ATYPICAL FRONTAL CONNECTIVITY ASSOCIATED WITH COGNITIVE DEFICITS IN CHILDREN WITH ASD: EVIDENCE FROM FNIRS STUDIES

CHAN MING CHUNG

PhD

The Hong Kong Polytechnic University

2024

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

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CHAN MING CHUNG

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

March 2024

CERTIFICATE OF ORIGINALITY

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_____Chan Ming Chung_____ (Name of student)

Abstract

This thesis aims to fill a research gap in the neurocognitive understanding of Autism Spectrum Disorder (ASD), a neurodevelopmental disorder marked by a spectrum of social, communicative, and behavioral challenges. Although ASD's behavioral aspects have been extensively studied, there remains a substantial void in comprehending the precise neural and executive functioning deficits that form the foundation of these challenges.

To address this, the thesis examines the interactions between executive dysfunction, abnormal prefrontal connectivity, and information processing challenges in ASD, utilizing functional near-infrared spectroscopy (fNIRS) alongside assessments of executive function. Initial findings reveal significant difficulties in tasks demanding cognitive flexibility, specifically tied to hypoconnectivity in the prefrontal cortex, particularly the bilateral lateral PFC. This condition underlies the compromised efficiency in information processing observed in individuals with ASD.

The work further delves into the impact of working memory load on prefrontal connectivity in children with ASD, unveiling distinct patterns of functional connectivity under varying memory demands. These insights shed light on the cognitive challenges linked to working memory and their broader implications for cognitive functioning within this population.

Finally, the thesis delves into the challenges individuals with ASD encounter in reading comprehension, underscoring that these difficulties may entrenched in executive dysfunctions. These challenges are closely linked to slower information processing speeds and diminished functional connectivity in the prefrontal cortex during complex cognitive

tasks, indicating a significant struggle among individuals with ASD in integrating complex information.

Although the focus of this research is on high-functioning individuals with ASD, it highlights the critical need for future studies to encompass a broader spectrum of ASD populations. The implications of these findings stretch beyond mere theoretical insights, paving the way for interventions and support mechanisms tailored to the nuanced needs of individuals with ASD.

Publications

Published Journal Articles

Chan, M. M., Chan, M. C., Yeung, M. K., Wang, S. M., Liu, D., & Han, Y. M. (2022). Aberrant prefrontal functional connectivity during verbal fluency test is associated with reading comprehension deficits in autism spectrum disorder: An fNIRS study. *Frontiers in Psychology*, *13*, 984777.

Chan, M. M., Chan, M. C., Lai, O. L. H., Krishnamurthy, K., & Han, Y. M. (2022). Abnormal prefrontal functional connectivity is associated with inflexible information processing in patients with Autism Spectrum Disorder (ASD): an fNIRS study. *Biomedicines*, *10*(5), 1132.

Han, Y. M., Chan, M. C., Chan, M. M., Yeung, M. K., & Chan, A. S. (2022). Effects of working memory load on frontal connectivity in children with autism spectrum disorder: a fNIRS study. *Scientific Reports*, *12*(1), 1522.

Please note that these publications form the basis of this thesis. Additional information is provided at the start of the relevant Chapters

Acknowledgments

First and foremost, I wish to extend my deepest gratitude to my supervisor, Dr. Yvonne Han, for her unwavering guidance, support, and mentorship throughout my PhD journey. Her expertise and insights have been invaluable, and her encouragement has motivated me to push boundaries. I am equally grateful to my co-supervisor, Prof. Kenneth FONG, You have all been a constant source of guidance and encouragement during my PhD.

Special appreciation goes to my classmates, Dr. Melody Chan and Dr. Karthikeyan Krishnamurthy. Sharing the same journey together through this academic venture has fostered intellectual growth and lasting friendships.

My time during the PhD would not have been the same without the camaraderie and support of countless peers and colleagues. To each one of you who contributed directly or indirectly to this journey, thank you.

To my family, I would like to thank my parents Tommy and Ruby and my brother Hei your unwavering belief in my abilities and your steadfast support have been the bedrock upon which this academic achievement stands. I owe this accomplishment to your love, encouragement, and sacrifices.

A heartfelt thank you to my girlfriend, Crystal. Your patience, understanding, and endless encouragement have been a constant source of strength. Your faith in me, even during the toughest times, has been a beacon of hope, and I am eager to see what our shared future brings.

In conclusion, this thesis, while an individual accomplishment, is a testament to the collective efforts, support, and belief of many. My gratitude to each one of you is immeasurable.

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Chapter 1: General Introduction

1.1 Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder that affects approximately one in 54 people worldwide (Maenner Shaw & Baio 2020). ASD is characterized by persistent social deficits and repetitive, restricted behaviors, activities, and interests that negatively impact daily occupational and social functioning (Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, 5th ed, 2013). Social communication deficits include reciprocal social interaction challenges, nonverbal social communication deficiencies (Papagiannopoulou et al., 2014), and difficulty preserving and comprehending relationships with others (Cohen, Leslie & Frith, 1985). Symptoms in the restricted and repetitive behaviors domain manifest in motor, verbal, nonverbal, and sensory modalities (south et al., 2005). Motor stereotypies, echolalia, insistence on sameness, ritualized behaviors, narrow interests, and hyperreactivity or hypoactivity toward sensory stimuli are examples of observed behaviors in the restricted and repetitive domain.

Since Leo Kanner's initial description in 1943, the conceptualization of autism has significantly evolved. Once viewed as a monolithic condition, it is now recognized as a spectrum of conditions ranging from mild to severe manifestations, with considerable heterogeneity within the ASD population. This recognition has led to a more nuanced understanding of ASD but also presents challenges in diagnosis and treatment, as individuals with ASD exhibit a diverse array of strengths, weaknesses, and needs. Long-term studies have demonstrated that developmental outcomes for individuals with autism vary significantly, even among those at the higher-functioning end of the spectrum. While some individuals with ASD achieve independence, obtain qualifications, and live fulfilling lives,

the majority struggle to attain self-sufficiency, secure full-time employment, or develop meaningful friendships (Howlin et al., 2004; Howlin et al., 2000; Szatmari et al., 1989).

Moreover, the increasing prevalence of ASD underscores its increasing significance as a public health concern (Baird et al., 2000 & Bertrand et al., 2001). The growing recognition of and changes in diagnostic criteria have likely contributed to this increase (Charman, 2002). The societal and economic impacts of ASD are profound and involve not only direct costs related to healthcare and educational services but also indirect costs such as lost productivity and family support needs. The lifetime cost per individual with ASD is estimated to exceed two million dollars, with national costs in the United States potentially surpassing ten trillion dollars in the next decade (Cakir et al., 2020). However, despite the high prevalence and social burden of ASD, the causes of this disease are not well understood, and there is currently no cure. Clinicians and educators have long debated the merits of different assessments and intervention strategies for treating ASD. However, the lack of knowledge of the causes and neurophysiological factors that underlie the cognitive deficits associated with ASD has made the development of innovative and effective interventions for children with ASD challenging. Hence, a greater understanding of the neural mechanisms and potential causes underlying the pervasive behavioral and cognitive dysfunctions associated with ASD is needed to develop effective strategies for helping children with this disorder.

1.2 Cognitive deficits in ASD

Autism spectrum disorder (ASD) has long been considered a disorder with significant variability in cognitive and behavioral presentations. This variability can be derived from the ASD diagnostic criteria, which are complex and change with development. For instance, some individuals with ASD do not smile or frown very much, and they also do not use gestures or express themselves verbally very often. Whereas some develop the ability to

produce productive speech and comprehend language, they may still struggle greatly with putting their language skills in social situations and/or have difficulty reading subtle nonverbal cues that regulate social relationships (Wozniak et al., 2017). Importantly, research indicates that these social interaction difficulties can persist or even worsen with age, potentially widening the social gap between individuals with ASD and their typically developing peers (Bal et al., 2015). Furthermore, behavioral rigidity is another challenge in individuals with ASD. A tendency toward repetitive behaviors and a strong preference for routine can significantly impact daily functioning and flexibility. Like social interaction difficulties, these behaviors can also become more pronounced with age, presenting ongoing challenges for individuals with ASD and their caregivers (Kissine et al., 2021).

These variations do not end in diagnosis-relevant characteristics but can also be observed in ASD-related cognitive functions. For example, individuals with high-functioning autism often present milder behavioral symptoms but may still encounter significant challenges in academic and social settings. Despite average or above-average intelligence, they may struggle with executive functioning, understand nuanced language such as humor, and adapt to new routines or environments. One explanation is that many core autism traits persist in these high-functioning children, such as rigidity, inflexibility, preference for rituals and repetitive behavior, and difficulty understanding complex language usage(Ozonoff et al., 2014).

Although the precise cognitive profile and underlying mechanisms governing cognitive processing in autism patients have not been determined, it is widely accepted that ASD involves abnormalities in various distinct yet related cognitive processes. Individuals with ASD have been shown to exhibit impairments in their 'theory of mind' (ToM), 'central coherence', and executive dysfunction. ToM refers to an individual's ability to attribute

mental states, such as beliefs, intentions, and desires, to themselves and others, as well as recognizing and respecting that others may hold different beliefs, intentions, and desires (Mitchell, 1997). The development of ToM is crucial for interpreting other people's mental and emotional states in everyday life, which in turn aids personal self-organization and self-regulation. Consequently, underdeveloped ToM hinders the understanding of the social world and the manifestation of socially accepted behaviors or the use of appropriate strategies in social settings (Doherty, 2008; Korkmaz, 2011). Similarly, the concept of 'weak central coherence' refers to the tendency in ASD to focus on details at the expense of the bigger picture, affecting the ability to process information in a holistic manner (Happe, 1999; Happe & Frith, 2006). These cognitive aspects, along with executive dysfunction, contribute significantly to the challenges faced by individuals with ASD in both social and nonsocial contexts.

1.3 Executive dysfunction in ASD

Since the 1960s, research has progressively revealed that individuals with autism spectrum disorder (ASD) often experience significant executive dysfunctions, which manifest as challenges in cognitive processes and behavior regulation. Early studies highlighted these differences, noting that individuals with ASD exhibited unique patterns in memory abilities and executive functioning compared to their typically developing counterparts. (O'Connor & Hermelin, 1967).

Executive function (EF) is a broad cognitive domain that encompasses various skills essential for executing complex behaviors and is mainly supported by the prefrontal cortex (Carlson et al., 2013). The processes of EF enable goal-directed and self-regulated behaviors, allowing us to make decisions, prioritize and sequence our actions, plan for the future, and cope with novel situations. (Miyake & Friedman, 2012). It is generally understood to be an umbrella

term encompassing a wide range of related but distinct cognitive processes, including working memory, inhibitory control, cognitive flexibility, fluency and planning (Demetriou et al., 2018; Diamond, 2013). Children with poor executive functioning often lack the necessary cognitive strategies to integrate and generalize what they have learned and to organize materials and tasks. Difficulties in planning and initiation, inability to multitask, problem adaptation to novel situations, poor self-regulation, or weak reasoning ability were observed in these children (El Wafa et al., 2020; Gordon et al., 2018).

Notably, the verbal memory of ASD individuals was found to be considerably weaker than that of age-matched and ability-matched controls (Boucher, 1981; Boucher & Lewis, 1989). Importantly, these cognitive shortcomings could not be solely explained by intellectual disability and were not confined to the verbal memory domain. A study by Ozonoff and Pennington (1991) demonstrated that even ASD individuals with average intelligence quotients (IQ) displayed deficits in both verbal memory and executive function (EF) when compared to control participants.

These findings are pivotal because they indicate that cognitive challenges in individuals with ASD are not solely attributable to intellectual disability and are not confined to a single domain, such as verbal memory.

In the subsequent sections, each mentioned executive function (EF) domain will be defined and accompanied by a brief overview of the neuropsychological research of ASD in these domains.

1.3.1 Working Memory. Working memory pertains to the short-term storage and processing of information. Baddeley's influential model of working memory (2012) identifies four main components: a phonological loop, a visuospatial sketchpad, an episodic buffer, and a central executive. The phonological loop manages and holds verbal and auditory information, while

the visuospatial sketchpad holds visual and spatial data. The episodic buffer combines data from both subsystems and long-term memory into a unified episodic representation, and the central executive ultimately brings this representation to conscious attention, modifies it as necessary, and returns it to the episodic buffer.

Although some studies report deficits in verbal or phonological working memory (Alloway et al., 2016; Andersen et al., 2013; Fried et al., 2016; Kiep & Spek, 2017; Minshew & Goldstein, 2001; Schuh & Eigsti, 2012), a significant body of research reveals that individuals with ASD, including children, adolescents, and adults, consistently demonstrate impairments primarily in visual and particularly visuospatial working memory (Barendse et al., 2013; Corbett et al., 2009; Funabiki & Shiwa, 2018; Geurts & Vissers, 2012; Goldberg et al., 2005; Sachse et al., 2013; Sinzig et al., 2008; Steele et al., 2007; Tse et al., 2019; Verté et al., 2005;). Happé et al. (2006) observed that spatial working memory discrepancies in childhood did not continue into adolescence. However, Luna et al. (2007) found that, compared to controls, people with ASD displayed weaker spatial working memory retention across all ages, even though their performance improved from childhood to adulthood. Conversely, Macizo et al. (2016) found no correlation between phonological working memory and age among children with ASD. However, recent meta-analyses have reported deficits in both visuospatial and verbal/phonological working memory in the ASD population (Habib et al., 2019; Lai et al., 2017).

1.3.2 Inhibition Inhibitory control is thought to include three distinct functions: prepotent response inhibition, interference control, and cognitive inhibition. Prepotent response inhibition involves restraining a dominant or automatic reaction. Interference control concentrates attention by disregarding immediate distractions. Cognitive inhibition

involves suppressing undesired thoughts and resisting interference from previously encountered information (Diamond, 2013; Friedman & Miyake, 2004). The extended literature presents varying conclusions regarding the specific inhibitory control impairments in autism spectrum disorder (ASD). Geurts et al. (2004) reported that while children with ASD had difficulties with prepotent response inhibition, their interference control abilities were comparable to those of typically developing children. Conversely, Adams and Jarrold (2012) reported that children with ASD showed competence in prepotent response inhibition tasks but faced challenges with interference control tasks. On the other hand, Christ et al. (2011) observed compromised interference control in children with ASD but noted intact response inhibition and proactive interference resistance. This finding is in contrast to that of earlier study (Christ et al., 2007). Ozonoff and Strayer (1997) found no differences between children with and without ASD in terms of response inhibition or interference control.

1.3.3 Flexibility. Cognitive flexibility is defined as the capacity to adapt one's thoughts or actions based on the demands of a given situation (Geurts, Corbett, & Solomon, 2009). Examples of cognitive flexibility behaviors include switching from one task to another or multitasking as well as changing behavior based on a new rule (Ionescu, 2012). While research has shown that individuals with ASD experience cognitive flexibility deficits linked to repetitive behaviors (South et al., 2007; Yerys et al., 2009), the findings are not consistent. Studies that have assessed cognitive flexibility in natural environments using the Behavior Rating Inventory of Executive Function (BRIEF) have indicated that individuals with ASD struggle with flexibility in everyday life (Gioia et al., 2002; Mackinlay et al., 2006).However, research conducted in clinical or research settings has produced more varied results regarding cognitive flexibility. In most studies that have identified cognitive flexibility deficits in individuals with autism, a clinical neuropsychological test called the Wisconsin Card Sorting Task (WCST) was used. Various studies employing the Wisconsin Card Sorting Task

(WCST) have shown deficits in altering sorting strategies among individuals with autism, encompassing various subtypes, ages, and cognitive abilities (Geurts et al., 2004; Goldstein et al., 2001; Pellicano et al., 2006; Tsuchiya et al., 2005). Additionally, a meta-analysis conducted by Willcutt and colleagues (2008) on the WCST revealed large differences in cognitive flexibility between individuals with autism and typically developing individuals. However, the majority of studies using other neuropsychological measures (e.g., the trail-making test) have reported mixed results. For instance, Lopez and colleagues (2005) found no difficulty with the trail-making test (TMT) in children and adults with ASD.

1.3.4 Fluency. Fluency, characterized by the capacity to produce original ideas or learned responses based on a specified rule (Bishop & Norbury, 2005), is considered a higher-order executive function (EF) (Vestberg et al., 2017; Vestberg et al., 2021). It involves working memory (Aita et al., 2018), inhibitory control (Escobar et al., 2018), and cognitive flexibility (Zhao et al., 2013). Past research has demonstrated that individuals with autism spectrum disorder (ASD) experience difficulty in semantic verbal fluency (Baxter et al., 2019; Yeung et al., 2019). In such tasks, participants are asked to voluntarily produce as many words as possible within a specified semantic category while refraining from providing repetitive and irrelevant responses. However, some have found no effect on the same task (Kenworthy et al., 2013). In addition, Baxter (2019) found an age-group interaction suggesting that the discrepancy in task performance between individuals with ASD and typically developing individuals diminishes after aging.

1.3.5 Planning. Planning refers to the process of selecting and executing a strategy in novel or familiar circumstances, where a series of coordinated actions need to be monitored, assessed, and adjusted according to a predetermined objective (Hill, 2004; Ward & Morris, 2005). This cognitive skill allows us to engage in adaptive behavior. From creating task lists

and scheduling meetings to managing our social lives and evaluating our actions (Dubbelink & Geurts, 2017). It is widely acknowledged that working memory has a crucial function in maintaining and coordinating planned sequences (Goela et al.,2001). Individuals with ASD are believed to face challenges in planning (e.g., Hill, 2004; Lopez et al., 2005; Van den Bergh et al., 2014). They often struggle to manage their daily routines, sustain (social) engagements, or deal with unstructured periods of time (Ozonoff et al., 2002). However, a review of studies examining planning performance in individuals with ASD using cognitive measures reveals inconsistent results, leading to uncertainty regarding the proficiency of this skill in individuals with ASD. For example, common neuropsychological tests used to evaluate planning, which indicate lower performance in individuals with autism spectrum disorder (ASD), include the Tower of London (Just et al., 2007) and the Tower of Cambridge (Ozonoff et al., 2004). However, Bolte and colleagues (2011) used the Tower of Hanoi to evaluate high-functioning individuals with ASD and found no differences in performance between typically developing individuals and individuals with ASD.

As seen in the above reviews, although executive dysfunction has been found to be one of the major components in explaining ASD deficits, not all the subdomains of multidimensional executive functions are affected in people with ASD (Liss et al., 2001; Pellicano, 2007) or not found in some ASD individuals. As such, numerous attempts have been made to delineate the specific executive deficits in ASD (Abbott et al., 2018; Cui et al., 2010; Geurts, Corbett, & Solomon, 2009; Geurts et al., 2004). In particular, Turner (1999) suggested that deficiencies in response inhibition, cognitive flexibility/set shifting, and generativity contribute to the manifestation of repetitive and restricted behaviors in individuals with ASD, and more recently, Lopez et al. (2005) found that a lack of cognitive flexibility best predicts the prevalence of ASD repetitive behaviors.

In addition, working memory is another area that has attracted much attention because it is thought to be involved in and underlie many of the cognitive deficits and behaviors observed in individuals with ASD, including cognitive flexibility, focusing, sustaining attention, abstract thinking, behavioral regulation, and learning abilities (Hughes et al., 1994; Ozonoff & McEvoy, 1994; Ozonoff et al.,1991). However, previous results were inconsistent with some research that found WM deficits in individuals with ASD (Crane et al., 2011; Happe et al., 2006; Joseph et al., 2005), while others found nonsignificant results (Gonzalez-Gadea et al., 2013; Koshino et al., 2008). The variability in findings across studies may be attributed to the lack of a standardized method of measuring EFs and differences in methodology, making it difficult to compare results (Liss et al., 2001). Others have suggested that individuals with ASD who have low and high functioning abilities may have distinct primary deficits underlying their executive dysfunctions, as indicated by the different types of repetitive and stereotyped behaviors they exhibit (Hughes, 2001; Turner, 1997). To better understand the underlying cognitive mechanisms that contribute to the development of ASD and to improve diagnostic accuracy and targeted interventions, it is important to determine the specificity of executive dysfunctions in ASD patients.

1.3.6 Building components of EFs

The exploration of specific executive dysfunctions in ASD, as discussed in the preceding sections, naturally leads to a broader inquiry into the foundational building blocks of executive functions. This holistic view is essential for understanding the interplay between various cognitive processes and how they collectively contribute to the executive function challenges observed in individuals with ASD.

The conceptualization of EF is diverse and multifaceted, with various models proposed to

elucidate its key components. These models serve as frameworks for understanding the intricate cognitive processes underpinning executive functioning and provide a basis for analyzing the specific deficits encountered in ASD.

One influential model in the study of EF is the work of Miyake and colleagues (2000), who utilized confirmatory factor analysis (CFA) to dissect the complex structure of EF. Their research identified three core components: inhibitory control, working memory, and cognitive flexibility (or shifting). These elements, while distinct, are interrelated and collectively contribute to the efficient functioning of higher-order cognitive processes. Later, Huizinga, Dolan, and van der Molen (2006) performed confirmatory factor analyses with participants of different ages (7, 11, 15, and 21 years old). Their analysis found partial support for Miyake's model, as only the WM/shifting measures (and no inhibition measures) loaded onto latent variables. Additionally, subsequent research by Miyake's group (2004) explored the two-factor model of EF and found that inhibitory control should be integrated within the constructs of working memory and cognitive flexibility. These models highlight the overlapping and interconnected nature of EF components, suggesting a more integrated approach to understanding executive dysfunction in ASD patients.

On the other hand, recent meta-analyses, such as those conducted by Lai et al. (2017) and Demetriou et al. (2018), have provided a comprehensive overview of EF impairments in individuals with ASD across multiple domains. These studies revealed that deficits in fluency/generation, working memory (WM), and cognitive flexibility are more pronounced in individuals with ASD than in individuals with other EF domains. Such impairments are particularly relevant in the context of social interaction and in moderating repetitive and stereotyped behaviors, as noted by Causton-Theoharis, Ashby, & Cosier (2009), and Geurts

et al. (2009). These deficits are intrinsically linked to the core symptoms of ASD, notably decreased socialization and increased restricted interests/stereotypic behaviors.

The impact of these EF deficits extends beyond social interactions, significantly influencing academic performance. As Han & Chan (2018) note, individuals with ASD, even those with normal intelligence, often face substantial challenges in acquiring and applying skills crucial for academic success. This is particularly evident in areas such as reading and writing, with reading comprehension being a notable area of difficulty. Despite having abilities in word reading that can sometimes surpass those of their typically developing peers, individuals with ASD often struggle with understanding and integrating complex textual information (Minguez et al., 2021). This challenge is compounded by the inherent difficulties in EF, as efficient reading comprehension involves not only decoding words but also the dynamic interplay of working memory, cognitive flexibility, and central executive control (Butterfuss & Kendeou, 2017). These processes are essential for organizing, integrating, and retrieving information from both the text and prior knowledge, as emphasized by McNamara & Magliano (2009).

Consequently, deficits in EF, particularly in managing and synthesizing information across different contexts, pose significant barriers to learning in individuals with ASD. The implications of these learning challenges are profound, affecting not only academic performance but also self-esteem and future opportunities in higher education and employment. As Friedman, Warfield, and Parish (2013) highlight, the educational struggles faced by children with ASD can have long-lasting effects, underscoring the need for tailored educational strategies that address these specific cognitive challenges. Therefore, understanding and supporting EF in ASD becomes crucial, not only for enhancing social and behavioral outcomes but also for facilitating academic achievement and lifelong learning."

1.4 Neural basis of executive dysfunction in ASD

Building on the discussion of executive dysfunctions in individuals with ASD in section 1.3, we now turn our attention to the underlying neurobiological mechanisms involved. This shift from observable behavioral patterns to realms of neurobiology is crucial. This study bridges our understanding of the outward manifestations of executive challenges observed in individuals with ASD and the internal neurophysiological processes that orchestrate these functions.

Neuroimaging and neurophysiological studies have consistently shown that significant executive function impairments in ASD patients are closely linked to aberrant processes in the frontal lobes (Ozonoff et al., 2004). Furthermore, during neuropsychological tasks assessing executive function (Hill, 2004; Neubauer & Fink, 2003), including visual planning (Minshew et al., 1997) and attentional and inhibitory processing (Raymaekers, Van der Meere, & Roeyers, 2004), individuals with ASD exhibit atypical activation, perfusion, and metabolic patterns in the frontal lobes. While it is widely accepted that the frontal cortex mediates central executive processes (Collette & Van der Linden, 2002), increasing evidence has shown that executive functioning in individuals with ASD also relies on the coordinated action of a broader network of brain regions (Han et al., 2013; Osaka et al., 2004). For example, frontal and parietal regions reportedly exhibit enhanced regional blood flow during nonverbal paired-associated tasks (Klingberg & Roland, 1998), and research using brain imaging has demonstrated that the fronto-parietal network is important in visuospatial working memory (McEvoy et al.,2001).

The complexity of these neural networks reflects the multifaceted nature of EF as an "on-line" coordination of various abilities essential for complex behaviors. As highlighted by

Denckla (2002) and further elaborated by Chan et al. (2011), the cognitive demand imposed by executive tasks—whether due to their inherent difficulty, semantic richness, or volume of information—directly influences the engagement and functioning of these neural networks. Therefore, if the tasks require mental effort or if the information is meaningful, semantically related, or in large quantities, this will result in greater cognitive demand for central executive processes (Chan et al., 2011).

1.5 Information processing speed and task complexity in ASD patients

Information processing speed, defined as the duration needed to process a set of information or the quantity of information that can be processed within a specific time frame, is a measure of how effectively the brain processes information, including registering and storing stimuli or retrieving previously stored information (Kail & Salthouse, 1994), is foundational to effective cognitive functioning. It significantly influences downstream cognitive abilities such as planning, memory, attention, and decision-making, primarily through its role in the integration of information (Salthouse, 1996).

ASD has been characterized as an information-processing disorder in which challenges in processing speed are a central feature (Minshew & Goldstein, 1998; Minshew et al., 1997). This is particularly evident in the difficulty individuals with ASD face in integrating multisensory information. For instance, children with ASD might struggle to follow instructions in a noisy environment due to their inability to filter out irrelevant stimuli, a task that involves simultaneous processing of auditory information and the exclusion of background noise (Kjelgaard & Tager-Flusberg, 2001; Just et al., 2004). Moreover, this processing difficulty is not uniform across all types of tasks. Individuals with ASD often exhibit disparities in processing complex versus simple information. While they may face

challenges in processing complex auditory or visual information, such as interpreting speech with nuanced meanings or recognizing facial expressions, they often retain, or even excel in, processing simpler forms of the same modality, such as pitch or shape recognition (Bonnel et al., 2010; Bertone et al., 2005; Dawson et al., 2004). This dichotomy extends to the realm of executive function, where tasks involving complex information processing, such as problem solving and reading comprehension, pose greater challenges than simpler tasks (Kenworthy et al., 2008).

Task complexity, therefore, acts as a cognitive load indicator. The brain's performance can be impacted when the cognitive load of a task exceeds the individual's processing capacity. In ASD, this manifests as increased difficulty with tasks that are inherently complex or complicated due to time constraints or volume (Williams et al., 2006). This observation aligns with findings suggesting that deficits in cognitive flexibility in ASD become more apparent in tasks demanding greater complexity, such as the Wisconsin Card Sorting Task (Eylen et al., 2011).

In addition, the pattern of slower reaction times or extended task completion durations in individuals with ASD, even in tasks where they perform comparably to typically developing peers, further supports this theory (Carmo et al., 2015; Carmo et al., 2017; Lever et al., 2015; Schmitt et al., 2019). This evidence collectively indicates that individuals with ASD may employ different information processing mechanisms, possibly underpinned by neurophysiological pathways distinct from those of their typical developing counterparts.

1.6 Disordered Connectivity in ASD Patients

Introduced in the 1970s, EF originally focused on cognitive processes associated with the frontal cortex, particularly those governing goal-oriented behavior and self-regulation (Posner et al., 2004). However, decades of research have expanded this understanding, illustrating

that EF relies on a sophisticated network of interconnected brain regions. For instance, working memory not only engages the dorsolateral cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) but also involves the medial premotor cortex, parietal cortex, and dorsal cingulate cortex, which form a widespread neural network (Owen et al., 2005). Similarly, cognitive flexibility, another key aspect of EF, is associated with the combined activity of the anterior cingulate cortex, inferior parietal lobule, and lateral prefrontal cortex (Buchsbaum et al., 2005). Moreover, substantial evidence points to frontal lobe dysfunction in ASD. For instance, a comprehensive neuroimaging meta-analysis revealed that children with ASD exhibited hypoactivation in the right inferior and anterior frontal gyri while performing executive function tasks that demanded switching and updating abilities (Zhang et al., 2020). In addition, Narita et al. (2012) observed atypical activation patterns in the left anterior prefrontal cortex of adults with ASD during a visuospatial delayed forgetting task. However, this represents only a portion of the broader picture; in recent years, research has begun to shift away from the view of ASD as a disorder localized to specific brain regions. Instead, it is increasingly conceptualized as involving multiple functional networks that span across the brain (Muller et al., 2011; Rippon et al., 2007). This perspective aligns with the information processing challenges in ASD. Given that both executive functions and daily social and cognitive behaviors involve communication between multiple brain regions, the disorder might stem from suboptimal neural pathways for processing both sensory and higher-order cognitive information. The atypical organization and communication between different brain regions in ASD might lead to inefficiencies in the integration and processing of sensory inputs, as well as higher-order cognitive functions such as reasoning, planning, and problem solving (Minshew & William, 2007; Belmonte et al., 2004). In fact, there is a growing body of evidence supporting alterations in functional connectivity within the brains of individuals with ASD, including the prefrontal cortex (PFC), during both task and resting

states. For example, Monk et al. (2009) reported underconnectivity between the posterior cingulate cortex and superior frontal gyrus in a resting-state condition among individuals with ASD. Han and Chan (2017) observed increased resting-state coherence in the frontal-parietal connections in individuals with ASD. Furthermore, Poustka et al. (2012) reported reduced frontal connectivity in individuals with ASD during working memory tasks, with the degree of connectivity significantly correlated with working memory performance and symptom severity. Nevertheless, it remains unclear whether these alterations can be categorized as global underconnectivity or local overconnectivity, as suggested by previous research (Hull et al., 2017; Just et al., 2012; Mohammad Rezazadeh et al.,2016). Despite this uncertainty, functional connectivity alterations in ASD patients are likely to play a critical role in the pathology of the disorder (Courchesne & Pierce, 2005; Just et al., 2004; Wass, 2011). Therefore, functional coupling both within and between brain regions, particularly the PFC, is essential for successful execution of executive function tasks. Altered functional connectivity in ASD patients may contribute to the observed deficits in executive function and information processing abilities.

Understanding the intricate relationship between altered neural connectivity and EF deficits in ASD patients is crucial. This understanding not only contributes to the body of knowledge about the neurodevelopmental underpinnings of ASD but also informs the development of targeted interventions. With these objectives in mind, the present study aimed to examine the relationship between functional connectivity alterations, specifically within the frontal cortex, and executive function impairment in individuals with ASD. By doing so, we seek to uncover the neural mechanisms that contribute to the observed cognitive and behavioral impairments in this population, potentially facilitating the development of effective treatments and interventions and identifying early neural markers for this disorder.

1.7 Mapping of functional near-infrared spectroscopy (fNIRS) to behavioral functioning

The fields of neurophysiology and neuroimaging have made substantial contributions to our knowledge of brain activity as well as of the neurological and psychiatric origins of a wide range of diseases**.** Electroencephalography (EEG), event-related brain potentials (ERPs), magnetoencephalography (MEG), positron emission tomography (PET), single positron emission computed tomography (SPECT), and functional magnetic resonance (fMRI) are some of the most frequently used imaging methods for greatly improving the understanding of a variety of brain-related disorders. However, there is still a great deal of understanding about these illnesses. This is largely attributable to the innate complexity of the neurobiological underpinnings of these illnesses and the mind itself. However, despite the complexity of the underlying mechanism, there are methodological strengths and limitations to each of the research approaches utilized to investigate brain function**.** As a result, we are hampered in our efforts to explain the neural underpinnings of neurological and psychiatric illnesses in both the laboratory and the real world. More complete knowledge of brain function and its disorders should result from the development of novel techniques that allow data to be obtained under more diverse situations than are achievable with existing neuroimaging systems**.**

Functional near-infrared spectroscopy, also known as fNIRS, is a noninvasive neuroimaging tool that measures changes in the concentrations of oxyhemoglobin and deoxyhemoglobin. fNIRS offers several features that allow neuroimaging investigations of

the cortex to be performed in clinical offices and under more natural, ecologically valid conditions. Because of its low cost, small size, portability, and wireless capability, fNIRS allows the construction of translational research and clinical investigations that have ecological validity beyond the reach of other neuroimaging technologies (Curtin & Ayaz, 2018).

1.7.1 Mechanism of fNIRS

In general, two of the physiological phenomena linked to brain activity can be measured with optical methods. First, the membrane potential of neurons fluctuates because of ionic fluxes (such as changes in sodium and potassium ions) across the cell membrane during neural activity. This kind of activity can be assessed using EEG or MEG. Another type of metabolism is glucose metabolism. Neuronal activity is fuelled by glucose metabolism, and an increase in neuronal activity will also increase the need for glucose and oxygen from the nearby capillary bed. In response to a decrease in blood sugar and oxygen levels, the brain increases cerebral blood flow (CBF) and cerebral blood volume (CBV) through a process known as neurovascular coupling. Over the course of a few seconds, the elevated CBF brings glucose and oxygen to the region, the latter carried by oxygenated hemoglobin in the blood. (Fox et al., 1988).

Changes in the concentrations of oxygenated and deoxygenated hemoglobin (oxyHb and deoxyHb, respectively) can be detected during neurovascular coupling via optical techniques due to their distinctive optical qualities in the visible and near-infrared light ranges (650–900 nm) (Chance et al., 1998). Most biological tissues are almost transparent to light in this light range, largely because water, a fundamental building component of most tissues, absorbs extremely little energy at these wavelengths (Felix, 2013). The majority of photons emitted by the fNIRS device are introduced at the scalp, where they either pass through the tissues or

are absorbed by oxy-Hb and deoxy-Hb. A consistent number of these photons return to the surface of the scalp in a banana-shaped pattern, where they can be measured using photodetectors. Changes in chromophore concentrations (oxy-Hb and deoxy-Hb) lead to variations in the number of photons absorbed and the quantity of photons scattered back to the scalp's surface. By selecting wavelengths optimized for the absorption of oxy-Hb and deoxy-Hb, these changes can be quantified using a modified Beer–Lambert law as an empirical explanation for optical attenuation in highly scattering media (Cope & Delpy, 1988). Therefore, by monitoring absorbance shifts at two or more wavelengths that are sensitive to oxy-Hb and deoxy-Hb, changes in relative Hb levels can be determined, allowing for the inference of brain activity.

1.7.2 fNIRS and Brain Activation

Since its inception, fNIRS has been utilized in numerous cognitive tests involving participants actively engaging in functional activities that require high-level cognitive functions (Chance et al., 1993; Hoshi & Tamura, 1993; Mirelman et al., 2014). Generally, the hemodynamic response to a stimulus peaks approximately 5 seconds after stimulus onset and returns to baseline approximately 16 seconds poststimulus (Pinti et al., 2018). The collected data are then prepared for subsequent data analysis, such as event-locked or task-locked averaging of selected portions of the continuous fNIRS signal. Statistical tests can then be applied to these average activations for different events.

To verify the validity of fNIRS, several studies have been conducted to compare the metabolic correlates of cerebral activity detected by fNIRS (increase in oxy-Hb and decrease in deoxy-Hb) with that detected by fMRI (blood oxygenation level-dependent (BOLD) response). Several significant associations were discovered between the BOLD signal and

oxy-Hb and between the BOLD signal and deoxy-Hb (Huppert et al., 2006; Cui et al., 2011; Scarapicchia et al., 2017).

1.7.3 fNIRS and Functional Connectivity

Interconnected neural networks in the brain mediate complex cognitive processes (Sporns, 2011). In addition to assessing brain activation, fNIRS can also be employed to evaluate functional connectivity between brain regions. Functional connectivity examines the relationship between regional fluctuations in slow signals (0.1 Hz) throughout the brain. Compared to that of fMRI, the sample rate of common fNIRS systems is 10 Hz, providing optimal data for connectivity measures with a reduced risk of aliasing higher frequency activities (such as heart rate, 1 Hz) into lower frequencies (<0.1 Hz) (Lu et al., 2010). Regarding data analysis, traditional techniques initially developed for fMRI have been adapted for fNIRS use. One such example is the seed-based correlation method, where a single fNIRS channel serves as the seed, and all potential channel pairings can then be analyzed for their correlation or coherence across various frequency bands (Sasai et al., 2011). Over the past decade, fNIRS has been utilized to assess functional coupling between brain areas, particularly the prefrontal cortex (PFC), in the performance of various tasks. For instance, fNIRS has been employed to measure functional connectivity between two cortical regions underlying motor performance (Varshney & Liapounova; Golestani et al., 2012) and to evaluate intrahemispheric or interhemispheric connectivity within the dorsolateral PFC and frontal pole in the n-back task for healthy young adults (Fishburn et al., 2014; Sun et al., 2019).

1.7.4 Advantages of fNIRS

fNIRS offers several distinct advantages over fMRI. First, fNIRS provides greater temporal resolution, routinely allowing brain signals to be observed with a temporal sampling precision of 0.01 seconds, which is considerably faster than that of fMRI (Franceschini & Boas, 2004). The hemodynamic response to brain activation occurs on a time scale of approximately 1-2 seconds, and the improved temporal resolution in fNIRS enables better signal separation from motion artifacts or systemic physiological signals.

Another advantage of fNIRS is its tolerance of motion and environmental conditions, which makes it suitable for use with awake, engaged infants or pediatric patients who might exhibit uncontrolled motion during experiments. In contrast, fMRI studies often require infants to be asleep or sedated, limiting the types of experiments that can be conducted. Furthermore, fNIRS technology is more cost-effective, portable, and user-friendly than fMRI (Wilcox & Blondi, 2015).

When comparing fNIRS to EEG/ERP methods, the primary advantage of fNIRS is its higher spatial resolution. With effects located within 1-2 cm of the activated area, fNIRS allows for more precise identification of regions where cortical responses are detected than electrophysiological techniques (Tak, & Ye, 2014).

These unique properties make fNIRS a suitable tool for studying functional connectivity during executive function tasks in pediatric populations (Jasdzewski et al., 2003) and an appropriate choice for investigating functional connectivity in children with ASD.

1.7.5 fNIRS and ASDs

The use of fNIRS in studying ASD has become increasingly popular due to its unique advantages, and several studies have employed this technique to investigate brain function and connectivity in individuals with ASD. In a study by Khan et al. (2015), fNIRS was utilized to examine cortical responses to social and nonsocial stimuli in children with ASD and their typically developing peers. The findings revealed reduced cortical activation in response to social stimuli in the ASD group, providing evidence for atypical social processing in ASD patients.

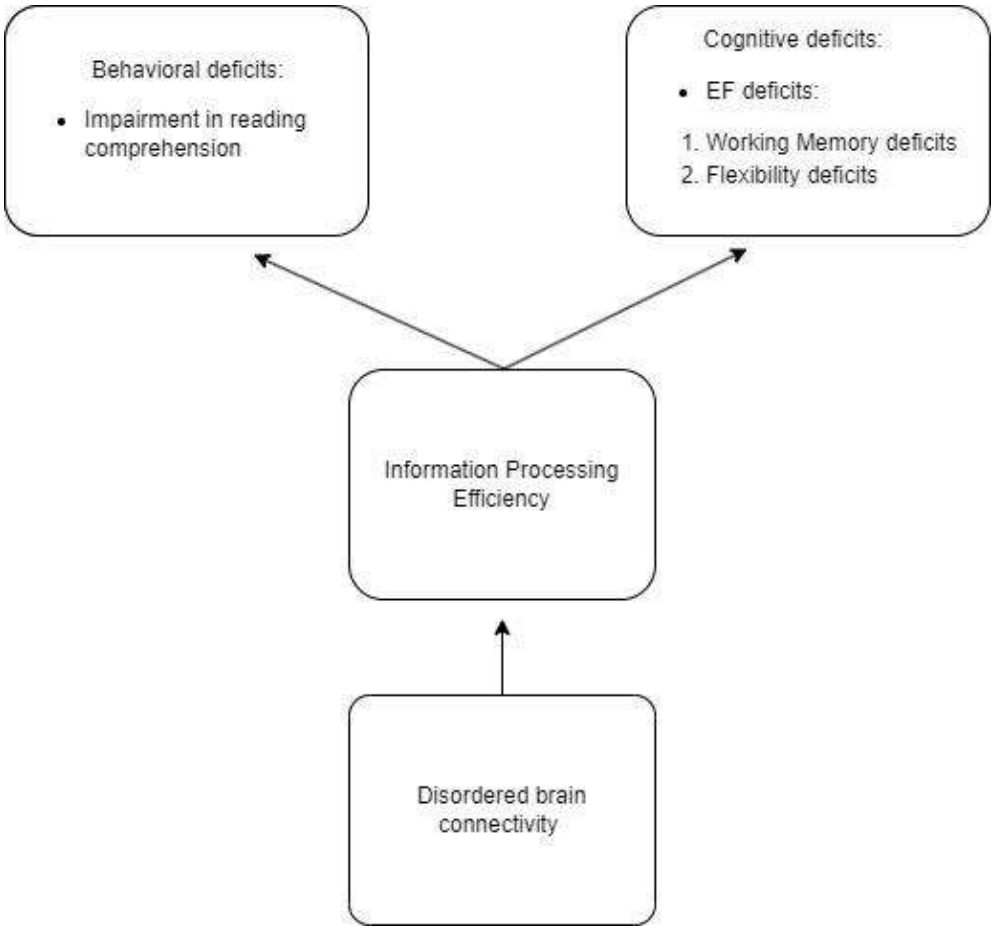
Similarly, Kita et al. (2011) employed fNIRS to investigate prefrontal cortex activation during a cognitive task in children with ASD. The study revealed that children with ASD exhibited atypical patterns of prefrontal activation, suggesting possible deficits in executive functioning.

In a study by Xiao et al. (2017), fNIRS was used to assess functional connectivity during a resting-state condition in children with ASD. The findings showed reduced functional connectivity within the frontal cortex and between the frontal and parietal regions, which could be related to the observed impairments in executive functioning and social cognition in ASD patients.

These studies highlight the potential of fNIRS as a valuable tool for investigating the neural correlates of ASD and for advancing our understanding of the underlying neurobiological mechanisms associated with this complex neurodevelopmental disorder.

1.8 Aims and objectives

Figure 1. *A diagram summarizing the conceptualization of the current thesis hypothesis*



The current thesis conceptualization is summarized in **Figure 1.** In summary, individuals with ASD exhibit a range of executive function problems, involving problems with working memory cognitive flexibility, and fluency is considered a core deficit in ASD. However, not all studies have shown impairments in these executive function domains in individuals with ASD. Individuals with ASD tend to have difficulty processing complex information but intact or even enhanced abilities for simple tasks, suggesting atypical information processing mechanisms and neurophysiology. Hence, atypical information processing problems, could affect higher-order behavioral aspects of ASD since these complex behaviors often involve

the ongoing transfer and observation of existing and updated data. These tasks rely heavily on central executive control and information processing abilities. Disrupted functional connectivity within the frontal lobe and between frontal and parietal regions has been well documented in the ASD literature, and abnormal organization and connectivity between various brain regions in individuals with ASD could result in inefficient processing and integration of sensory information. In other words, atypical neural pathways for processing information in the brains of individuals with ASD might impair the ability to combine and make sense of sensory inputs. Hence, these disorders can affect ASD both cognitively and behaviorally. However, the exact connection between changes in neural connectivity, particularly in frontal regions, and executive function (EF) deficits in individuals with ASD is not well understood. To address these existing gaps in related research, multiple related studies have been carried out, and the findings are presented across various chapters in this thesis. A brief overview of the rationales and aims of these studies can be found below.

To explore the above objectives, **chapter 2** sets out to investigate the association between altered prefrontal connectivity and cognitive inflexibility in individuals with ASD. Flexibility is one of the major components of EFs and serves as a basis for other EFs. It is crucial to better understand the neural underpinnings of the atypical information-processing mechanisms observed in ASD. **Chapter 3** aims to examine the impact of varying working memory demands on frontal connectivity in children with ASD. Since working memory is another core component of EFs, by assessing how changes in working memory load affect functional connectivity, this study seeks to reveal potential differences in neural mechanisms related to working memory in individuals with ASD compared to typically developing individuals. **Chapter 4** focuses on understanding the link between disrupted functional connectivity and executive function deficits that contribute to reading comprehension difficulties in individuals with ASD. Reading comprehension, an important skill in everyday

life, affects different areas of life, as well as quality of life, in ASD patients. In essence, reading comprehension, as a higher-order cognitive skill, depends on the efficient integration of various executive functions, such as working memory and flexibility, as well as the ability to process complex information. In individuals with ASD, atypical neural connectivity and information processing may directly impact their ability to understand and interpret text, leading to challenges in reading comprehension. As such, it is essential to examine the role of disrupted functional connectivity and executive function deficits in understanding the nature of reading comprehension difficulties in individuals with ASD, hence opening up new directions for developing effective strategies and treatment.

Chapter 2: Abnormal prefrontal functional connectivity is associated with inflexible information processing in individuals with autism spectrum disorder (ASD): An fNIRS study

A version of this chapter has been published in a peer-reviewed journal:

Chan, M. M., Chan, M. C., Lai, O. L. H., Krishnamurthy, K., & Han, Y. M. (2022). Abnormal prefrontal functional connectivity is associated with inflexible information processing in patients with Autism Spectrum Disorder (ASD): an fNIRS study *Biomedicines*, *10*(5), 1132.

2.1 Abstract

Individuals with autism spectrum disorder (ASD) are characterized by impairments in flexibly acquiring and maintaining new information, as well as in applying learned information for problem solving. However, the neural mechanism underpinning such impairments remains unclear. This study investigated the flexibility of the acquisition and application of visual information in individuals with ASD (aged 14–21 years) via the Wisconsin Card Sorting Test (WCST). Behavioral data, including response accuracy and latency and prefrontal hemodynamic data measured by functional near-infrared spectroscopy (fNIRS), were collected when individuals performed the WCST. Canonical general linear model and functional connectivity analyses were performed to examine the prefrontal activation and synchronization patterns, respectively. Although ASD individuals (n = 29) achieved comparable accuracy rates to those of age- and intelligence quotient (IQ)-matched typically developing (TD; n = 26) individuals ($F_{1,53} = 3.15$, $p = 0.082$), ASD individuals needed significantly more time to acquire and apply WCST card sorting rules ($F_{1,53} = 17.92$, p

< 0.001). Moreover, the ASD individuals showed significantly lower prefrontal functional connectivity than did the TD individuals during the WCST ($F_{1,42} = 9.99$, $p = 0.003$). The hypoconnectivity in ASD individuals was highly significant in the right lateral PFC in the acquisition condition ($p = 0.005$) and in the bilateral lateral PFC in the application condition ($ps = 0.006$). Furthermore, a shorter WCST reaction time was correlated with lower bilateral lateral PFC functional connectivity only in the application condition ($p = 0.003$) but not in the acquisition condition. Impairment in information acquisition and application is evident in ASD individuals and is mediated by processing speed, which is associated with lower functional connectivity in the bilateral lateral PFC when individuals apply learned rules to solve novel problems.

2.2 Introduction

Chapter 1 provides a comprehensive introduction to autism spectrum disorder (ASD), outlining its clinical features, the complexity of its cognitive deficits, and the challenges it presents in both social and occupational functioning. Drawing on this foundational understanding, Chapter 2 ventures into a specific exploration of the neurobiological aspects of ASD, focusing on the role of prefrontal functional connectivity in the disorder's cognitive abilities.

Autism spectrum disorder (ASD) patients exhibit marked impairment in adjusting behaviors to accommodate different social situations (Russell et al., 2012) and demonstrate strong adherence to inflexible routines (Han & Chan, 2018). Given that the ability to adjust behaviors to ever-changing daily situations has been shown to be associated with cognitive flexibility (Duncan, 2010), some researchers have hypothesized that deficits in cognitive flexibility may underpin the behavioral manifestations of ASD (Memari et al., 2013; Van Eylen et al., 2011).

Cognitive flexibility has long been conceptualized as a vital ability for humans to process daily environmental information; this ability comprises cognitive processes to acquire and maintain new information and to apply learned information for problem solving (Armbruster-Genç et al., 2016; Duncan, 2010; Kehagia et al., 2010; Vatansever et al., 2017). The Wisconsin Card Sorting Task (WCST) is one of the many neuropsychological tests tapping into cognitive flexibility that has been extensively used in both healthy and clinical populations (Miles et al., 2021; Uddin, 2021; Westwood et al., 2016). The WCST requires participants to sort the response cards correctly with several stimulus cards through feedback given to them based on a rule (Coulacoglou & Saklofske, 2017). This task can be operationally stratified into substages tapping into an individual's ability to process information, in particular, the acquisition and maintenance of new information, as well as the application of learned information (Vatansever et al., 2017). For ASD individuals, the WCST has been revealed to be the only cognitive flexibility task that has reflected consistent deficits in this aspect (Landry & Al-Taie, 2016). Specifically, Van Eylen et al. (2011) showed that, compared to their typically developing (TD) counterparts, ASD individuals tend to produce more perseveration errors and require more processing time to respond when the card sorting rules change. A neurophysiological study conducted by Yeung, Han, Sze, and Chan (2016) further showed that abnormal neurophysiological findings in the frontal cortex of ASD

patients were associated with reduced accuracy and increased latency in WCST task performance. These studies collectively imply that cognitive flexibility deficits in ASD patients represented by a reduction in WCST task accuracy are possibly modulated by information processing speed, as reflected by an increased latency to complete tasks, and that impaired performance may be associated with abnormal frontal cortex functioning in these individuals.

A previous meta-analysis has shown that during both the rule acquisition and application stages of the WCST, brain regions within the prefrontal cortex (PFC), which includes the bilateral inferior, middle and superior/medial frontal gyri, as well as the anterior cingulate gyrus, are predominantly activated (Buchsbaum et al., 2005). Increasing evidence reveals that integrated activities, specifically the neural connectivity between these brain regions, underpin WCST performance (Carrillo-De-La-Pena & García-Larrea, 2007; Zhang et al., 2017). Given the strong dependence on the integrated actions of frontal brain regions for the WCST, for individuals with ASD who are known to have frontal lobe abnormalities (Teffer & Semendeferi, 2012; Yeung et al., 2016) and abnormal neural connectivity (Han & Chan, 2017), it is reasonable to speculate that altered neural connectivity in the frontal brain regions could also be observed during the WCST, which is possibly associated with the observed cognitive flexibility deficits in these individuals. Indeed, previous studies have documented aberrant frontal cortex activation in individuals with ASD during various cognitive flexibility tasks (Gilbert et al., 2008; Yerys et al., 2015); however, the differences in frontal activation and neural connectivity during the WCST between ASD individuals and their TD counterparts, as well as the relationships between neurophysiological and behavioral parameters, have not been determined.

One of the parameters reflecting neural connectivity is functional connectivity. Pearson's correlation between the filtered signals recorded from different parts of the brain reflects the degree of nondirectional synchrony between two brain regions (Friston, 2011). To measure functional connectivity, an increasing number of studies have utilized functional near-infrared spectroscopy (fNIRS), an optical neuroimaging tool that has been widely applied to study the hemodynamic responses evoked by neuronal activity (Villringer & Chance, 1997) in the prefrontal cortex of healthy individuals (Huang, Chou, Wei, & Sun, 2015) and clinical populations such as ASD patients (Yeung, Lee, & Chan, 2019). Given that previous evidence has shown that cognitive flexibility deficits in individuals with ASD are associated with abnormal frontal functioning, this study aimed to investigate frontal cortex functioning, in terms of activation and functional connectivity, in individuals with ASD during the WCST. The psychophysiological correlates of impaired WCST performance in ASD patients will also be explored. We hypothesize that ASD individuals have an impaired ability to flexibly acquire and apply new information, as reflected by poorer WCST behavioral performance than TD individuals. We further hypothesize that the observed behavioral impairment is associated with abnormal prefrontal activation and functional connectivity as measured by fNIRS.

2.3 Method

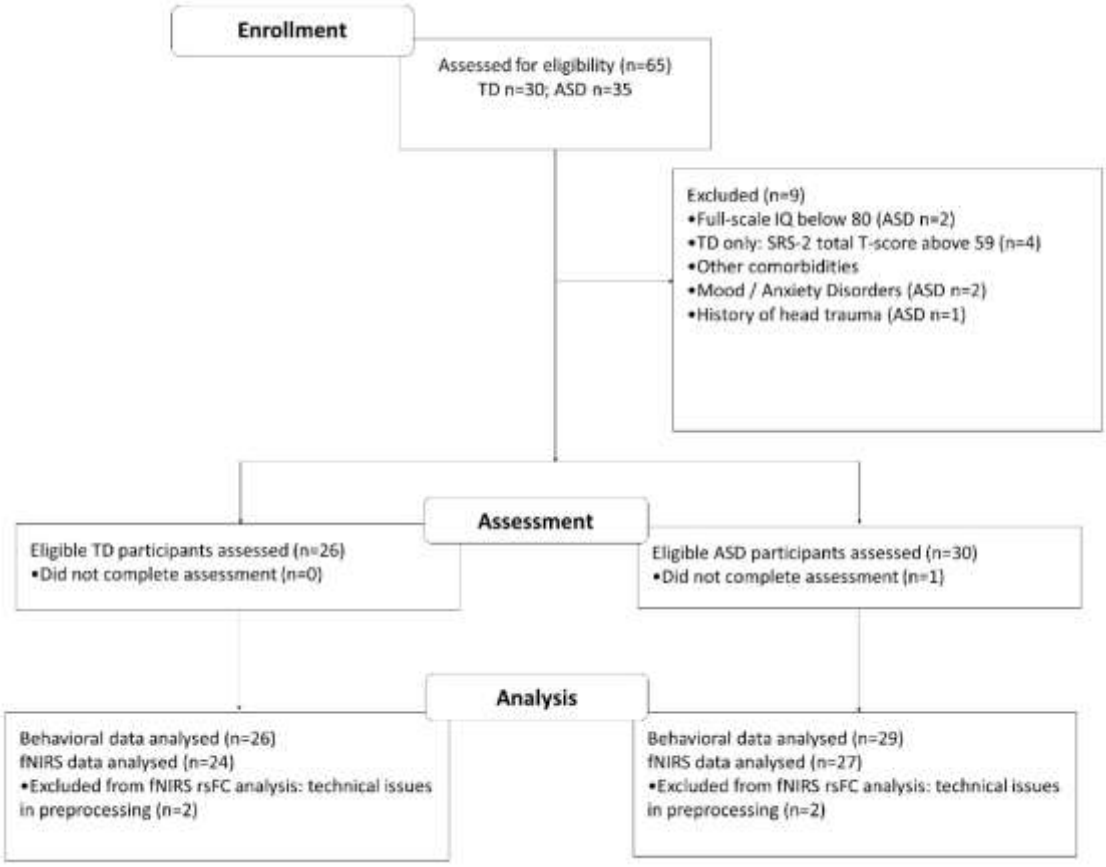
2.3.1 Participants

This study was approved by the Human Subjects Ethics Sub-Committee of Hong Kong Polytechnic University and was conducted in accordance with the Declaration of Helsinki. Twenty-nine

individuals with ASD and 26 TD individuals aged 14–21 years participated in this study. All participants achieved a full intelligence quotient (IQ) ≥ 80, as measured by either the short form of the Hong Kong Wechsler Intelligence Scale for Children – fourth edition (WISC–IV–HK:SF; Wechsler, 2010) for participants aged less than 15:11 or the short form of the Wechsler Adult Intelligence Scale – fourth edition (WAIS–IV–HK:SF; Wechsler, 2010) for those aged 16 or older. Given that previous research has shown that individuals with ASD exhibit sex–dependent differences in nonsocial cognitive domains involving executive function (Lai et al., 2012), we included only males in our sample. Furthermore, as prior studies have shown that handedness influences the brain network organization underlying executive functioning (Gao, Wang, Yu and Chen, 2015), we included only right–handed individuals whose handedness was confirmed by scoring over +80 on the Edinburgh Handedness Inventory short form (Oldfield, 1971). The diagnosis of ASD among the participants was confirmed by the Autism Diagnostic Interview–Revised (ADI–R; Lord, Rutter & Le Couteur, 2003). The social functioning of TD individuals was screened by the second edition of the Social Responsiveness Scale (SRS–2; Constantino & Gruber, 2012), with all included TD individuals obtaining a total score equal to or less than 59 out of a

maximum score of 195, indicating that they had normal daily social functioning. A total of 65 individuals potentially suitable for inclusion in this study were recruited from multiple sources, including a child psychiatry clinic at a public hospital, a private autism clinic run by allied health professionals, and social media (i.e., Facebook local peer support group, WhatsApp). All of the recruited individuals were assessed for eligibility. Nine individuals were excluded from the study because they did not fulfill the inclusion criteria listed above. Twenty-nine individuals with ASD and 26 TD individuals aged 14–21 years completed the assessment, and their data were included in the final analysis. The participants' flow is illustrated in **Figure 2.**

Figure 2. *A flowchart showing the participants' enrollment, assessment, and analysis of this study.*



2.3.2 Procedure and Materials

Before the commencement of the experiment, the procedures and potential risks and benefits of the study were first explained to the participants and their parents, and written informed consent was subsequently obtained from all the participating parents of the recruited individuals. All the children underwent two assessments, namely, an IQ assessment and an fNIRS measurement. The sequence of assessments was counterbalanced across subjects to minimize order effects. While the parents of all the children were asked to complete the SRS-2, the parents of the children with ASD were involved in a structured interview in which the ADI-R was administered in addition to the completion of the SRS-2. The WISC/WAIS-IV-HK:SF and ADI-R were administered by a clinical psychologist who was blinded to the

hypothesis of the study. The fNIRS measurements were conducted by trained research assistants.

2.3.3 fNIRS measurements

fNIRS measurements were taken for each of the participants before and when they performed the WCST. Before the commencement of the WCST paradigm, participants were asked to focus on a fixation cross for 30 seconds, such that the baseline neural activity could be recorded. A computerized version of the WCST—64-card version (Kongs, Thompson, Iverson, & Heaton, 2000)—was subsequently presented using E-prime 3 software (Psychology Software Tools, 2016). The WCST experimental design adopted from Vatansever et al. (2017) is illustrated in **Figure 3.** A 52-channel fNIRS optical topography system (ETG-4000; Hitachi Medical Co., Tokyo, Japan) was used to measure the changes in brain signals during the task with a sampling rate of 10 Hz. Before wearing the probe set, landmarks in the 10-20 system (Jasper, 1958) were identified by measuring the head circumference, distance between the incision and nasion, and distance between the left and right auricular. To ensure measurement consistency, this procedure was performed by the same experienced research assistant. The probe set with thirty-three NIR emitters and detectors was mounted on a 3x11 grid with the emitter-detector distance fixed at 3 cm and was then worn on a participant's head using an elastic headband with detector 26 placed at FpZ, emitter 24 placed midway between F8, and emitter 27 placed midway between F7. The channels were grouped to represent the medial and lateral PFC in the left and right hemispheres to increase the signal-to-noise ratio (Yeung et al., 2019). The arrangements of channels, NIR emitters and detectors as well as the channel groupings are illustrated in **Figure 4.**

Figure 3. *Experimental design. The WCST-64 paradigm consists of six blocks with 10 trials for each block. Participants were asked to sort the stimulus card by a rule (color, shape, number) that was not disclosed to them. The rule changes after every 10 trials and the rule order were counterbalanced among subjects. In every trial, participants were presented with one stimulus card (below) and four reference cards (top row); the information was not changed throughout the whole paradigm. The order of the stimulus cards was random. Feedback indicating choice accuracy was given immediately after each response was made.*

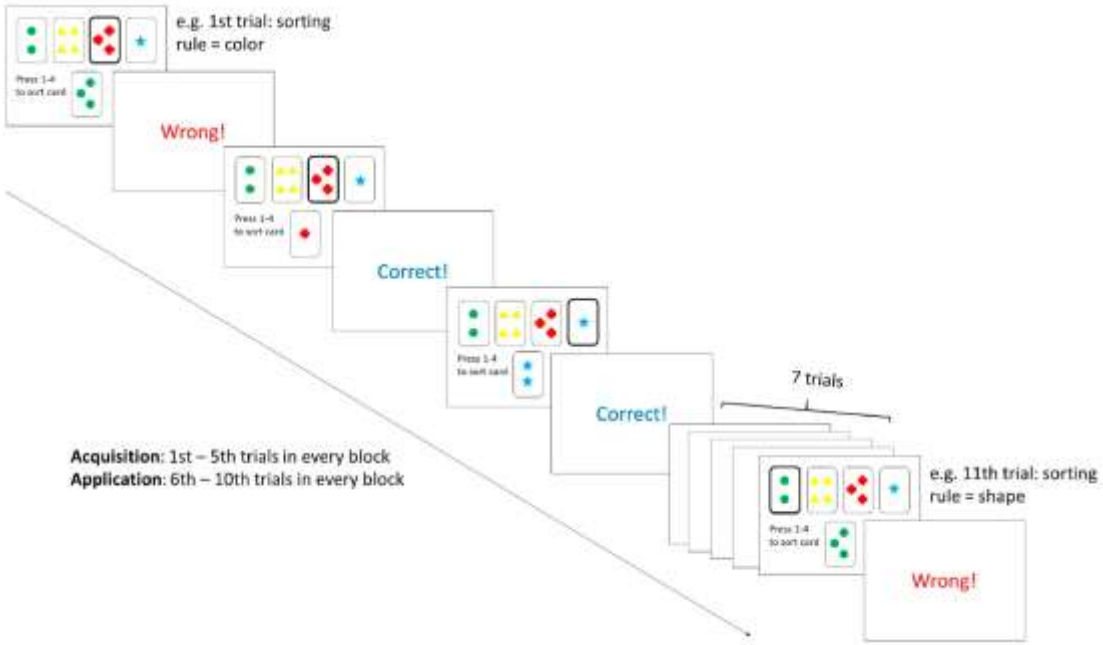
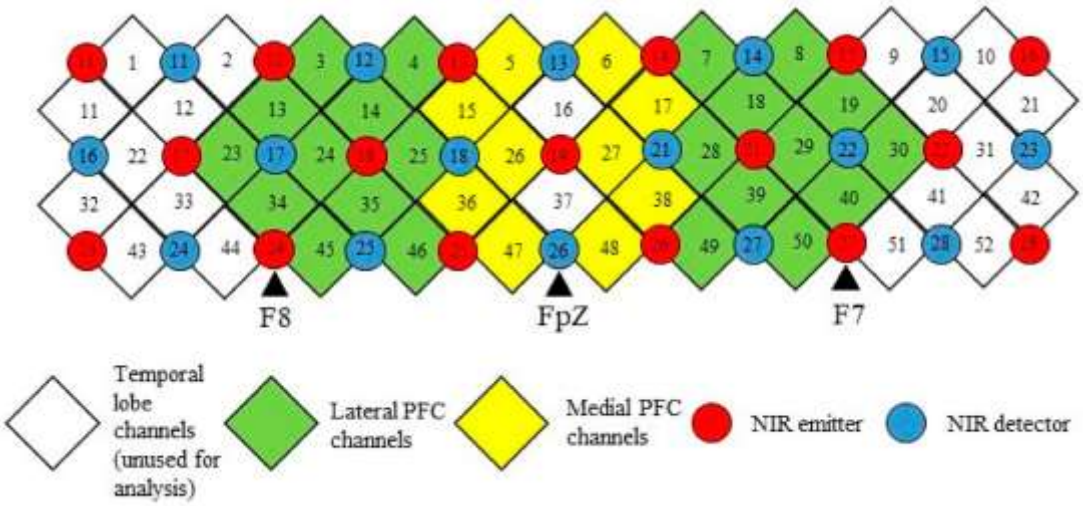


Figure 4. *The arrangements of near-infrared channels, emitters, and detectors, as well as the channel groupings.*



2.3.4 Data analysis

fNIRS preprocessing fNIRS data preprocessing was performed using the AnalyzIR toolbox (Santosa et al., 2018) in MATLAB 2019a (The Mathworks, Natick, MA), and the preprocessing pipeline is illustrated below. The light intensity data for each participant collected during the baseline and WCST conditions were extracted from the ETG-4000 machine. Saturated or flatlined channels were replaced with high variance noise using the FixSatChans or FixFlatChans modules, respectively. The resample module was subsequently adopted to downsample the data to 1 Hz using a Nyquist filter. The resampled data were converted to optical density using the OpticalDensity module and then to oxyhaemoglobin

(HbO), deoxyhaemoglobin (HbR) and total hemoglobin (HbT) concentrations using the modified Beer–Lambert Law (Delpy et al., 1988). For statistical analysis, only HbO data were used in this study given that HbO has been found to be a more sensitive measure than HbR for detecting task-related neural changes in patients with neurological disorders, including ASD (Yeung & Lin, 2021).

fNIRS first-level analysis. To estimate the differences in fNIRS activation between the experimental (i.e., acquisition/application) and baseline (i.e., focusing on a fixation cross) conditions while also controlling for the type I errors caused by slow systemic physiology and motion artifacts, a general linear model (GLM) with an autoregressive prewhitening approach using iteratively reweighted least-squares (AR-IRLS; Barker, Aarabi, & Huppert, 2013) was performed for the HbO data of each of the participants. The GLM yielded a regression coefficient (β) for each channel, and the β values were averaged within each region of interest (i.e., left medial PFC, right medial PFC, left lateral PFC and right lateral PFC) for both animal and transport conditions. These averaged values were subsequently used in the second-level fNIRS activation analysis.

To estimate the differences in functional connectivity between experimental (i.e., acquisition/application) and baseline (i.e., focusing on a fixation cross) fMRI data, GLM with AR-IRLS followed by robust regression (Santosa et al., 2017) was conducted for the HbO data of each of the participants. Although AR-IRLS has been shown to effectively reduce type-I errors in fNIRS activation analyses, shifting-type motion artifacts, which usually result from an individual's abrupt and excessive movement causing the shift of the entire probe set, could still appear as extreme statistical outliers (Barker et al., 2013), yielding high but spurious correlations that influence the interpretation of functional connectivity data as a result (Santos et al., 2017). Robust regression was hence adopted to reduce the effect of these

statistical outliers on the data analysis by assigning a lesser weighting to the outliers to normalize the noise distributions. A Z-transformed correlation coefficient (Z) was calculated for each of the possible channel pairs, and the Z values were averaged within each region of interest (i.e., left medial PFC, right medial PFC, left lateral PFC and right lateral PFC) for both animal and transport conditions. These averaged values were subsequently used in the second-level functional connectivity analysis.

Second-level analysis. Group-level analyses of the behavioral and fNIRS data were performed using IBM SPSS Statistics Version 26.0 (IBM Corp, Armonk, NY). The normality of the data was first checked with the Shapiro–Wilk test. To examine whether the TD and ASD groups were matched, independent sample t tests (or Mann–Whitney tests for nonnormal data) were performed for age, IQ and SRS-2 data. To test for differences in WCST performance between the two groups during the acquisition and application stages, accuracy in terms of correct response percentage and reaction time (ms) were analyzed with 2 (group) × 2 (category) mixed ANOVA. To investigate the difference in prefrontal fNIRS activation patterns between the two groups under different conditions (i.e., acquisition/application) on the WCST in the medial/lateral PFC of the left/right hemisphere, a 2 (group) × 2 (category) × 2 (region) × 2 (hemisphere) mixed ANOVA was performed with the averaged β-values of the medial/lateral PFC of each hemisphere. To investigate the difference in prefrontal fNIRS functional connectivity between the two groups under different conditions (i.e., acquisition/application) on the WCST within the medial/lateral PFC of the left/right hemisphere, a 2 (group) × 2 (category) × 2 (region) × 2 (hemisphere) mixed ANOVA was performed with the averaged Z values of the medial/lateral PFC of each hemisphere. Post hoc t tests were performed when significant interactions or main effects were found for the above analyses. To explore the relationship between brain hemodynamic changes and behavioral performance, Spearman's rank order correlational analyses (two-

tailed) were conducted for parameters found to be significant in the group comparisons. Bonferroni corrections were applied to all post hoc and correlational analyses unless otherwise specified.

2.4 Results

2.4.1 Demographic details

The demographic details of the participants are listed in **Table 1.** Independent sample t tests revealed that the ASD and TD groups were age-matched (p =.259) and full-scale IQ (p =.293) with the age distributions of each group shown in **Figure 5.** The ADI-R domain scores were all above the cutoff for our ASD sample, with this group of individuals also showing markedly impaired current social functioning when compared to their TD counterparts, as indicated by a significantly greater SRS-2 total score (p <.001).

Figure 5. *Histograms showing the age distributions of the TD (left) and ASD (right) groups.*

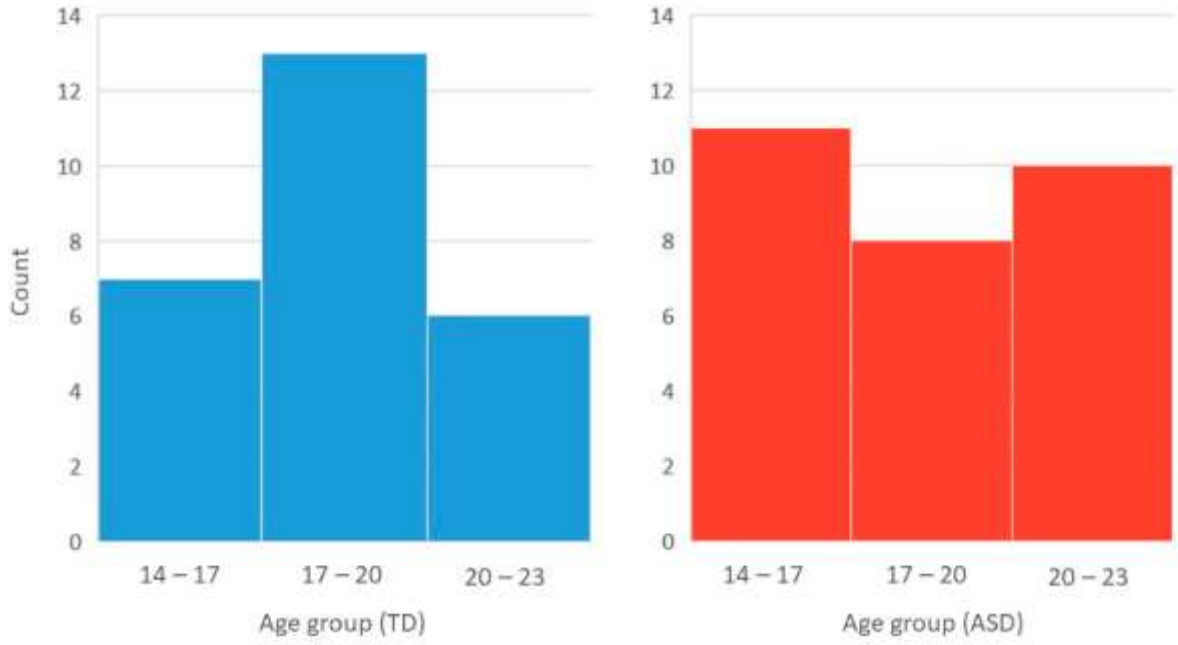


Table 1. *Participants' demographic information.*

Parameters	Group				
	ASD	**TD**	***t***	***df***	***p***
Mean chronological age in years (S.D.)	17.75 (2.31)	18.47 (2.36)	1.14	53	0.259
Mean full Scale IQ (S.D.)	97.93 (15.98)	101.73 (8.95)	1.07	53	0.293
Mean SRS-2 total score (S.D.)	98.86 (25.15)	55.60 (24.29)	−6.00 ***	53	<0.001
Mean ADI-R domain scores (S.D.)					
Social interaction	19.30 (3.60)	N/A		N/A	
Communication	14.67 (4.29)				
Restricted, repetitive behavior	3.30 (1.92)				

Note: All participants (ASD, *n*= 29; TD, *n*= 26) were right-handed and male; SRS: Social Responsiveness Scale-2; ADI-R: Autism Diagnostic Interview-Revised; ****p*< 0.001.

2.4.2 WCST behavioral performance

The results of the WCST behavioral performance are listed in **Table 2.** In terms of performance accuracy, a 2x2 mixed ANOVA showed a nonsignificant group*condition interaction effect (F1,53 =.342, p =.561) with a nonsignificant main effect of group (F1,53 = 3.15, p =.082). A 2x2 mixed ANOVA showed a highly significant main effect of group (F1,53 = 17.92, p <0.001), and post hoc independent sample t tests indicated that individuals with ASD took significantly longer to respond during both acquisition (p <0.001) and application. The group*condition interaction effect was nonsignificant (F1,53 =.026, p =.872).

Table 2. *WCST behavioral performance.*

Parameters	Group				
	ASD	**TD**	***t***	***df***	***p***
			Accuracy (% of correct responses)		
Acquisition	55.17 (12.07)	60.03 (12.63)	1.46	53	0.151
Application	76.97 (14.47)	83.77 (15.20)	1.70	53	0.095
			Reaction time (ms)		
Acquisition	1882.33 (581.46)	1346.39 (394.43)	3.95 ***	53	<0.001
Application	1647.53 (597.26)	1123.10 (291.22)	4.20 ***	53	<0.001

Note: ****p*< 0.001 (Bonferroni-corrected).

2.4.3 fNIRS prefrontal activation during the WCST

Four-way mixed ANOVA revealed a nonsignificant group*condition*region*hemisphere interaction effect (F1,49 =.315, p =.577) and a nonsignificant main effect of group (F1,49

=.599, p =.443) on prefrontal activation during the WCST. The descriptive statistics are shown in **Table 3.**

Table 3. *fNIRS prefrontal activation during the WCST in ASD and TD individuals (beta values).*

	Right Hemisphere		**Left Hemisphere**	
	Group		**Group**	
	ASD	**TD**	**ASD**	**TD**
		Condition 1: Acquisition		
Medial	1.58 (40.83)	7.86 (38.89)	9.85 (34.54)	7.97 (40.32)
Lateral	1.60 (35.96)	16.35 (35.88)	7.86 (36.96)	8.40 (46.22)
		Condition 2: Application		
Medial	2.40 (40.50)	8.27 (39.67)	7.96 (37.41)	6.22 (40.67)
Lateral	−0.24 (37.33)	16.00 (35.66)	8.21 (38.23)	6.54 (45.37)

Note: *n*= 51 (2 fNIRS data points from the TD group and 2 data points from the ASD group could not be preprocessed due to technical issues).

2.4.4 fNIRS prefrontal functional connectivity during the WCST

Regarding intrahemispheric functional connectivity within the medial and lateral PFC (**Table 4**), a 4-way mixed ANOVA revealed a highly significant main effect of group (F1,49 = 9.99, p =.003) and a nonsignificant group*condition*region*hemisphere interaction (F1,49 = 1.82, p =.185). In the acquisition condition, ASD individuals exhibited lower functional connectivity in the right lateral PFC (p =.005), while in the application condition, the bilateral PFC exhibited lower functional connectivity (right: p =.006; left: p =.006).

Table 4. *fNIRS prefrontal functional connectivity during the WCST in ASD and TD individuals (r).*

	Right Hemisphere					Left Hemisphere				
	Group					Group				
	ASD	TD	*t*	*df*	*p*	ASD	TD	*t*	*df*	*p*
Condition 1: Acquisition										
Medial	0.22 (.15)	0.31 (.17)	2.04	49	0.047	0.19 (0.09)	0.24 (0.10)	1.95	49	.057
Lateral	0.21 (.17)	0.34 (.17)	2.91 **	49	0.005	0.21 (0.13)	0.30 (0.12)	2.69	49	0.010
Condition 2: Application										
Medial	0.22 (.14)	0.34 (.18)	2.56	49	0.014	0.20 (0.08)	0.25 (0.12)	1.86	49	0.069
Lateral	0.25 (.16)	0.38 (.16)	2.89 **	49	0.006	0.21 (0.13)	0.32 (0.11)	2.89 **	49	0.006

Note: *n*= 51 (two fNIRS data points from the TD group and two data points from the ASD group could not be preprocessed due to technical issues). ***p*< 0.0063 (Bonferroni-corrected).

2.4.5 Brain-behavior relationships

The relationships between the WCST reaction time, right PFC functional connectivity during the acquisition condition, and bilateral PFC functional connectivity during the application condition were examined. Correlations between WCST reaction time during the acquisition condition and fNIRS measurements were significant at the p =.05 (uncorrected) level but did not survive Bonferroni corrections (rhos > -.362, ps >.01, uncorrected; **Table 5**). In turn, highly significant negative correlations between WCST reaction time during the application condition and bilateral lateral PFC functional connectivity were found (rhos = < -.415, ps =.003, Bonferroni-corrected; **Table 5; Figure 6**).

Figure 6. *Scatter plots showing the brain-behavior relationships between WCST response latency during WCST application and lateral PFC functional connectivity in the (a) right and (b) left hemispheres. The red dots represent the data from the ASD group, and the blue dots represent the data from the TD group.*

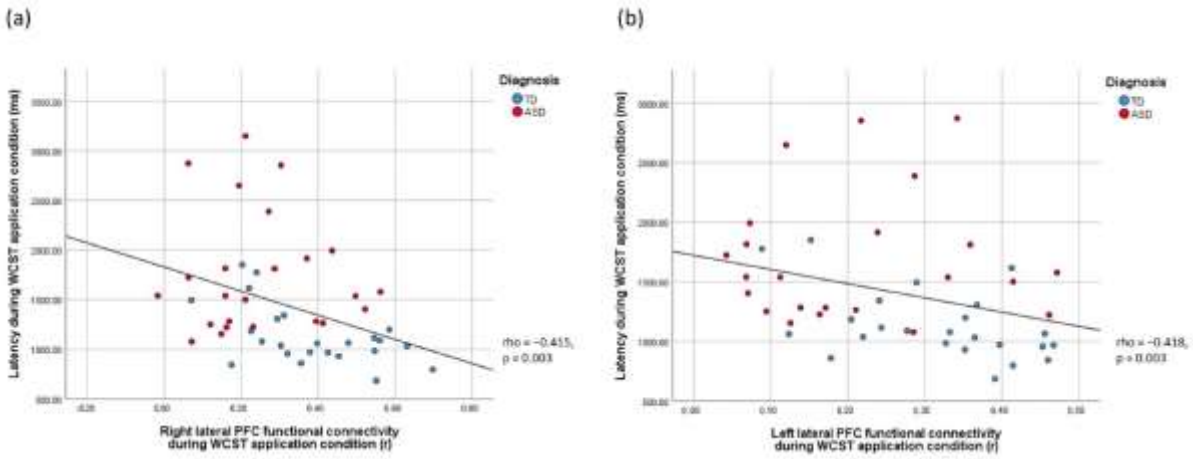


Table 5. *Correlation between WCST reaction time and PFC FC parameters (whole-group analysis).*

Parameters	R_lPFC_Acquisition	R_lPFC_Application	L_lPFC_Application
RT_acquisition	−0.348	−0.362	−0.344
RT_application	−0.353	−0.415 **	−0.418 **

Note: n = 51 (listwise)*; **p*< 0.0083 (Bonferroni-corrected).

2.5 Discussion

This study aimed to investigate the neuropsychological and neurophysiological functions of individuals with ASD who were performing a well-known cognitive flexibility task, the WCST. Behavioral and fNIRS data from 29 individuals with ASD were compared with those

from 26 age- and IQ-matched TD counterparts. Although individuals with ASD achieved accuracy rates comparable to those of TD individuals, they needed significantly more time to acquire and apply the WCST card sorting rules. Moreover, individuals with ASD showed significantly lower functional connectivity in the right lateral PFC during the acquisition condition and in the bilateral lateral PFC during the application condition. Furthermore, a shorter WCST reaction time was correlated with lower bilateral lateral PFC functional connectivity only in the application condition but not in the acquisition condition.

Consistent with the findings of previous studies, individuals with ASD were found to exhibit impairments in all cognitive processes supporting cognitive flexibility, namely, information acquisition and maintenance, as well as information application for problem solving. For instance, Young, Hudry, Trembath, and Vivanti (2016) showed that children with ASD demonstrated a reduction in information acquisition behavior when they were asked to learn novel actions in response to different social scenarios. For information maintenance, Miller et al. (2015) showed that children with ASD exhibited marked difficulties in maintaining learned rules for task completion, and such impairment was positively correlated with increased severity of restricted, repetitive behaviors. Regarding information application for problem solving, Yeung et al. (2019) showed that individuals with ASD exhibited marked impairment when they were asked to produce learned words that were relevant to a semantic rule. In particular, as shown by our results, these individuals took significantly longer to yield comparable performance accuracy to that of their peers, which was also consistent with previous findings showing that information application deficits in ASD patients reflected by other executive functioning tasks (e.g., verbal fluency tasks) were revealed only when there was limited time (Yeung, Lee, & Chan, 2019) but not adequate time (Ehlen et al., 2020) given for task completion. Our results imply that the impairment of cognitive flexibility subprocesses in ASD patients is mediated by information processing speed, providing

evidence, alongside a number of previous studies (e.g., Haigh et al., (2018); Eack et al. (2013); Faja et al., (2009)) to support the notion that there is a fundamental impairment in speed that affects information processing in individuals with ASD, such that they exhibit abnormalities, especially when demand for information processing is high (e.g., complex behavior, including social communication and interaction; Haigh et al., 2018).

Previous studies have shown that information processing efficiency is underpinned by the strength of functional connectivity between regions within and between functional brain networks (Silva et al., 2020). For example, visual information processing speed has been shown to be associated with functional connectivity within the cingulo-opercular (Ruiz-Rizzo et al., 2019) and right frontoparietal (Haupt et al., 2020) networks, as well as between these two networks and the occipital network (Küchenhoff et al., 2021). Individuals with impaired information processing speed, such as those with ASD, are postulated to exhibit aberrant functional connectivity (Zimmerman et al., 2008). Indeed, many previous studies have documented altered functional connectivity in individuals with ASD, both during the resting state (Fishman et al., 2014; Han & Chan, 2017) and during many neuropsychological tests requiring complex information processing, including working memory (Koshino et al., 2005; Krishnamurthy et al., 2020), face recognition (Koshino et al., 2008) and mentalizing (Cole, Barraclough, & Andrews, 2019). Consistent with these studies, we provided new evidence to support aberrant functional connectivity in ASD patients during demanding cognitive tasks. In particular, we showed that individuals with ASD exhibited PFC hypoconnectivity during the WCST, with the right lateral PFC showing hypoconnectivity when participants acquired a new rule through trial and error and the bilateral lateral PFC showing hypoconnectivity when participants were asked to apply the learned rules for problem solving. The finding of condition-independent right lateral PFC hypoconnectivity during the WCST in ASD patients in our study is consistent with the findings of a recent large-scale lesion study showing that

lesions in the right lateral PFC underlie impaired performance in the WCST (Gläscher et al., 2019). We further showed that in the context of ASD, slower information processing speed during the WCST is correlated with lower functional connectivity in the right lateral PFC, particularly when individuals are asked to apply rules for problem solving. These results collectively imply that reduced right lateral PFC functional connectivity is the neural correlate for speed-mediated cognitive flexibility deficits in ASD, which particularly affects the application of rules for solving novel problems and manifests in daily situations such as social communication in these individuals (Williams et al., 2014). Interestingly, we also observed hypoconnectivity in the left, on top of the right, lateral PFC in ASD patients, specifically during the rule application condition, which was also highly correlated with WCST behavioral performance. This domain-specific left lateral PFC impairment might be attributed to the greater extent of left hemisphere abnormalities in ASD patients reported in previous studies (D'Cruz et al., 2009; Rinehart et al., 2002). Although abnormal PFC brain activation in ASD patients during cognitive flexibility tasks was shown in previous neuroimaging studies (Gilbert et al., 2008; Yerys et al., 2015), we detected nonsignificant differences in brain activation between ASD patients and TD individuals during the WCST. The nonsignificant difference between the two groups might be attributed to the large standard deviations in beta values representing brain activation in both groups, possibly because different brain regions were recruited when participants employed different cognitive strategies for WCST task completion (Müller et al., 2015).

In this study, we showed that information processing speed mediates cognitive flexibility task performance in ASD patients and is associated with decreased functional connectivity in the right lateral PFC. Given these findings, it is reasonable to postulate that treatments that enhance functional connectivity in this region can promote information processing in individuals with ASD, hence alleviating their cognitive flexibility deficits and associated

social and behavioral impairments. Transcranial direct current stimulation (tDCS), a noninvasive neuromodulation technique, might be a potentially promising candidate. A previous meta-analysis showed that prefrontal anodal tDCS could enhance functional connectivity in the right anterior cingulate cortex in humans (Chan, Yau, & Han, 2021). In addition, multiple studies conducted in healthy (Plewnia et al., 2015) and clinical (Gögler et al., 2017) populations have shown that tDCS can enhance information processing speed. Thus, the effectiveness of anodal tDCS over the right lateral PFC may be a possible direction of future research.

2.5.2 Conclusion

This study investigated the neuropsychological and prefrontal neurophysiological functions of individuals with ASD who acquired and applied new information during a well-established cognitive flexibility task, the WCST. Behavioral and fNIRS data collected during the WCST from 29 ASD individuals aged 14-21 were compared with those from 26 IQ- and age-matched TD individuals. The results revealed impairment in information acquisition and application in ASD that was mediated by processing speed. Furthermore, lower functional connectivity in the bilateral lateral PFC was shown to be associated with slower processing speed when individuals with ASD were asked to apply learned rules to solve novel problems. Future studies might consider investigating the neural correlates of the WCST beyond the PFC, as well as the effectiveness of neuromodulation techniques in enhancing lateral PFC functional connectivity to improve information processing efficiency and associated social communication deficits in these individuals.

Chapter 3: Effects of Working Memory Load on Frontal Connectivity in Children with Autism Spectrum Disorder: a fNIRS Study

A version of this chapter has been published in a peer-reviewed journal:

Han, Y. M., Chan, M. C., Chan, M. M., Yeung, M. K., & Chan, A. S. (2022). Effects of working memory load on frontal connectivity in children with autism spectrum disorder: a fNIRS study. *Scientific Reports*, *12*(1), 1522.

3.1 Abstract

Individuals with autism spectrum disorder (ASD) perform poorly on visuospatial working memory (WM) tasks, and some studies have suggested that impaired performance is modulated by WM load. While some neuroimaging and neurophysiological studies have reported altered functional connectivity during WM processing in these individuals, it remains largely unclear whether such alterations are moderated by WM load. The present study aimed to examine the effect of WM load on functional connectivity within the prefrontal cortex (PFC) in ASD patients using functional near-infrared spectroscopy (fNIRS). Twenty-two children with high-functioning autism aged 8–12 years and 24 age-, intelligence quotient (IQ)-, sex- and handedness-matched typically developing (TD) children performed a number n-back task with three WM loads (0-back, 1-back, and 2-back). Hemodynamic changes in the bilateral lateral and medial PFC during task performance were monitored using a multichannel fNIRS device. The results showed that children with ASD demonstrated slower reaction times, specifically during the "low load" condition, than did TD children. In addition, the ASD and TD groups exhibited differential load-dependent functional connectivity changes in the lateral and medial PFC of the right hemisphere but not in the left hemisphere. These findings indicate that WM impairment in high-functioning autism patients is paralleled by load-dependent alterations in right, but not left, intrahemispheric connectivity during WM processing in children with ASD. A disruption of functional neural connections that support different cognitive processes may underlie poor performance in WM tasks in ASD patients.

3.2 Introduction

Following Chapters 2, this chapter explores the complexities of autism spectrum disorder (ASD) and its executive dysfunction at the neurophysiological level. While Chapter 2 focused on the inflexibility of information processing and its linkage to prefrontal

connectivity, Chapter 3 shifted the focus toward another crucial aspect of executive functions—working memory (WM). In this chapter, we explore how variations in WM load influence frontal connectivity in children with ASD. This exploration is vital because WM not only is a core component of executive functions but also plays a significant role in many higher-order cognitive processes.

It has been suggested that deficiencies in working memory (WM), which is the temporary storage system that serves as a basis for complex cognitive functions (Baddeley, 2012), and associated executive functioning deficits (Demetriou et al., 2018), contribute to ASD symptom manifestation and daily dysfunction. (Cui et al., 2010; deVries & Geurts, 2014; Kleinhans et al., 2005; Lemon et al., 2011). Specifically, individuals with ASD are found to exhibit specific facial recognition impairments when they are asked to recall faces presented a few trials before (Behrmann et al., 2006; Deruelle et al., 2004) but not when they are asked to perform face matching tasks (McPartland et al., 2011). Moreover, when children with ASD learn, they are presented with difficulties integrating and generalizing learned knowledge, especially when the complexity of knowledge increases (Han & Chan, 2018). Many individual studies have demonstrated deficient WM in individuals with ASD, but the findings have been inconsistent: some studies have found a significant difference in WM task performance between individuals with ASD and typically developing (TD) controls (Corbett et al., 2009; Gabig, 2008; Sinzig et al., 2008; Williams et al., 2006), whereas others have not (Geurts et al., 2004; Happé & Frith, 2006; Ozonoff & Strayer, 2001). Nevertheless, a recent meta-analysis confirmed the presence of WM deficits in individuals with ASD (Habib et al., 2019), with previous researchers suggesting that the level of WM impairment might be associated with the increase in the complexity of information and the demand for WM capacity involved in a task (Barendse et al., 2013; Habib et al., 2019).

It is well established that the frontal lobe is involved in WM. Evidence for this possibility comes from studies of the n-back task, one of the most widely adopted paradigms reflecting WM ability in cognitive neuroscience. For instance, an aggregate of studies has shown bilateral activation in the dorsolateral and ventrolateral PFC, dorsal cingulate cortex, medial premotor cortex, and parietal cortex during the n-back task (Owen et al., 2005). Additionally, functional coupling between frontal and parietal regions (Ma et al., 2012) and between the left and right PFC (Sun et al., 2019) increases during processing, which requires increased WM demand. These studies provide evidence to support the notion that WM is mediated by the PFC and its distributed neural networks (Fletcher & Henson, 2001; Smith & Jonides, 1999), which also implies that good performance in a WM task requires an efficient flow of information between these brain areas to maintain and integrate information.

Frontal lobe dysfunction in ASD has long been documented in the literature. For example, a neuroimaging meta-analysis showed that children with high-functioning ASD had hypoactivation in the right inferior frontal gyrus and right anterior cingulate gyrus during cognitive tasks involving inhibition, switching and updating components (Zhang et al., 2021). In addition, Narita et al. (2012) reported abnormal activation patterns in ASD adults over the left dorsolateral prefrontal cortex (PFC) during a visuospatial delayed recall task, a task reflecting participants' WM capacity. These studies collectively imply that abnormal frontal activity might be associated with impaired cognitive performance in individuals with ASD.

Furthermore, converging evidence suggests altered functional connectivity of the brain involving the PFC in both resting and task states in ASD patients, although it is still controversial whether these alterations are best characterized as global underconnectivity and/or local overconnectivity (Just et al., 2012; Mohammad-Rezazadeh et al., 2016). Since functional coupling between and within regions in the brain, especially the PFC, is important

for the execution of WM tasks, altered connectivity of the brain may underlie the WM deficits exhibited by individuals with ASD. Indeed, some studies have reported altered functional connectivity during n-back tasks in individuals with ASD. Several early fMRI studies have shown that adults with ASD exhibit overall underconnectivity between the PFC and parietal regions during a letter 2-back task (Koshino et al., 2005) and between the frontal and fusiform or parietal areas across different WM load levels in a facial n-back task (Koshino et al., 2008). Additionally, a more recent magnetoencephalography study revealed reduced synchronization within frontotemporal networks during a visuospatial 2-back task in children with ASD compared to that in TD children (Urbain et al., 2016). Despite these findings, it remains largely unclear whether the altered functional connectivity during WM task performance in individuals with ASD is moderated by WM load. Thus, the aim of the present study was to examine the effect of WM load on functional connectivity in ASD patients.

Functional near-infrared spectroscopy (fNIRS) is a noninvasive neuroimaging technique that monitors changes in the concentrations of oxyhemoglobin (HbO) and deoxyhemoglobin (HbR), which are associated with activities in the cerebral cortex (Villringer & Chance, 1997). During fNIRS recording, an fNIRS device emits at least two near-infrared signals with wavelengths ranging from 650–900 nm into the scalp. The lights then penetrate the scalp, skull, cerebrospinal fluid, and brain tissue in a banana-shaped trajectory, and the exiting lights are recorded by a receiver. Variations in optical density caused by changes in brain metabolism can then be used to estimate changes in hemoglobin concentration in sampled brain tissue via the modified Beer–Lambert law (Delpy et al., 1988). Over the last decade, fNIRS has been used to assess the functional coupling of brain regions, especially the PFC, during the performance of a wide variety of tasks. For example, fNIRS has been used to measure functional connectivity between two cortical areas that underlie motor performance

(Varshney et al., 2012). It has also been used to measure intrahemispheric and/or interhemispheric connectivity within the dorsolateral PFC and frontal pole during the n-back task in healthy young adults (Fishburn et al., 2014).

It is widely agreed that fNIRS possesses adequate temporal and spatial resolution and relatively high tolerance to motion and environmental conditions (Boas, Dale, & Franceschini, 2004). These unique properties make fNIRS a suitable tool for studying functional connectivity in pediatric populations. In the present study, we utilized fNIRS to examine functional connectivity within the PFC during the n-back task with three WM loads in children with high-functioning ASD. We hypothesized that, compared to TD controls, children with ASD would exhibit WM impairment and altered PFC connectivity that is load dependent during n-back task performance.

3.3. Method

3.3.1. Participants

This study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Human Subjects Ethics Sub-Committee of Hong Kong Polytechnic University. Twenty-two children with ASD and 24 TD children aged 8-12 years voluntarily participated in this study. These children were recruited through advertisements sent to parent groups via social media (e.g., WhatsApp and Facebook) and posted in the rehabilitation clinic at Hong Kong Polytechnic University, as well

as through invitation letters sent to teachers of local primary schools. All potential participants were screened for eligibility prior to the study, and those with a history of epilepsy or head trauma were excluded. A participant was included in the high-functioning ASD group if he or she fulfilled the following criteria: 1) he or she had received a diagnosis of ASD based on the Diagnostic and Statistical Manual of Mental Disorders–5th Edition (DSM-5; APA, 2013) from psychiatrists before the commencement of this study and scored above the cutoff points in all subscales in the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), which was conducted by a registered clinical psychologist during the screening session for this study; and 2) a full-scale intelligence quotient (IQ) ≥ 80 on the Hong Kong version of the Wechsler Intelligence Scale for Children-Fourth Edition short form [WISC-IV (HK); Wechsler, 2003], which was also administered by a clinical psychologist during the screening session. For a participant to be included in the TD group, he or she should have no history of developmental delay or any other neurological/psychiatric disorders.

3.3.2 Procedure and Materials

All the children and their parents attended individual screening and neuropsychological/neurophysiological measurement sessions at The Hong Kong Polytechnic University. Prior to the screening and assessment, the children and their parents were informed about the assessment procedures, and informed consent was obtained from the children and parents. All of the child participants were administered the Tumbling "E" test to ensure that they had normal or corrected-to-normal vision before any cognitive assessment or fNIRS testing. The child participants were screened for intellectual functioning by a clinical psychologist, followed by fNIRS recording sessions conducted by trained research assistants. These procedures were conducted in separate rooms. Short breaks were given to the participants every 30 minutes, and the entire experiment lasted for approximately two hours for each participant.

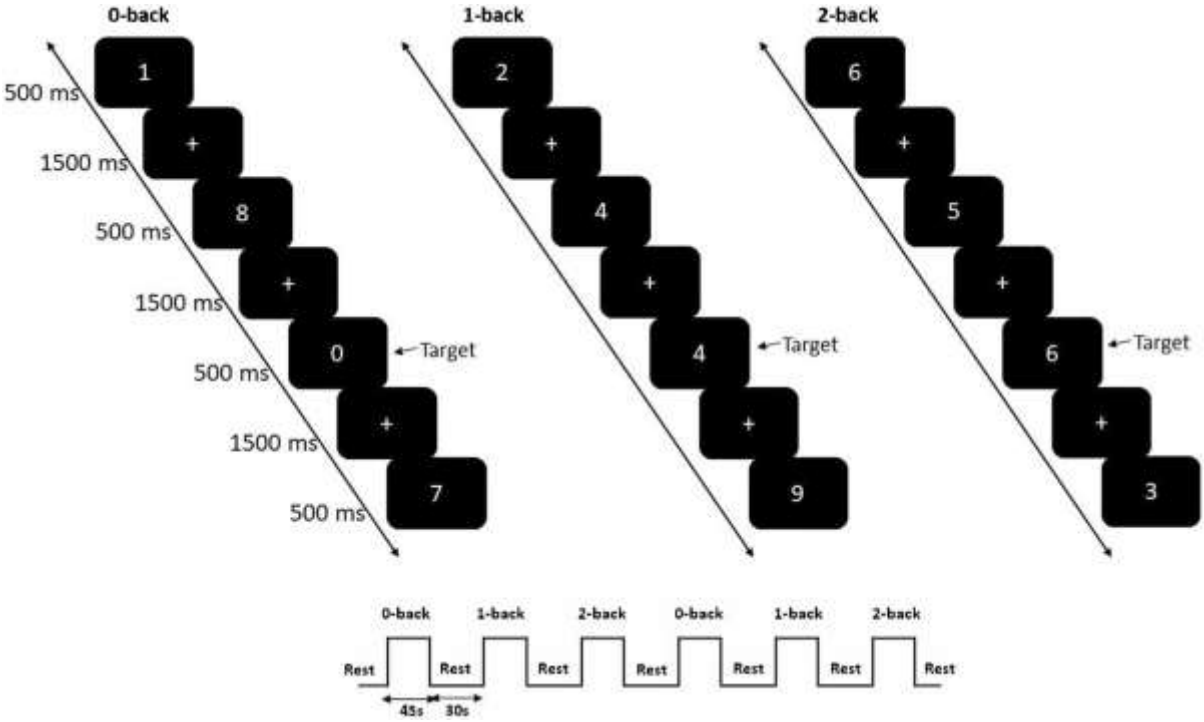
The demographic information of the participants was collected during interviews conducted by a clinical psychologist with parents in a separate room. Notably, we collected the medication history of the participants to delineate any possible mediating effects of some psychiatric medications on EF functioning, especially for working memory (e.g., medication for alleviating attention deficit/hyperactivity symptoms in ASD; Rosenau et al., 2021), during our data analysis. To measure participants' level of autistic traits in both the ASD and TD groups, the Social Responsiveness Scale–Second Edition (SRS-2) was administered (Constantino & Gruber, 2012). The SRS-2 is a sensitive measure of children's social impairment related to ASD over the past six months. The SRS-2 consists of five subscales that measure social awareness, social cognition, social communication, social motivation, restricted interests and repetitive behavior. Each item is rated on a four-point Likert scale from 1 (not true) to 4 (almost always true). Higher total scores indicate greater difficulties in

socialization. For the assessment of IQ, the WISC-IV (HK) short form was adopted in this study; this form comprises two verbal subtests, digit span and similarities, and two performance subtests, matrix reasoning and coding, yielding a full IQ score with a mean of 100 and a standard deviation of 15.

N-back paradigm

Each participant performed the n-back task, which was run with E-prime 2.0 Software (Psychology Software Tools, Pittsburgh, PA, USA), while prefrontal hemodynamic changes were recorded via fNIRS. The n-back task was adapted from previous fNIRS studies (Ehlis et al., 2008; Yeung, Lee, & Chan, 2019; Yeung et al., 2016) and consisted of 0-back (i.e., low WM load), 1-back (i.e., medium WM load), and 2-back (i.e., high WM load) conditions (Figure 7). Each condition was presented twice, and the three tasks alternated in blocks (i.e., 0-1-2-0-1-2, 0-2-1-0-2-1, 1-0-2-1-0-2, 1-2-0-1-2-0, 2-0-1-2-1 or 2-1-2-2-1-0) and were separated by 30-second rest blocks during which the participants sat still with their eyes open. The order was counterbalanced across participants to prevent order effects. Each task block consisted of a 5-second instruction cue that introduced the task, followed by 20 trials (5 target and 15 nontarget trials) presented in a pseudorandom manner.

Figure 7. *The number n-back paradigm used in this study.*



In the 0-back condition, the participants were instructed to press the left button of a mouse when the digit "0" (i.e., target) appeared but to press the right button for other digits. In the 1-back condition, the participants were instructed to press the left button when the presented digit was identical to the digit presented in the previous trial (i.e., target) or otherwise, the right button. In the 2-back condition, the participants were instructed to press the left button when the presented digit was identical to the digit presented two trials before (i.e., target) or otherwise, the right button. Each digit was presented for 500 milliseconds, followed by an interstimulus interval of 1500 milliseconds. Each task block lasted for 45 seconds, for a total duration of 8 minutes.

fNIRS measurements

The fNIRS recording session was conducted in a quiet, dim-lighted room. Each participant sat 60 cm away from a 15'' LCD monitor that was used for stimulus display. Head dimensions (nasion–inion and left–right periauricular points) were measured to facilitate offline spatial registration of fNIRS channels (Singh et al., 2005), where the channel positions

were transformed into Montreal Neurological Institute (MNI) space and projected onto the surface of a volume-rendered child brain template chosen according to participant age and head dimensions (Sanchez et al., 2012).

Prefrontal hemodynamics during the n-back task were measured by a 52-channel fNIRS optical topography system (ETG-4000; Hitachi Medical Co., Tokyo, Japan). This dataset consisted of 17 sources of two wavelengths (695 and 830 nm) and 16 detectors. A custom-built headband mounted with optical emitters and receivers, which were arranged in a 3 × 11 matrix, was placed on the children's heads based on the 10–10 system (Jurcak et al., 2007), an extension to the international 10–20 system (Jasper, 1958). The probe in the center of the lowest row was placed at Fpz, guided by a reference point marked on the headband that was standardized to be placed over the nasion of all subjects. The sampling frequency was 10 Hz. Each pair of sources and detectors was 3 cm apart; therefore, brain activity was measured approximately 15–20 mm beneath the scalp (Cui et al., 2011).

3.3.3 Statistical analysis

Behavioral data

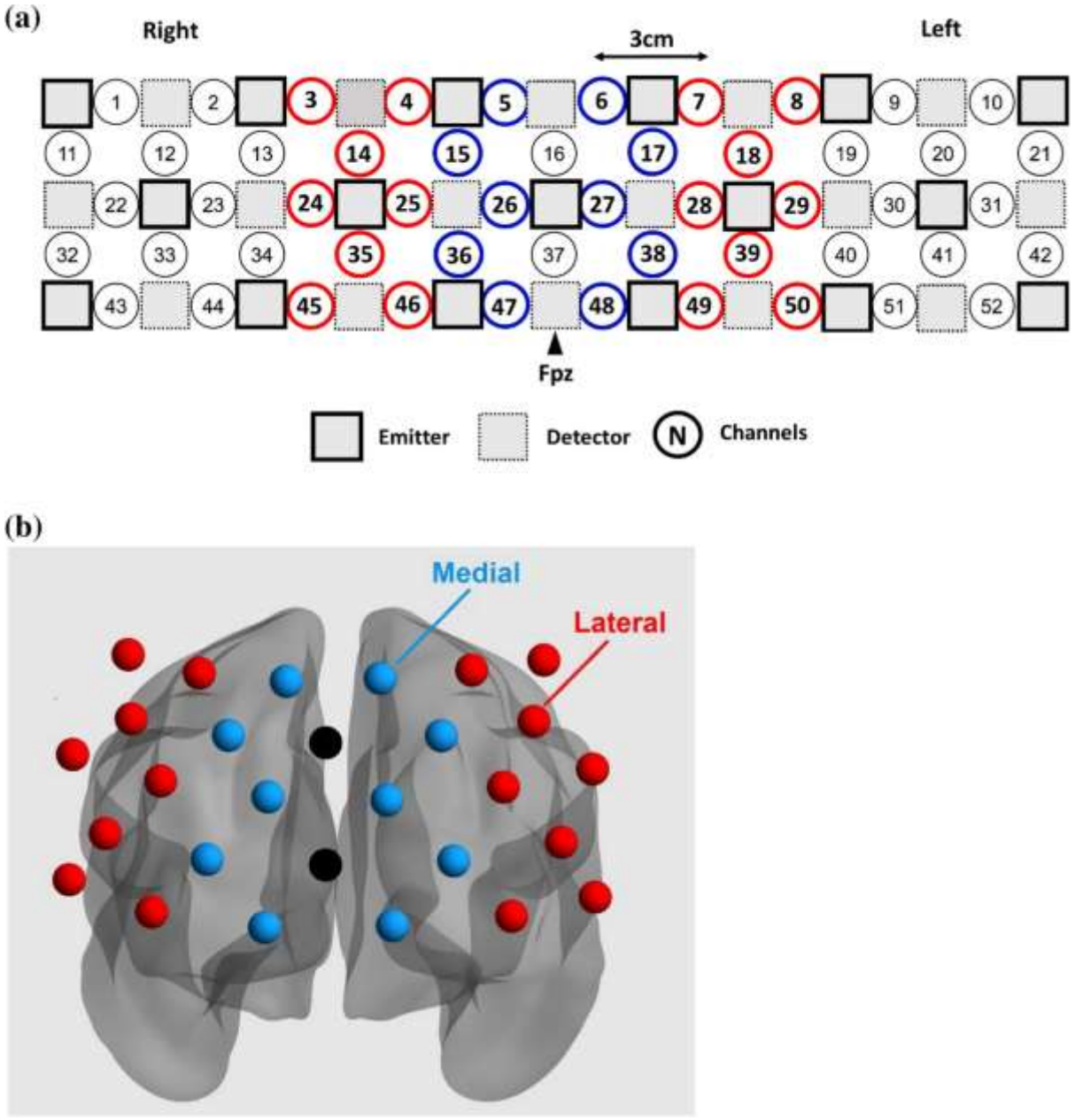
The mean latency time for all correct trials for each subject was calculated and named the mean reaction time (RT), and the percentage of correct trials as accuracy (ACC) for the n-back task was analyzed. We first inspected the normality of the RT and ACC distributions with Shapiro–Wilk tests. Because the RT variables in all three conditions were positively skewed, they were log-transformed. Given that most log-transformed RT variables no longer

violated the normal distribution ($p > 0.05$), parametric tests were used for analysis. For each n-back condition, the ACC and mean RT were separately analyzed via two-way mixed-design analysis of variance (ANOVA) with load (low, medium, or high) as the within-subjects factor and group (ASD or TD) as the between-subjects factor.

fNIRS preprocessing

We performed functional connectivity followed by activation analyses. For both analyses, the raw fNIRS signals were first converted to optical density changes and subsequently transformed into changes in HbO and HbR using the modified Beer–Lambert law (Delpy et al., 1988). Since HbO has a higher signal-to-noise ratio than HbR (Cui et al., 2011; Kamran, Mannan, & Jeong, 2016; Strangman, Culver, Thompson, & Boas, 2002), only the HbO data were analyzed. While we focused on the lateral PFC because this region has been implicated in n-back task performance (Owen et al., 2005), the medial frontopolar region was also examined to assess the specificity of the results. Based on the virtual registration of channels (Singh et al., 2005), eight and five channels represented the lateral PFC and medial frontopolar cortex on each side, respectively (Figure 8). Channels 7, 8, 18, 28, 29, 39, 49, and 50 represented the left lateral PFC; channels 3, 4, 14, 24, 25, 35, 45, and 46 represented the right lateral PFC; channels 6, 17, 27, 38, and 48 represented the left medial PFC; and channels 5, 15, 26, 36, and 47 represented the right medial PFC. The outermost channels covering the temporal lobe regions were not analyzed because of poor optode–scalp contact for most of the children.

Figure 8. *Arrangement of channels (a) in the sensor space and (b) in the brain space. The channels in red and blue represent the lateral and medial prefrontal cortex, respectively.*



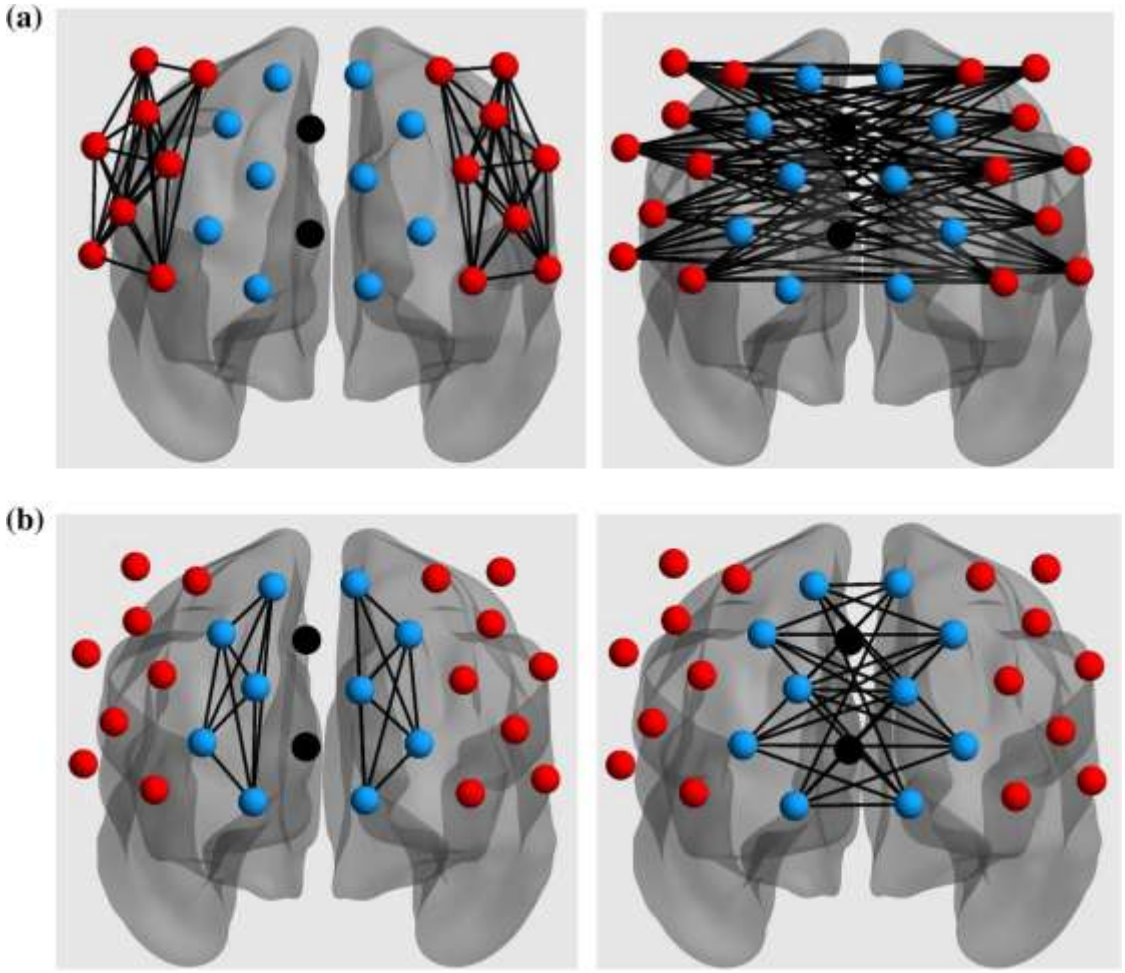
Functional connectivity analysis

The connectivity patterns during the n-back task were analyzed using the NIRS Brain Analyses Toolbox (Santosa et al., 2018) for MATLAB (The MathWorks, Natick, MA). The traditional approach to connectivity analysis computes the Pearson correlations between possible pairs of channels; however, this approach does not address systemic physiological noise or head motion, which are temporally correlated (colored) with the fNIRS signals and may affect the accuracy of the results (Santosa et al., 2017). In this case, a prewhitening filter can be used to remove the autocorrelation and whiten the frequency content of the signal (Barker et al., 2013). First, temporally correlated physiological artifacts were corrected by applying an autoregressive prewhitening filter to the signal (Y) received by each channel, defined as $Y_{\{t\}} = \sum_{i=1}^{P} \quad a_i \cdot Y_{\{t-i\}} + \epsilon_{\{t\}}$ and $\epsilon_{\{t\}} \in N(0, \sigma^2)$, where t indicates the sample point, a_i is the autoregressive coefficient of the model, and P is the model order that was selected based on Bayesian information criterion (BIC). This equation states that the current sample point (Y{t}) can be predicted based on the last several time points (a1.Y{t−1}). . . ap.Y{t−p}) and the newly added information at that time point, which are the innovations and are denoted as (ε{t}). These innovations can be considered new information that is added to the total signal at each time point. This method yields prewhitened signals without autocorrelations with time (Barker et al., 2013; Huppert, 2016; Santosa et al., 2018). The prewhitened signals were then processed using the procedure described in Santosa et al. (2017) to remove motion artifacts. Then, correlation coefficients (R) between two prewhitened and preweighted signals

(denoted as AS,W and BS,W below) were calculated using the equation $R = b_1 \cdot \frac{\sigma_A}{\sigma_B}$ (where σ_A and σ_B are the standard deviations of the signals A and B) after obtaining the value b_1 estimated by applying a least-square solution to the regression model $A_{S,W} = b_0 + B_{S,W} \cdot b_1$. This process was repeated until the correlation coefficients of all possible channel pairs were calculated. The correlation coefficients for each channel pair were Fisher's Z-transformed before averaging across channel pairs.

Intrahemispheric and interhemispheric connectivity were examined separately for the lateral and medial PFC. Figure 9 presents the channel pairs for each connectivity measure. First, a mixed ANOVA with load (low, medium, and high), region (medial and lateral) and hemisphere (left and right) as within-subjects factors and group (ASD and TD) as a between-subjects factor was conducted on the mean Z-transformed correlation coefficients for intrahemispheric connectivity. Then, another mixed ANOVA with load and region as within-subjects factors and group as a between-subjects factor was conducted on the mean Z-transformed correlation coefficients for interhemispheric connectivity.

Figure 9. *Channel pairs for the intrahemispheric (left) and interhemispheric (right) connectivity measures in the (a) lateral (red) and (b) medial (blue) prefrontal cortexes.*



Activation analysis

To complement the connectivity analysis, task-related changes in HbO were also examined. The fNIRS signals between each source and detector pair were analyzed using a general linear regression model (GLM) to test for differences between the baseline (30-s rest period at the beginning of the experiment) and the task conditions. This can be expressed by the equation $Y = X \times \beta + e$, where X is the timing of stimulus events, β is the coefficient (weight)

of the stimulus condition, and Y is the vector of measurements. Several modules can be used to obtain β, and the AR-IRIS method is the one we used in the paper; this method can remove artifacts and control type-I errors in the fNIRS model (see Santosa et al., 2018 for details). These values were then averaged across repetitions for each WM load and across channels for the lateral and medial PFC separately. For each region, a mixed ANOVA with load, hemisphere and region as within-subjects factors and group as a between-subjects factor was conducted on β.

For significant interactions and main effects of group on the behavioral and neurophysiological measures, if any, post hoc independent or paired sample t tests with Bonferroni corrections for three WM-load conditions (i.e., $p < 0.017$ for each condition) were conducted.

Correlation analysis

To explore the association between the activation/functional connectivity pattern during the WM task and ASD symptomatology, Spearman's rank-order correlations were performed between SRS-2 scores and significant fNIRS activation/functional connectivity results. Given that this analysis is exploratory in nature, no statistical adjustments were applied.

3.4 Results

3.4.1 Sample characteristics

Table 6 shows the demographic, intellectual, and clinical characteristics of the participants. Independent-sample t tests and chi-square tests showed that the TD and ASD groups did not significantly differ in age ($p = .93$), IQ ($p = .22$), sex ($p = .20$) or handedness ($p = .086$).

Regarding autism symptomatology indicated by the SRS-2, the children with ASD had a significantly greater SRS-2 total score than did the TD individuals (p <.001). All the ASD children fulfilled the diagnostic criteria for ASD with above-cutoff scores in all the ADI-R subdomains. Eight ASD participants were receiving psychiatric medication.

Table 6. *Demographic, intellectual, and clinical characteristics of TD (n = 24) and ASD (n = 22) individuals.*

	Group			
	TD	**ASD**	***t*/*χ*2**	***p***
	***M* (*SD*)**	***M* (*SD*)**		
Age (years)	10.2 (0.8)	10.1 (1.0)	0.09	.927
Intelligent quotient (IQ)	107.9 (9.2)	102.7 (17.0)	1.26	.218
Sex (male:female)a	17:7	19:3	1.63	.202
Handedness (R:L)	21:3	22:0	2.94	.086
SRS-2 total score	43.2 (16.6)	81.2 (18.8)	7.56	< .001***
Medication (Y:N)	–	8†:14	–	–
ADI-R Social Interaction (N = 19)	–	13.1 (8.3)	–	–
ADI-R Communication (N = 19)	–	10.6 (5.5)	–	–
ADI-R Restricted, Repetitive Behavior (N = 19)	–	4.7 (2.8)	–	–

ADI-R, Autism Diagnostic Interview-Revised; SRS-2, Social Responsiveness Scale–Second Edition.
aGroup comparison was conducted by the likelihood ratio test.
****p* < .001.
†Medication for alleviating attention deficit/hyperactivity, n = 7; antipsychotics for alleviating inflexibility, n = 1.

3.4.2 Behavioral performance

Table 7 presents the WISC-IV (HK) forward and backward digit span data, n-back ACC and mean (log-transformed) RT in each group. Both forward and backward digit span data were not significantly different between the two groups (p>0.40). For the ACC, a mixed 3 (load) × 2 (group) ANOVA showed a significant main effect of load (F2,88 = 69.71, p <.001,.61). The

main effect of group was not significant (F1,44 = 1.87, p =.18,.04), and no significant load × group interaction effect was observed. Analysis of all TD (n=24) and drug-free ASD (n=14) individuals also yielded nonsignificant results (ACC main effect of group: F1,36 =.45, p =.51; ACC load × group interaction: F2,72 =.76, p =.47).

For the mean log-transformed RT measure, a 3 (load) × 2 (group) mixed ANOVA showed significant main effects of load (F2,88 = 35.84, p <.001,.45) and group (F1,44 = 6.53, p =.014,.13), with the ASD group having a slower mean log-transformed RT than the TD group. The interaction between group and load was not significant (F2,88 = 0.33, p =.72,.008). Post hoc t tests with Bonferroni corrections showed that the ASD group had significantly slower mean log-transformed RTs than did the TD group in the 0-back condition (p =.009) and that trends toward significance in the 1-back (p =.030) and 2-back (p =.025) conditions did not survive Bonferroni corrections. Analysis of all TD (n=24) and drug-free ASD (n=14) individuals also yielded similar trends (log-transformed RT main effect of load: F1,36 = 36.50, p <.001; log-transformed RT main effect of group: F1,36 = 1.51, p =.23; log-transformed RT load × group interaction: F2,72 = 11.68, p =.002).

Table 7 *Working memory performance of TD (n = 24) and ASD (n = 22) individuals in our sample.*

	Group				
	TD	**ASD**	***t***	***p***	***d***
	***M* (*SD*)**	***M* (*SD*)**			
WM capacity					
WISC-IV (HK) Forward digit span	12.8 (2.3)	13.0 (3.1)	0.208	0.836	0.07

	Group				
	TD	**ASD**	***t***	***p***	***d***
	***M* (*SD*)**	***M* (*SD*)**			
WISC-IV (HK) Backward digit span	9.2 (3.1)	8.4 (3.4)	0.845	0.403	0.25
0-back					
Accuracy (%)	93.6 (5.1)	93.6 (5.6)	0.12	0.99	0.00
Raw RT (ms)	483.6 (121.1)	580.7 (150.7)	–	–	–
Log-transformed RT (a.u.)	2.67 (0.09)	2.75 (0.10)	2.73	0.009**	0.84
1-back					
Accuracy (%)	90.1 (7.9)	86.0 (13.4)	1.27	0.21	0.37
Raw RT (ms)	562.0 (142.6)	677.7 (202.5)	–	–	–
Log-transformed RT (a.u.)	2.74 (0.11)	2.81 (0.13)	2.24	0.030*	0.58
2-back					
Accuracy (%)	80.6 (8.3)	75.9 (10.7)	1.67	0.10	0.49
Raw RT (ms)	592.5 (186.8)	741.9 (253.1)	–	–	–
Log-transformed RT (a.u.)	2.75 (0.12)	2.85 (0.15)	2.32	0.025*	0.74

WISC-IV (HK), Hong Kong version of the Wechsler Intelligence Scale for Children-Fourth Edition short form; WM, working memory.
*$p < .05$, ** $p < .01$.

3.4.3 Effect of n-back load on prefrontal functional connectivity

To clarify the neural mechanisms underlying n-back task performance, we analyzed connectivity within and between the left and right medial and lateral PFC (Table 8), which were the regions of interest (ROIs) defined in our study (Figure 10). Regarding intrahemispheric connectivity, a 2 (hemisphere) × 3 (load) × 2 (region) × 2 (group) mixed ANOVA showed a significant hemisphere × load × region × group effect (F2,88 = 4.478, p =.014,.09). The main effects were significant for hemisphere (F1,44 = 4.350, p =.043,.09) and region (F1,44 = 4.194, p =.047.09). A follow-up 3 (load) × 2 (region) × 2 (group) mixed

ANOVA was conducted for each hemisphere to explore how different loads in the n-back task mediated functional connectivity of the medial and lateral PFC on each side of the brain. In the right hemisphere, a significant load × region × group interaction ($F_{2,88} = 6.073$, $p = .003$, .12) and a significant main effect of region ($F_{1,44} = 7.351$, $p = .010$, .14) were found. Thus, the ASD and TD groups exhibited different changes in connectivity in the right hemisphere with loads in the lateral and medial PFC. A post hoc paired-sample t test showed a trend toward significance between 0-back and 1-back connectivity in the right medial regions of the ASD group ($p = .030$), which did not survive Bonferroni correction. On the left side, neither a significant main effect nor a significant interaction was found (ps >.24). Analysis of all TD (n=24) and drug-free ASD (n=14) individuals showed similar results (hemisphere × load × region × group 4-way interaction: $F_{2,72} = 3.48$, $p = .036$; right PFC load × region × group 3-way interaction: $F_{2,72} = 4.75$, $p = .012$). For the functional connectivity laterality index (Table 9), a 2 (region) × 3 (load) × 2 (group) mixed ANOVA was performed. The main effect was significant for region ($F_{1,44} = 4.118$, $p = .049$, $\eta p2 = .09$), and none of the other main effects, including the main effect of group, were significant. There was also a significant load × region interaction effect ($F_{2,88} = 4.314$, $p = .016$, $\eta p2 = .09$), and none of the other interaction effects with group were significant.

Table 8 *Connectivity measures indicating (a) intrahemispheric and (b) interhemispheric functional connectivity in the lateral and medial prefrontal cortexes during the n-back task in TD (n = 24) and ASD (n = 22) individuals.*

	Left hemisphere		**Right hemisphere**	
	TD	**ASD**	**TD**	**ASD**
	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**
(a) Intrahemispheric				
Medial region				
0-back	0.238 (0.177)	0.228 (0.137)	0.197 (0.136)	0.154 (0.083)
1-back	0.238 (0.092)	0.216 (0.090)	0.160 (0.095)	0.162 (0.104)
2-back	0.264 (0.167)	0.221 (0.094)	0.194 (0.138)	0.181 (0.123)
Lateral region				
0-back	0.277 (0.173)	0.209 (0.148)	0.221 (0.199)	0.239 (0.143)
1-back	0.241 (0.174)	0.193 (0.161)	0.241 (0.151)	0.192 (0.097)
2-back	0.264 (0.142)	0.221 (0.152)	0.244 (0.148)	0.228 (0.155)
	Medial		**Lateral**	
	TD	**ASD**	**TD**	**ASD**
	***M* (*SD*)**	***M* (*SD*)**	***M (SD)***	***M (SD)***
(b) Interhemispheric				
0-back	0.270 (0.143)	0.279 (0.119)	0.227 (0.197)	0.190 (0.094)
1-back	0.264 (0.121)	0.243 (0.123)	0.190 (0.093)	0.161 (0.116)
2-back	0.280 (0.132)	0.286 (0.134)	0.214 (0.167)	0.182 (0.124)

Figure 10 *Effect of the n-back task load on the (a) left lateral, (b) left medial, (c) right lateral and d) right medial intrahemispheric functional connectivity changes in the prefrontal cortex in TD and ASD patients.*

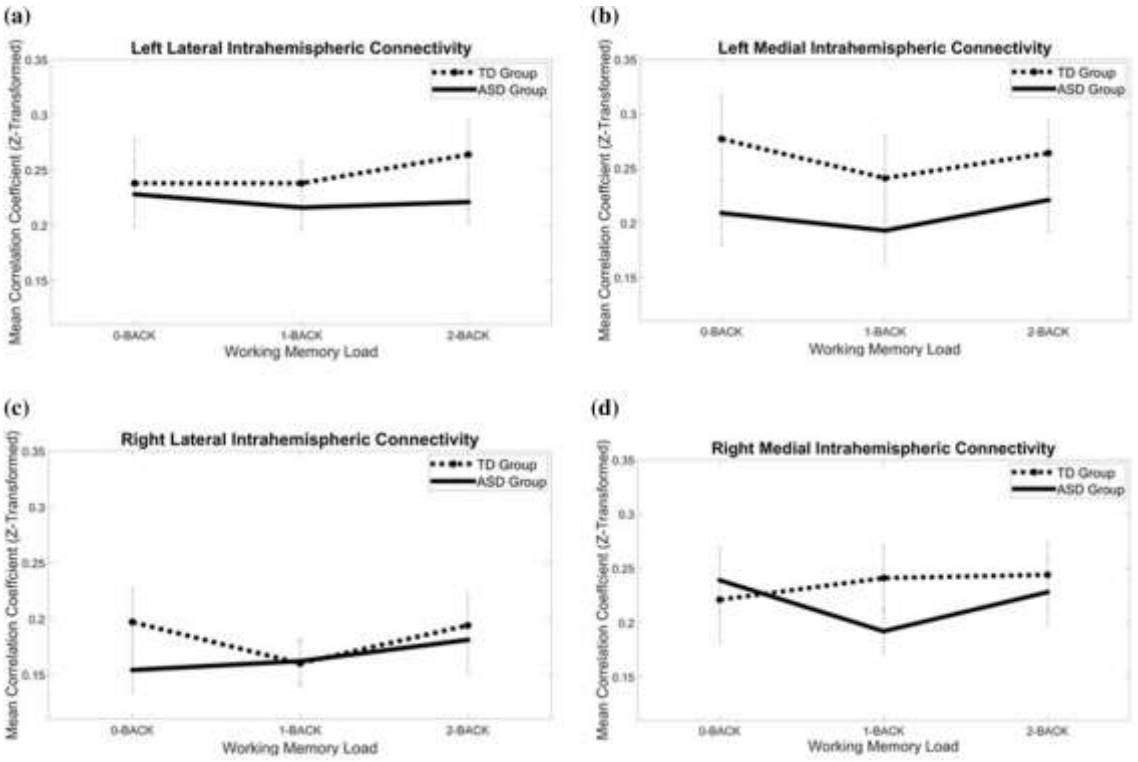
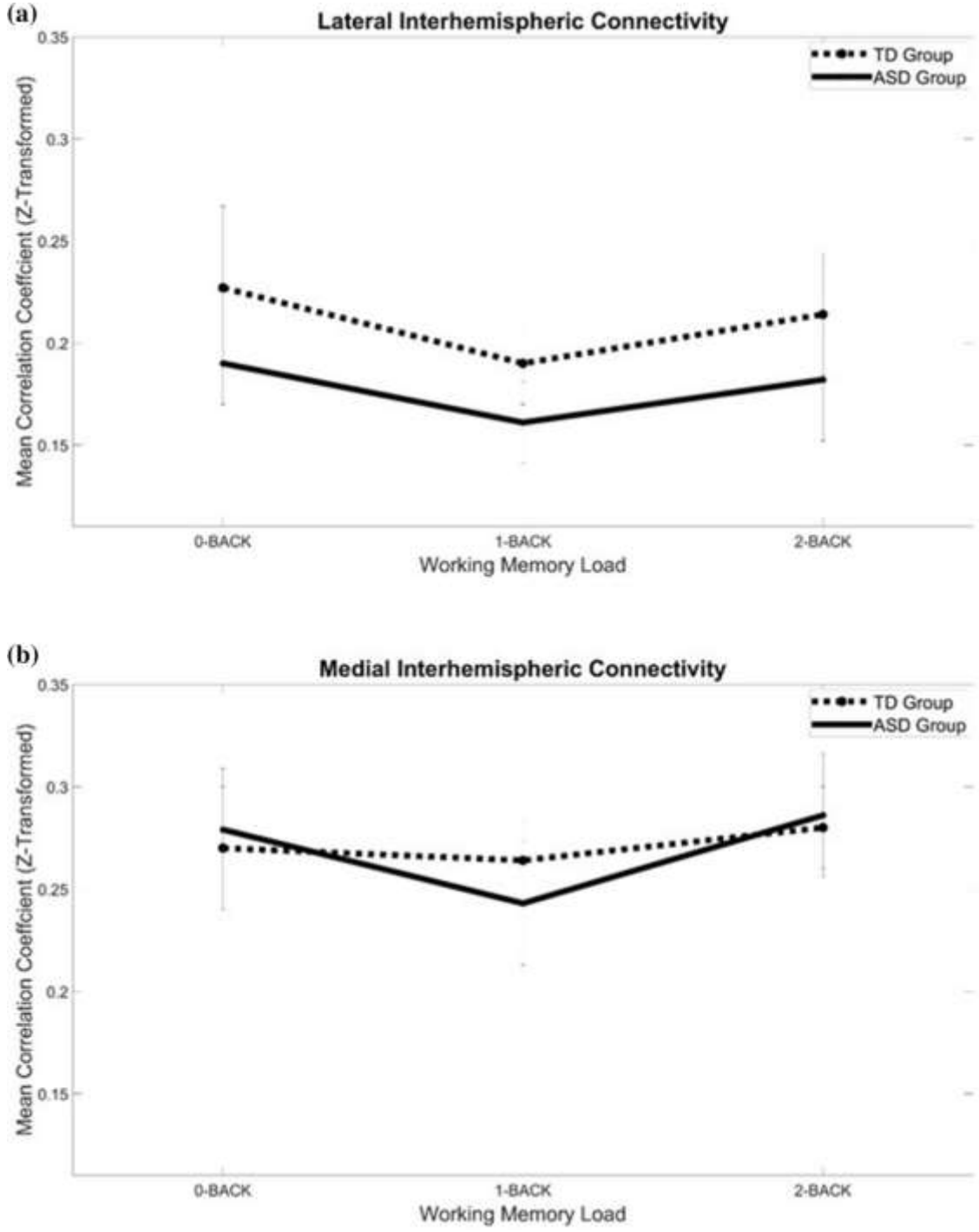


Table 9 *Functional connectivity laterality indices of ASD and TD individuals during the n-back task.*

	Laterality Index			
	Medial		**Lateral**	
	TD	**ASD**	**TD**	**ASD**
	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**
0-back	0.123 (0.467)	− 0.042 (0.441)	0.041 (0.417)	0.100 (0.392)
1-back	− 0.005 (0.504)	− 0.143 (0.465)	0.169 (0.369)	0.213 (0.418)
2-back	0.060 (0.384)	− 0.108 (0.445)	0.131 (0.446)	0.146 (0.437)

Regarding interhemispheric connectivity (Figure 11), a 3 (load) × 2 (region) × 2 (group) mixed ANOVA showed that only the main effects of load ($F_{2,88}$= 3.22, p =.045,.07) and region ($F_{1,44}$= 30.26, p <.001,.41) were significant. None of the effects involving groups were significant (p >.27).

Figure 11 *Effect of n-back task load on (a) lateral and (b) medial interhemispheric functional connectivity changes in the prefrontal cortex in TD and ASD patients.*



3.4.4 Effects of n-back load on prefrontal activation

To complement the functional connectivity analysis, mean changes in HbO levels (i.e., activation) in the PFC during the n-back task were examined (Table 10). A 3 (load) × 2 (hemisphere) × 2 (region) × 2 (group) mixed ANOVA showed a significant main effect of group (F1,44= 6.879, p =.012,.14), with the ASD group showing greater activation than the TD group during the n-back task. Post hoc t tests showed that higher activation in the ASD group was statistically significant only in the right medial region during the 0-back condition (p =.012) and in the right lateral region during the 1-back condition (p =.003); there were no differences in any ROIs in the 2-back condition (ps >.039). Analysis of all TD (n=24) and drug-free ASD (n=14) individuals showed similar trends (hemisphere × load × region × group 4-way interaction: F2,72 = 4.30, p =.045).

Table 10 *Mean changes in oxyhaemoglobin concentration (beta values) during the n-back task in TD (n = 24) and ASD (n = 22) individuals.*

	Left Hemisphere		**Right Hemisphere**	
	TD	**ASD**	**TD**	**ASD**
	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**	***M* (*SD*)**
0-back				
Medial	1.184 (21.35)	9.608 (23.76)	− 8.035 (13.90)	8.300 (26.78)
Lateral	0.076 (15.55)	8.313 (40.26)	− 1.418 (23.07)	8.568 (27.02)
1-back				
Medial	− 1.972 (21.78)	4.931 (21.95)	− 6.214 (18.62)	− 1.714 (32.96)
Lateral	3.150 (20.88)	− 1.377 (33.97)	− 6.658 (17.12)	12.037 (22.88)
2-back				
Medial	1.938 (15.74)	12.644 (18.29)	− 2.661 (19.12)	9.921 (31.11)
Lateral	− 1.578 (19.17)	4.594 (27.09)	5.683 (20.95)	5.638 (31.14)

3.4.5 Association between prefrontal functional connectivity and ASD symptomatology

Given that a significant interaction effect between group and WM load was identified in the right PFC, the functional connectivity values in the right medial and lateral PFC during the WM task were correlated with the SRS-2 total score. A significant positive correlation (rho =.460, p =.031) between the SRS-2 total score and right lateral PFC functional connectivity during the 0-back condition was detected in the ASD group only; other correlations remained nonsignificant (ps >.05).

3.5 Discussion

The present study used fNIRS to examine the effects of WM load on PFC connectivity during the number n-back task in children aged 8-12 with high-functioning ASD. Compared to age-, IQ-, sex- and handedness-matched TD children, children with ASD exhibited slower performance only during the "low load" (i.e., 0-back) condition. Additionally, there were differential load-dependent functional connectivity changes in the lateral and medial PFC, specifically in the right hemisphere but not in the left hemisphere. Our results suggest that individuals with ASD exhibit WM deficits, which is specifically mediated by the reduced information processing efficiency underpinned by abnormal functional connectivity in the right prefrontal cortex.

From the behavioral data, our finding of overall increased RTs during the n-back task among the children with ASD was consistent with previous observations of slower processing speed across various cognitive tasks in ASD (Goldstein et al., 1994; Nydén et al., 2001; Ozonoff & Strayer, 2001). It is well known that RT is a measure of the speed of information processing (Vartanian et al., 2007; Vernon, 1983) and represents the maximum rate at which a cognitive operation can be executed (Kail & Salthouse, 1994). In the present study, the children with

ASD needed more time to achieve a similar performance level as the TD children did, a pattern that corroborates the findings of a large-scale n-back study of adults with ASD (Lever et al., 2015). Despite showing a significant between-group difference with ANOVA, we are aware of the nonsignificant between-group differences in RTs (after Bonferroni corrections) for medium and high WM load conditions. The lack of a significant between-group difference might be attributed to the limited sample size and inherent heterogeneity within the ASD population regarding WM functioning , which is subject to further research. The difference in reaction time between the ASD and TD groups is consistent with previous findings when ASD individuals perform other executive functioning tasks (e.g., verbal fluency tasks). For instance, impaired verbal fluency is evident only when there is limited time given to ASD individuals; when they are given adequate time for task completion (Ehlen et al., 2020), they can perform equally well when compared to their TD counterparts. These findings imply that the impairment of WM in ASD patients is mediated by abnormal information processing in the brain, providing evidence in combination with a number of previous studies (e.g., Haigh et al., 2018; Eack et al., 2013). However, the accuracy across different WM loads was not significantly different between the two groups, which was consistent with the findings of previous studies involving individuals with high-functioning autism (Koshino et al., 2008). This could be explained by the phenomenon that high-functioning ASD individuals tend to complete complex WM tasks by utilizing their general intellectual capacities as compensation (Barendse et al., 2013; Barendse et al., 2018).

According to the fNIRS data, compared with TD controls, the children with ASD exhibited aberrant load-dependent intrahemispheric functional connectivity and activation patterns within the right PFC. Specifically, when comparing the 0- and 1-back loads, visual inspection of the data showed an increasing trend in functional connectivity in the right medial PFC in the TD group, while the ASD group showed a decreasing trend in right medial

intrahemispheric connectivity on load (Figure 4d). The right medial PFC has been documented to be the key hub for WM maintenance (Smith et al., 2018), learning and recalling learned associations between context, events and corresponding adaptive responses (Euston et al., 2012). Additionally, the right hemisphere has been heavily implicated in vigilance or sustained attention (Petersen & Posner, 2012). Thus, disrupted connectivity within the right medial PFC may interfere with these cognitive processes and underlie the overall slowing of information processing in ASD patients. In fact, our finding of right-lateralized abnormalities during the WM task is consistent with the findings of previous studies showing abnormal lateralization patterns in individuals with ASD (Floris et al., 2021). More importantly, our results revealed a positive correlation between functional connectivity in the right lateral PFC during the 0-back task and the SRS-2 total score, indicating that more impaired overall social functioning is associated with greater right lateral PFC functional connectivity during the low WM load condition. Given that the low-load condition in the n-back task corresponds to a two-alternative forced choice task tapping simple visual information processing (Gajewski et al., 2018) and that a more connected neural network reflects more effortful information processing (Engstrom et al., 2013), our results may be interpreted as a more effortful processing of incoming information for individuals with more impaired social functioning, which is consistent with the theory attributing ASD behavioral manifestations to abnormal information processing (Williams et al., 2015). However, it should be noted that we did not find a significant difference in the laterality indices between the ASD and TD groups. This could be because laterality indices vary greatly among ASD individuals, with both high and low scores (Floris et al., 2021), as reflected by the large standard deviation of our laterality index data. However, further studies are warranted to improve the understanding of the abnormal laterality pattern observed during WM tasks. Interestingly, our results showed that trending functional connectivity differences occurred in

the 1-back load for the right medial PFC, while a significant difference in reaction time (after Bonferroni correction) occurred in the 0-back load. A possible explanation for this discrepancy is that the 1-back condition might also be challenging for TD children, and a previous large-scale normative study has shown that n-back performance varies greatly in TD children aged between 8 and 12 (Pelegrina et al., 2015), the age group of our current sample. The inherently large heterogeneity in the 1-back condition may contribute to a less significant difference between TD individuals and ASD individuals.

This study is one of the first to apply fNIRS to clarify neural processing during WM processing in ASD patients. Consistent with previous fMRI studies of adults with ASD (Koshino et al., 2005, 2008), one recent study by Yeung et al. (2019) showed that adolescents with ASD exhibited increased right lateralization of PFC activation, which was positively associated with WM abilities, in response to increasing WM load (2-back > 0-back) during an n-back task similar to the one employed in the present study. Specifically, the present study revealed significant right lateral PFC hyperactivation in the 1-back condition. Given the role of the lateral PFC in error monitoring, which is the process of checking task performance over time for quality control and adjusting behavior (Stuss & Alexander, 2007), our results could imply an overall increase in effort for error monitoring in ASD patients during the n-back task. Interestingly, we did not observe between-group differences in the 2-back condition, which was in contrast to the findings of previous studies. This discrepancy in findings is likely due to age differences. Given the large heterogeneity of n-back task behavioral performance in children aged 8-12 (Pelegrina et al., 2015), it is reasonable to expect that the frontal activation pattern also changes with age, although how age modulates the frontal activation pattern during the n-back task remains poorly understood. Taken together, the evidence suggests the potential importance of considering the developmental context when studying WM processing in ASD patients. To our knowledge, this study is the

first to apply fNIRS to study cortical connectivity and to report altered PFC connectivity during WM processing in individuals with ASD. Because fNIRS possesses adequate temporal and spatial resolution and can be readily used in a natural setting, it is a promising tool for studying cortical connectivity in individuals with ASD.

3.5.1 Conclusion

The present study reported WM deficits and altered PFC connectivity during an n-back task in children with ASD. Because WM load influenced the pattern of PFC connectivity within the right but not the left PFC, this study highlights the importance of considering WM load to clarify the neural mechanisms underlying WM processing in ASD patients. Taken together, the literature implicates the right PFC in WM functioning in ASD (Koshino et al., 2005; Yeung et al., 2019). There is some preliminary evidence that transcranial direct current stimulation (Osório & Brunoni, 2019) and transcranial magnetic stimulation (Barahona-Corrêa et al., 2018) improve clinical and cognitive symptoms in individuals with ASD. Given that WM supports a variety of complex cognitive functions (Baddeley, 2012), future research exploring the effectiveness of neurostimulation over the right PFC for mitigating WM problems in ASD patients is warranted.

Chapter 4: Aberrant prefrontal functional connectivity during verbal fluency test is associated with reading comprehension deficits in autism spectrum disorder: An fNIRS study.

A version of this chapter has been published in a peer-reviewed journal:

Chan, M. M., Chan, M. C., Yeung, M. K., Wang, S. M., Liu, D., & Han, Y. M. (2022). Aberrant prefrontal functional connectivity during verbal fluency test is associated with reading comprehension deficits in autism spectrum disorder: An fNIRS study. *Frontiers in Psychology*, *13*, 984777.

4.1 Abstract

Children with autism spectrum disorder (ASD) exhibit marked difficulty in reading comprehension, a complex cognitive skill fundamental to successful daily functioning that is associated with core executive functions. However, the neurophysiological mechanisms underlying reading comprehension deficits in these children have not been elucidated. Twenty-one right-handed males with high-functioning ASD (mean age = 10.24 years) and 23 age-, IQ-, educational level-, sex- and handedness-matched typically developing (TD; mean age = 10.14 years) individuals underwent a reading comprehension test and a semantic verbal fluency test that assessed core executive functions underlying reading comprehension during concurrent prefrontal functional near-infrared spectroscopy (fNIRS) measurements. Participants' information processing efficiency was also assessed. High-functioning ASD children exhibited good reading comprehension [main effect of group: $F(1,40) = 7.58$, $p = 0.009$], selective verbal fluency deficits [group × category interaction: $F(1,42) = 4.90$, $p = 0.032$] and slower processing speed ($t42 = 2.36$, $p = 0.023$). Regarding the hemodynamics of

the prefrontal cortex (PFC), although ASD individuals showed patterns of PFC brain activation comparable to those of their healthy counterparts, lower PFC intrahemispheric (main effect of group: $F(1,42) = 11.36$, $p = 0.002$) and interhemispheric (main effect of group: $F(1,42) = 7.79$, $p = 0.008$) functional connectivity were evident during the semantic verbal fluency test. At the whole-group level, poorer reading comprehension performance was associated with poorer performance on the semantic verbal fluency test ($r42 = 0.508$, $p < 0.001$). Moreover, poorer semantic verbal fluency test performance was associated with slower information processing speed ($r42 = –0.312$, $p = 0.044$), which was associated with reduced left medial PFC functional connectivity ($r42 = –0.319$, $p = 0.040$). Abnormal intrahemispheric and interhemispheric prefrontal hypoconnectivity is associated with deficits in executive processes essential for reading comprehension in ASD patients. Our study has important implications for the neuropsychological and neurophysiological mechanisms underlying reading comprehension deficits in individuals with ASD.

4.2 Introduction

This chapter builds upon the foundational work presented in the earlier chapters of this thesis, which have collectively illuminated various aspects of executive functioning in autism spectrum disorder (ASD). While the initial chapters provided a comprehensive overview of executive dysfunctions and their neurobiological underpinnings in ASD, with a particular focus on flexibility and information processing (Chapter 2) and the impact of working memory load on frontal connectivity (Chapter 3), Chapter 4 shifts the lens to the domain of reading comprehension.

In this chapter, we investigate the neurophysiological mechanisms underlying reading comprehension deficits in children with high-functioning ASD, specifically examining the role of prefrontal functional connectivity during a verbal fluency test. This study is grounded

in the understanding that reading comprehension is a complex cognitive skill fundamentally associated with core executive functions. The focus on verbal fluency in relation to reading comprehension is particularly relevant. Verbal fluency, a task that taps into the core executive functions of updating, inhibition, and shifting, is crucial for reading comprehension and involves integrating and executing a variety of cognitive and executive function processes.

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder characterized by language and communication deficits as well as repetitive, stereotyped behaviors (American Psychological Association, 2013). Although individuals with ASD have been shown to possess intact simple language abilities, such as word recognition (Venker et al., 2021) and phonetic decoding of nonwords (Gabig, 2010), they encounter great difficulties in reading comprehension (Jones et al., 2009; see Brown et al., 2012 for a meta-analysis), a foundation skill for language learning in academic settings (Asberg et al., 2010). Previous neuropsychological studies have suggested that reading comprehension is a complex cognitive process involving the integration and execution of different cognitive-perceptual processes (Christopher et al., 2012; Kendeou et al., 2016). For example, when comprehending a written sentence, after individuals are visually recognized, these words are temporarily stored in the brain for matching with the learned phonological, orthographic and semantic representations, followed by combining these representations to form an understanding of the sentence (Chirstopher et al., 2012). For the successful comprehension of a longer sentence or even a passage with multiple paragraphs conveying several ideas, not only does a reader have to process more information, but he also has to maintain new information while disengaging from old information (Martin et al., 2020). In other words, the demand for cognitive-perceptual processes increases when the comprehension task becomes more complicated.

Previous studies have shown that all core components of EFs, namely, updating, inhibition and shifting (Miyake et al., 2000), are involved in reading comprehension. For instance, a review conducted by Butterfuss and Kendeou (2018) concluded that updating supports comprehension by maintaining relevant information in the working memory system, inhibition supports comprehension through the suppression of irrelevant text information and the prevention of irrelevant thoughts from intruding upon the working memory system, and shifting aid attention allocation to different features of the text. Given that many previous studies have revealed executive dysfunctions in individuals with ASD (see Demetriou et al., 2018 for a meta-analysis), it is reasonable to postulate that impairments in updating, inhibition and shifting in individuals with ASD may underpin reading comprehension difficulties in those with ASD.

Among many executive function tasks, the semantic verbal fluency (VF) task, for which a task taker is required to voluntarily generate as many words as possible with a given semantic category and to avoid giving repetitive and irrelevant answers (Lezak et al., 2012), has been shown to be sensitive for tapping updating (Aita et al., 2018), inhibition (Escobar et al., 2018) and shifting (Zhao et al., 2013) abilities. Evidence from neuroimaging meta-analyses has shown that semantic VF tasks activate brain networks that primarily involve the frontal lobe. While the left medial, superior and inferior frontal gyri are activated in response to VF tasks performed in nontonal language (e.g., English; Wagner et al., 2014), bilateral activations involving the superior, middle and inferior frontal gyri are found when VF tasks are performed in tonal language (i.e., Chinese; Wu et al., 2012). Evidence from functional connectivity studies shows that the semantic VF task involves prefrontal functional connectivity changes. Specifically, Paschoal et al. (2021) showed that there is a left-lateralized increase in connections accompanied by an increase in cerebral blood flow in the superior (BA6), middle (BA6) and inferior (BA9, 45, 47) frontal gyri during semantic VF

tasks compared to baseline (Paschoal et al., 2021). Multiple studies from lesion studies have shown that functional segregation of the medial and lateral prefrontal cortex (PFC) is evident for semantic VFs. For instance, while the lateral PFC has been shown to be associated with the strategic retrieval of words (Reverberi et al., 2006), the superior and medial prefrontal cortices have been shown to be involved in the voluntary generation of new words relevant to the given cues (Robinson et al., 2012).

Several previous studies have provided evidence to support semantic VF impairment in individuals with ASD. Specifically, Yeung et al. (2019) and Inokuchi & Kamio (2013) showed that individuals with ASD exhibited significantly poorer performance than did typically developing (TD) individuals only for the living (i.e., animal) but not the nonliving (i.e., transport) category, suggesting a category-dependent impairment in semantic VF in individuals with ASD. However, Ehlen et al. (2020) showed that ASD individuals have an intact ability to live-category semantic VFs. Similar conflicting results have been documented in neurophysiological and neuroimaging studies. For instance, a previous functional magnetic resonance imaging (fMRI) study showed that individuals with ASD exhibited reduced activation in the left inferior and middle frontal gyri (Kenworthy et al., 2013), and another fMRI study showed enhanced activation in the left inferior frontal gyrus during a similar semantic VF task (Beacher et al., 2012). For functional near-infrared spectroscopy (fNIRS) studies, although Yeung et al. (2019) showed that ASD individuals exhibited a significantly altered activation pattern in the medial and lateral PFC when compared to TD individuals, Ota et al. (2020) revealed nonsignificant differences between ASD and TD individuals in prefrontal activation with a similar fNIRS paradigm.

Some preliminary evidence has shown that the time allowed for semantic VF task completion might contribute to the above inconsistent results. For instance, Carmo et al. (2015) showed

that, compared with TD individuals, ASD individuals only exhibited impairment when less time was given for task completion, indicated by a reduced number of words generated in the animal category only in the first 30 seconds of the task but not in the late task period (i.e., 31-60 seconds of the task). Given that ASD has long been construed as an information processing disorder (Han & Chan, 2018) indicated by an increased amount of time needed for information to travel across the brain, it is not surprising to see that slow processing speed underpins semantic VF performance. A number of studies have shown that slow processing speed is associated with abnormal structural and functional connectivity (da Silva et al., 2020), and previous studies have shown that functional connectivity is altered in individuals with ASD during the resting state (Han & Chan, 2017; King et al., 2019) and cognitive task performance (e.g., working memory; Koshino et al., 2005).

As reviewed above, given that the semantic VF task 1) is sensitive to tapping into core executive functions (i.e., updating, inhibition and shifting) that are fundamental to reading comprehension, 2) requires intact functioning of the medial and lateral PFC, and 3) is influenced by information processing efficiency contributed by functional connectivity in the brain, it is reasonable to postulate that altered functional connectivity in the medial and/or lateral PFC during semantic VF tasks could be the possible neurophysiological mechanism underpinning reading comprehension deficits in ASD patients. However, to the best of our knowledge, the prefrontal functional connectivity of ASD patients during semantic VF tasks and its behavioral correlates have not been investigated in previous studies. This study aimed to investigate the neurophysiological mechanism underlying reading comprehension performance in children with high-functioning ASD. It is hypothesized that, when compared to typically developing (TD) individuals, ASD individuals exhibit impaired reading comprehension performance, especially when task difficulty increases, which is associated with impaired semantic VF performance. In turn, impaired semantic VF performance in ASD

patients is associated with reduced information processing efficiency, which is underpinned by altered prefrontal functional connectivity but not abnormal prefrontal activation patterns.

4.3 Method

4.3.1 Participants

This study was approved by the Human Subjects Ethics Sub-Committee of Hong Kong Polytechnic University and was conducted in accordance with the Declaration of Helsinki. Twenty-one individuals with ASD and 23 TD individuals aged 8-12 years who were studying Grade 3-5 in local mainstream primary schools participated in this study. All participants achieved a full intelligence quotient (IQ) ≥ 80 according to the short form of the Hong Kong Wechsler Intelligence Scale for Children – fourth edition (WISC-IV-HK:SF; Wechsler, 2010). Given that previous research has shown that individuals with ASD exhibit sex-dependent differences in nonsocial cognitive domains involving executive function (Lai et al., 2012), we included only males in our sample. Furthermore, as prior studies have shown that handedness influences the neural connectivity underlying Chinese semantic language processing (Gao, Wang, Yu and Chen, 2015), we included only right-handed individuals whose handedness was confirmed by scoring over +80 on the Edinburgh Handedness Inventory short form (Oldfield, 1971). The diagnosis of ASD in participants was confirmed

by the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter & Le Couteur, 1994), which was administered by a clinical psychologist blinded to the hypothesis of the study. The social functioning of TD individuals was assessed by the second edition of the Social Responsiveness Scale (SRS-2; Constantino & Gruber, 2012). A total of 59 out of a maximum score of 195 was obtained for all included TD individuals, indicating that they had normal daily social functioning.

4.3.2 Procedure and Materials

Before the commencement of the experiment, the procedures and potential risks and benefits of the study were first explained to the participants and their parents, and written informed consent was subsequently obtained from all the participating parents of the recruited individuals. All the children underwent three assessments, namely, the WISC-IV-HK:SF IQ, a series of behavioral assessments and fNIRS measurements. The sequence of assessments was counterbalanced across subjects to minimize order effects. While the parents of all the children were asked to complete the SRS-2, the parents of the children with ASD were involved in a structured interview in which the ADI-R was administered in addition to the completion of the SRS-2. The WISC-IV-HK:SF and ADI-R were administered by a clinical psychologist. The behavioral assessments and fNIRS measurements were conducted by trained research assistants.

Behavioral assessments

Behavioral assessments were also conducted to examine the participants' reading comprehension ability and information processing efficiency.

The reading comprehension test consists of three parts with increasing difficulty. The first part, which consisted of three short sentences of 20-35 words, assessed children's pronunciation resolution ability. The second part consisted of a 50-word short descriptive paragraph, from which participants were required to answer two questions asking for the identification of specific details from the paragraph. The third part consisted of two passages with multiple paragraphs. The first passage was a story behind a Chinese idiom with conversations between two people embedded in the story. Children were asked not only to identify specific details from the passage but also to make logical conclusions and infer the symbolic meanings of a word and the whole passage. The second passage was a 200-word metaphorical description of the Great Wall of China, with all six questions testing the participants' understanding of the metaphors used in the passage. There was no time limit for test completion. A higher score obtained during the test indicates better reading comprehension performance.

Participants' information processing efficiency was assessed by the five-choice reaction time (RTI) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Fray et al., 1996). This is a standardized computerized test tapping participants' mental processing speeds by eliminating the effect of movement execution time (Sachse et al., 2013). The five-choice mean reaction time, a commonly adopted measure reflecting information processing efficiency (e.g., Hadanny et al., 2020, Cabeca et al., 2018), was used. A higher mean reaction time indicates less efficient information processing.

fNIRS measurements

fNIRS measurements were taken for each of the participants when they performed the semantic verbal fluency task. The paradigm is adapted from previous studies (i.e., Huang et al., 2016; Yeung et al., 2016; Yeung et al., 2019), and the task design is illustrated in Figure 12. During the experimental blocks, a category word (i.e., "animal" or "transport") was shown in the center of the screen. Participants were instructed to orally produce as many words relevant to the given category as possible without repeating their ideas in 60 seconds. The order of the experimental blocks was counterbalanced across individuals. During the control blocks, participants were instructed to repeat the phrase "1, 2, 3, 4" slowly and continuously during the given period of time (i.e., 30 seconds for the first control block and 60 seconds for the second and third control blocks). The visual stimuli were presented using E-prime 3 (Psychology Software Tools, 2016). A 52-channel fNIRS optical topography system (ETG-4000; Hitachi Medical Co., Tokyo, Japan) was used to measure the changes in brain signals during the task with a sampling rate of 10 Hz. Before wearing the probe set, landmarks in the 10-10 system (Chatrian et al., 1988) were identified by measuring the head circumference, distance between the incision and nasion, and distance between the left and right auricular. To ensure measurement consistency, this procedure was performed by the same experienced research assistant. The probe set with thirty-three NIR emitters and detectors was mounted on a 3x11 grid with the emitter-detector distance fixed at 3 cm, which was then worn on a participant's head using an elastic headband with detector 26 placed at FpZ, emitter 24 placed midway between F8 and FC8, and emitter 27 placed midway between F7 and FC7 for children aged 8-11 years old with an average head circumference of 52 cm in our sample. The channels were grouped to represent the medial and lateral PFC in the left and right hemispheres to increase the signal-to-noise ratio (Yeung et al., 2019). The arrangements of channels, NIR emitters and detectors as well as the channel groupings are illustrated in Figure 13.

Figure 12 *Semantic verbal fluency task design*

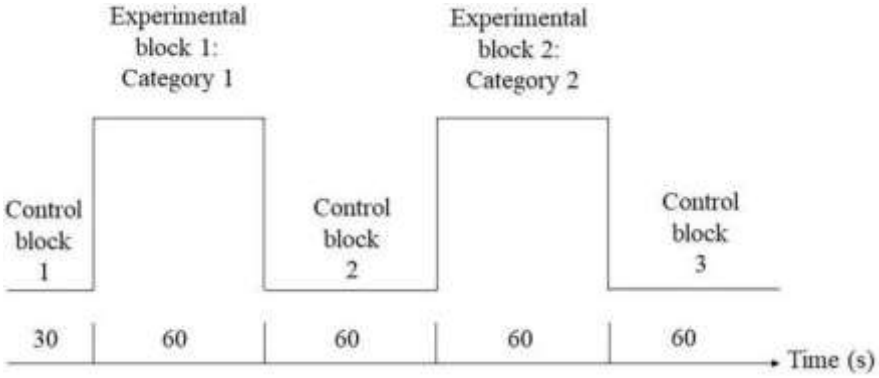
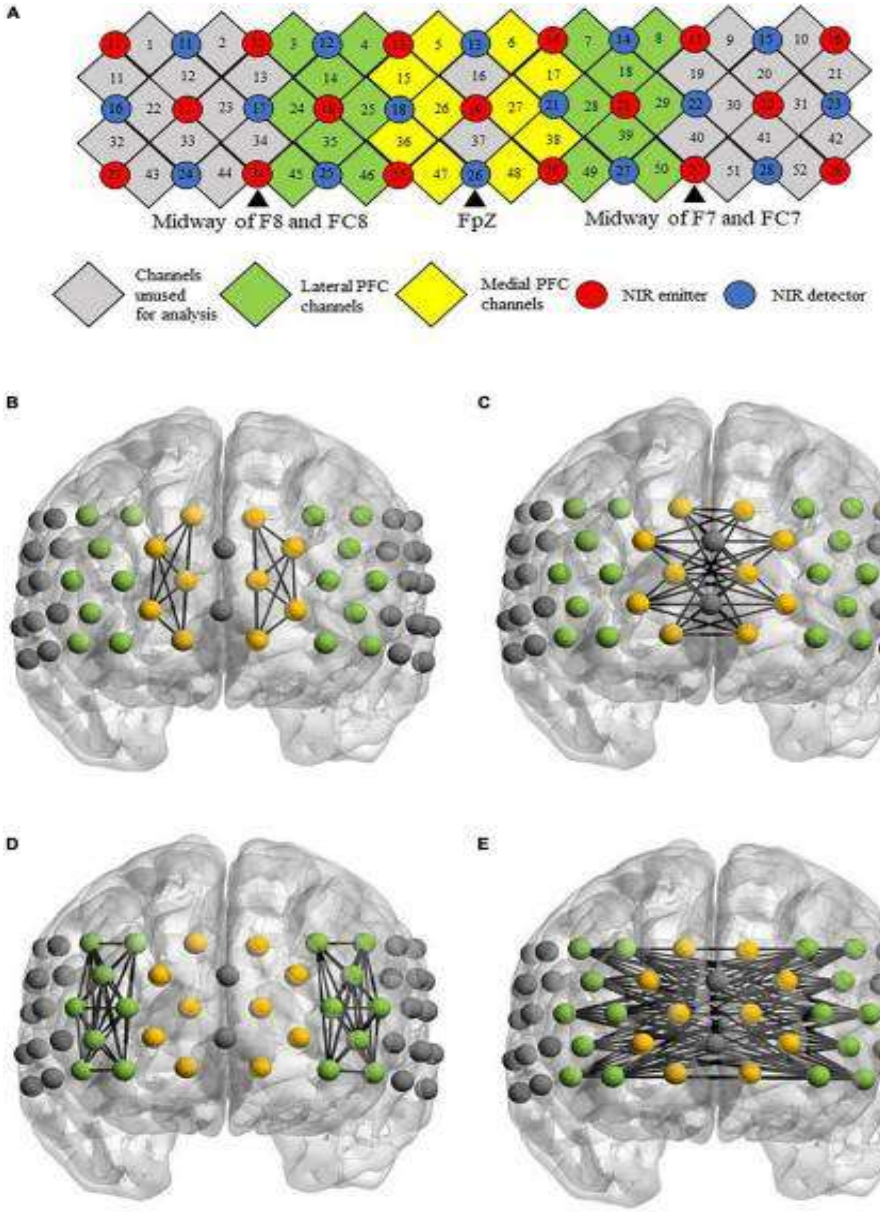


Figure 13 *(A) Arrangements of channels, near-infrared (NIR) emitters, detectors and channel groupings. (B–E) Images showing the location of channels on a brain template. The figures define the functional connectivity of the (B) intrahemispheric and (C) interhemispheric medial PFC, as well as the functional connectivity of the (D) intrahemispheric and (E) interhemispheric lateral PFC.*



4.3.3 Data analysis

fNIRS preprocessing

fNIRS data preprocessing was performed using the AnalyzIR toolbox (Santosa et al., 2018) in MATLAB 2019a (The Mathworks, Natick, MA), and the preprocessing pipeline is illustrated below. The light intensity data for each participant collected during the sematic verbal fluency task were extracted from the ETG-4000 machine. Saturated or flatlined channels were replaced with high variance noise using the FixSatChans or FixFlatChans modules, respectively. The resample module was subsequently adopted to downsample the data to 1 Hz using a Nyquist filter. To remove excessive baseline signals before and after the

task, the TrimBaseline module was applied to keep the first control block the baseline only. The resampled and trimmed data were converted to optical density using the OpticalDensity module and then to oxyhaemoglobin (HbO), deoxyhaemoglobin (HbR) and total hemoglobin (HbT) concentrations using the modified Beer–Lambert Law (Delpy et al., 1988). For statistical analysis, only HbO data were used in this study given that HbO has been found to be a more sensitive measure than HbR for detecting task-related neural changes in patients with neurological disorders, including ASD (Yeung & Lin, 2021).

fNIRS first-level analysis

To estimate the differences in fNIRS activation between the experimental (i.e., animal/transport word generation) and baseline (i.e., number repetition) conditions while also controlling for type I errors caused by slow systemic physiology and motion artifacts, a general linear model (GLM) with an autoregressive prewhitening approach using iteratively reweighted least squares (AR-IRLS; Barker et al., 2013) was generated for the HbO data of each of the participants. The GLM yielded a regression coefficient (β) for each channel, and the β values were averaged within each region of interest (i.e., left medial PFC, right medial PFC, left lateral PFC and right lateral PFC) for both animal and transport conditions. These averaged values were subsequently used in the second-level fNIRS activation analysis.

To estimate the differences in functional connectivity between the experimental (i.e., animal/transport word generation) and baseline (i.e., number repetition) conditions, GLM with AR-IRLS followed by robust regression (Santosa et al., 2017) was conducted for the HbO data of each of the participants. Although AR-IRLS has been shown to effectively reduce type-I errors in fNIRS activation analyses, shifting-type motion artifacts, which usually result from an individual's abrupt and excessive movement causing the shift of the entire probe set, could still appear as extreme statistical outliers (Barker et al., 2013), yielding

high but spurious correlations that influence the interpretation of functional connectivity data as a result (Santosa et al., 2017). Robust regression was hence adopted to reduce the effect of these statistical outliers on the data analysis by assigning a lesser weighting to the outliers to normalize the noise distributions. A Z-transformed correlation coefficient (Z) was calculated for each of the possible channel pairs, and the Z values were averaged within each region of interest (i.e., left medial PFC, right medial PFC, left lateral PFC and right lateral PFC) for both animal and transport conditions. These averaged values were subsequently used in the second-level functional connectivity analysis.

Second-level analysis

Group-level analyses of the behavioral and fNIRS data were performed using IBM SPSS Statistics Version 26.0 (IBM Corp, Armonk, NY). The normality of the data was first checked with the Shapiro–Wilk test. For nonnormal behavioral and fNIRS data, the aligned rank transform contrasts (ART-C; Elkin et al., 2021) procedure was used to facilitate the administration of omnibus tests (illustrated below).

To examine whether the TD and ASD groups were matched, independent sample t tests (or Mann–Whitney tests for nonnormal data) were performed for age, IQ, educational level and SRS-2 score. To test for differences in reading comprehension performance between two groups across different levels of difficulty (H1), we analyzed subscores (from different levels) from the reading comprehension test with 2 (group) × 3 (level of difficulty) mixed ANOVA. To test for the difference in semantic verbal fluency performance between two groups across different word categories (H2), the total number of correct words generated for each category (i.e., animal or transport) was analyzed with 2 (group) × 2 (category) mixed ANOVA. To test for differences in information processing efficiency between two groups (H3), an independent sample t test (or Mann–Whitney test for nonnormal data) was

performed for the five-choice mean reaction time from the CANTAB reaction time test. To investigate the difference in prefrontal fNIRS activation patterns between the two groups during different categories in the semantic verbal fluency test in the medial/lateral PFC of the left/right hemisphere (H4), a 2 (group) × 2 (category) × 2 (region) × 2 (hemisphere) mixed ANOVA was performed with the averaged β-values of the medial/lateral PFC of each hemisphere. To investigate the difference in prefrontal fNIRS functional connectivity between the two groups during different categories in the semantic verbal fluency test within the medial/lateral PFC of the left/right hemisphere (H5), a 2 (group) × 2 (category) × 2 (region) × 2 (hemisphere) mixed ANOVA was performed with the averaged Z values of the medial/lateral PFC of each hemisphere. To explore the relationship between brain hemodynamic changes and behavioral performance, Pearson's correlation analyses were performed for parameters found to be significant in the group comparison. To correct for multiple comparisons, Bonferroni corrections were applied to each of the hypotheses.

4.4 Results

4.4.1 Demographic details

The demographic details of the participants are listed in Table 11. Independent sample t tests revealed that the ASD and TD individuals were matched for age, full-scale IQ score and education level ($p > .158$). Our ASD sample also showed markedly impaired current social functioning compared to that of their TD counterparts, as indicated by a significantly greater SRS-2 total score ($p < .001$).

Table 1 1 *Patient demographic information.*

Parameters	Group				
	ASD	TD	*t*	*df*	*p*
Mean chronological age in years (*S.D.*)	10.24 (1.16)	10.14 (0.90)	0.339	42	0.736
Mean full scale IQ (*S.D.*)	100.76 (16.04)	105.74 (12.11)	1.17	42	0.249
Educational level (*S.D.*)	3.90 (1.00)	4.30 (0.82)	1.46	42	0.153
Mean SRS-2 total score (*S.D.*)	84.00 (22.32)	42.89 (14.92)	6.64***	42	<0.001
Mean ADI-R domain scores (*S.D.*)					
Social interaction	14.26 (7.58)	N/A	N/A		
Communication	10.84 (5.87)				
Restricted, repetitive behavior	4.63 (2.17)				

All participants (ASD, n = 21; TD, n = 23) were right-handed males.

SRS, Social Responsiveness Scale-2; ADI-R, Autism Diagnostic Interview-Revised.

***p < 0.001.

4.4.2 Behavioral performance

Regarding reading comprehension performance (Table 2), a 2x3 mixed ANOVA showed a highly significant main effect of group (F1,42 = 9.85, p =.003) with a nonsignificant group*level interaction effect (F1.59,63.68 =.221, p =.751). Post hoc independent t tests with Bonferroni corrections showed that ASD individuals performed markedly poorer on questions of high level than did TD individuals (p =.016; Table 12). Regarding semantic verbal fluency performance (Figure 14), a 2x2 mixed ANOVA showed a significant group*condition interaction effect (F1,42 = 4.90, p =.032) with a nonsignificant main effect of group (F1,42 = 2.04, p =.161). Post hoc t tests with Bonferroni corrections showed that ASD individuals performed poorer in animals (t42 = 2.33, p =.024) but not in transport (t42 = -.265, p =.792) or word generation. Regarding information processing efficiency, ASD individuals exhibited slower processing speed in the CANTAB RTI five-choice mean

reaction time (ASD mean = 473.87 ms, s.d. = 60.19 ms; TD mean = 430.24 ms, s.d. = 59.49 ms; t42 = 2.36, p =.023).

Table 1 2 *Reading comprehension performance.*

Parameters	Group				
	ASD	TD	*t*	*df*	*p*
Reading comprehension total score					
Main effect of group: *F*(1, 40) = 7.58, *p* = 0.009**					
ART-C reading comprehension (low level) subscore (S.D.)	50.34 (36.84)	71.76 (34.83)	2.15	40	0.038
ART-C reading comprehension (medium level) subscore (S.D.)	61.39 (44.20)	88.35 (38.06)	2.30	40	0.027
ART-C reading comprehension (high level) subscore (S.D.)	49.52 (29.98)	68.78 (19.90)	2.95*	40	0.016

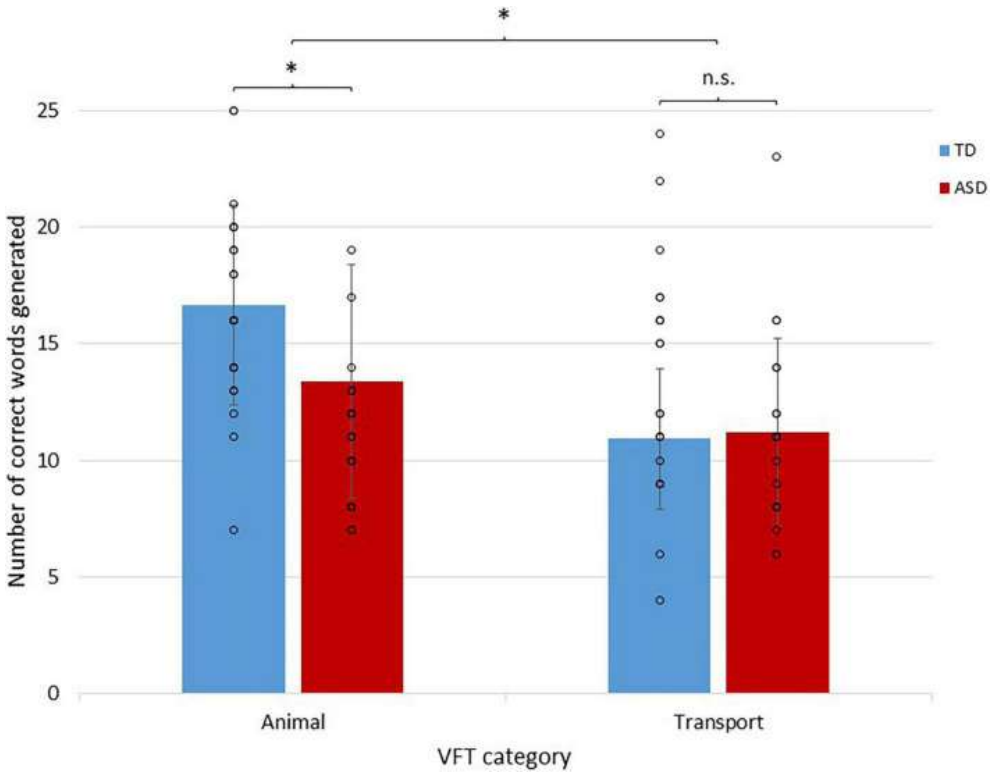
ART-C, aligned rank transform contrast.

ASD, n = 19; TD, n = 23; two sets of data from the ASD group were missing.

*p < 0.017 (Bonferroni-corrected).

**p < 0.01 (Bonferroni-corrected).

Figure 1 4 *A bar chart showing semantic fluency performance in ASD and TD individuals during different semantic categories. Individual data points are represented by circles. Error bars represent ± 1 standard deviation of the mean. *p <0.05.*



4.4.3 fNIRS prefrontal activation during the semantic verbal fluency task

A 4-way (group*condition*region*hemisphere) mixed ANOVA revealed nonsignificant interaction effects across all levels ($p > .066$) and a nonsignificant main effect of group ($F_{1,42} = .149$, $p = .701$) for prefrontal activation during the semantic verbal fluency task.

4.4.4 fNIRS prefrontal functional connectivity during the semantic verbal fluency task

Regarding intrahemispheric functional connectivity within the medial and lateral PFC (Table 13), a 4-way (group*condition*region*hemisphere) mixed ANOVA revealed a highly significant main effect of group ($F_{1,42} = 11.36$, $p = .002$) and a significant region*group interaction ($F_{1,42} = 6.92$, $p = .012$). In both animal and transport word generation, ASD individuals exhibited lower PFC functional connectivity in all subregions in both

hemispheres, but only the lower intrahemispheric functional connectivity in the left medial PFC during animal (t42 = 2.92, p =.006) and transport (t42 = 3.13, p =.004) word generation survived Bonferroni corrections. The other interaction effects remained nonsignificant (p > 0.085).

Table 13 *Intrahemisphere within-region functional connectivity during verbal fluency tasks in ASD and TD individuals (Z-transformed coherence values).*

	Left hemisphere					Right hemisphere				
	Group					Group				
	ASD	TD	*t*	*df*	*p*	ASD	*TD*	*t*	*df*	*p*
Main effect of group: *F*(1, 42)= 11.36.*p*= 0.002**										
Group*condition*region*hemisphere: *F*(1, 42)= 0.364,*p*= 0.550										
Condition 1: Animal word generation										
Medial	0.12 (0.12)	0.27 (0.22)	2.93**	42	0.006	0.17 (0.11)	0.26 (0.13)	2.65	42	0.011
Lateral	0.12 (0.10)	0.19 (0.12)	2.15	42	0.037	0.10 (0.09)	0.14 (0.07)	1.61	42	0.114
Condition 2: Transport word generation										
Medial	0.14 (0.12)	0.30 (0.21)	3.03**	42	0.004	0.12 (0.11)	0.22 (0.18)	2.27	42	0.029
Lateral	0.15 (0.11)	0.22 (0.14)	2.03	42	0.049	0.11 (0.09)	0.12 (0.07)	0.451	42	0.655

** p < 0.0063 (Bonferroni-corrected).

Regarding interhemispheric functional connectivity (Table 14), a 3-way (Group × Condition × region) mixed ANOVA revealed a highly significant main effect of group [F(1,42) = 7.79, p = 0.008] and a significant region × group interaction [F(1,42) = 4.35, p = 0.043]. ASD individuals exhibited lower interhemispheric functional connectivity in the lateral PFC during animal word generation (t42 = 2.73, p = 0.009), while lower interhemispheric medial PFC

functional connectivity was observed in the transport word generation condition (t42 = 2.75, p = 0.008). The other interaction effects remained nonsignificant (p > 0.076).

Table 1 4 *Interhemispheric functional connectivity (FC) during verbal fluency tasks in ASD and TD individuals (Z-transformed connectivity index).*

Prefrontal brain region	Group				
	ASD	TD	*t*	*df*	*p*
Main effect of group: *F*(1,42)= 7.79, *p*= 0.008**					
Group*condition*region: *F*(1, 42)= 4.35,*p*= 0.043					
Condition 1: Animal word generation					
Medial	0.18 (0.11)	0.27 (0.15)	2.37	42	0.023
Lateral	0.09 (0.08)	0.15 (0.08)	2.73**	42	0.009
Condition 2: Transport word generation					
Medial	0.16 (0.10)	0.28 (0.17)	2.75**	42	0.008
Lateral	0.11 (0.08)	0.15 (0.09)	1.54	42	0.13

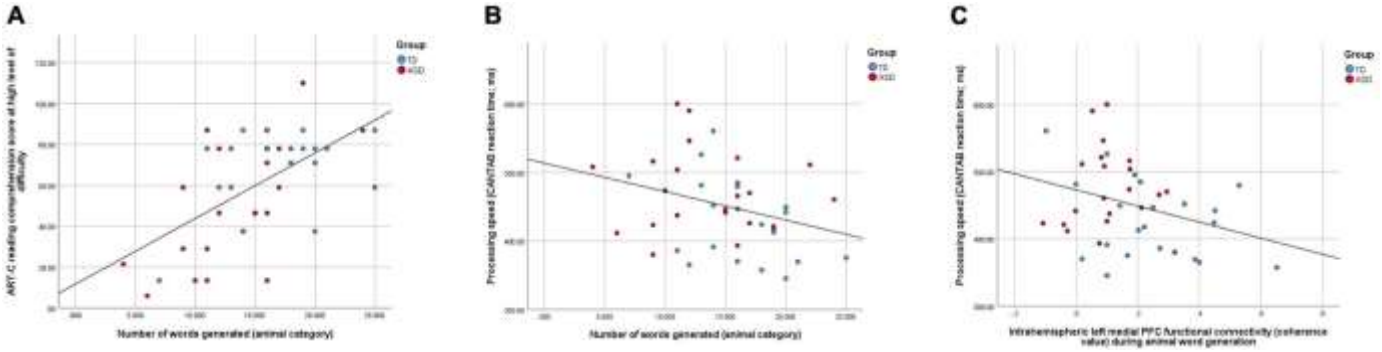
** p < 0.0125 (Bonferroni-corrected).

4.4.5 Brain-behavior relationships

The relationships between the strength of intrahemispheric functional connectivity in the left medial PFC and interhemispheric functional connectivity in the lateral PFC during animal word generation, processing speed, animal category verbal fluency performance and reading comprehension performance were examined. At the whole-group level, better animal word generation ability was strongly associated with better reading comprehension performance at a high level of difficulty (r42 = 0.508, p < 0.001; Figure 15A), which was also correlated with faster processing speed (r42 = –0.312, p = 0.044; Figure 15B). In turn, faster processing speed was significantly correlated with greater left medial PFC functional connectivity during

animal word generation (r42 = –0.319, p = 0.040; Figure 15C). Subgroup analyses of the TD group revealed marginal significance in the correlation between RT and reading comprehension performance at a high level of difficulty (r22 = –0.42, p = 0.058) as well as between RT and the total number of animal words generated (r22 = 0.389, p = 0.067). For the ASD group, a greater total number of animal word generations was significantly associated with better reading comprehension performance at a high level of difficulty (r20 = 0.61, p = 0.006). The other correlations remained nonsignificant (p > 0.1).

Figure 1 5 *(A) A scatter plot showing a highly significant positive correlation between reading comprehension performance and a high level of difficulty and semantic verbal fluency performance in the animal category (r42 = 0.508, p < 0.001); (B) a scatter plot showing a significant negative correlation between semantic verbal fluency performance and processing speed (r42 = –0.312, p = 0.044); (C) a scatter plot showing a significant negative correlation between processing speed and left medial PFC functional connectivity during animal word generation (r42 = –0.319, p = 0.040).*



4.5 Discussion

Our results showed that high-functioning ASD children performed markedly poorer on the reading comprehension test, especially at the high difficulty level, and that this was accompanied by a significantly slower information processing speed and fewer correct words generated in only the living things category (i.e., animal) in the semantic verbal fluency test. Although a nonsignificant difference was found in PFC activation in our fNIRS

measurements, we found that ASD patients exhibited markedly lower functional connectivity in the left medial PFC during the animal word generation task, which was significantly correlated with a slower processing speed, provided that such a reduction in processing speed was also correlated with poor animal word generation performance, a parameter that was highly correlated with poorer reading comprehension performance at a high level of difficulty. We discuss the above results in the following paragraphs.

Consistent with previous findings (Brown et al., 2013), our ASD sample exhibited significantly poorer reading comprehension than did their TD counterparts. Our results further indicated that ASD individuals exhibited significant impairment only when comprehending longer passages (approximately 100-200 words) involving social context (i.e., conversations between two people) and abstract concepts (i.e., metaphorical descriptions for an object) but were able to perform comparably with TD individuals in pronoun resolution from a short sentence (approximately 20-35 words) and identification of specific details from a short paragraph (approximately 50 words). Indeed, previous studies have revealed that school-age children with high-functioning ASD could identify correct information from written text when only short paragraphs (i.e., three sentences) were given (Saldana & Frith, 2007) but were found to perform poorly in passages with more than one paragraph and even more poorly when they were asked to answer inferential questions (Myles & Simptoms 2002). A meta-analysis conducted by Brown et al. (2013) also showed that reading comprehension impairment was more severe when participants were asked to comprehend social contexts than when they were not. This evidence, together with our findings, collectively suggests that reading comprehension deficits in individuals with high-functioning ASD are complex and dependent, which has also been hypothesized by previous researchers (O'Connor & Klein, 2004; Williamson et al., 2012). Given that ASD has long been regarded as an information processing disorder (Belmonte et al., 2004; Williams et al.,

2006; Rudie et al., 2012; Han & Chan, 2017; Haigh et al., 2018), it is reasonable to only see impairments in high-functioning ASD individuals when more information has to be integrated as comprehension task demand increases (e.g., longer passages and more abstract concepts were given).

Consistent with the findings of another local study of verbal fluency ability in adolescents with ASD (Yeung et al., 2019) and another study from another country (Inokuchi & Kamio, 2013), we found category-dependent semantic verbal fluency impairment in children with high-functioning ASD. Importantly, we further revealed that poorer semantic verbal fluency was associated with poorer reading comprehension performance at a high level of difficulty and less efficient information processing. Taken together with our observation of reading comprehension performance in ASD patients discussed above, we can conclude that selective reading comprehension impairment in ASD patients may be associated with deficits in information processing. In addition, our findings help explain why semantic verbal fluency impairment was not observed in some studies, such as Ehlen et al. (2020). In Ehlen et al. (2020), participants were given 120 seconds, rather than 60 seconds, during the verbal fluency task. It could be possible that with more time given, demand for information processing is reduced, which might result in comparable performance observed in ASD individuals compared to TD individuals.

We further investigated the neurophysiological mechanism underlying information processing deficits during semantic verbal fluency tasks and found that ASD individuals exhibited category-independent, significantly lower functional connectivity in the left medial PFC. The significant negative correlation between functional connectivity in the left medial PFC and reaction time (i.e., an indicator of information processing efficiency) implies that left medial PFC hypoconnectivity could be the possible neuropsychological mechanism

underlying deficient information processing during the verbal fluency task. Previous studies have shown that the medial PFC is the key hub for learning and recalling learned associations between context, events and corresponding adaptive responses (Euston et al., 2012). In the context of semantic fluency, the left medial PFC facilitates the recall of words that are relevant to a particular given category (i.e., animal, transportation), which are considered learned associations. As individuals with ASD were found to have hypoconnected left medial PFC, they may have less efficient retrieval of relevant responses when semantic cues are given during a task, resulting in slower responses and fewer correct words (i.e., poor performance) within a limited time (i.e., 60 seconds). If we apply the same logic to contextualize the hypoconnected left medial PFC during transport word generation, we should also expect significantly poorer behavioral performance in ASD individuals than in TD individuals. Interestingly, our results showed that the number of correct transport words generated by ASDs was comparable to that generated by TD individuals. A possible explanation could be as follows. For TD individuals, transport word generation is consistently found to be more difficult for local populations (Chan & Poon, 1999; Chan & Chen, 2004). Moreover, different types of transportation are commonly found to be a theme of restricted interest in many ASD individuals (Mancil & Pearl, 2008). It could be possible that individuals with high-functioning ASDs, who are often found to have intact, or even greater, vocabulary reserves than TD individuals (Kim & Lord, 2013), are more knowledgeable in words relevant to transportation, which in turn masks the expected deficits in verbal fluency.

Although aberrant prefrontal activation patterns have been identified in ASD individuals during verbal fluency tasks in previous fMRI (Kenworthy et al., 2013; Beacher et al., 2012) and fNIRS (Yeung et al., 2019) studies, we found nonsignificant between-group differences in fNIRS prefrontal activation during this task, consistent with the findings of an fNIRS study by Ota et al. (2020). In contrast to Yeung et al. (2019), who recruited ASD males and females

aged 12-18 years, we recruited a younger group of right-handed ASD males. Previous studies have shown sex differences in ASD patients during language processing (Kauschke et al., 2016). Moreover, the neural connectivity between brain regions differs between Chinese males and females during semantic tasks (Gao, Wang, Yu, & Chen, 2015). Moreover, a previous fMRI study revealed a differential lateralization pattern in children compared to adults during a VF task (Holland & Plante, 2001). However, additional studies are needed to confirm whether prefrontal activation is altered during verbal fluency tasks in ASD children aged 8-12 years.

4.5.1 Conclusion

This study aimed to investigate the neurophysiological mechanism underlying reading comprehension performance in children aged 8-12 with high-functioning ASD. Twenty-one right-handed boys with high-functioning ASDs and 23 age-, IQ-, educational level-, sex- and handedness-matched TD individuals underwent a reading comprehension test, an information processing efficiency test and a semantic verbal fluency test with concurrent fNIRS measurements. The results showed that high-functioning ASD children had impaired reading comprehension when task difficulty increased, which was strongly associated with poorer performance in semantic VFs, a task tapping core executive functioning component underpinning reading comprehension ability. In addition, poorer semantic VF performance was associated with slower information processing speed, which was contributed by reduced left medial PFC functional connectivity. Our study has important implications for the neuropsychological and neurophysiological mechanisms underlying reading comprehension deficits in individuals with ASD.

Chapter 5: General Discussion

In this chapter, the main findings of the thesis (Chapter 2-Chapter 4) are summarized, and limitations are examined and discussed.

5.1 Summary of the main findings

5.1.1 Prefrontal Dysfunction and Cognitive Inflexibility in ASD

Chapter 2 delves into the relationship between abnormal prefrontal functional connectivity and cognitive inflexibility in individuals with ASD. The study utilized functional near-infrared spectroscopy (fNIRS) in conjunction with the Wisconsin Card Sorting Test (WCST) to assess cognitive flexibility in individuals with ASD. FNIRS and behavioral data were collected from a group of 29 adolescents and adults with ASD and 26 age-matched (14-22 years) and IQ-matched controls. Behaviorally, ASD patients were found to exhibit impairments in all cognitive processes supporting cognitive flexibility; specifically, ASD individuals took a significantly longer time to achieve comparable performance accuracy with that of their peers. These findings are in line with previous studies (Young et al., 2016; Miller et al., 2015). On the other hand, individuals with ASD exhibited hypoconnectivity in the prefrontal cortex (PFC) during the Wisconsin Card Sorting Test (WCST). Specifically, hypoconnectivity was observed in the right lateral PFC when participants were learning new rules through trial and error and on both sides of the lateral PFC when they were required to use these learned rules for problem-solving tasks. This neural pattern (in the bilateral lateral PFC) was correlated with slower information processing speed during the WCST. These findings are consistent with previous studies showing that information processing efficiency is underpinned by the strength of functional connectivity between functional brain networks (Silva et al., 2020; Ruiz-Rizzo et al., 2019).

5.1.2 Working Memory Load and Frontal Connectivity in Children with ASD

Chapter 3 discusses the effects of working memory (WM) load on prefrontal connectivity in children with autism spectrum disorder (ASD). This study employed functional near-infrared spectroscopy (fNIRS) and the n-back task to analyze how varying WM loads affect frontal lobe activity and connectivity in these children. The data were gathered from a group of 22 children with ASD and a control group of 22 children matched for age (8-12 years) and IQ. In line with prior research and findings from Chapter 2, children with ASD displayed longer reaction times during the n-back task, echoing findings from Ozonoff & Strayer (2001) and Goldstein, Minshew, & Siegel (1994). The fNIRS data revealed distinctive patterns in intrahemispheric functional connectivity and activation within the right prefrontal cortex (PFC) in children with ASD compared to typically developing (TD) controls. Notably, under the 0- and 1-back conditions, the TD group exhibited an upward trend in right medial PFC functional connectivity, while the ASD group showed a downward trend in this area as the load increased. The right medial PFC is crucial for working memory maintenance and for learning and recalling associations between context, events, and adaptive responses, as noted by Smith et al. (2018) and Euston, Gruber & McNaughton (2012).

This chapter's findings of right-lateralized abnormalities during the WM task align with other research indicating atypical lateralization in ASD patients (Floris, 2021). Notably, a positive correlation was discovered between the right lateral PFC functional connectivity during the 0-back task and the SRS-2 total score. This finding suggested that individuals with more severe social functioning impairment exhibit greater right lateral PFC functional connectivity in low WM-load situations. Considering that the low-load condition mirrors a simple visual information processing task (Gajewski et al., 2018) and that a more connected neural network signifies more effortful information processing (Engstrom, Landtblom, & Karlsson, 2013),

these findings imply that individuals with more pronounced social difficulties may process incoming information more laboriously.

5.1.3 Reading comprehension, verbal fluency, and prefrontal connectivity in ASD patients

Chapter 4 bridges executive dysfunctions with complex cognitive skills, focusing on reading comprehension in the context of ASD. The study utilized functional near-infrared spectroscopy (fNIRS) during a verbal fluency task to assess executive function (EF) and evaluated reading comprehension skills to investigate the relationships between ejection fraction (EF), functional connectivity, and reading comprehension proficiency. The data were gathered from a group of 21 children with ASD and a control group of 23 children matched for age (8-12 years) and IQ. Our findings indicated that children with high-functioning ASDs exhibited significant challenges in reading comprehension, coupled with a notably slower information processing speed and a reduced number of correctly identified words in the semantic verbal fluency task, specifically in the living things category (e.g., animals). Moreover, a positive correlation was identified between the quantity of words generated in the animal category and reading comprehension skills, echoing the findings of a previous study that highlighted a direct link between executive function and reading comprehension in individuals with autism (Micai et al., 2021).

In addition, the study showed that individuals with ASD demonstrated reduced intrahemispheric and interhemispheric connectivity in the prefrontal cortex (PFC) during the verbal fluency task. This observation aligns with prior neuroimaging research (Anderson et al., 2011; Zhu et al., 2014; Lee et al., 2016; Guo et al., 2020). At a broader group level, diminished functional connectivity in the left medial PFC was significantly associated with slower processing speeds in the VFT. This reduction in processing speed correlated with

lower performance in generating animal-related words, a metric strongly linked to decreased reading comprehension ability, particularly at higher difficulty levels.

5.2 Limitations

5.2.1 Gender, Handedness and Power in the ASD Group

We acknowledge various limitations in the studies conducted for this thesis. First, our studies did not impose specific requirements on handedness or sex, although these factors did not significantly differ between individuals with autism spectrum disorder (ASD) and typically developing (TD) individuals. However, the literature highlights the importance of considering handedness due to its association with brain lateralization, particularly in language processing. It is well established that most right-handed individuals have language functions predominantly in the left hemisphere, a pattern less consistent among left-handers (McManus, 2002). Furthermore, studies suggest that brain asymmetry and lateralization might differ in individuals with ASD, suggesting potential variability in cognitive and language functions (Geschwind & Behan, 1982; Annett, 1997). Additionally, sex differences in individuals with ASD could influence brain structure and function. Research indicates varying prevalence rates and manifestations of ASD symptoms between males and females, suggesting potential underlying neurobiological differences (Turner et al., 2015; Polyak et al., 2015). In fact, the differences in symptom presentation and cognitive profiles between males and females with ASD emphasize the need for a sex-specific approach in both research and clinical practice. For instance, females with ASD often exhibit less pronounced stereotypical behaviors and may have better social imitation skills than males, which can lead to underdiagnosis or misdiagnosis in females (Lai et al., 2015; Hull et al., 2017). This gender disparity also extends to the realm of cognitive abilities and sensory processing, where differences in profiles have been noted (Kirkovski et al., 2013; Lai et al., 2015). Moreover,

neuroimaging studies have shown that males and females with ASD may exhibit different patterns of brain connectivity and structural organization (Beacher et al., 2012; Lai et al., 2013). For example, females with ASD might demonstrate brain connectivity patterns that align more closely with those of typically developing males than with those of females. Additionally, the findings reported in this thesis are derived from a relatively low number of participants diagnosed with ASD (29 in chapter 2, 22 in chapter 3 and 21 in chapter 4). Our findings should therefore be treated with caution and may not be generalizable to the entire ASD spectrum. The relatively low participant numbers may have contributed to inadequate statistical power in some instances; for example, the marginally significant 1-back and 2-back reaction time post hoc t tests reported in chapter 3 and prefrontal functional connectivity analysis during the WCST in chapter 4. Taken together, in future research on ASD, it is crucial to incorporate a more systematic approach to understanding sex and handedness differences. This included stratifying study participants by sex/handedness to uncover distinct or shared patterns in brain structure and function, which might be obscured in mixed-gender/handedness analyses. Nonetheless, the novel analysis approaches presented throughout this thesis have identified interesting differences between ASD patients and control participants, many of which were hypothesized based on previous findings (see Chapter 1 and Kessler et al., 2016). This thesis therefore provides important pilot findings for future research, which should include greater numbers of participants.

5.2.2 Inclusion of Only High-Functioning ASD Individuals

Chapters 2 through 4 of this thesis focus exclusively on participants with high-functioning ASDs. This selection was primarily driven by practical considerations. Participants with

high-functioning ASDs generally facilitate smoother execution of experimental procedures, yield higher-quality neuroimaging data, and can engage in a greater number of experimental trials before experiencing fatigue. This aspect is particularly crucial for studies involving functional connectivity analysis, which are sensitive to the signal-to-noise ratio differences between groups (Bastos & Schoffelen, 2016).

This approach has notable limitations. By focusing solely on high-functioning individuals with ASD, studies may overlook the vast spectrum of cognitive and neurodevelopmental variations that characterize ASD. This selection bias limits the generalizability of our findings, potentially restricting their applicability to the broader ASD population, especially those with more pronounced symptoms or additional cognitive challenges.

Recognizing this limitation, we emphasize the need for future research to include a more diverse range of participants within the autism spectrum, particularly those with lower functioning levels. Such inclusive research is essential for fully comprehending the complexities of ASD and ensuring that our findings are representative and applicable across the entire spectrum.

5.3 Implication and Future Directions

Overall, the findings from this thesis contribute to our understanding of executive dysfunction and its neurobiological underpinnings in autism spectrum disorder (ASD). The research outlined in the chapters highlights critical aspects of cognitive inflexibility, working memory challenges, and reading comprehension difficulties associated with ASD.

5.3.1 Executive Dysfunction and Information Processing Disorder in ASD

Chapter 1 of this thesis delved into existing research on executive dysfunction and information processing in autism spectrum disorder (ASD). Our literature review suggested

that the core of executive function deficits in ASD patients is closely tied to inherent challenges in information processing. In particular, we observe that ASD individuals face increased cognitive challenges when confronted with tasks that either present a high volume of information or require simultaneous engagement of multiple cognitive or sensory modalities (i.e., increased task complexity). This situation can increase the processing demand on our brain and adversely affect brain performance.

Supporting this theory, our empirical findings indicate a pattern of delayed reaction times in ASD participants across various tasks. In Chapter 2, individuals with ASD displayed significantly longer response times in both the acquisition and application conditions of the WCST task than did typically developing (TD) controls. Chapter 3 revealed a similar trend, with the ASD group showing slower reaction times in the 0-back, 1-back, and 2-back tasks. Chapter 4 further substantiated these observations, demonstrating slower processing speeds in ASD individuals on the CANTAB RTI five-choice mean reaction time than in TD individuals.

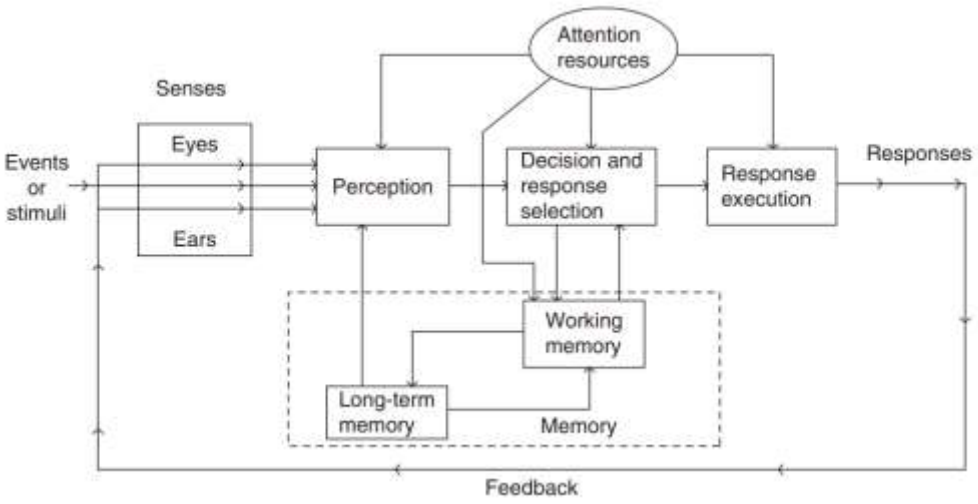
These results collectively point toward a generalized trend of slower information processing in individuals with ASD, which aligns with findings from previous studies (Baisch et al., 2017; Schmitz et al., 2007; Inui et al., 1995; Antao et al., 2020; Morrison et al., 2018). However, this observation is not universally supported, as indicated by studies that did not find significant differences in reaction times (Ferraro, 2016; Foti et al., 2015; Karalunas et al., 2014). This discrepancy in results might be attributed to the presence or absence of time constraints in the tasks. For instance, Yeung et al. (2019) suggested that information processing deficits in individuals with ASD may become more apparent under time-limited conditions. Consistently, our studies in Chapters 2 to 4 incorporated time constraints in

behavioral tasks, potentially revealing this facet of information processing challenges in individuals with ASD.

Conversely, we could only find a marginal group effect on performance in working memory ($p = .18$) and flexibility ($p = .08$) tasks. This could be because of the limited power explained in the limitation section or because the tasks themselves may not be complex enough to create sufficient cognitive load to see the difference. This can be attributed to the fact that a significant group effect can be observed in reading comprehension performance. This task, presumed to be adequately complex in engaging multiple executive functions (Butterfuss and Kendeou 2018), illustrates the challenges present in ASD.

Wickens' information-processing model (2021; Figure 16) provides a framework for understanding these challenges. The initial challenge is in the perceptual stage, where atypical sensory processing, a characteristic feature of ASD (Tomchek & Dunn, 2007; Crane et al., 2009; Marco et al., 2011), can lead to inaccurate or distorted interpretation of sensory stimuli. This impairment in sensory interpretation, combined with documented challenges in memory systems (Desaunay et al., 2020), may obstruct the smooth transition of information from perception to the decision-making phase. The decision-making stage is further compromised when tasks necessitate integrating multiple sources of information. In fact, individuals with ASD have been shown to have a slower decision-making process (Vella et al., 2018) under time constraints, where the need for rapid decision-making can lead to increased stress and lower performance.

Figure 16 *Model of human information processing. (Source: Adapted from Wickens & Carswell 2021.)*



5.3.2 Information Processing and Disorder Connectivity in ASD Patients

Disordered connectivity in individuals with autism spectrum disorder (ASD) has been consistently noted across various neurophysiological tools, both during specific tasks and in resting states (Hull et al., 2017; Just et al., 2012; Mohammad-Rezazadeh et al., 2016; Yeung, Lee, & Chan, 2019). Our findings corroborate these observations, revealing reduced intrahemispheric functional connectivity in the frontal cortex of the ASD group compared to that in the frontal cortex of typically developing (TD) individuals during both the Wisconsin Card Sorting Test (WCST) and verbal fluency tasks. The altered connectivity observed in ASD patients is thought to stem from atypical brain structures, such as decreased white matter integrity (Rane et al., 2015; Schmitz et al., 2007). Given these structural and functional disparities, it is plausible that such abnormalities impede information flow within the ASD brain, both within and between hemispheres.

Numerous studies have demonstrated the impact of both functional and structural connectivity on information processing efficiency and speed (Silva et al., 2020). For instance, white matter pathways have been identified as key to processing speed (Kail & Salthouse, 1994; Gold et al., 2007; Turken et al., 2008), and genetic factors also play a significant role in

altering white matter and synaptic structures and hence the flow of information (Giddaluru, 2016; Penke et al., 2010; Chiang et al., 2011). Notably, mutation of SHANK3, a gene frequently implicated in ASD research, is known to affect synaptic function and neural connections (Eyring & Geschwind, 2021). Additionally, single nucleotide polymorphisms (SNPs) have been linked to ASD, influencing axon growth and information processing (Giddaluru, 2016).

Our research findings in Chapter 2 align with these findings, revealing significant correlations between Wisconsin Card Sorting Test (WCST) reaction times during the acquisition phase and connectivity measures, notable at the p =.05 level (uncorrected). However, these correlations did not withstand Bonferroni corrections. More importantly, we found significant negative correlations between WCST reaction times during the application phase and the functional connectivity of the bilateral lateral prefrontal cortex (PFC).

The lateral PFC is known to play a critical role in various cognitive processes, including action planning, working memory, attentional regulation, executive control of behavior, temporal sequencing, and response inhibition (Tanji & Hoshi, 2007; Petrides, 1995; Postle et al., 2003; Ninokura et al., 2003). Additionally, previous studies have shown that damage to the lateral PFC results in impaired performance on the WCST, likely due to difficulties in the inhibition process (Passingham, 1972; Barcelo & Knight, 2007). Therefore, the altered functional connectivity in the lateral PFC that we observed in individuals with ASD could interfere with or slow the inhibitory processes in the ASD brain, thereby impacting their task performance and overall cognitive efficiency.

5.3.3 Disorder connectivity and reading comprehension

Chapter 4 highlights the interplay between executive function (EF), prefrontal cortex (PFC) connectivity, and reading comprehension in children with autism spectrum disorder (ASD). Our results indicated that children with ASD particularly struggled with reading comprehension tasks of greater complexity involving extended passages and abstract concepts. This observation is consistent with previous literature suggesting that reading comprehension in individuals with ASD may be disproportionately affected as the cognitive demands of the task increase (Nation et al., 2006).

The Kintsch construction-integration (CI) model (1988) provides a useful framework for understanding this phenomenon. According to this model, reading comprehension involves two critical phases: the construction phase, where readers activate information from both the text and their background knowledge; and the integration phase, where these concepts are interconnected to form a coherent mental representation of the text. These phases heavily rely on EF components such as working memory, inhibition, and cognitive flexibility. For instance, the integration phase demands continual updating of the developing mental model with new information, thus placing a greater burden on working memory. As a result, the increased complexity of reading tasks can strain these EF traits, potentially leading to the poorer reading comprehension performance observed in ASD patients.

In addition, our study revealed a significant correlation where reduced intrahemispheric connectivity in the left medial PFC during a semantic verbal fluency task was linked to poorer reading comprehension performance in ASD children, specifically with tasks of greater difficulty. Interestingly, these children performed worse in the animal category but not in the transport category of the verbal fluency task. This finding suggested that PFC connectivity patterns in ASD patients might not only be task specific but also dependent on

the cognitive complexity of the task. For instance, the animal category might pose greater cognitive demands for ASD individuals. Thus, the observed decrease in PFC connectivity may imply a struggle to integrate complex cognitive processes, not only in specific tasks but also as a broader cognitive challenge.

Reading comprehension, particularly of complex texts, necessitates the integration of multiple cognitive processes and efficient information processing. Therefore, the observed patterns of neural connectivity in ASD patients during the verbal fluency task might be indicative of the underlying neural mechanisms contributing to their difficulties in reading comprehension. This interpretation is further supported by the finding that better comprehension performance at higher difficulty levels correlated with faster processing speeds, as measured by the five-choice reaction time test, which in turn correlated significantly with increased left medial PFC functional connectivity during animal word generation.

5.3.4 Implication

Transcranial direct current stimulation (tDCS)

The findings from this thesis have implications for the use of transcranial direct current stimulation (tDCS) in treating ASD. tDCS, a noninvasive brain stimulation technique, has shown promise in modulating neuroplasticity and cognitive functions in various neurological conditions (Imburgio, & Orr, 2018; Doruk et al., 2014; Dubreuil-Vall et al., 2019). Given the observed altered connectivity in the PFC and its correlation with cognitive deficits in ASD patients, tDCS could be explored as a tool to modulate cortical activity and connectivity. Targeted stimulation of the PFC might aid in improving Efs and creating more efficient flow of information in the brain, particularly in tasks requiring complex cognitive functions.

Educational and Intervention Strategies

The challenges in reading comprehension and information processing in ASD patients underline the need for tailored educational strategies. Interventions focusing on enhancing EFs could benefit reading comprehension skills, particularly in handling complex texts. Educational programmes might incorporate exercise to strengthen working memory, cognitive flexibility, and inhibitory control. Additionally, considering the slower information processing in individuals with ASD, educational material should be structured to allow sufficient time for comprehension, avoid overload and provide opportunities for repeated exposure and practice.

5.4 Conclusion

In conclusion, this thesis systematically explored the complex interplay between executive dysfunction, abnormal prefrontal connectivity, and information processing challenges in individuals with autism spectrum disorder (ASD). Utilizing functional near-infrared spectroscopy (fNIRS) alongside a range of cognitive and executive function assessments, our research sheds light on the intricate neurophysiological aspects of ASD.

Key findings from this body of work reveal that individuals with ASD face considerable difficulties in tasks requiring cognitive flexibility. This is evident in their performance on the Wisconsin Card Sorting Test (WCST) and is intimately connected to hypoconnectivity in the prefrontal cortex, specifically in the bilateral lateral PFC. This hypoconnectivity is a crucial indicator of compromised information processing efficiency, which is a central challenge in individuals with ASD.

Our studies also highlighted the significant impact of working memory load on prefrontal connectivity in children with ASD. Distinct patterns of functional connectivity emerge under different working memory demands, providing valuable insights into working memory-related cognitive challenges and their broader implications for cognitive functioning in individuals with ASD.

A notable aspect of this research is the examination of reading comprehension difficulties among individuals with ASD. These findings indicate that these challenges not only are rooted in executive dysfunctions but are also closely associated with slower information processing speeds and reduced functional connectivity in the prefrontal cortex during complex cognitive tasks, such as the verbal fluency test.

Acknowledging these limitations, including the focus on high-functioning individuals with ASD and the lack of specific attention given to sex and handedness differences, this thesis underscores the need for future research to encompass a more diverse ASD population and systematically address these factors.

The implications of these findings extend beyond theoretical insights, offering practical avenues for intervention and support. These findings open up possibilities for investigating neuromodulation techniques such as transcranial direct current stimulation (tDCS) to potentially enhance cognitive functions in ASD patients. Furthermore, these insights can inform the development of specialized educational strategies and interventions tailored to the unique cognitive challenges faced by individuals with ASD.

In summary, this thesis contributes a comprehensive and nuanced understanding of the cognitive and neurobiological aspects of ASD. This study not only enriches our theoretical knowledge but also lays the groundwork for future research and practical applications that could lead to more effective support and treatment strategies for individuals with ASD.

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