage. (c – g) Electric field distribution [(c) front view; (d) top view; (e) bottom view; (f) left view; (g) right view] generated by left dlPFC (cathode) – right supraorbital region (anode) montage.

5.6. Data Screening and Analysis

Data screening was conducted with normality assumption using Shapiro–Wilk test. Data with nonnormality were log-transformed, but if it was revealed violating normality

again, then nonparametric tests were used. SPSS software (version 25; IBM Corp., Armonk, NY, USA) was utilized to conduct data screening and analyses.

5.6.1. Data Analyses of Demographic Variables

Two groups (cathodal and sham tDCS) of demographic variables "age, IQ, and SRS-2" met with normality assumptions; hence, these variables were analyzed using independent sample t tests. Simultaneously, the categorical variables sex and handedness were analyzed using chi-square tests.

5.6.2. Data Analyses of Questionnaires and Neuropsychological Measures

The SRS-2 total score and IPE composite and CF composite scores for the two groups (cathodal and sham tDCS) met normality assumptions; hence, they were analyzed using 2x2 repeated-measures ANOVA. The group comparison yielding significant *group*time* interactions proceeded with follow-up post hoc analyses using paired t tests with Bonferroni corrections. To comprehend the group comparison and specific effects following post hoc t tests, partial eta squared with 90% confidence interval (CI) and Cohen's d were reported.

5.6.3. Pre-processing and First-level Analyses of the fNIRS Data

Pre-processing of the fNIRS data was conducted using the AnalyzIR toolbox (Santosa et al., 2018) in MATLAB 2019a (The MathWorks, Natick, MA, USA), and the corresponding pipeline of the toolbox is described below. The raw fNIRS data of each participant during the resting state were extracted from the Hitachi ETG-4000 machine. The raw data containing saturated, flat-channel, and not-a-number issues were resolved and replaced with high variance noise using FixSatChans, FixFlatChans, and FixNotaNum" modules, respectively. Then, resampling was performed for downsampling the data from 10

Hz to 1 Hz using a Nyquist filter. Subsequently, baseline correction was performed to remove excessive baseline before and after the rest block using the TrimBaseline module. The resampled and trimmed data were then converted to optical density using the OpticalDensity module and further proceeded to obtain oxyhaemoglobin (HbO), deoxyhaemoglobin (HbR), and total hemoglobin (HbT) using the modified Beer–Lambert Law. Since HbO is a relatively more sensitive measure than HbR for detecting neural changes in individuals with neurological disorders, including autism (Yeung & Lin, 2021), the study used only HbO for the statistical analysis. Subsequently, first-level analysis was conducted using the robust autoregressive whitened correlation method in the advanced general linear model and measured correlation coefficient (r) between possible channel pairs. The r-values were then averaged within the left medial PFC, right medial PFC, left lateral PFC and right lateral PFC, which were eventually used for the second-level functional connectivity analyses.

5.6.4. fNIRS Functional Connectivity Analyses

To examine the effects of tDCS on PFC rsFC changes between the two groups of ASD participants, 2x2 repeated-measures ANOVA was conducted on the mean coherence (r) of the medial/lateral PFC of each hemisphere, with the familywise error rate maintained at alpha =.05 (i.e., p =.05/4 =.0125) for a significant effect for each ROI.

5.6.5. Brain-behavior Relationship

To explore the relationships among social functioning with information processing speed, CF, and rsFCT before and after the tDCS intervention, Pearson's correlation analyses were conducted at the whole group and subgroup levels by maintaining alpha =.05. Since the correlation analyses were exploratory, trends toward false discovery rate (FDR)-corrected significance at p <.1 were also reported.

5.7. Results

5.7.1. Demographic, Clinical, and Intellectual Profiles

The demographic, clinical and IQ profiles in Table 5.1 show that the cathodal and sham groups were matched by age, t (28) = 0.38, p = 0.71; IQ, t (28) = 0.39, p = 0.70; gender, χ^2 = 1.20, p = 0.27; handedness, χ^2 = 1.42, p = 0.23; and social skill, t (28) = 0.28, p = 0.78.

Table 5.1. Demographic, intellectual, and clinical characteristics of the ASD groups receiving cathodal, and sham stimulation.

Demographic Details	**Group**		**Statistics**		
	Cathode (n=15)	Sham (n=15)	t/χ^2	*df*	*p*
Mean chronological age in years (S.D.)	17.37 (2.26)	17.68 (2.18)	0.383	28	0.705
IQ (S.D.)	86.53 (19.48)	83.87 (18.01)	0.389	28	0.700
Gender (M:F)	12:03	14:01	[a]1.20	1	0.273
Handedness (R:L)	14:01	15:00	[a]1.42	1	0.233
Mean SRS-2 Total (S.D.)	105.27 (28.32)	108.13 (27.43)	0.282	28	0.780

Note:
Gender (M=male; F=female); Handedness (R=right-handed; L=left-handed); SRS-2: Social Responsiveness Scale- 2
[a] *The group comparison was conducted by Likelihood Ratio*

5.7.2. EC, Executive, Social, and Resting State Functional Connectivity of the PFC

The 2x2 repeated-measures ANOVA revealed that there was a significant *group*time* interaction on the activation control component of EC, F(1,26) = 4.37, p =.046, η_p^2 = 0.13. The follow-up post hoc paired t test with Bonferroni correction indicated that the enhancement of activation control was significant in the cathodal group, t(14) = 2.66, p =.019, d = 1.18, and in the sham group, t(12) = 2.38, p =.022, d = 1.23. The main and interaction effects for other EC subcomponents, including attention, inhibitory control, and

total score, were all nonsignificant (p >.05). There was also a significant interaction effect for social behavior measured using the SRS-2 total score, F(1,28) = 4.47, p =.043, η_p^2 = 0.13, and the subsequent post hoc paired t test indicated that cathodal stimulation induced significantly more social behavior, t(14) = 4.09, p =.007, d = 0.48, than sham stimulation, t(14) = 2.20, p =.034, d = 0.29. Additionally, there were also significant interaction effects on information processing efficiency, F(1,28) = 7.13, p =.012, η_p^2 = 0.22, cognitive flexibility F(1,28) = 7.81, p =.009, η_p^2 = 0.27, and the resting state functional connectivity of medial PFC, F(1,28) = 6.95, p =.025, η_p^2 = 0.09. The concurrent post hoc paired t test revealed that only cathodal stimulation induced significantly enhanced processing speed, t(14) = 2.23, p =.032, d = 0.65, cognitive flexibility, t(14) = 5.26, p =.000, d = 1.25, and rsFC, t(14) = -3.44, p =.007, d = 0.80. The post hoc paired t test for sham stimulation on processing speed, cognitive flexibility, and rsFC were nonsignificant (p >.05; Table 5.2).

Table 5.2: Comparison of changes in outcome measures between cathode and sham tDCS groups

Domain	Outcome measure	Group				Statistics	
		Cathode pre	Sham pre	Cathode post	Sham post	F (group*time interaction)	Post hoc t
Effortful control	Activation control	21.14 (2.01)	21.58 (1.90)	23.58 (2.11)	24.02 (2.05)	$F_{1,26} = 4.37$*	C: t(14) = 2.66* S: t(12) = 2.38*
	Attention control	14.56 (0.99)	15.17 (0.96)	16.08 (0.98)	16.69 (0.94)	$F_{1,26} = .061$	Not needed Not needed
	Inhibitory control	21.31 (2.17)	21.82 (2.06)	22.82 (2.32)	23.33 (2.21)	$F_{1,26} = 1.68$	Not needed Not needed
	EC-total	19.01 (1.40)	19.52 (1.33)	20.82 (1.46)	21.34 (1.39)	$F_{1,26} = 0.24$	Not needed Not needed
Social behavior	SRS-2 total score (S.D.)	105.27 (28.32)	104.60 (26.31)	91.07 (29.87)	97.67 (21.36)	$F_{1,28} = 4.47$*	C: t(14) = 4.09** S: t(14) = 2.20*
Processing speed	Processing speed composite (S.D.)	.91 (.99)	1.17 (1.44)	.34 (.68)	1.30 (1.53)	$F_{1,28} = 7.13$*	C: t(14) = 2.23* S: n.s.
Cognitive flexibility	Flexibility composite (S.D.)	1.40 (1.12)	.58 (1.22)	.13 (.86)	.21 (1.53)	$F_{1,28} =$ 7.81**	C: t(14) = 5.26*** S: n.s.
rsFC	Z-transformed coherence value (S.D.)	.27 (.16)	.35 (.21)	.40 (.14)	.31 (.22)	$F_{1,28} = 6.95$*	C: t(14) = -3.44** S: n.s.

Note: * p <.05; ** p<.01; ***p<.001*; C = Cathode; S = Sham; n.s. = not significant.*

5.7.3. Brain-behavior Relationship

Correlation analyses demonstrated that the cathodal-induced improvement in rsFC of the right medial PFC was significantly associated with information processing efficiency (p =.021) and cognitive flexibility (p =.015) enhancement. Additionally, information processing efficiency improvement was highly correlated with enhancement of cognitive flexibility in the cathodal tDCS group alone but not in the sham tDCS group (p =.003).

5.8. Discussion

This double-blind randomized pilot study aimed to examine the effectiveness of repetitive cathodal versus sham tDCS stimulations on temperamental EC and its associated constructs, including executive and social functions, in adolescents and adults with ASD. The study also aimed to understand cathodal and sham stimulation-induced resting-state PFC connectivity in autism. The current findings demonstrated that repetitive cathodal stimulation is an effective treatment modality for improving activation control of EC components, social communication, and flexible behavior in adolescents with ASD. Such observed effects were highly correlated with resting-state connectivity in the right medial PFC. The results of this study supported our hypotheses. First, repetitive cathodal tDCS improved social functioning in individuals with ASD. The result was consistent with previous preliminary findings, such that 20 min of inhibitory tDCS (1.5 mA) for 10 sessions enhanced autistic behaviors indexed by the Aberrant Behavior Checklist in adult participants with autistic disorder (D'Urso et al., 2015). Similarly, 15 min cathodal stimulation (2 mA) for 10 sessions could decrease stereotypic behavioral patterns and behavioral dysexecution in adults with high functioning autism. The observed improvement in social function is attributed to the development of cognitive flexibility skill, which utilizes flexible reasoning approaches while socializing people with various circumstances (Wang, Liu, & Feng, 2021). Put differently, our study implies that cathodal stimulation over the left dlPFC might increase flexible problem-solving skills across various social situations and eventually lead to improvement in overall social functioning.

Second, as expected, only cathodal stimulation over the left dorsolateral prefrontal cortex significantly increased resting state functional connectivity of the right medial prefrontal cortex, and the result was consistent with the neuroimaging meta-analytical findings showing that transcranial direct current stimulation over the left dorsolateral

prefrontal cortex promoted resting state connectivity of the right medial prefrontal cortex belonging to the default mode network (Chan, Yau, & Han, 2021). Moreover, the cathodal group alone showed a significant correlation among enhanced information processing efficiency with improvement in cognitive flexibility, social communication, and resting state functional connectivity of the right medial prefrontal cortex. In line with these correlation findings, previous studies have demonstrated that brain functional connectivity was associated with information processing efficiency (Gao et al., 2020; Küchenhoff et al., 2021). Previous studies also declared that individuals with ASD demonstrated slower information processing (Haigh, Walsh, Mazefsky, Minshew, & Eack, 2018) and displayed aberrant corticocortical connectivity both at rest (Murias, Webb, Greenson, & Dawson, 2007) and while performing cognitive tasks, including cognitive flexibility (Doesburg et al., 2013). Notably, the medial prefrontal cortex is considered a key region for information processing and was found to be hypo-connected in individuals with autism (Padmanabhan et al., 2017). Given these propositions, our findings imply that cathodal stimulation causes flexible processing of social information and thereby yields clinically noticeable improvement in social functioning. In addition to cathodal stimulation-induced neuropsychological mechanisms, the neurophysiological mechanism related to the E:I ratio in people with ASD was found to be heightened in the medial PFC (Trakoshis et al., 2020). Relatedly, a study on mice claimed that a higher E:I ratio in the medial PFC reduced the processing of synaptic information and social behavior (Yizhar et al., 2011). Therefore, it is reasonable to assert that cathodal stimulation over the left dlPFC could reduce the E. I ratio in the right medial PFC, which has yet to be verified in future RCTs.

Third, our findings about lack of group differences between sham and cathodal stimulations on total, attention and inhibitory control scores in EC index suggest that the electrical stimulations on the left DLPFC (F3) region might not tap EC functions in autism.

This notion has been supported by our recent fMRI meta-analysis on neural substrates underlying temperamental EC deficits in autism, which found that individuals with ASD showed deactivation in the left inferior frontal, left fusiform, and left precentral gyri during attention control; left anterior cingulate during inhibitory control; and left inferior frontal gyrus, left anterior cingulate, and left precuneus during cognitive flexibility tasks. Likewise, the anterior cingulate, dorsal-medial frontal cortex (DMFC), and left inferior frontal gyri were found to be neurological bases for social orientation, interindividual communications, joint attention, and perceiving emotions of other human beings (Chan & Han, 2020; Mundy, 2003). This finding suggests that EC deficits in autism were widely attributed to deactivation of the left inferior frontal and the left anterior cingulate gyri. Therefore, electrical stimulations on either of these brain sites might yield noticeable outcomes of EC function in individuals with ASD. Furthermore, it should be noted that PFC dysfunction was pronounced to have more attentional loading deficits in autism (Christakou et al., 2013), and thus cathodal and sham stimulations at this brain site might have produced comparable effects between the two groups on the attention control component of EC.

This pilot study was the first to compare the effect of repetitive cathodal versus sham stimulations on temperamental EC and its related measures, including EF and social functions, by examining the underlying mechanism of rsPFC functional connectivity in adolescents and adults with ASD. Since the two groups of participants were matched for age, IQ, sex, handedness, baseline social function and severity of ASD symptoms, 10 consecutive sessions of repetitive cathodal stimulation over the left dlPFC were a harmless and effective treatment for adolescents with autism. Nevertheless, the study shared a significant contribution for comprehending the effects of tDCS on ASD, and it was limited in several aspects. First, the study included neuropsychological tests that required a moderate level of comprehending guidelines; it included individuals with a full-scale IQ > 60, and they

constituted approximately 50% of the ASD population (Charman et al., 2011). Second, since the E:I ratio was only observed in males but not in females with ASD, the effects of cathodal tDCS were masked with real effects. Third, the small sample size allowed us to interpret the findings as a general trend but not as conclusive evidence. Fourth, the study lacked an actual control group; hence, improvements in cognitive, behavioral, and PFC connectivity domains could not be compared with the control group to determine whether such enhancements were free from learning effects and ensure that the findings are not mediated by the natural developmental patterns of autism. Fifth, the study included adolescents and adults within the age range of 14 to 21; thus, findings were limited to interpreting within this age group only. Finally, although gender was matched, the proportion of males versus females was large in the study, i.e., the number of male participants was relatively higher than the number of female participants in both the cathodal and sham groups. Hence, the findings will be interpreted with caution for female participants.

5.9. Conclusion

This double-blind preliminary RCT study compared the effects of cathodal and sham stimulations on effortful control, executive, social, and PFC functioning in adolescents and adults with autism. The study showed that repetitive cathodal and sham stimulations over the left dlPFC were effective and safe treatments for adolescents with ASD. The resultant outcome was influenced by the enhancement of functional connectivity in the right medial PFC, which is a key region for processing socially relevant information. Future studies incorporating larger males and broader IQ would be helpful to understand the E:I modulation and neurophysiological mechanism associated with cathodal stimulation.

CHAPTER 6: THESIS IMPLICATIONS

6.1. Overall Conclusion and Summary

This thesis has been entitled to pursue three primary aims: a) to study the neural bases of temperamental EC deficits in autism by synthesizing whole-brain fMRI studies, b) to examine EC and its association with EF, socioemotional, and PFC functioning in Chinese-Hong Kong children, adolescents, and adults with ASD, and c) to compare the effectiveness of tDCS versus sham stimulation on EC, EF, socioemotional, and PFC functioning in individuals with ASD.

The study addressing the first aim showed a significant reduction in brain activities across all EC components in the autism group compared to the HC group. Specifically, hypoactivation was apparent in the left inferior frontal gyrus (opercular part; VAN), left precentral gyrus (SMN), left fusiform gyrus (DAN), right cerebellum crus II (FPN), and right superior occipital gyrus (VN) during attention control; left anterior cingulate (DMN) and right angular gyri (DAN) during inhibitory control; and left anterior cingulate (DMN), left inferior frontal gyrus (FPN), and left precuneus (DAN) during cognitive flexibility tasks. The autism group further demonstrated age-increased deactivation in the right precentral gyrus, left inferior frontal gyrus during attention control, and left anterior cingulate cortex during cognitive flexibility tasks.

The study for the second aim revealed that children, adolescents, and adults with ASD showed poorer EC, executive, and socioemotional functions than healthy individuals. The children with ASD further demonstrated increased overall PFC activation and decreased right frontal connectivity during the frontal sensitive n-back task. Adolescents and adults with ASD only showed a significant reduction in intra- and interfrontal connectivity during the WCST. The EC status was not associated with PFC activation or connectivity during the n-back task in children or the WCST task in adolescents and adults with ASD. However, EC

was significantly correlated with social functioning alone in children and social and attention functions (reaction time task) in adolescents and adults.

The study for the third aim showed that cathodal tDCS elicited significantly increased activation control of EC, social, processing speed, cognitive flexibility profiles. Cathodal stimulation also induced more synchronization in the right medial PFC at rest, and such connectivity was associated with flexible behavior and efficient processing of information in patients with ASD.

6.2. Overall Implications of the Findings

The findings from the first study have yielded new insight into the neural bases underlying temperamental EC deficits in individuals with autism. Notably, the deactivation patterns found in the brain regions during attention control, inhibitory control, and cognitive flexibility components would serve as a potential site for noninvasive brain stimulation techniques to facilitate corresponding temperamental EC subcomponents in autism. The second and third studies have expanded prior knowledge that individuals with high-functioning autism significantly present with a greater degree of impairment in EC, EF, socioemotional, and PFC activations and connectivity. Such findings have been extended to Chinese-Hong Kong children, adolescents, and adults with high-functioning ASD. The association between significant EC deficits and social dysfunction (in children, adolescents, and adults) and attention skill impairment in adolescents and adults with autism provide a therapeutic basis for addressing EC deficits and would improve social and attention skills in the respective age groups, and vice versa. Nevertheless, the final study using tDCS stimulation showed a positive trend on improving activation control of EC, social function, cognitive flexibility, and processing speed in adolescents and adults with ASD, the observed

effects are still preliminary. Hence, definitive conclusion cannot be warranted for the utility of tDCS against sham stimulation to address issues related to EC, EF, socioemotional, and PFC functioning domains.

APPENDICES

7.1. Supplementary table 1: Between-group fMRI meta-analysis and meta-regression on EC components (attention, inhibitory control, and flexibility) with age as a covariate and regressor, respectively: Emotional components excluded and included only neutral stimuli

Brain regions with significant peak activation							Cluster breakdown	
Anatomical regions	ASD > TD/ASD < TD	Total voxels	MNI coordinates	SDM-Z	*p* (uncorrected)	*p* - TFCE corrected	Anatomical regions (Broadmann areas)	Network parcellation
Meta-analysis of attention with age as a covariate (n = 10)								
Left inferior frontal gyrus, triangular part	ASD > TD	31	-42,34,26	3.289	<.0005	n.s.	Left middle frontal gyrus (BA45, BA46) Left inferior frontal gyrus, triangular part (BA45, BA46) Corpus callosum	FPN
Right precentral gyrus	ASD > TD	15	34, 18,56	3.024	<.005	n.s.	Right precentral gyrus (BA4, BA6)	SMN
Left cerebellum, crus I	ASD < TD	192	-20, 78, 30	-3.392	<.0005	n.s.	Left cerebellum, crus I, II, (BA18) Left cerebellum, hemispheric lobule VI, VIIB	
Right cerebellum, hemispheric lobule	ASD < TD	137	24, 66, 20	-3.480	<.0005	n.s.	Right cerebellum, hemispheric lobule VI, (BA18, BA19, BA37) Right fusiform gyrus (BA19, BA37) Right inferior network, inferior longitudinal	

							fasciculus.	
Right cuneus cortex	ASD < TD	133	18, 74,36	-3.401	<.0005	n.s.	Right superior occipital gyrus (BA7, BA19, BA18) Right cuneus cortex (BA19, BA18, BA7)	
Left middle occipital gyrus	ASD < TD	63	-32, 72,24	-3.313	<.0005	n.s.	Left middle occipital gyrus (BA19, BA39) Left inferior network, inferior longitudinal fasciculus	VN
Left precentral gyrus	ASD < TD	40	-34, 16,60	-3.279	<.005	n.s.	Left superior longitudinal fasciculus I Left precentral gyrus (BA4, BA6)	SMN
Left inferior occipital gyrus	ASD < TD	40	-42, 76, 10	-2.998	<.005	n.s.	Left inferior occipital gyrus (BA19, BA37) Left temporal gyrus (BA37) Left fusiform gyrus (BA19)	VN
Right parahippocampal gyrus	ASD < TD	36	28, 34, 12	-3.045	<.005	n.s.	Right parahippocampal gyrus (BA20, BA37) Right hippocampus (BA20, BA37)	
Left fusiform gyrus	ASD < TD	6	-40, 62, 16	-2.689	<.005	n.s.	Left fusiform gyrus (BA37)	DAN (Top-down)
Left inferior temporal gyrus	ASD < TD	5	-42, 60, 10	-2.787	<.005	n.s.	Left inferior network, inferior longitudinal fasciculus Left inferior temporal gyrus (BA37)	
Left inferior frontal gyrus, opercular part	ASD < TD	5	-58,12,16	-2.741	<.005	n.s.	Left inferior frontal gyrus, opercular part (BA6, BA44)	VAN (Bottom-

up)

Meta-regression of attention with age as a regressor ($p < 0.05$)								
Right precentral gyrus	Decreasing activation with increasing age	86	28, 24,58	-2.216	0.013	n.s.	Right precentral gyrus (BA4, BA6)	SMN
Meta-analysis of inhibition with age as a covariate (n = 8)								
Right angular gyrus	ASD < TD	196	48, 72,30	-3.333	<.0005	n.s.	Right angular gyrus (BA19, BA39, BA7) Right middle occipital gyrus (BA19, BA39)	DAN (Top-down)
Left anterior cingulate/paracingulate gyri	ASD < TD	70	-2,26,20	-3.406	<.0005	n.s.	Left anterior cingulate/paracingulate gyri (BA24, BA32) Right anterior cingulate/paracingulate gyri (BA24) Left median network, cingulum	DMN
Meta-analysis of flexibility with age as a covariate (n = 8)								
Left anterior cingulate/paracingulate gyri	ASD < TD	388	0,40,16	-3.148	<.005	n.s.	Right and left anterior cingulate/paracingulate gyri (BA24,32) Left superior frontal gyrus, medial (BA32) Right median cingulate/paracingulate gyri (BA32)	DMN

Corpus callosum	ASD < TD	8	-18,46,28	-3.021	<.005	n.s.	Corpus callosum Left middle frontal gyrus (BA9)	
Left inferior frontal gyrus, triangular part	ASD < TD	7	-42,30,26	-2.888	<.005	n.s.	Left inferior frontal gyrus, triangular part (BA45, BA46, BA48) Left middle frontal gyrus (BA45, BA46)	FPN
Left precuneus	ASD < TD	3	-8, 70,48	-2.664	<.005	n.s.	Left precuneus (BA7)	DAN (Top-down)
Left inferior frontal gyrus, triangular part	ASD < TD	2	-44,28,20	-2.623	<.005	n.s.	Left inferior frontal gyrus, triangular part (BA48)	FPN
Meta-regression of flexibility with age as a regressor ($p < 0.05$)								
Left median cingulate/paracingulate gyri	Increasing activation with increasing age	13	-6, 38,54	1.705	0.044	n.s.	Left median cingulate/paracingulate gyri Left precuneus Left paracentral lobule	DMN
Left anterior cingulate/paracingulate gyri	Decreasing activation with increasing age	93	0,44,4	-2.064	0.019	n.s.	Left anterior cingulate/paracingulate gyri (BA10, BA32) Right anterior cingulate/paracingulate gyri, BA(10) Right superior frontal gyrus, medial (BA10)	DMN

Note: FPN = Fronto Parietal Network; SMN = Somato Motor Network; VN = Visual Network; DAN = Dorsal Attention Network; VAN = Ventral Attention Network; DMN = Default Mode Network.

7.2. fNIRS data analysis script (Adopted and modified from the AnalyzIR toolbox for obtaining individual participant's activation and connectivity)

```
folder='C:\Users\Dr. K. Karthikeyan\Desktop\n-back experiment';

raw=nirs.io.loadDirectory(folder,{'subject'});

% to create demographic table
nirs.createDemographicsTable(raw)

%% These codes fix "not a number, flat and saturated channels issues" that specially happen in Hitachi ETG4000

job = nirs.modules.FixNaNs;
job = nirs.modules.FixFlatChans(job);
job = nirs.modules.FixSatChans(job);

rawf = job.run(raw);

%% to get stim name for all listed subjects
nirs.getStimNames(raw)
% to get the stim name for single (the first) subject
nirs.getStimNames(raw(1))

%% Fix the stimulus information
j=nirs.modules.RenameStims;
j.listOfChanges={'Mark_2','zeroback'; 'Mark_3','oneback';...
    'Mark_4','twoback'};
rawf=j.run(rawf);
cond={'zeroback','oneback','twoback'};
for j=1:length(cond)
    for i=1:length(rawf);
        st=rawf(i).stimulus(cond{j});
        if(length(st.onset)<4)
            st.onset=[1; st.onset];
            st.dur=[0; st.dur];
            st.amp=[1; st.amp];
        end
```

```
        st.dur=st.onset([2 4])-st.onset([1 3]);
        st.onset([2 4])=[];
        st.amp([2 4])=[];
        rawf(i).stimulus(cond{j})=st;
    end
end

demo=readtable('daniel_demo.xlsx');
flds=demo.Properties.VariableNames;
for j=1:length(flds)
    for i=1:height(demo);
        if(iscellstr(demo.(flds{j})))
        demo.(flds{j}){i}(find(double(demo.(flds{j}){i})==39))=[];
        end
    end;
end
demo=unique(demo);
job=nirs.modules.AddDemographics;
job.varToMatch='ID';
job.demoTable=demo;
rawf=job.run(rawf);



%% default first level stats model (imported from nirs.viz.jobsmanager )


% STEP 1 ----  Import Data
job = nirs.modules.ImportData();
   job.Input = 'raw';
   job.override = 0;


% STEP 2 ----  Remove Files w/o Stim
job = nirs.modules.RemoveStimless(job);
```

```
% STEP 3 ----  Fix NaNs
job = nirs.modules.FixNaNs(job);
   job.ifFailReplaceWith = 1;


% STEP 4 ----  Resample
job = nirs.modules.Resample(job);
   job.Fs = 1;


% STEP 5 ----  Optical Density
job = nirs.modules.OpticalDensity(job);


% STEP 6 ----  Beer-Lambert Law
job = nirs.modules.BeerLambertLaw(job);
   job.PPF = 0.1;


% STEP 7 ----  Export Data
job = nirs.modules.ExportData(job);
   job.Output = 'Hb';


% STEP 8 ----  Trim Pre/Post Baseline
job = nirs.modules.TrimBaseline(job);
   job.preBaseline = 30;
   job.postBaseline = 30;


% STEP 9 ----  GLM via AR(P)-IRLS
job = nirs.modules.GLM(job);
   job.type = 'AR-IRLS';
```

```
  job.options = [];
  basis=Dictionary();
      default=nirs.design.basis.Canonical;
          default.peakTime=4;
          default.uShootTime=16;
          default.peakDisp=1;
          default.uShootDisp=1;
          default.ratio=0.16667;
          default.duration=32;
          default.incDeriv=0;
      basis('default')=default;
  job.basis=basis;
  job.verbose = 1;
  job.trend_func = @nirs.design.trend.constant;
  job.goforit = 0;


% STEP 10 ----  Export Data
job = nirs.modules.ExportData(job);
  job.Output = 'SubjStats';


job.run(rawf);

% Individual Subject Statistics for activation (beta and t-stats) is obtained by
nirs.util.write_xls('Yf3_nb_act.xls',SubjStats(1,1).table,'Sheet1')

%% Indiavidual Subject Statistics for connectivity (R and Z scores) is obtained by
job=advanced.nirs.modules.GLMResiduals;
job.GLMjob;
res=job.run(Hb);
res(1).draw;
job;
job=nirs.modules.Connectivity;
job.divide_events=true;
```

```
job.min_event_duration=30;
job.ignore=5;
ConnStats=job.run(res);

% To obtain individual subject connectivity statistics
nirs.util.write_xls('Yf26_nb_con.xls',ConnStats(1,1).table,'Sheet1')
```

7.3: Description and customized MATLAB scripts for estimating a subject wise region of interest (ROI) connectivity

Connectivity value is simply the measure of correlation between two channels' activation, which falls between -1 and 1. Connectivity is estimated by the Matlab based NIRS toolbox called "AnalyzIR" which measures channel by channel correlation at first, e.g., channel 1 to 2,3,4, 5…52; channel 2 to 3, 4, 5 …. 52; 52; The channel 2 to 3, 4, 5…52; The channel 3 to 4, 5, 6…52 and so on for the remaining 52 channels (The MATLAB script is given in the supplementary 2). Secondly, the channels (ch) located on the right inferior frontal gyrus (IFG; ch3, ch14, ch24, ch35, ch45) and left IFG (ch8, ch18, ch29, ch39, ch50); right middle frontal gyrus (MFG; ch4, ch25, ch46) and left MFG (ch7, ch28, ch49); and right superior frontal gyrus (SFG; ch5, ch26, ch47) and left SFG (ch6, ch27, ch48) were determined and defined as preferrable region of interests.

The individual connectivity data of listed channels in the specified ROIs was then utilized to produce six patterns of connectivity such as intra-hemisphere within ROI (Right & left), intra-hemisphere between ROI (right and left), inter-hemisphere within ROI, and inter-hemisphere between ROIs for every participant using custom made MATLAB script (Given in the appendices A, B, C, D). The channel pairs of each connectivity pattern differ from one another, for example, the right and left intra-hemisphere within ROI is the grand average of channel pairs within SFG, MFG, and IFG itself on the respective frontal sides. The right and left intra-hemisphere between ROI are the mean estimation of channel pairs between one ROI to the other ROI (s) on the respective frontal sides, e.g., channels of SFG with MFG and IFG, and channels of MFG with IFG. The inter-hemisphere connectivity is derived by estimating channel pairs between right and left frontal lobes, such that, the inter-hemisphere within ROI is an estimation of grand average between the channel pairs of right and left SFG, right and left MFG, and right and left IFG. Finally, the inter-hemisphere between ROI is the grand average of channel pairs combining the right SFG with left MFG and left IFG; right MFG with left SFG and left IFG; and right IFG with left SFG and left MFG (Supplementary 3a, 3b, 3c, & 3d).

7. 3a) Intrahemispheric Within ROI Connectivity (Figure 3.4 a)

```
%% Determine channels which correspond to certain pairs of sources and detectors

% Connectivity denotes correlations between different channels. However,
% original files don't include channel information. So first we need to
% determine channels according to pairs of sources and
% detectors,e.g.channel 11 corresponds to source 1 and detector 6.

% load template data to determine origin and destination channels.You can
% open this file to check. This template comes from sorted file 'Yt2_1_1Mpost_rest_con.xls'.
Data1 = readtable('Template.xls'); % Attention: do not put this template into 'fileFolder' mentioned in Line 53.
Data2 = Data1(:,[4 5 8 9]); % extract useful columns with information of locations
Rows = strcmpi(Data2.TypeOrigin,Data2.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
Data3 = Data2(Rows,:); % extract marked data

% Mark ROI in analysis of connectivity 1. The following pairs can be found
% in Picture 1 to 3. It is a short range connectivity 1.
Location_FM_R = (Data3.originChannels==4 & Data3.destinationChannels==25)... % Frontal middle_Right
        + (Data3.originChannels==4 & Data3.destinationChannels==46)...
        + (Data3.originChannels==25 & Data3.destinationChannels==46);
Location_FM_L = (Data3.originChannels==7 & Data3.destinationChannels==28)... % Frontal Middle_ Left
        + (Data3.originChannels==7 & Data3.destinationChannels==49)...
        + (Data3.originChannels==28 & Data3.destinationChannels==49);
Location_FS_R = (Data3.originChannels==5 & Data3.destinationChannels==26)... % Frontal Superior_Right
        + (Data3.originChannels==5 & Data3.destinationChannels==47)...
        + (Data3.originChannels==26 & Data3.destinationChannels==47);
Location_FS_L = (Data3.originChannels==6 & Data3.destinationChannels==27)... % Frontal Supeiror_Left
        + (Data3.originChannels==6 & Data3.destinationChannels==48)...
        + (Data3.originChannels==27 & Data3.destinationChannels==48);
Location_FI_R = (Data3.originChannels==3 & Data3.destinationChannels==14)... % Frontal Inferior_Right
        + (Data3.originChannels==3 & Data3.destinationChannels==24)...
        + (Data3.originChannels==3 & Data3.destinationChannels==35)...
        + (Data3.originChannels==3 & Data3.destinationChannels==45)...
        + (Data3.originChannels==14 & Data3.destinationChannels==24)...
        + (Data3.originChannels==14 & Data3.destinationChannels==35)...
```

```
        + (Data3.originChannels==14 & Data3.destinationChannels==45)...
        + (Data3.originChannels==24 & Data3.destinationChannels==35)...
        + (Data3.originChannels==24 & Data3.destinationChannels==45)...
        + (Data3.originChannels==35 & Data3.destinationChannels==45);
Location_FI_L = (Data3.originChannels==8 & Data3.destinationChannels==18)... % Frontal Inferior_ Left
        + (Data3.originChannels==8 & Data3.destinationChannels==29)...
        + (Data3.originChannels==8 & Data3.destinationChannels==39)...
        + (Data3.originChannels==8 & Data3.destinationChannels==50)...
        + (Data3.originChannels==18 & Data3.destinationChannels==29)...
        + (Data3.originChannels==18 & Data3.destinationChannels==39)...
        + (Data3.originChannels==18 & Data3.destinationChannels==50)...
        + (Data3.originChannels==29 & Data3.destinationChannels==39)...
        + (Data3.originChannels==29 & Data3.destinationChannels==50)...
        + (Data3.originChannels==39 & Data3.destinationChannels==50);

%% Calculate the first kind of connectivity

% Load all the files with raw fNIRS data.
fileFolder=fullfile('E:\Data ana_project4_fnirs\wisconsin\Yt2_wis_connectivity result');% The file folder should only have all files requiring analysis.
dirOutput=dir(fullfile(fileFolder,'*.xls'));
fileNames={dirOutput.name}';
Size_files = size(fileNames);
Connec_bho_1 = zeros(Size_files(1),6); % initiate matrix of connectivity results.
Connec_bhr_1 = zeros(Size_files(1),6); % initiate matrix of connectivity results
% calculate data of each subject
for i = 1:Size_files(1)
    filename = fileNames{i};
    Data1 = readtable(filename); % load data
    Data1 = sortrows(Data1,4); % sort raw data in the column of TypeOrigin.You can find that the template data also has been sorted.
    Data1 = sortrows(Data1,7); % sort raw data in the column of TypeDest.
    Rows = strcmpi(Data1.TypeOrigin,Data1.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
    Data2 = Data1(Rows,:); % extract marked data

    % Extract data of ROI. Because the template data has been sorted, so we
    % can use these locations directly. For the sake of check, you can
```

```
    % compare the columns of SourceOrigin, DetectorOrigin,
    % SourceDest,DetectorDest between template and any files having been
    % sorted with Line 63 and 64.
    Connec_R = Data2(logical(Location_FM_R + Location_FS_R + Location_FI_R),8:9); % 8:9 means we extract these two columes of numbers.
    Connec_L = Data2(logical(Location_FM_L + Location_FS_L + Location_FI_L),8:9);
    Connec_ALL = Data2(logical(Location_FM_L + Location_FS_L + Location_FI_L +...
            Location_FM_R + Location_FS_R + Location_FI_R),8:9);

    % Calculate three kinds of connectivity averages
    Connec_hbo_1(i,1:2) = mean(Connec_R{1:size(Connec_R,1)/2,:});
    Connec_hbo_1(i,3:4) = mean(Connec_L{1:size(Connec_L,1)/2,:});
    Connec_hbo_1(i,5:6) = mean(Connec_ALL{1:size(Connec_ALL,1)/2,:});
    Connec_hbr_1(i,1:2) = mean(Connec_R{size(Connec_R,1)/2+1:end,:});
    Connec_hbr_1(i,3:4) = mean(Connec_L{size(Connec_L,1)/2+1:end,:});
    Connec_hbr_1(i,5:6) = mean(Connec_ALL{size(Connec_ALL,1)/2+1:end,:});
end

% Make the connectivity result more readable.
Connectivity_hbo_1 = array2table(Connec_hbo_1,'VariableNames',{'R1', 'R2', 'L1', 'L2', 'ALL1', 'ALL2'});
Connectivity_hbo_1.Name = fileNames;
Connectivity_hbo_1 = movevars(Connectivity_hbo_1,'Name','Before','R1'); % THIS IS THE FINAL RESULT.
Connectivity_hbr_1 = array2table(Connec_hbr_1,'VariableNames',{'R1', 'R2', 'L1', 'L2', 'ALL1', 'ALL2'});
Connectivity_hbr_1.Name = fileNames;
Connectivity_hbr_1 = movevars(Connectivity_hbr_1,'Name','Before','R1'); % THIS IS THE FINAL RESULT.
% writetable(Connectivity_hbo_1,'The first kind of hbo connectivity.xls'); % If necessary, you can save the result as excel-type file.
% writetable(Connectivity_hbo_1,'SC1_rest_oxy.xls')
 writetable(Connectivity_hbo_1,'SC1_wis_oxy.xls')
% writetable(Connectivity_hbr_1,'The first kind of hbr connectivity.xls'); % If necessary, you can save the result as excel-type file.
% writetable(Connectivity_hbr_1,'SC1_rest_deoxy.xls')
 writetable(Connectivity_hbr_1,'SC1_wis_deoxy.xls')
```

7. 3b) Intrahemispheric Between ROI Connectivity (Figure 3.4 b)

```
%% Determine channels corresponded to certain pairs of sources and detectors
% The procedures of this analysis is same as Connectivity_mean_1.m. They
% are just different from each other in Locations of ROI. So please read
% comments in Connectivity_mean_1.m if you want to know how this analysis works.

Data1 = readtable('Template.xls'); % load template data to determine origin and destination channels
Data2 = Data1(:,[4 5 8 9]); % extract useful columns
Rows = strcmpi(Data2.TypeOrigin,Data2.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
Data3 = Data2(Rows,:); % extract marked data

% Mark ROI in analysis of connectivity 2. The following pairs can be found
% in Picture 4 to 7. It is a short range connectivity 2.
Location_R = (Data3.originChannels==4 & Data3.destinationChannels==5)...
        + (Data3.originChannels==4 & Data3.destinationChannels==26)...
        + (Data3.originChannels==4 & Data3.destinationChannels==47)...
        + (Data3.originChannels==4 & Data3.destinationChannels==3)...
        + (Data3.originChannels==4 & Data3.destinationChannels==14)...
        + (Data3.originChannels==4 & Data3.destinationChannels==24)...
        + (Data3.originChannels==4 & Data3.destinationChannels==35)...
        + (Data3.originChannels==4 & Data3.destinationChannels==45)...
        + (Data3.originChannels==25 & Data3.destinationChannels==5)...
        + (Data3.originChannels==25 & Data3.destinationChannels==26)...
        + (Data3.originChannels==25 & Data3.destinationChannels==47)...
        + (Data3.originChannels==25 & Data3.destinationChannels==3)...
        + (Data3.originChannels==25 & Data3.destinationChannels==14)...
        + (Data3.originChannels==25 & Data3.destinationChannels==24)...
        + (Data3.originChannels==25 & Data3.destinationChannels==35)...
        + (Data3.originChannels==25 & Data3.destinationChannels==45)...
        + (Data3.originChannels==46 & Data3.destinationChannels==5)...
        + (Data3.originChannels==46 & Data3.destinationChannels==26)...
        + (Data3.originChannels==46 & Data3.destinationChannels==47)...
        + (Data3.originChannels==46 & Data3.destinationChannels==3)...
        + (Data3.originChannels==46 & Data3.destinationChannels==14)...
        + (Data3.originChannels==46 & Data3.destinationChannels==24)...
```

```
        + (Data3.originChannels==46 & Data3.destinationChannels==35)...
        + (Data3.originChannels==46 & Data3.destinationChannels==45)...% upto heare R-FMG (chs 4,25, 46)
                                                                       % is connected with R-SFG and R-IFG.
        + (Data3.originChannels==5 & Data3.destinationChannels==3)...
        + (Data3.originChannels==5 & Data3.destinationChannels==14)...
        + (Data3.originChannels==5 & Data3.destinationChannels==24)...
        + (Data3.originChannels==5 & Data3.destinationChannels==35)...
        + (Data3.originChannels==5 & Data3.destinationChannels==45)...
        + (Data3.originChannels==26 & Data3.destinationChannels==3)...
        + (Data3.originChannels==26 & Data3.destinationChannels==14)...
        + (Data3.originChannels==26 & Data3.destinationChannels==24)...
        + (Data3.originChannels==26 & Data3.destinationChannels==35)...
        + (Data3.originChannels==26 & Data3.destinationChannels==45)...
        + (Data3.originChannels==47 & Data3.destinationChannels==3)...
        + (Data3.originChannels==47 & Data3.destinationChannels==14)...
        + (Data3.originChannels==47 & Data3.destinationChannels==24)...
        + (Data3.originChannels==47 & Data3.destinationChannels==35)...
        + (Data3.originChannels==47 & Data3.destinationChannels==45); % Upto here R-SFG (chs 5, 26, 47) connected with R-IFG

Location_L = (Data3.originChannels==6 & Data3.destinationChannels==7)...
        + (Data3.originChannels==6 & Data3.destinationChannels==28)...
        + (Data3.originChannels==6 & Data3.destinationChannels==49)... % L-SFG (ch6) to L-MFG
        + (Data3.originChannels==6 & Data3.destinationChannels==8)...
        + (Data3.originChannels==6 & Data3.destinationChannels==18)...
        + (Data3.originChannels==6 & Data3.destinationChannels==29)...
        + (Data3.originChannels==6 & Data3.destinationChannels==39)...
        + (Data3.originChannels==6 & Data3.destinationChannels==50)... % L-SFG (ch6) to L-IFG
        + (Data3.originChannels==27 & Data3.destinationChannels==7)...
        + (Data3.originChannels==27 & Data3.destinationChannels==28)...
        + (Data3.originChannels==27 & Data3.destinationChannels==49)...% L-SFG (ch27) to L-MFG
        + (Data3.originChannels==27 & Data3.destinationChannels==8)...
        + (Data3.originChannels==27 & Data3.destinationChannels==18)...
        + (Data3.originChannels==27 & Data3.destinationChannels==29)...
        + (Data3.originChannels==27 & Data3.destinationChannels==39)...
        + (Data3.originChannels==27 & Data3.destinationChannels==50)...% L-SFG (ch27) to L-IFG
```

```
    + (Data3.originChannels==48 & Data3.destinationChannels==7)...
    + (Data3.originChannels==48 & Data3.destinationChannels==28)...
    + (Data3.originChannels==48 & Data3.destinationChannels==49)...% L-SFG (ch48) to L-MFG
    + (Data3.originChannels==48 & Data3.destinationChannels==8)...
    + (Data3.originChannels==48 & Data3.destinationChannels==18)...
    + (Data3.originChannels==48 & Data3.destinationChannels==29)...
    + (Data3.originChannels==48 & Data3.destinationChannels==39)...
    + (Data3.originChannels==48 & Data3.destinationChannels==50)...% L-SFG (ch48) to L-IFG
    + (Data3.originChannels==7 & Data3.destinationChannels==8)...
    + (Data3.originChannels==7 & Data3.destinationChannels==18)...
    + (Data3.originChannels==7 & Data3.destinationChannels==29)...
    + (Data3.originChannels==7 & Data3.destinationChannels==39)...
    + (Data3.originChannels==7 & Data3.destinationChannels==50)... % L-MFG (ch7) to L-IFG
    + (Data3.originChannels==28 & Data3.destinationChannels==8)...
    + (Data3.originChannels==28 & Data3.destinationChannels==18)...
    + (Data3.originChannels==28 & Data3.destinationChannels==29)...
    + (Data3.originChannels==28 & Data3.destinationChannels==39)...
    + (Data3.originChannels==28 & Data3.destinationChannels==50)... %L-MFG (ch28) to L-IFG
    + (Data3.originChannels==49 & Data3.destinationChannels==8)...
    + (Data3.originChannels==49 & Data3.destinationChannels==18)...
    + (Data3.originChannels==49 & Data3.destinationChannels==29)...
    + (Data3.originChannels==49 & Data3.destinationChannels==39)...
    + (Data3.originChannels==49 & Data3.destinationChannels==50); % L-MFG (ch49) to L-IFG

%% Calculate the first kind of connectivity
fileFolder=fullfile('E:\Data ana_project4_fnirs\wisconsin\Yt2_wis_connectivity result');
dirOutput=dir(fullfile(fileFolder,'*.xls'));
fileNames={dirOutput.name}';
Size_files = size(fileNames);
Connec_hbo_2 = zeros(Size_files(1),6);
Connec_hbr_2 = zeros(Size_files(1),6);
% calculate data of each subject
for i = 1:Size_files(1)
    filename = fileNames{i};
    Data1 = readtable(filename); % load data
```

```
    Data1 = sortrows(Data1,4);
    Data1 = sortrows(Data1,7);
    Rows = strcmpi(Data1.TypeOrigin,Data1.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
    Data2 = Data1(Rows,:); % extract marked data


    % Extract data of ROI
    Connec_R = Data2(logical(Location_R),8:9);
    Connec_L = Data2(logical(Location_L),8:9);
    Connec_ALL = Data2(logical(Location_L + Location_R),8:9);

    % Calculate three kinds of connectivity averages
    Connec_hbo_2(i,1:2) = mean(Connec_R{1:size(Connec_R,1)/2,:});
    Connec_hbo_2(i,3:4) = mean(Connec_L{1:size(Connec_L,1)/2,:});
    Connec_hbo_2(i,5:6) = mean(Connec_ALL{1:size(Connec_ALL,1)/2,:});
    Connec_hbr_2(i,1:2) = mean(Connec_R{size(Connec_R,1)/2+1:end,:});
    Connec_hbr_2(i,3:4) = mean(Connec_L{size(Connec_L,1)/2+1:end,:});
    Connec_hbr_2(i,5:6) = mean(Connec_ALL{size(Connec_ALL,1)/2+1:end,:});
end

% Make the connectivity result more readable.
Connectivity_hbo_2 = array2table(Connec_hbo_2,'VariableNames',{'R1', 'R2', 'L1', 'L2', 'ALL1', 'ALL2'});
Connectivity_hbo_2.Name = fileNames;
Connectivity_hbo_2 = movevars(Connectivity_hbo_2,'Name','Before','R1'); % THIS IS THE FINAL RESULT.
Connectivity_hbr_2 = array2table(Connec_hbr_2,'VariableNames',{'R1', 'R2', 'L1', 'L2', 'ALL1', 'ALL2'});
Connectivity_hbr_2.Name = fileNames;
Connectivity_hbr_2 = movevars(Connectivity_hbr_2,'Name','Before','R1'); % THIS IS THE FINAL RESULT.
% writetable(Connectivity_hbo_2,'The second kind of hbo connectivity.xls'); % If necessary, you can save the result as excel-type file.
%writetable(Connectivity_hbo_2,'SC2_rest_oxy.xls')
writetable(Connectivity_hbo_2,'SC2_wis_oxy.xls')
% writetable(Connectivity_hbr_2,'The second kind of hbr connectivity.xls'); % If necessary, you can save the result as excel-type file.
%writetable(Connectivity_hbr_2,'SC2_rest_deoxy.xls')
writetable(Connectivity_hbr_2,'SC2_wis_deoxy.xls')
```

7. 3c) Interhemispheric Connectivity Within ROI (Figure 3.4 c)

```
%% Determine channels corresponded to certain pairs of sources and detectors
% The procedures of this analysis is same as Connectivity_mean_1.m. They
% are just different from each other in Locations of ROI. So please read
% comments in Connectivity_mean_1.m if you want to know how this analysis works.

Data1 = readtable('Template.xls'); % load template data to determine origin and destination channels
Data2 = Data1(:,[4 5 8 9]); % extract useful columns
Rows = strcmpi(Data2.TypeOrigin,Data2.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
Data3 = Data2(Rows,:); % extract marked data

% Mark ROI in analysis of connectivity 3. The following pairs can be found
% in Picture 8 to 9. It is a long range connectivity I
Location_FM = (Data3.originChannels==4 & Data3.destinationChannels==7)...
        + (Data3.originChannels==4 & Data3.destinationChannels==28)...
        + (Data3.originChannels==4 & Data3.destinationChannels==49)... % R-MFG(ch4) to L-MFG(ch7,28,49)
        + (Data3.originChannels==25 & Data3.destinationChannels==7)...
        + (Data3.originChannels==25 & Data3.destinationChannels==28)...
        + (Data3.originChannels==25 & Data3.destinationChannels==49)...% R-MFG(ch25) to L-MFG(ch7,28,49)
        + (Data3.originChannels==46 & Data3.destinationChannels==7)...
        + (Data3.originChannels==46 & Data3.destinationChannels==28)...
        + (Data3.originChannels==46 & Data3.destinationChannels==49); % R-MFG(ch46) to L-MFG(ch7,28,49)
Location_FS = (Data3.originChannels==5 & Data3.destinationChannels==6)...
        + (Data3.originChannels==5 & Data3.destinationChannels==27)...
        + (Data3.originChannels==5 & Data3.destinationChannels==48)...% R-SFG(ch5) to L-SFG(ch6,27,48)
        + (Data3.originChannels==26 & Data3.destinationChannels==6)...
        + (Data3.originChannels==26 & Data3.destinationChannels==27)...
        + (Data3.originChannels==26 & Data3.destinationChannels==48)...% R-SFG(ch26) to L-SFG(ch6,27,48)
        + (Data3.originChannels==47 & Data3.destinationChannels==6)...
        + (Data3.originChannels==47 & Data3.destinationChannels==27)...
        + (Data3.originChannels==47 & Data3.destinationChannels==48);% R-SFG(ch5) to L-SFG(ch6,27,48)
Location_FI = (Data3.originChannels==3 & Data3.destinationChannels==8)...
        + (Data3.originChannels==3 & Data3.destinationChannels==18)...
```

```
    + (Data3.originChannels==3 & Data3.destinationChannels==29)...
    + (Data3.originChannels==3 & Data3.destinationChannels==39)...
    + (Data3.originChannels==3 & Data3.destinationChannels==50)...% R-IFG (ch3) to L-IFG (ch8,18,29,39,50)
    + (Data3.originChannels==14 & Data3.destinationChannels==8)...
    + (Data3.originChannels==14 & Data3.destinationChannels==18)...
    + (Data3.originChannels==14 & Data3.destinationChannels==29)...
    + (Data3.originChannels==14 & Data3.destinationChannels==39)...
    + (Data3.originChannels==14 & Data3.destinationChannels==50)...% R-IFG (ch14) to L-IFG (ch8,18,29,39,50)
    + (Data3.originChannels==24 & Data3.destinationChannels==8)...
    + (Data3.originChannels==24 & Data3.destinationChannels==18)...
    + (Data3.originChannels==24 & Data3.destinationChannels==29)...
    + (Data3.originChannels==24 & Data3.destinationChannels==39)...
    + (Data3.originChannels==24 & Data3.destinationChannels==50)...% R-IFG (ch24) to L-IFG (ch8,18,29,39,50)
    + (Data3.originChannels==35 & Data3.destinationChannels==8)...
    + (Data3.originChannels==35 & Data3.destinationChannels==18)...
    + (Data3.originChannels==35 & Data3.destinationChannels==29)...
    + (Data3.originChannels==35 & Data3.destinationChannels==39)...
    + (Data3.originChannels==35 & Data3.destinationChannels==50)...% R-IFG (ch35) to L-IFG (ch8,18,29,39,50)
    + (Data3.originChannels==45 & Data3.destinationChannels==8)...
    + (Data3.originChannels==45 & Data3.destinationChannels==18)...
    + (Data3.originChannels==45 & Data3.destinationChannels==29)...
    + (Data3.originChannels==45 & Data3.destinationChannels==39)...
    + (Data3.originChannels==45 & Data3.destinationChannels==50);% R-IFG (ch45) to L-IFG (ch8,18,29,39,50)

%% Calculate the first kind of connectivity
fileFolder=fullfile('E:\Data ana_project4_fnirs\wisconsin\Yt2_wis_connectivity result');
dirOutput=dir(fullfile(fileFolder,'*.xls'));
fileNames={dirOutput.name}';
Size_files = size(fileNames);
Connec_hbo_3 = zeros(Size_files(1),8);
Connec_hbr_3 = zeros(Size_files(1),8);

% calculate data of each subject
for i = 1:Size_files(1)
   filename = fileNames{i};
```

```
    Data1 = readtable(filename); % load data
    Data1 = sortrows(Data1,4);
    Data1 = sortrows(Data1,7);
    Rows = strcmpi(Data1.TypeOrigin,Data1.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
    Data2 = Data1(Rows,:); % extract marked data

    % Extract marked data
    Connec_FM = Data2(logical(Location_FM),8:9);
    Connec_FS = Data2(logical(Location_FS),8:9);
    Connec_FI = Data2(logical(Location_FI),8:9);
    Connec_ALL = Data2(logical(Location_FM + Location_FS + Location_FI),8:9);

    % Calculate three kinds of averages
    Connec_hbo_3(i,1:2) = mean(Connec_FM{1:size(Connec_FM,1)/2,:});
    Connec_hbo_3(i,3:4) = mean(Connec_FS{1:size(Connec_FS,1)/2,:});
    Connec_hbo_3(i,5:6) = mean(Connec_FI{1:size(Connec_FI,1)/2,:});
    Connec_hbo_3(i,7:8) = mean(Connec_ALL{1:size(Connec_ALL,1)/2,:});
    Connec_hbr_3(i,1:2) = mean(Connec_FM{size(Connec_FM,1)/2+1:end,:});
    Connec_hbr_3(i,3:4) = mean(Connec_FS{size(Connec_FS,1)/2+1:end,:});
    Connec_hbr_3(i,5:6) = mean(Connec_FI{size(Connec_FI,1)/2+1:end,:});
    Connec_hbr_3(i,7:8) = mean(Connec_ALL{size(Connec_ALL,1)/2+1:end,:});
end

% Make the connectivity result more readable.
Connectivity_hbo_3 = array2table(Connec_hbo_3,'VariableNames',{'FM1', 'FM2', 'FS1', 'FS2', 'FI1', 'FI2','ALL1','ALL2'});
Connectivity_hbo_3.Name = fileNames;
Connectivity_hbo_3 = movevars(Connectivity_hbo_3,'Name','Before','FM1'); % THIS IS THE FINAL RESULT.
Connectivity_hbr_3 = array2table(Connec_hbr_3,'VariableNames',{'FM1', 'FM2', 'FS1', 'FS2', 'FI1', 'FI2','ALL1','ALL2'});
Connectivity_hbr_3.Name = fileNames;
Connectivity_hbr_3 = movevars(Connectivity_hbr_3,'Name','Before','FM1'); % THIS IS THE FINAL RESULT.
% writetable(Connectivity_hbo_3,'The third kind of hbo connectivity.xls'); % If necessary, you can save the result as excel-type file.
% writetable(Connectivity_hbo_3,'LC1_rest_oxy.xls')
writetable(Connectivity_hbo_3,'LC1_wis_oxy.xls')

% writetable(Connectivity_hbr_3,'The third kind of hbr connectivity.xls'); % If necessary, you can save the result as excel-type file.
```

```
% writetable(Connectivity_hbr_3,'LC1_rest_deoxy.xls')
writetable(Connectivity_hbr_3,'LC1_wis_deoxy.xls')
```

7. 3d) Interhemispheric Connectivity Between ROI (Figure 3.4 d)

```
%% Determine channels corresponded to certain pairs of sources and detectors
% The procedures of this analysis is same as Connectivity_mean_1.m. They
% are just different from each other in Locations of ROI. So please read
% comments in Connectivity_mean_1.m if you want to know how this analysis works.

Data1 = readtable('Template.xls'); % load template data to determine origin and destination channels
Data2 = Data1(:,[4 5 8 9]); % extract useful columns
Rows = strcmpi(Data2.TypeOrigin,Data2.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
Data3 = Data2(Rows,:); % extract marked data
 % Mark ROI in analysis of connectivity 4. The following pairs can be found
% in Picture 10.
LFI2RSF = (Data3.originChannels==8 & Data3.destinationChannels==5)... % Left Frontal Inferior to Right Superior Frontal
          + (Data3.originChannels==8 & Data3.destinationChannels==26)...
          + (Data3.originChannels==8 & Data3.destinationChannels==47)...
          + (Data3.originChannels==18 & Data3.destinationChannels==5)...
          + (Data3.originChannels==18 & Data3.destinationChannels==26)...
          + (Data3.originChannels==18 & Data3.destinationChannels==47)...
          + (Data3.originChannels==29 & Data3.destinationChannels==5)...
          + (Data3.originChannels==29 & Data3.destinationChannels==26)...
          + (Data3.originChannels==29 & Data3.destinationChannels==47)...
          + (Data3.originChannels==39 & Data3.destinationChannels==5)...
          + (Data3.originChannels==39 & Data3.destinationChannels==26)...
          + (Data3.originChannels==39 & Data3.destinationChannels==47)...
          + (Data3.originChannels==50 & Data3.destinationChannels==5)...
          + (Data3.originChannels==50 & Data3.destinationChannels==26)...
          + (Data3.originChannels==50 & Data3.destinationChannels==47);
 LFI2RMF = (Data3.originChannels==8 & Data3.destinationChannels==4)... % Left Frontal Inferior to Right Middle Frontal
          + (Data3.originChannels==8 & Data3.destinationChannels==25)...
          + (Data3.originChannels==8 & Data3.destinationChannels==46)...
          + (Data3.originChannels==18 & Data3.destinationChannels==4)...
```

```
        + (Data3.originChannels==18 & Data3.destinationChannels==25)...
        + (Data3.originChannels==18 & Data3.destinationChannels==46)...
        + (Data3.originChannels==29 & Data3.destinationChannels==4)...
        + (Data3.originChannels==29 & Data3.destinationChannels==25)...
        + (Data3.originChannels==29 & Data3.destinationChannels==46)...
        + (Data3.originChannels==39 & Data3.destinationChannels==4)...
        + (Data3.originChannels==39 & Data3.destinationChannels==25)...
        + (Data3.originChannels==39 & Data3.destinationChannels==46)...
        + (Data3.originChannels==50 & Data3.destinationChannels==4)...
        + (Data3.originChannels==50 & Data3.destinationChannels==25)...
        + (Data3.originChannels==50 & Data3.destinationChannels==46);
LFM2RFS = (Data3.originChannels==7 & Data3.destinationChannels==5)... % Left Frontal Medial to Right Frontal Superior
        + (Data3.originChannels==7 & Data3.destinationChannels==26)...
        + (Data3.originChannels==7 & Data3.destinationChannels==47)...
        + (Data3.originChannels==28 & Data3.destinationChannels==5)...
        + (Data3.originChannels==28 & Data3.destinationChannels==26)...
        + (Data3.originChannels==28 & Data3.destinationChannels==47)...
        + (Data3.originChannels==49 & Data3.destinationChannels==5)...
        + (Data3.originChannels==49 & Data3.destinationChannels==26)...
        + (Data3.originChannels==49 & Data3.destinationChannels==47);
LFM2RFI = (Data3.originChannels==7 & Data3.destinationChannels==3)... % Left Frontal Middle to Right Frontal Inferior
        + (Data3.originChannels==7 & Data3.destinationChannels==14)...
        + (Data3.originChannels==7 & Data3.destinationChannels==24)...
        + (Data3.originChannels==7 & Data3.destinationChannels==35)...
        + (Data3.originChannels==7 & Data3.destinationChannels==45)...
        + (Data3.originChannels==28 & Data3.destinationChannels==3)...
        + (Data3.originChannels==28 & Data3.destinationChannels==14)...
        + (Data3.originChannels==28 & Data3.destinationChannels==24)...
        + (Data3.originChannels==28 & Data3.destinationChannels==35)...
        + (Data3.originChannels==28 & Data3.destinationChannels==45)...
        + (Data3.originChannels==49 & Data3.destinationChannels==3)...
        + (Data3.originChannels==49 & Data3.destinationChannels==14)...
        + (Data3.originChannels==49 & Data3.destinationChannels==24)...
        + (Data3.originChannels==49 & Data3.destinationChannels==35)...
        + (Data3.originChannels==49 & Data3.destinationChannels==45);
```

```
LFS2RMF = (Data3.originChannels==6 & Data3.destinationChannels==4)... % Left Frontal Superior to Right Middle Frontal
        + (Data3.originChannels==6 & Data3.destinationChannels==25)...
        + (Data3.originChannels==6 & Data3.destinationChannels==46)...
        + (Data3.originChannels==27 & Data3.destinationChannels==4)...
        + (Data3.originChannels==27 & Data3.destinationChannels==25)...
        + (Data3.originChannels==27 & Data3.destinationChannels==46)...
        + (Data3.originChannels==48 & Data3.destinationChannels==4)...
        + (Data3.originChannels==48 & Data3.destinationChannels==25)...
        + (Data3.originChannels==48 & Data3.destinationChannels==46);
LFS2RFI = (Data3.originChannels==6 & Data3.destinationChannels==3)...% Left Frontal Superior to Right Frontal Inferior
        + (Data3.originChannels==6 & Data3.destinationChannels==14)...
        + (Data3.originChannels==6 & Data3.destinationChannels==24)...
        + (Data3.originChannels==6 & Data3.destinationChannels==35)...
        + (Data3.originChannels==6 & Data3.destinationChannels==45)...
        + (Data3.originChannels==27 & Data3.destinationChannels==3)...
        + (Data3.originChannels==27 & Data3.destinationChannels==14)...
        + (Data3.originChannels==27 & Data3.destinationChannels==24)...
        + (Data3.originChannels==27 & Data3.destinationChannels==35)...
        + (Data3.originChannels==27 & Data3.destinationChannels==45)...
        + (Data3.originChannels==48 & Data3.destinationChannels==3)...
        + (Data3.originChannels==48 & Data3.destinationChannels==14)...
        + (Data3.originChannels==48 & Data3.destinationChannels==24)...
        + (Data3.originChannels==48 & Data3.destinationChannels==35)...
        + (Data3.originChannels==48 & Data3.destinationChannels==45);
%% Calculate the first kind of connectivity
fileFolder=fullfile('E:\Data ana_project4_fnirs\wisconsin\Yt2_wis_connectivity result');
dirOutput=dir(fullfile(fileFolder,'*.xls'));
fileNames={dirOutput.name}';
Size_files = size(fileNames);
Connec_hbo_4 = zeros(Size_files(1),2);
Connec_hbr_4 = zeros(Size_files(1),2);

% calculate data of each subject
for i = 1:Size_files(1)
   filename = fileNames{i};
```

```
    Data1 = readtable(filename); % load data
    Data1 = sortrows(Data1,4);
    Data1 = sortrows(Data1,7);
    Rows = strcmpi(Data1.TypeOrigin,Data1.TypeDest); % mark data with same type in TypeOrigin and TypeDest(e.g.'hbo'and 'hbo')
    Data2 = Data1(Rows,:); % extract marked data

    % Extract marked data
    Connec_ALL = Data2(logical(LFI2RSF+LFI2RMF+LFM2RFS+LFM2RFI+LFS2RMF+LFS2RFI),8:9);

    % Calculate three kinds of averages
    Connec_hbo_4(i,1:2) = mean(Connec_ALL{1:size(Connec_ALL,1)/2,:});
    Connec_hbr_4(i,1:2) = mean(Connec_ALL{size(Connec_ALL,1)/2+1:end,:});
end
 % Make the connectivity result more readable.
Connectivity_hbo_4 = array2table(Connec_hbo_4,'VariableNames',{'R', 'Z'});
Connectivity_hbo_4.Name = fileNames;
Connectivity_hbo_4 = movevars(Connectivity_hbo_4,'Name','Before','R'); % THIS IS THE FINAL RESULT.
Connectivity_hbr_4 = array2table(Connec_hbr_4,'VariableNames',{'R', 'Z'});
Connectivity_hbr_4.Name = fileNames;
Connectivity_hbr_4 = movevars(Connectivity_hbr_4,'Name','Before','R'); % THIS IS THE FINAL RESULT.
% writetable(Connectivity_hbo_4,'The forth kind of hbo connectivity.xls'); % If necessary, you can save the result as excel-type file.
% writetable(Connectivity_hbo_4,'LC2_rest_oxy.xls')
writetable(Connectivity_hbo_4,'LC2_wis_oxy.xls')
% writetable(Connectivity_hbr_4,'The forth kind of hbr connectivity.xls'); % If necessary, you can save the result as excel-type file.
% writetable(Connectivity_hbr_4,'LC2_rest_deoxy.xls')
writetable(Connectivity_hbr_4,'LC2_wis_deoxy.xls')
```

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