Deficient Attentional and Inhibitory Control with associated Neurophysiologic Abnormalities of Frontal Area and Anterior Cingulate Cortex in ASD Children

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ABSTRACT

Objectives:

To investigate neurophyiologic abnormalities in frontal and anterior cingulate cortex underlying attentional and inhibitory control in children with Autism Spectrum Disorder (ASD).

Methods:

20 children with high-functioning ASD [Mean Age (SD): 10.75 years old (2.07 years); Mean IQ(SD): 101.4 (16.8)] and age- and IQ- matched normal children (NC) [Mean Age (SD): 9.80 years old (1.88 years); Mean IQ (SD): 110.7(17.8)] were investigated electrophysiologically during performance of a visual Go/NoGo task. An electrophysiological source localization method was employed to further analyze the data. Several different neurospsychological tests were also performed to provide behavioral measures on attention and inhibition.

Results:

ASD children showed a significantly task-related lower frontal theta activity. This effect was associated with a significantly reduced activation of the anterior cingulate cortex (ACC). Both groups also differ significantly regarding the behavioral aspects of attention and inhibition.

Conclusion:

The results suggest that ASD children have deficits in attentional and inhibitory control. Frontal dysfunction and weak ACC engagement in ASD were supported as the underlying neuronal inefficiency.

摘要

目的：

過往的研究曾指出，自閉症兒童的行為問題源於腦神經網絡的失調。本研究是探討自閉症兒童在專注及抑制功能上腦電波的異常狀況。

方法：

二十位智力正常的自閉症兒童及二十位年齡與智力水平相約的正常兒童參與研究，他們的平均年齡為十歲，研究智能屬於合齡程度。研究在電腦研究活動(Go/NoGo)進行時，會同時錄取被試者的腦電波數據，並運用根源定位方法來分析所收集的數據。研究並會使用其他幾項腦功能測試來量度兒童的在行為上的抑制能力。

結果：

Go/NoGo 活動的表現結果顯示，自閉症兒童的大腦前額葉在 theta 波段上的活動顯注地低於正常兒童的平均水平，並同時連繫著顯注地低的前額葉及前扣帶皮質活動。在多項腦功能測試來量度專注及抑制能力行為指數上，自閉症兒童與正常兒童表現也有相當差距。

總結：

結果顯示，自閉症兒童呈現專注及抑制能力上的缺失，在一般的反應控制上亦有缺失。大腦前額葉和前扣帶皮質的活動失調可能是失效原因。

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INTRODUCTION

Overview

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition currently diagnosed based on a triad of qualitative impairments, namely the social interaction, social communication, and restricted repetitive and stereotypic patterns of behaviours (American Psychiatric Association, 2000). It is a lifelong disorder. While its etiology is not well understood, substantial evidence has suggested that frontal regions and its pathways to other brain areas are abnormal in ASD anatomically (Abell et al., 1999; Courchesne et. al., 2005a, 2005b; Haznedar et. al., 1997, 2000; McAlonan et al., 2005), metabolically (Horwitz et al., 1988) and functionally (Silk et al., 2006). In mediating frontal lobe functions, anterior cingulate cortex (ACC) is evidenced to be functionally significant (Koski et al., 2000). It lies on the medial surfaces of the frontal lobes, and is anatomically connected with virtually all areas of the frontal cortex as well as other brain areas making it a central station for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain

(Braver et al., 2001; Mundy, 2003). Various types of brain imaging studies have also consistently implicated focal abnormalities associated with cingulate cortex in autism [Morphometric studies (Henderson, 2006, Haznedar et al., 2000; Mundy 2003); Diffusion Tensor Imaging study (Barnea-Goraly, 2004); and postmortem studies (Bauman and Kemper, 1994, 2003)].

The frontal and ACC play an essential role in mediating attention and inhibitory control in healthy people (Garavan et al., 1999, 2002; Rubia et al., 2005, 2006) and patients with acquired damage to the frontal lobes are typically impaired in neuropsychological processes such as planning, impulse control, inhibition and set shifting as well as the initiation and monitoring of action (Barkley, 1997;Denckla, 1996; Lezak, 2004; Stuss, 2002). ACC is involved in efficient allocation of attention to accomplish an effortful cognitive task (Mulert et al., 2005; Sauseng et al., 2007). It is also an active component in detecting and monitoring errors, evaluating the degree of the error, and then suggesting an appropriate form of action to be implemented by the motor system (Botvinick et al., 2004; Braver et al., 2001; Garaven et al., 2002; Menon et al., 2001). Lesions in the ACC lead to inability to detect errors, severe difficulty in resolving stimulus conflict, inattention, emotional instability, and akinetic mutism. (Bush, G., Luu, P. & Posner, M., 2000; Posner M. & DiGirolamo G., 1998).

Based on the documented abnormalities of the frontal cortex and ACC in ASD

and the reported association between these two brain areas with attention and inhibitory control, it is reasonable to infer that ASD might have deficits in attention and inhibition (for detailed reviews of executive function in autism, see Hill, 2004; Russell et al., 1999; Ozonoff, 1997; and for the link between deficits in executive function and the clinical symptoms of ASD, see Hill & Bird, 2006), although the degree of behavioural impairment may vary with other factors such as the ability level and the age of the group, the complexity and modality of the inhibition task. On the other hand, consistent neural-based difference in inhibition circuitry are indicated (Bishop & Norbury, 2005; Russell et. al., 1999; Schmitz et al., 2006). Given the essential roles of attention in information processing and inhibition in suppressing irrelevant thoughts and interference during executive tasks, it has been postulated that primary deficits in attentional and inhibitory controls may account for the executive dysfunctions that underlie many of the repetitive, stereotyped and rule-bound behaviors in ASD (Burack, 1994; Goldstein et al., 2001; Nyden et al., 1999). With demonstrated inability to inhibit inappropriate actions or verbalizations in terms of timing or circumstances, these kinds of higher-order cognitive dysfunctions might further explain why even the most able ASD individuals are often times unable to achieve at a level comparable to their intellectual levels and show poorer overall adaptations in their real life situations.

In laboratory tests, indices often used to measure attention and inhibitory control include omission and commission errors (Hummel et al., 2002; Serrien et. al., 2005) and digit span. Increased number of false alarms can also be considered as a useful index of poor inhibition since it reflects an inability to differentiate interference (Chiappe et al., 2000). Behavioural rating reflecting naturalistic situations are always investigated also in order to meaningfully measure the effect of this cognitive construct on daily life. In our present study, both laboratory measures and ratings on daily life would be taken into account.

Up till present, investigations on the neural basis of attention and response inhibition with ASD are few, especially for the young clinical group. So far, results from neurobiological studies on ASD adults proposed that abnormal neurobiological processes in the frontal lobes and hypoactivation of ACC that underlie this deficit (Mundy 2003; Schmitz et al., 2006), and functional imaging studies have also found altered patterns of activation, perfusion, and glucose metabolism in various areas of the frontal lobes in ASDs during inhibitory process (Ohnishi et al., 2000; Pierce et al., 2004; Schmitz et al., 2006). The present study is an attempt to investigate the electrophysiological basis of deficiency in attention and inhibitory control in ASD using EEG analysis coupled with Go/NoGo task. Given its association with frontal and ACC abnormalities evidenced, it is reasonable to hypothesize that

electrophysiological patterns associated with attentional and inhibitory deficits in ASD would involve altered patterns of activation in the frontal cortex and ACC.

Mitchell et al. (2008) in their review, pointed out that there have been accumulating evidence postulating that increased frontal theta activity in EEG analysis is a prominent feature linking to increased cognitive demands, in particular in those that require attention or working memory (Chabot & Serfontein, 1996; Gevins et al., 1997; Jensen & Tesche, 2002; Onton et al., 2005). It is often studied during mental arithmetic (Inanaga, 1998; Ishihara and Yoshii, 1972; Ishii et al., 1999; Mizuki et al., 1980; Sasaki et al., 1996 Smith et al., 1999), error detection (Luu et al., 2003, 2004), goal conflict resolution (Moore et al., 2006) and execution and inhibition of movement (Morris & Hagen, 1983). Kirmizi-Alsan et al. (2006) in their Go/NoGo experiment observed that both Go condition and NoGo condition evoked theta activity suggesting that theta activity reflected attention and response inhibition.

Within the manifestation of theta rhythm, frontal midline distribution is generally supported with the notion that human ACC is involved in its generation. This accrues from a comparison of the electrophysiological and metabolic neuroimaging literature including studies on focused attention (EEG: Asada et al., 1999; metabolic Davis et al., 1997); on task difficulty (EEG: Gevins et al., 1997; metabolic: Murtha et al., 1996), on orienting response (EEG: Dietl et al., 1999; Williams et al., 2000). Previous

studies of concurrent measurements coupling frontal midline theta activity and other neuro-imaging tests have further revealed positive correlations between electrophysiological and hemodynamic data in the anterior cingulate cortex and various frontal regions which were recorded simultaneously (Pizzagalli D.A., Oakes, T.R., & Davidson, R.J., 2003). The use of a tomographic source localization technique for the EEG data enables localizing the source of the brain electrical activity. For example, Fallgatter et al. (2004) have employed Low-resolution electromagnetic tomography analysis (LORETA) to analyze the EEG data obtained during a continuous performance test in their study with ADHD boys, and has revealed that there is a significantly diminished electrical activity in the anterior cingulate of ADHD group and in no other region of the brain during NoGo condition.

In brief, as Gevins et al.(2007) have suggested, Fm[theta] is an indicator of neuropsychological processes, it is most likely generated in the ACC, and LORETA as an electrophysiological method can effectively localize its source.

In this present study, both frontal lobe and anterior cingulate cortex were identified as the two regions of interest as they are both significant in functioning of attention and inhibition as based on the literature reviewed above. The purpose of the study was to examine the neurophysiologic activity of these two regions in ASD upon tasks demanding attention and inhibitory control. We also examined the behavioural

performance of ASD children in attention and inhibitory control both on the neuropsychological tasks and everyday situation through a parent rating form, we hypothesized that ASD children would perform significantly poorer than normal children on behavioral indices, and this hypothesized dysfunction was associated with their abnormalities of frontal activity as measured by frontal theta power, and also abnormalities in ACC using an EEG source localization technique. These hypotheses were tested by assessing its neurophysiologic activities while the participants were performing a task requiring attentional and inhibitory control - a Go/NoGo task. Relationship of performance in Go/NoGo with age and IQ was also tested. To my understanding, all the EEG studies with ASD in the past were done at resting cortical state only, this present study is an attempt to extend to the event-related changes in EEG power during a Go/NoGo task, giving further information about the cortical electro-physiological activity of ASD in relation to attention and inhibitory control. Besides, most of the ASD studies previously done with investigation on ACC engagement were limited to the adolescent or adult population only, this present study serves the gap of understanding and explore into the children population.

Literature Review

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition currently diagnosed based on a triad of qualitative impairments, namely the social interaction,

social communication, and restricted repetitive and stereotypic patterns of behaviours (American Psychiatric Association, 2000). It is a lifelong disorder. Increasing rates of prevalence have been reported for autistic disorder / ASD. According to Blaxill (2004), the rate of autistic disorder was reported to be <3 per 10,000 children in the 1970s and rose to >30 per 10,000 in the 1990s. Recent data suggests that it affects at least 0.6% of the population in U.S. studies (Centers for Disease Control and Prevention, 2007) making it the sixth most common disability classification in the United States. A prevalence rate of 16.1 per 10,000 children aged 15 years old and less during the period of 1986 to 2005 is also indicated in a local epidemiological study (Wong, 2008). The dramatic rise in the numbers of children classified as ASD highlights the need for further research to be conducted into this population.

Abnormalities of Frontal Cortex and Anterior Cingulate Cortex in ASD

While etiology of ASD is not well understood, Carper & Courchesne (2002, 2005) have documented that ASD children have abnormally large frontal lobes that may reflect a lack of synaptogenesis early in life (Belmonte et al., 2004). Substantial evidence has also suggested that frontal regions and its pathways to other brain areas are abnormal in ASD anatomically (Abell et al., 1999; Courchesne, 2001; Haznedar et. al., 1997, 2000; McAlonan et al., 2002), metabolically (Horwitz, 1988) and functionally (Silk et al., 2006). The anterior cingulate cortex (ACC), lying on the

medial surfaces of the frontal lobes,it is the frontal part of the cingulated cortex, which resembles the 'collar' of the corpus callosum; it is anatomically connected with virtually all areas of the frontal cortex as well as other brain areas making it a central station for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain (Braver et al., 2001; Mundy, 2003). Functionally, it is significant in mediating frontal lobe functions (Koski et al., 2000). Various types of brain imaging studies on ASD have also consistently shown focal abnormalities associated with cingulate cortex in autism Anatomical studies proposed grey matter reductions in prefrontal lobe of ASD (Abell et al., 1999); abnormally large frontal lobes that may reflect a lack of synaptogenesis early in life (Courchesne et al., 2001); and that the whole brain volumetric analysis showed a significant reduddction in total grey matter volume and a significant increase in cerebral spinal fluid volume within the fronto-striatal and parietal networks (McAlonan et al., 2005). Morphometric studies have proposed that dorso-medial frontal cortex and ACC might constitute a neural-substrate for socio-cognitive deficits in autism, with activity in dorso-medial frontal cortex (Brodmann's area 8/9) and ACC (Brodmann's area 24) may be a correlate of both joint attention skills in infants (Henderson, 2002,Haznedar et al., 2000; Mundy 2003) and theory of mind task performance in children and adults of typical and atypical development (Frith & Frith, 1997, 2001, 2003); DTI study in

autism has reported reduced myelin integrity in the ventromedial prefrontal cortex and the anterior cingulate and also at the temporoparietal junctions suggesting disrupted connections between the involved regions (Barnea-Goraly, 2004); and postmortem studies have indicated that the ACC of ASD are smaller in size (Bauman and Kemper, 1994). All the above findings have consistently shown abnormalities in terms of the structue, the metabolic state, the neurophysiological activities and its connection with other neural areas in ASD.

Role of Frontal Region and ACC in Mediating Attention and Inhibition

Attention and inhibitory process are among the most well studied constructs in cognitive science. Robertson, Manly, Andrade, Baddeley & Yiend, (1997) defined that attention is the endogenous ability to mindfully and consciously process stimuli, whose non-arousing qualities would otherwise lead to habituation and distraction, it is a control process that enables the individual to select, from a number of alternatives, the task he will perform or the stimulus he will process, and the cognitive strategy he will adopt to carry out these operations. It is therefore not a unitary cognitive function but a multidimensional factor involving different specific functions and different anatomical brain areas. Posner (1998) has identified at least three processes, namely, alerting, orienting, and executive control, the alerting network includes thalamic and cortical sites related to the brain's norepinephrine system; the orienting network is

centered on parietal sites and the executive network inclues the anterior cingulate and other frontal areas (Fan, McCandiss, Fosselis, Flombaum, Posner, 2005). Inhibition can generally be defined as the withholding or suppressing of attention or responses to irrelevant, non-target, or distracting stimuli (Enticott, Ogloff, & Bradshaw, 2006; Friedman & Miyake, 2004; Nigg, 2000) and is believed to be playing an important role in cognition and in the control of social and emotional behaviour (Bjorklund & Harnishfeger, 1995), it demands a good amount of coordination including preparation for responding, monitoring performance, and detecting errors (Barkley, 1997). Based on numerous studies, one of the most prominent brain regions implicated which mediate attention and inhibitory control in healthy people is the frontal cortex and its connections to other brain areas (Garavan et al., 2006; Rubia et al., 2005). Patients with acquired damage to the frontal lobes are typically impaired in executive functions (Barkley, 1997; Lezak, 1982; Rowe, 2001; Richter, 2001; Stuss, 2005) that refers to neuropsychological processes such as planning, working memory, impulse control, inhibition and set shifting as well as the initiation and monitoring of action (Denckla, 1996; Lezak, 2004; Stuss, 2002) and the lack of good coordination of these various processes to achieve effective goal-directed behaviours (Welsh & Pennington, 1988).

ACC studies have indicated that it is especially involved when effort is needed to

carry out a task such as in early learning and problem solving, it is involved in efficient allocation of attention to accomplish an effortful cognitive task (Mulert et al., 2005; Sauseng et al., 2007). It is also an active component in detecting and monitoring errors, evaluating the degree of the error, and then suggesting an appropriate form of action to be implemented by the motor system (Botvinick et al., 2004; Braver et al., 2001; Garaven et al., 2002; Menon et al., 2001). Lesions in the ACC lead to inability to detect errors, severe difficulty in resolving stimulus conflict, inattention, emotional instability (Bush, G., Luu, P. & Posner, M., 2000; Posner M. & DiGirolamo G., 1998). Cincinnati Lead Study, which is a longitudinal MRI study on a group of adults who had suffered from high levels of lead poisoning during their childhood, has shown that when they grew up, these adults have decreased brain size, and the decrease was most pronounced in the ACC (Cecil et al., 2008). It is interpreted that the specific impact on ACC growth and development is critically and significantly relating to their subsequent cognitive and behavioural deficits.

Deficits in Attention and Inhibitory Control Process in ASD

Given the documented abnormalities of the frontal cortex and ACC in ASD and the reported association between these two brain areas with attention and inhibitory control, it is reasonable to infer that ASD might have deficits in attention and inhibition. This would be reviewed at the following two levels:

At Behavioural Level. Vigorous reviews to examine the different dimensions of executive function within autism and other neurodevelopmental disorders that are considered to implicate frontal lobe function have been made (for detailed reviews of executive function in autism, see Hill, 2004; Russell, 1997; Ozonoff, 1997; and for the link between deficits in executive function and the clinical symptoms of ASD, see Hill, 2004). Amongst the different dimensions examined. attention and inhibition are the key dimensions being researched on, and amongst those behavioural studies, most have indicated such deficits in ASD individuals (Bishop & Norbury, 2005; Hughes et al., 1994;; Luna et al., 2002; Nyden et al., 1999, 2004; Russell et. al., 1999), although there are a few inconsistent findings in inhibitory control (Ozonoff & Jensen, 1999).

Hill (2004) in his review has pointed out that when the attention and inhibition demanding tests such as a Go/NoGo task that involved a primed response and some degree of cognitive flexibility, ASD individuals are impaired in relation to age, gender and IQ matched normally developing counterparts. Russell has postulated that when the rules of inhibition tests appear arbitrary to autistic individuals, they perform with difficulties (Russell, 2002). Furthermore, on studies with more complicated paradigms such as those involving an additional element of working memory or set shifting on top of simple response inhibition, ASD individuals showed significant difference in test performance (Happe et al., 2006). These authors have argued that when the

paradigm gets more complex, even the high functioning ASD would more readily reveal this underlying deficit, it is only when the inhibition task is simple in presentation, that the high functioning adult ASD may successfully use other internal resources to compensate for this deficit. It is therefore reasonable to infer that ASD group does indicate consistently neural-based difference in inhibition circuitry as compared to normal developing individuals, and as far as the behavioral level of impairment is concerned, it varies with other factors such as the ability level and the age of the group, and the complexity and modality of the inhibition task.

Given the essential roles of attention in information processing and inhibition in suppressing irrelevant thoughts and interference during executive tasks, it has been postulated that primary deficits in attentional and inhibitory controls may account for the executive dysfunctions that underlie many of the repetitive, stereotyped and rule-bound behaviors in ASD (Burack, 1994; Goldstein et al., 2001; Nyden et al., 1999). With demonstrated inability to inhibit inappropriate actions or verbalizations in terms of timing or circumstances, these kinds of higher-order cognitive functions might further explain why even the most able ASD individuals are often times unable to achieve at a level comparable to their intellectual levels and show poorer overall adaptations in their real life situations, because they are weak in controlling their impulses, keeping goals in mind and prioritizing actions, and finally

launching out an integrated course of actions appropriately.

In laboratory tests, indices often used to measure attention and inhibitory control include omission and commission errors (Hummel et al., 2002; Serrien et. al., 2005) and digit span. Increased number of false alarms can also be considered as a useful index of poor inhibition since it reflects an inability to differentiate interference (Chiappe et al., 2000) Behavioural rating reflecting naturalistic situations are always investigated also in order to meaningfully measure the effect of this cognitive construct on daily life. In our present study, both laboratory measures and ratings on daily life would be taken into account. We also aimed to study the young ASD children group instead of the adolescent or adult group that most of the previous neural-based studies have focused on.

At Neural Activity Level. In a recent fMRI study with high functioning ASD adults Schmitz et al. (2006), result has revealed that despite that the ASD adults performed with a similar level of behavioural performance on the response inhibition task, they achieved this behavioral level with an elevated frontal activation than their normal counterparts,. The authors interpreted that ASD adults in his study have been paying extra mental effort as a compensatory mechanism in order to achieve the same level of result as the normal controls since in NC adults, R prefrontal brain regions have been shown to mediate inhibitory control (Rubia et al., 2001, 2005). However

since the study was one with ASD adults, it is unsure whether this interpretation can extend to ASD children or not, since abnormalities in frontal region and anterior cingulate cortex can be a consequence to deviated development in childhood, or it might also be a cause leading to subsequent abnormal development in adulthood. Up till present, integrated behavioural and neural-based studies on this aspect are not many especially for young clinical group. Nevertheless, results from neurobiological studies on individuals with ASD does have proposed abnormal neurobiological processes in the frontal lobes that underlie this deficit (Mundy 2003; Schmitz et al., 2006), and functional imaging studies have also found altered patterns of activation, perfusion, and glucose metabolism in various areas of the frontal lobes in ASDs during inhibitory process (Ohnishi et al., 2000; Pierce et al., 2004; Schmitz et al., 2006). In a recent fMRI study done by Kana et al. (2007), the authors have investigated the neural basis of attention and response inhibition with high functioning autistic adults using Go/NoGo paradigms, Results have indicated that autistic participants showed less brain activation in ACC than control participants and its connectivity with other brain regions were atypical also during this attention and inhibition demanding task. The present study was an attempt to serve this gap of understanding, and aimed to study on the young clinical group.It was to examine the neural basis of deficient attention and inhibitory control in ASD children using

EEG .This could be achieved by coupling EEG investigation ith an attention/ inhibitory demanding task – Go/NoGo task.

Review of Inhibitory Control of other types of Neuropsychological Disorders

Inhibitory control is an important component of executive function that allows for the suppression of actions and resistance to interference from irrelevant stimuli. Dysfunctional inhibitory control is increasingly being recognized, as an important component to a number of neuropsychiatric disorders, among them is Attention Deficit/Hyperactivity Disorder, ADHD. Before continuing on to look into the electrphysiological aspect of attention and inhibition of ASD in relation to attention and inhibitory control, it is worth taking to have a brief review of the related neuroimaging findings of ADHD and also the several other types of paediatric neuro-psychiatric disorders which has a dysfunctional inhibitory control as a key component.

ADHD. It is a neurodevelopmental disorder that by definition, the affected children are much more inattentive, and impulsive than are typical for their age. Different studies have reflected the different natures of the underlying problem in attentional control in ADHD, Barkley (1997) has postulated that the core attentional problem is in executive control; Swanson et al (1998) have suggested that alerting and orienting functions are also impaired in ADHD children; and Nigg (2001) has

pinpointed that inhibition of processing is the main aspect that is disrupted. In terms of neural regions, various regions of the attentional network appear to be dysfunctional in ADHD. For instance, studies have indicated that hypometabolism of frontal regions is associated with the lack of executive control (Zametkin et al., 1993), and dysfunction of parietal regions is associated with difficulties in orienting (Sieg, Gaffney, Preston, and Hellings, 1995), besides, dysfunction of inferior prefrontal regions and the striatrum (Rubia et al., 1999) during motor inhibition, and dysfunction of the anterior cingulate in monitoring performance (Bush et al., 1999, 2005; Tamm et. al., 2004) have been reported also. More recent work has also started to search for cerebellar abnormalities in ADHD (Seidman et al., 2005; Valera et al, 2005).

While the suggested involved neural regions are diffused and varied, recent review of data from neuroimaging, neuropsychological, genetic, and neurochemical studies have generally implicated frontostriatal network abnormalities as the likely cause contributing to the pathophysiology of ADHD (Castellanos, 1997; Durston, 2003; Lou, 1996;Tannock, 1998). Casey (1997) has suggested further that the right prefrontal cortex plays a role in suppressing responses to salient, but otherwise irrelevant events while the basal ganglia appears to be involved in executing these behavioural responses. Neurochemically, numerous evidence have suggested a link specifically to a problem in the dopaminergic transmitter system., This dopaminergic

system anatomically originates in brain stem regions and projects diffusely to any target areas, frontal cortex is one area that receives many dopaminergic projections. In effect, first-line ADHD medication such as methylphenidate and amphetamine work to affect the dopaminergic neurotransmitter system by either slowing the rate of dopamine reuptake on postsynaptic sites or increase in the release of dopamine. Brain imaging studies have further revealed that the frontostriatal circuity and the dopaminergic system interact together in the clinical picture of ADHD, by that the drugs affect activation of the frontal-striatal system, remedying the hypoperfusion in the caudate, putamen, globus pallidus and the frontal regions of ADHD children (Spencer et al., 2005). Genetic studies also link ADHD to domaminergic system. DAT-1, a dopamine transporter gene which may be linked to the hyperactive reuptake of dopamine (Cook et al., 1995), and DRD4 gene which may be linked to subsensitivity of the postsynaptic receptor (LaHoste et al., 1996). In both cases, it is assumed that disruption of dopaminergic transmission is linked to ADHD.

Tourette's Syndrome (TS). It is a neuropsychiatric disorder characterized by chronic vocal and motor tics (APA, 2000), which usually present at 5-7 years old (Robertson, 2000). A number of symptoms in TS such as echolalia, echopraxia, copropraxia, repetitive movement, urge to perform socially inappropriate acts, and other 'disinhibited' behaviours suggest a failure of inhibitory control (Cohen &

Leckman, 1992; Kurlan et al., 1996). As such it has been supported that the impaired inhibitory control may relate to the core symptoms of TS (Rankins et al., 2006). TS patients are impaired in interrupting the execution of intended movements, inhibiting both motor and verbal prepotent responses (Baron-Cohen, 1994) and have difficulty in not processing irrelevant distracter stimuli when instructed to do so (Ozonoff et al., 1998). Neuroimaging findings have indicated that tic suppression is related to activity in the basal ganglia and thalamus and the prefrontal cortex (Peterson et al., 1998). Functionally, it depends on cortical-striato-thalmo-cortical circuitry. In particular, activity in subcortical regions correlated more significantly with the symptom severity. Structurally, abnormalities have been found in the orbital frontal cortex (Peterson et al., 2001), with its size and more specifically, the volumetric decrease in the left deep frontal white matter correlated with the symptom severity again (Goldman-Rakic, 1987, Kates et al, 2002) suggesting the importance of disrupted orbitofrontal inhibitory control mechanisms in TS.

Obsessive-Compulsive Disorder (OCD). It is a mental illness characterized by obsessions and compulsions that are inappropriate, frequent, and sufficiently intense to cause distress (APA, 2000). It has long been hypothesized to be the result of a dysfunction in inhibitory control mechanisms (Chamberlain et al., 2005). Many of the keys symptoms and clinical features of OCD such as intrusive and troubling thoughts

and compulsive and repetitive behaviours strongly suggest inhibitory impairment (Kirkorian et al., 2004). Patients with OCD performed impaired inhibitory control on a number of different tasks, including the oculomotor tasks requiring the suppression of eye movements (Rosenberg et al., 1997); response inhibition task committing more errors (Bannon et al., 2002); and on the cognitive inhibition Stroop test (Penades et al., 2005) and on the Go/NoGo task with poorer performance (Penades et val., 2007; Watkins et al., 2005). In paediatric obsessive-compulsive disorder, findings support the hypothesis that paediatric OCD is characterized by a dysregulation of frontostriatothalamic brain regions including the anterior cingulate gyrus necessary for motor inhibition, and also demonstrate dysfunction of temporoparietal and frontocerebellar attention networks during more cognitive forms of inhibition. (Woolley, Heyman, Brammer, Brammer, Frampton, McGuire and Rubia, 2008; Szeszko et al., 2004).

Neurophysiological Investigation on Attention and Inhibition

A major task of Electroencephalographic (EEG) analysis is to determine the source and functional significance, if any, of the observed rhythms. Amongst different wavebands, theta rhythm is one the most commonly studied area and some relationships of it with behaviours have been established. Mitchell et al. (2008) in their review, pointed out that there have been accumulating evidence postulating that

increased frontal theta activity in EEG analysis is a prominent feature linking to increased cognitive demands, in particular in those that require attention or working memory (Chabot & Serfontein, 1996; Gevins et al., 1997; Onton et al., 2005; Loo et al., 2009). It is often studied during mental arithmetic (Inanaga, 1998; Ishihara and Yoshii, 1972; Ishii et al., 1999; Mizuki et al., 1980; Sasaki et al., 1996 Smith et al., 1999), error detection (Luu et al., 2003, 2004), working memory tasks (Gevins et al., 1997; Krause et al., 2000; Onton et al., 2005), goal conflict resolution (Moore et al., 2006; McNaughton, 2000) and execution and inhibition of movement (Morris & Hagen, 1983). Kirmizi-Alsan et al. (2006) in their Go/NoGo experiment, observed that both Go condition and NoGo condition evoked theta activity suggesting that theta activity reflected attention and response inhibition.

Within the manifestation of theta rhythm, frontal midline distribution is generally supported with the notion that human ACC is involved in its generation which is always fronto-central with a maximum at, or just anterior to Fz and is thought to be elicited by an inhibitory mechanism that blocks out information when trying to retain something in working memory or when focusing attention (Ishii, 1999; Asada et al, 1999). This accrues from a comparison of the electrophysiological and metabolic neuroimaging literature. This includes studies on focused attention (EEG: Asada et al., 1999; metabolic Davis et al., 1997); on task difficulty (EEG: Gevins et al., 1997;

metabolic: Murtha et al., 1996), on orienting response (EEG: Dietl et al., 1999; Williams et al., 2000). Previous studies of concurrent measurements coupling frontal midline theta activity and other neuro-imaging tests have further revealed positive correlations between electrophysiological and hemodynamic data in the anterior cingulate cortex and various frontal regions which were recorded simultaneously (Pizzagalli D.A., Oakes, T.R., & Davidson, R.J., 2003). The use of a tomographic source localization technique for the EEG data enables localizing the source of the brain electrical activity. For examples, Fallgatter et al. (2004) have employed Low-resolution electromagnetic tomography analysis (LORETA) to analyze the EEG data obtained during a continuous performance test in their study with ADHD boys, and has revealed that there is a significantly diminished electrical activity in the anterior cingulate of ADHD group and in no other region of the brain during NoGo condition, while Sauseng et al. (2007) also used LORETA to study the source of FM-theta during a motor working memory task and has revealed that it came from the anterior cingulate gyrus and the cingulate motor area. In a recent study done by Dopplemayr et al. (2008), they have investigated the brain correlates of attention and behavioural inhibition using rifle shooting in his experimental paradigm, in view that rifle shooting is a sports with a high demand of executive inhibition and release at right timing (Losel & Funk, 1995). They studied the time course of frontal midline

theta (Fm[theta]) during the aiming period in rifle shooting. 2 groups were tested, one was the expert group and another the novices. Results showed that the expert group exhibited a significantly stronger frontal theta activation at electrode location Fz and also a generous increase (not to a significant level) at electrode location Cz (the 2 electrode locations normally identified as contributing to Fm[theta]). Again, subsequent analysis using LORETA suggested that the difference in theta activity between the two experimental groups was significant at region corresponding to frontal midline (BM 32, 9, and 6) and anterior cingulate areas (BM 24 and 33).

In brief, as Gevins et al.(2007) have suggested, Fm[theta] is an indicator of neuropsychological processes, it is most likely generated in the ACC, and LORETA as an electrophysiological method can effectively localize its source. Using EEG in this present study, frontal theta activity and ACC activation would be investigated.

Hypotheses

In this present study, both frontal lobe and anterior cingulate cortex were identified as the two regions of interest as they are both significant in functioning of attention and inhibition as based on the literature reviewed above. The purpose of the study was to examine the neurophysiologic activity of these two regions in ASD upon tasks demanding attention and inhibitory control.

We examined the behavioural performance of ASD children in attention and inhibitory control both on the neuropsychological tasks and everyday situation through a parent rating form, as well as their neurophysiological activity as reflected by the theta power using EEG, which is clinically much more easier to apply to ASD children since the setting is more friendly, and the procedure is non-invasive and less costly as compared to other neuroimaging techniques despite that its spatial resolution is lower. We hypothesized that ASD children would perform significantly poorer than normal children on behavioral indices of attention and inhibition, and this hypothesized dysfunction was associated with their abnormalities of frontal activity as measured by frontal theta power, and also abnormalities in ACC using an EEG source localization technique. These hypotheses were tested by assessing its neurophysiologic activities while the participants were performing a task requiring attentional and inhibitory control - a Go/NoGo task. We hypothesized that on Go/NoGo task, ASD's behavioural performance was poorer than age peers and based on the literature reviewed, its relationship with age and IQ was also tested. Neurophyiologically, ASD was hypothesized with hypoactivation on frontal and ACC areas. To my understanding, all the EEG studies with ASD in the past were done at resting cortical state only. The present study is an attempt to extend to the event-related changes in EEG power during a Go/NoGo task, giving further

information about the cortical electro-physiological activity of ASD in relation to attention and inhibitory control. Besides, most of the ASD studies previously done with investigation on ACC engagement were limited to the adolescent or adult population only, this present study serves the gap of understanding and explore into the children population. It is hopeful that with better understanding of any altered electrophysiological pattern in this patient group, it might lead to more feasible and effective intervention at that level.

METHODS

Recruitment of Participants

Initially, 41 children previously diagnosed by pediatricians of Child Assessment Centres to have ASD were recruited either through the Parents' Association of Pre-School Handicapped Children in Hong Kong, or from the subject database of our Neuropsychological Laboratory. They were previously diagnosed by pediatricians of Child Assessment Centres in Hong Kong based on DSM-IV-TR criteria (American Psychiatric Association, 2000) and/or Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2003). Their diagnosis was then re-confirmed again by a clinical psychologist in our Laboratory who again conducted a standard clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed., text rev.; DSM-IV-TR; supplemented with Autism Diagnostic Interview-Revised (ADI-R; Rutter, LeCouteur, & Lord, 2003). The parent interview also included a comprehensive developmental history taking, which included early developmental history, medical history, school and psychiatric history, if any.

50 normal control (NC) children were recruited from local primary schools by sending invitation letters to their parents. Parents were invited to complete and return the consent form to the research team if they agreed to have their children participate in the project. Again, a clinical psychologist in our Laboratory interviewed

the parent of each child with a standard questionnaire on the developmental history of the child.

Exclusion criteria included current or past psychiatric and neurological disorders , birth injury, mental deficiency, acquired brain injury, learning difficulties, and medical disorders (e.g. epilepsy, fragile-X syndrome) with implication for impairment in the central nervous system or those requiring regular medication. Potential control participants were also screened to exclude those with a family history of autism. As the result of this exclusion, 11 ASD children and another 11 normal children were excluded from the present study. There remained altogether 30 ASD children and 39 NC children at this stage of selection.

Matching ASD Group and NC Group

Since studies have shown that performance in attention and inhibitory control is generally affected by age and level of intelligence (Doppelmayr, Klimesch, Sauseng, Hodlmoser, Stadler, & Hanslmayr, , 20082005) and besides, human scalp EEG data has also been evidenced to vary with age (Harmony, et la., 1995; Somsen, Van-Klooster, Van-der-Molen, & Van-Leeuwen, 1997), to control their effects on the performance in attention and inhibitory control to be measured, the potential ASD participants and potential control participants were further tested with Test of

Nonverbal Intelligence, 3rd Edition (TONI-III; Brown, Sherbenou, & Johnson, 1992). After matching the age, IQ as measured by TONI-III, gender and handedness, ASD group composed of 22 children and NC group composed also of 22 children were finally drawn for further analysis.

Finalizing the Subject Pool after Removing Outliers

22 ASD children and 22 age- and IQ- matched normal controls were evaluated. Behavioural assessment in Go/NoGo task was administered and 19-channel scalp EEGs were recorded both during eyes opened resting and on task states.

As this first step, the participants' behavioural performances in Go/NoGo were reviewed. 2 children from the NC were identified as outliers in the Black Press (Go) condition, being fallen out of 3 box lengths of boxplot. They were subsequently taken out of the subject pool. Correspondingly, another 2 age- and IQ –matched participants were also removed from the ASD subject pool, resulting in a total sample size of 20 participants in each group. These two groups were matched on age, t=-1.510, IQ t = 1.695, gender t= .588, and handedness, t=.000, all ps>.05. The two groups were similar in age range (NC: mean ages was 9.8 years old with age ranging from 7 to 13; ASD: mean age was 10.75 years old with ages ranging from 7 to14) and IQ range (NC: mean IQ was 110.7 with IQs ranging from 88 to 148; ASD: mean IQ was 101.4 with IQs ranging from 80 to 140). As compared, NC had a slightly smaller mean age

and higher mean IQ than the ASD group, again, differences on both were not at significance level (*ps* >.05) Their demographical data were compared as per table 1 .

Procedure

After obtaining written informed consent from the participants' parents, participants underwent a battery of neuropsychological tests and concurrent EEG recording with Go/NoGo task taken place, following a protocol pre-approved by the Clinical Research Ethics Committee of The Chinese University of Hong Kong. The sequence of neuropsychological assessment and EEG recording was counter balanced to avoid order effect. Parent ratings of the children's everyday behaviour were explained to the parents and they completed the form privately in another room. The following was the list of instruments used in the study.

Neuropsychological Instruments

Test of Non-Verbal Intelligence (3rd edition) (TONI-III)

The TONI-III (Brown, Sherbenou & Johnson., 1992) is one of the most commonly psychometric tests used in assessing non-verbal intelligence primarily tapping on abstract visual reasoning and problem solving in a language-free context. It is a non-timed, multiple-choice type of test. It consists of two forms, Form A was administered in this study. Raw scores were converted to deviation quotients with a

mean of 100 and one standard deviation of 15 points with reference to age-matched cohorts provided in the test manual. The obtained deviation quotients were used for inclusion / exclusion into the study.

Hong Kong List Learning Test (HKLLT)

HKLLT (2nd ed.; Chan, 2006) is a Chinese word list learning test popularly used in Hong Kong. It measures the frontal lobe functions of learning strategies, organization, and vulnerability to interference on top of the verbal memory and recall power.. The test consists of 2 16-word lists, one for random condition where the items were presented in an disorganized format, and another for blocked condition where items are presented in an organized format. 3 learning trials on each condition are given to the participants. After recall, a verbal recognition task consisting of 32 items within which 16 are target words and 16 are distracters are presented after the 30-minute delayed recall trial, the number of false positives generates the False Alarm Score, it is commonly used as a useful index of poor inhibition in neuropsychological measure (Chiappe et al., 2000; Cummingham et al., 1997; De Beni and Palladino, 2004; Mahone et al., 2001; Schnider et al., 1996; Stuss et al., 1994). The higher the score, the poorer the performance in inhibition indicates.

Object Recognition Task (OR)

This test consists of 24 line drawings taken from the Snodgrass and Vanerwart's

object database (1980), modified and validated by Rossion and Pourtois (2004). The line drawings were placed in an array of 6 x 4 layout and displayed on a computer screen for 3 minutes, participants were instructed to try their best to memorize as many items as possible for a later recognition task which consisted of 12 target line drawings mixed with 12 distractors on another 6 x 4 layout. Incorrect identification of the line drawings shown were counted as False Alarms, a commonly used neuropsychological measure of commission error or inhibition (Chiappe et al., 2000; Cornoldi & Mammarella, 2006), The scores ranged from 0 to12, again the higher the score, the poorer the performance in inhibition indicates.

Digit –Span (DS)

This is a verbal subtest taken from Hong Kong Wechsler Intelligence Scale for Children. Strings of numbers of increasing length are read to the participants at a rate of one digit per second, once for each string, and immediately after it is read to them, they are required to repeat the string of numbers accurately and in the same order. This task is considered to measure efficiency in attention.

Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF (parent form) (Gioia et al., 2000) assesses executive function regarding daily life adaptations in children and adolescents at home situation. It is useful in evaluating children aged 5 to 18 years with a wide range of developmental

and acquired neurological conditions such as learning disabilities, Attention-Deficit /Hyperactivity Disorder, traumatic brain injury, low birth weight, Tourette's Disorder, and Pervasive Developmental Disorders/Autism. The summary score, the Behavioural Regulation Index (BRI) comprise of scores on inhibition, shift of attention, and emotional control. Higher score on the Scale correspond to lower inhibition.

Event-related Behavioural Task -Go/NoGo task

In this study, Go/NoGo task is administered simultaneously with the EEG measures taken. It is a type of Continuous Performance neuropsychological test commonly used to explore complex functions of response inhibition and sustained attention. The Go/NoGo paradigm designed in this study consists of a series of two different stimuli -- black or red balls. In this Go/NoGo discrimination paradigm, overall brain activity seems to involve several subprocesses, some of them common to both conditions, namely, sustained and selective attention, discrimination between stimuli, deciding whether or not to move, and some specific to each condition – initiation or inhibition of motor actions.

Black or red balls were displayed one at a time, in the center of the computer screen, and showed up for 500 msec, then blank interval for 1000 msec before another ball showed up again. The participants were instructed to press a button with their

index finger for every black ball (Go stimulus) shown up but not for the red ball (No-Go stimulus). There were altogether 240 balls with 192 black ones and 48 red ones. These 2 types of stimuli were presented randomly at a ratio of 4:1. The total testing time was approximately 6 minutes.

Each participant was initially given time to familiarize with the set up and allowed for practice before formal testing taken place. There were altogether 4 time-locking event types. Correct Hit meant the blackball/press (Go condition), Correct No-Hit meant red ball/No press (NoGo condition); while false alarm was red ball/press and omission was blackball/No-press. They were all marked with coloured lines on the EEG graphs during the recording process (For EEG recording, please see the following session). Reaction time (RT) measuring the time taken from appearance of the Reaction Stimulus to the push of the button was also recorded by the computer.

EEG Recording

Before the EEG assessment, each child and parent were briefly explained on the hookup and recording procedure with the help of a written description and a series of illustration photos.

During the EEG assessment, each child was tested individually in a sound- and light-attenuated room using the DEYMED Diagnostic TruScan 32. An electrode cap

with 19 electrodes, based on the International 10-20 System (Jasper, 1958) referenced to linked ears, was used to obtain the EEG data of each child at a sampling rate of 256 Hz. The level of impedance on each electrode site was kept at 10 kOhm or below.

Immediately after the hookup procedure, children were recorded for 5-minute continuous EEG signals under eyes-opened resting condition. In order to keep the children engaged and awake, they were asked to focus on a computer screen displaying a figure (e.g., a car) and to signal when the figure transformed into another form (e.g., a ship). After the eyes-opened condition, EEG recording continued during the Go/NoGo task.

Throughout the entire EEG recording process, the child's behavior was observed by an experienced research assistant to record the time when the child demonstrated behaviors that might cause artifacts, such as stereotypical behavior, excess motor movement, and eye blinking. These artifacts are visually reviewed off-line and pruned prior to further analysis. At least 1-minute artifact-free EEG data were selected with a high-frequency limit pass band of 30 Hz (John et al., 1988 for discussion of qEEG method).

EEG Data Reduction. The raw data of each participant has to be first transformed by excel application before they are imported into EEGLAB of MatLab 7.1, the software used to capture correct events and epochs. In general, normal people

takes around 90 msec to perceive the appearance of a visual object, then cognitive appraisal follows, leading to the motor action. The average reaction time for normal children /adult was set at around 300 to 400 msec. To ensure that the selected EEG would adequately bracket the EEG data corresponding to inhibition task, epoch limit was set as 50msec as the start and 900 msec as the end. Artifacts in epoched data were then pruned by visual inspection and rejection method on EEG Plot. All incorrect hits were also deselected. At this stage, the transformed data were ready to be exported into readable format for Neuroguide analysis.

Using Neuroguide software, EEG data were reduced. Signals were filtered three ways: low-pass filter set at (30) Hz, high-pass filter set at (0.5) Hz, and (70) Hz notch filter.

Source Analysis using LORETA

LORETA (low resolution electromagnetic tomography) (Pascual-Marqui, Michel, & Lehmann, 1994, Pascual-Marqui et al., 1999) is a voxel-based 3D representation of the cortical generators of an EEG signal and has a good estimation in localizing the sources, even when they arise in deep cortical structures. This technique has recently received important cross-modal validation, as summarized elsewhere (Pizzagalli et al., 2001).

It has been widely used as an electrophysiologically source localization method to analyze the EEG data obtained in the study.(Fallgatter et al. 2004; Mulert et al., 2001, 2003, 2005; Strik et al., 1998; Pizzagalli D.A., Oakes, T.R., & Davidson, R.J., 2003; Sauseng et al., 2007;Charalabos et al., 2009) Without postulating a pre-specified number of generating sources, this approach combines the high time resolution with a source localization method. LORETA computes a unique source distribution under the assumption that neighboring neurons are simultaneously and synchronously active. That is to say, LORETA does not make assumption about the number of sources contributing to the scalp potentials. The only pre-assumption made is that neighbouring voxels have a maximally similar electrical activity. This solution space (2,394 voxels; voxel size: 7x7x7mm3) was restricted to cortical gray matter and hippocampus of a reference brain, as defined by the digitized MNI probability atlases. Consequently, all coordinates reported in the present study are in MNI space. Subsequently, the Structure-Probability Maps atlas (Lancaster et al., 1997) was used to label gyri and Brodmann area(s). Since the Structure-Probability Maps atlas requires Talairach coordinates, MNI coordinates were converted to Talairach coordinates (Talairach & Tournoux, 1988) using the corrections proposed by Brett et al. (2002). Low-resolution electromagnetic tomopgraphy (LORETA) was employed in this study to determine the cortical sources of theta activity and differences in this

activity between ASD group and normal control group across 3 conditions (eyes-opened resting condition, Black Press (Go) condition, Red No-Press (NoGo) condition). (Pascual-Marqui, Michel & Lehmann, 1994; Pascual-Marqui et al., 1999).

Data Analysis

5 Scores from BRIEF, HKLLT, OR, and DS were compared between NC and ASD groups using independent *t*-tests. To cross validate the Go/NoGo paradigm designed for the present study, correlation analysis was conducted with the scores obtained in the Go/NoGo and those from the neuropsychological tests that were used in the study to measure attention and inhibitory control. To compare the between group (NC and ASD) difference of correct hits with black ball/press and the reaction time during the GO condition, and correct no-hit with red ball /No-Press during the NoGo condition, independent *t*-tests were performed. % Correct-Hit and % Correct-NoHit were used instead of the absolute number of Correct Hits or No-Hits for easier reference because of the numbers of the black balls and red balls shown were different in a ratio of 4:1. To investigate the relationship between IQ, and age with performances in Go condition and NoGo condition, Pearson's correlation analyses were conducted. It was generally supported that relative power (the percentage of total power contributed by the frequency band) instead of absolute

power (the amount of energy measured) was normally a better reference since individual variations in the amount of energy in that frequency band can be eliminated by calculating its percentage in the overall power (Chan et al., 2007) and relative power measurements also tend to give larger estimates for the dominant frequency range (Klimesch 1999). Theta power was selected for analysis based on previous literature review with its demonstrated relevance to attention and inhibitory control and ACC activation. Relative power for theta waveband was therefore calculated (4 -7.5 Hz) in anterior region (F3, F4, Fz, F7, F8) and posterior region (T5, P3, Pz, P4, T6, O1, O2) was also calculated for reference. They were averaged to obtain grand means for both regions. Repeated measures of analysis of variances were used to examine to effects of the groups (NC and ASD) and conditions (Go condition, and NoGo condition), and post hoc *t*-test to examine the differences. To investigate the relationship between indices of functioning in attention and inhibitory control and event-related frontal theta activity, Pearson's correlation analyses were examined. Partial Eta Squared values were checked.

For the calculation of cross spectra in LORETA, a fixed frequency range from 4 to 7 Hz was applied for all participants in both groups. Single-trial theta power (4-7Hz) was calculated in LORETA, and current source density was estimated for 2394 cortical voxels. Voxel-wise statistical non-parametrical mapping was performed and

ASD and normal control groups were contrasted. Voxel-wise were tested two-tailed on the 5% significance level after correction for multiple comparisons. (Tabacknick et al., 1989). The sources of the theta band computed from scalp electrical potentials are expressed as the three-dimensional cortical current density according to the Talairach brain atlas; and ALL EEG data for FFT were analyzed with LORETA for each task condition..

RESULTS

On Neuropsychological Measures

5 scores from BRIEF, HKLLT, OR and DS were compared between NC and ASD groups with results tabulated in Table 2. Obtained effect sizes all ranged from medium to large.

Hong Kong List Learning Test (HKLLT)

ASD group performed with significantly more False Alarms both on random and blocked conditions (ts=-2.761 and -2.042, ps<.01) than the age- and IQ- matched normal controls suggesting poorer inhibition.

Object Recognition Test (OR)

False Alarms on OR was also significantly higher (t=-4.035, p<.005) for ASD group suggesting poorer inhibition.

Digit Span (DS)

ASD group performed with significantly lower score suggesting poorer efficiency in attention (t=2.977, p=.007).

Behavioural Rating Inventory of Executive Function (BRIEF)

As reported by the parents of the children, ASD group scored significantly higher on Behavioural regulation (t =-4.500, p<.001) suggesting poorer executive functions

which included sub-domains on inhibition and attention in their everyday life behaviour.

On Event-related Go/NoGo Behavioural Performance

The Go/NoGo paradigm designed for this study was tested showing significant correlations with the neuropsychological measures on attention and inhibitory control employed (BRIEF, HKLLT-False Alarms, OR- False Alarms, and DS) as shown on Table 3. The % Correct Hit correlated negatively with HKLLT-Random False Alarm ($p<.001$), HKLLT- Blocked False Alarm ($p<.001$), OR- false Alarm ($p<.000$), and positively with DS ($p<.01$); while the % Correct-No-Hit also correlated negatively with BRIEF-BRI ($p<.05$), HKLLT-Random False Alarm ($p<.05$), HKLLT- Blocked False Alarm ($p<.05$), OR- false Alarm ($p<.01$), and positively with DS ($p<.05$). This lent support that the Go/NoGo paradigm designed was measuring the constructs on attention and inhibition. On this task, ASD children performed poorer on all the measured indicators. These included a significantly lower mean percentage of Correct Hit on the appearance of the blackball during the Go condition ($p=.015$), a significantly lower mean percentage of Correct No-Hit on the appearance of the redball during the NoGo condition ($p=.049$), and a non-significant slower reaction time than the control group ($p=.163$, partical eta sq.=.051, small effect size). Results

were summarized as in Table 4. Such results indicated that ASD did poorer in Go and NoGo condition that were not compromised by a faster reaction time.

Cross-sectional analyses of % Correct Hit during Go condition across age and IQ were also done. The strength of association was estimated by Pearson's correlation, the NC group revealed non-significant correlation between both age and % Correct Hit (r = .176, p=.458); and non-significant also for IQ and % Correct Hit (r = .037, p=.877). On the other hand, the associations both for age and IQ were significant in the ASD group, with r = .561, p=.01 for age, and r = .466, p=.038 for IQ.

Similar cross-sectional analyses of % Correct No-Hit during NoGo condition across age and IQ were done. The strength of association was again estimated by Pearson's correlation, NC group revealed non-significant correlation between the age and % Correct No-Hit, nor IQ and % Correct No-Hit, (r = .116, p=.627 for age, and r = .083, p=.729 for IQ; and ASD group revealed a marginally significant correlation with age but not with IQ (r = .428, p=.051 for age, and r = .268, p=.253 for IQ).

The strengths of association between reaction time with age and IQ were again estimated by Pearson's correlation, both were found significant for both NC and ASD groups. (NC: r = .683, p=.001 for age, and r = .527, p=.017 for IQ; ASD: r = .705, p=.001 for age, and r = .583, p=.007 for IQ). Figures 1(a) and (b) were the scatterplots showing the relationships between the % Correct Hit with age, and IQ for

the 2 groups during Go condition; and Figures 2(a) and (b) were the scatterplots showing the relationships between the % Correct No-Hit with age, and IQ for the 2 groups during NoGo condition.

On Neurophysiological Measures

Relative Theta

Maps showing the regional relative theta power of the ASD and NC groups were presented in Figure 3. Visual inspection reflected that relative theta power was lowered across multiple channels in the ASD group. For between group comparisons, it was further examined as shown in Figure 4. For anterior region, repeated measures ANOVA results showed a non-significant *condition* (Go, NoGo) by *group* (NC, ASD) interaction effect , F=.423, p>.05, □2=.025 indicating a small effect size, and a significant between-subject effect, F=.16.13, p<.000. Subsequent t-tests with the adjusted alpha level of p< .01 to control for inflated type I error indicated that ASD consistently demonstrated significantly lower relative theta than normal children for both Go and NoGo conditions, t=3.796, p<.001 for Go condition; and t=2.831, p<.01 for NoGo condition. (Fig.4(a)).

As for the posterior region, repeated measures ANOVA results showed a non-significant *condition* (Go, NoGo) by *group* (NC, ASD) interaction effect ,

F=.126, p>.05, partial eta sq.=.008 indicating a small effect size. Subsequent t-tests indicated that difference in relative theta between normal children and ASD were not significant across both conditions although ASD generally had a lower relative theta, t=1.217, p=.231 for Go condition; and t=1.917, p=.063 for NoGo condition (Fig. 4(b)).

Correlation between Frontal Theta Activity with the Neuropsychological Performances

Given that both the relative theta power at anterior region and some neuropsychological indices on attention and inhibition were significantly different between ASD and NC children, we examined the association between them using Pearson correlations. Both the values of relative theta at anterior region Go condition and NoGo condition were examined. Results were tabulated in Table 5. They indicated that the relative theta on Go Condition was significantly correlated with BRIEF Behavioral Regulation Index (r=-.485, p<.05), HKLLT Random –False Alarm (r=-498, p<.05), Blocked – False Alarm (r=-.500, p<.05), OR-False Alarm (r=-.566, p<.05) and DS (r=566, p<..005). Correlations with the relative theta on NoGo Condition were similar and even more pronounced on some indices, with BRIEF-Behavioral Regulation Index (r=-.532, p<.05), OR-False Alarm (r=-613, p<.005) and DS (.r=-571, p<.01).

Localization of Theta Activity

LORETA analysis of the difference in the theta activity between the 2 groups (NC, ASD) across both conditions (Go condition, NoGo condition) was computed as voxel-by-voxel *t* value for comparison, with result as shown in Figure 5. It revealed that the difference in theta activity at anterior cingulate cortex at Tarlairach coordinates (-3,24,22) became significant during the Go condition [BA 24; t= 4.138 (p<0.05)] and also during the NoGo condition [BA 24; t=2.715, (p<0.05)] with the activities significantly lower in the ASD group. It was noted that significant difference was also revealed in a region corresponding to parietal region during NoGo condition at Precuneus [(BA7; t=3.01, (p<0.05)] where ASD also had the theta activity much less than the NC there.

DISCUSSION

Summary of Findings

The main purposes of the present study were to examine the deficiencies on attention and inhibitory control in children with ASD, high functioning type; the associated difference in EEG pattern generated as compared to normal peers; and whether these changes in EEG pattern was associated with the frontal activity and ACC engagement.

Firstly, our results replicated those of the previous studies on ASD showing that even high functioning ASD was deficient in attentional and inhibitory control on behavioural performance both in laboratory tests and daily life adaptations. This study showed that young ASD children performed poorer on measures of attention including Digit Span test, and committing significantly more omission errors on "Go" trials; and on measures of inhibitory control including making more false alarms on HKLLT and OR, and committing more commission errors on "NoGo" trials. Real life adaptations as revealed by the parent report in BRIEF was also significantly worse than normal children of their age and IQ.

With great significant correlations established between the Go/NoGo performances and the other neuropsychological indices employed, the event-related

Go/NoGo paradigm so designed for the study is deemed able to reflect the neurophysiologic activity underlying attentional and inhibitory control. Results from the present study showed reliable group differences suggesting hypofrontality and underactivaton in ACC in electrophysiological activity upon attentional and inhibitory processes in young ASD children. They indicated significantly lower theta activity in the anterior region and reduced activation in ACC in both the "Go" and "NoGo" trials, such finding is in accordance with the previous fMRI findings.

Further examination indicated that the frontal theta activity was significantly associated with the performance in attention and inhibitory behavioural measures. Further scrutiny showed that the frontal activity correlated better with Object Recognition Task – False Alarms than with the HKLLT - False Alarms which is probably because Go/NoGo and Object Recognition Task are both visually mediated tasks sharing more similarities between them. On Go condition, the frontal activity also correlated significantly with all the neuropsychological indices tapped including those inhibition indices like False Alarms, this lends support that attention plays an essential role in all complex information processing (Goldstein et al., 2001); In general, the greater the frontal activity, the better the functions for both attention and inhibitory control. The above findings are in line with the intensive studies of frontal lobe pathology in ASD, which have proposed that it is the underlying cause of clinical

symptoms of autism. Its impacts may not just be limited to executive dysfunctions such as perseveration and loss of purposive behaviours, most theorists also share the view that it may lead to defective social cognitions which manifest in forms of inflexibility in social communications, inferiority in socially perceptive power, poor regard for feeling of others, and altered emotional attachments (Frith, 2001; Happe 1999, 2001; Smith, 1996). Bishop (2005) has further speculated the possible relationship between executive dysfunction and mind blindness in ASD with frontal dysfunction as the common underlying cause.

In congruence with this 2-dimensional topgraphical difference between the 2 groups, our finding suggested a significantly reduced activation of the ACC in ASD children compared to NC children, with the results from EEG-based Source Localization Analysis showing that the significantly increased theta activity during Go/NoGo task was generated by the anterior cingulate cortex. This is in accordance with the previous fMRI findings in high functioning ASD adults that showed a significant reduced activation of ACC during Go/NoGo, MRI-based morphometric studies indicating that ASD adults have ACC reliably smaller that the control group (Haznedar et al, 1997, 2000) and postmortem studies (Bauman and Kemper 1994) indicating abnormalities associated with cingulate cortex in ASD adults. The present finding of hypoactivation in the ACC electrophysiologically in our ASD children adds

further evidence to the abnormalities associated with this region in autism population, and this abnormality is probably apparent since a very young age. A point of note is the result has also revealed that significant difference between the 2 groups was also found at region corresponding to the parietal area during NoGo condition, where it is implicated as part of the inhibition circuit. This result is consistent with previous findings that inferior parietal regions, in conjunction with activation in ACC, have been related to error detection (Carter et al., 1998); response conflict (Braver et al., 2001); and visual-spatial alerting and orienting (Corbetta et al., 2000). Garavan et al. (2002) has futher proposed that ACC system is involved in relatively faster and urgent inhibition, whereas the frontal-parietal system is involved in more deliberate and controlled inhibition. In healthy controls, these two inhibition systems seem to work together as an integrated system recruiting and allocating attentional resources appropriately. Although our result consistently showed that task-related activity at both of these brain regions were significantly higher in healthy control group than in ASD group, further studies would still be necessary to confirm this proposition.

Our present findings supports the view that ASD is not only deficient specifically for inhibitory processes, but more generally on processes of prefrontal response control, which encompass both initiation of action and monitoring of conflict, as proposed by Fallgatter (1999, 2000, 2004) and Carter et al (2000). Since the ASD

children don't merely indicate significant differences in inhibition-related neuropsychological and electrophysiological measures during NoGo condition, significance were also observed during Go condition, where ASD children did significantly poorer in the Go trials of Go/NoGo committing with significantly more omission errors, in parallel, frontal theta activity was less activated and ACC was hypoactivated during Go condition. Indeed, on Go/NoGo discrimination paradigm, there are in fact many factors in common to the Go condition and NoGo condition, for instance, they both require sustain attention, discrimination between stimuli, detection of conflict, decision to press or not to press the button. At the same time, there are cognitive processes specific only to Go condition -- initiation of action; and only to NoGo condition -- inhibition of motor action. Prefrontal cortex and ACC are also widely documented to play an important part in these general cognitive processes (Ehlis, A., 2005; Fallgatter 1999, 2000, 2004; Plichta, M., 2009).

A further point of note is on the observed significant positive correlations between performance in our experimental Go/NoGo paradigm with age and IQ in ASD children which is not seen in their normal peers with comparable age and IQ, which suggested that the >8 year-olds with IQ 80 or above in our NC group in general were already able to perform adequately as well as the older children in terms of accuracy on our experimental Go/NoGo paradigm (only that the older and higher IQ

children did faster as shown in the correlations with reaction time), ASD group of similar age and IQ ranges suggested that their accuracy in performance still improved significantly with their age and IQ. In this light, such inferiority in attentional and inhibitory control may relate to a maturational lag or a deviation in its development. If it is a matter of maturational lag, then the degree of deficiency would not be observed to the same degree at all ages, and that the gap in performance with their normal counterparts might narrow down as they grow older. This might explain why Schmitz et al's study (2006) in ASD did not reflect inhibition problem on behavioural measures as they were studying the adult Asperger's group and not the children group. Besides, their study was limited to those diagnosed with Asperger's. It was speculated that the Asperger's group by virtue had no significant language delay, and they might therefore be using internal verbalizaton as compensatory mechanism during Go/NoGo task which in fact was congruent with his neuro-imaging finding that the Asperger's group demonstrated heightened left frontal activation as compared with the normal control group despite similar level of behavioural performance. In our present study confining to young ASD children and with diagnosis not primarily Asperger's, our finding is in agreement with the notion that ASD children does reveal deficient attentional and inhibitory control as an executive dysfunction. Further studies on the effect of age on subtypes of ASD would be worthwhile to better understand the course

of development of attentional and inhibitory control in this ASD population.

Clinical implications

Previous studies have depicted that ACC is a region playing a central role in several functions associated with attention-demanding activity, and activities demanding detection of conflict between competing responses which are required both during Go and NoGo conditions (Botvinick, 2004; Asada et al., 1999. Ishii et al. 1999, Pizzagalli et al., 2003). Thus, our present findings have further delineated that poorer attention and inhibition in ASD children are associated with their underactivation in ACC. As these functions are part of the type of complex information processing in which ASD individuals have difficulty (Minshew et al, 1997), where they often exhibit disturbances in resolving conflict between different strategies and monitoring and switching strategies to achieve goals in their daily life basis, lower activation in ACC in ASD might be the source of difficulty in these functions. This account leads to a crucial point, that to some degree, ACC activation may effectively predict subsequent performance in executive functions on daily life basis and may possibly be used as an index to evaluate program effectiveness. Specifically, strong ACC engagement should be followed by enhancement of goal-directed behaviours and weak ACC engagement by poorer goal-directed

behaviours. As has been employed in a design of a research-based educational program on attentional networks for 4-year-old children, where the authors have incorporated the use of EEG to evaluate if the training has effect in the underlying brain network, and has effectively altered activity in ACC so that it more closely resembled normal adults' pattern (Posner et al., 2006; Van Veen and Carter, 2002).

Furthermore, imaging studies of adults have also shown that adjacent areas in anterior cingulate are involved not just in regulation of behaviours, but also in social cognition and emotions. Rothbart (2004) has found that during childhood, performance on conflict tasks is correlated with parental reports of their child's effortful control on temperament questionnaires, in turn, effortful control is associated with the ability to delay gratification, and a development of feeling for others. In this connection, training on conflict tasks might effect development of feelings for others because these functions might be sharing similar underlying neural mechanism involving ACC. Training studies of monkeys have also observed that the animals' mastery of cognitive training has also led to decreases in aggressive behaviours and improvement in emotional control. These all suggest possibility of extensive generalization in training due to the change of the same underlying neural network the different functions are sharing. In this light, attention and inhibition training to ASD might benefit not just an increase in attentional and inhibitory control if effective, but

also positively influencing the child's ability in his social adaptation. Indeed, a previous study of electrically stimulating the ACC of a patient group has shown supportive findings about this possible therapeutic effect. Mayberg and her collaborators have applied this onto their group of depressed people. They were individuals whom have virtually catatonic with depression despite years of talk therapy, drugs, and even shock therapy. They placed pacemakelike electrodes in Area 25 of ACC, whom they have identified as an area as a key conduit of neural traffic between the "thinking" frontal cortex and the phylogenetically older central limbic region that gives rise to emotion, and it has appeared to be overactive in these depressed people, which Mayberg has described this phenomenon as " like a gate left open" allowing negative emotions to overwhelm thinking and mood. By appropriately stimulating this Area 25 with low dosages of electric current to close this gate, they have rapidly alleviated the depression of two-thirds of their trial's patients (Mayberg, H.S., Lozano, A.M. & Veen,V., et al., 2005). Although the intervention sounds invasive and probably not mature yet to apply to other clinical group, it at least points to a promising direction that neural mechanisms and behavioural manifestations are closely inter-related, and it is possible and feasible to change one aspect by the other and alleviate the various difficulties faced by our ASD population given continual investigations in this direction.

While results showed that in general, the frontal activity as measured by theta activity correlated with many of the behaviuoral indices, as compared between the deviance in terms of the performance in neuropsychological tasks tested (HKLLT, OR) with the measure on naturalistic daily life (BRIEF), it appears that ASD children were considerably more impaired in the complex executive functions involved in daily life adaptations as reflected by BRIEF than when the specific domains of cognitive processes were tapped by individual clinical instruments, since often times, the laboratory setting and the standardized test instructions have already provided a crucial structure to the ASD children to follow in response to the external task demand. This echoes Stuss and Benson's (1986) observation that " in the context of standardized assessment, the examiner and testing situation function as prosthetic frontal lobes". On one hand, this might explain why executive dysfunction or frontal lobe dysfunction are difficult to test out solely basing on clinical test instruments (Donders, 2007; Chan et al, 2009) and why even the most able with high IQ ASD individuals can be chaotic in managing his daily life. On the other hand, this might also suggest that one of the key therapeutic directions in training ASD children or others with frontal lobe pathology is to give them well-defined structures and boundaries, detailed timetables, precise final and substage objectives, simple course of actions with little leeway for options or bargaining, explicit guidelines and

explanation even on social matters, and controlled complexities on learning materials in order that they can maximize the educational gains cognitively, behaviorally and even socially. It is well accepted that a better understanding of the elements of executive dysfunction and its neural correlates in ASD can aid development of effective therapies for this debilitating disorder. Compensatory mechanisms to help ameliorate the consequences of executive dysfunction in their daily lives are one of the possible methods. (Schmitz et al., 2006)

EEG is contributive to the understanding of the underlying cortical dysfunctioning of ASD brains. With continual effort, it is hopeful that the related knowledge can extend to intervention, and neuro-feedback training to 'stretch' ASD's electro-physiological coping limits and re-shape their response patterns might become an effective intervention. Indeed, recent evidence-based neuro-feedback interventions on some clinical populations have been producing preliminary yet exciting findings. Normalizing brain electrical signals of attention-deficit / hyperactivity disorder (ADHD) has been found to be effective in reducing deficits in their cognitive /behavioral problems (Lubar, Swartwood & O'Donnell, 1995); and manipulating the theta/beta ratio in electrical activation on children with ASD has been documented to result with sustained improvements both in executive functions and social behaviours in a post-year follow-up study when compared to the wait-list control group (Kouijzer

et al., 2009a, 2009b). Further explorations are still necessary to delineate the exact relationship between the specific impacts of different manipulations of bandpowers and the various aspects of functioning, and also the durability of the induced enhancing effects. In the future, increased understanding of how individual neural region functions and how networks are developed and shaped by experience can provide insights into designs of more effective training programs for clinical population or even into establishment of new school subjects for normal school students to benefit from research. Moreover, the methods need not be limited to cognitive development, but can promote children's social adaptation. Given that inattention and disinhibition can severely disturb ASD's learning and social interaction, increase of knowledge on the neurophysiological systems in ASD brain might be a promising direction that can indirectly but essentially facilitate their learning ability and social functioning,

Lastly a point on the possible comorbidity of clinical diagnoses of ASD and ADHD, although traditionally in clinical practice, deficient attentional and inhibitory control are more commonly recognized to be inherent to ADHD, this present result shows that ASD as a group is also sharing attentional and inhibition difficulties with significant difference from his age peers, and there probably has great variability among ASD individuals within this patient group, this brings to mind an interesting

theoretical considerations on symptom profile and comorbidity of ASD and ADHD despite it is basically beyond the scope of the present study. While in past diagnostic tradition that if a child is conferred a diagnosis of autism, ADHD will not be considered present in that child., many accumulating studies on ASD have found that they show various degrees of attentional deficits, impulsivity and problems regulating activity level (Sturm, 2004), with percentage of comorbidity could be high as 85% (Yoshida & Uchiyama, 2004) for children in their PDD group of study. If additional research supports these suggestions, it calls into question the current exclusionary practice of offering a diagnosis of ADHD in PDD and adds to the growing literature suggesting a serious re-consideration of the DSM-IV nomenclature, that ADHD can possibly co-exist with ASD and dual diagnoses might be more meaningful in those situations. Besides, in terms of neural basis, there are evidence as mentioned in the literature review that both of these two groups are disrupted with abnormalities in frontal and anterior cingulate cortex, of which the present study has essentially revealed that

they are the neural regions associated with attentional and inhibitory control.

Limitation and Suggestions for Future Research

The main limitation of the present study is the relatively small sample sizes that

hamper a detailed analysis with regard to different degrees of severity and subtypes of ASD. The sample was also limited to a small age range between 7 and 14 years old and a narrow range also in terms of intellectual level. These factors limit the generalizability of the findings. Since age and IQ are factors affecting performance of our ASD group but not our NC group, it would be interesting to know if older ASD children and younger NC children are also recruited and tested whether the age effect will be different for them. Ideally, a longitudinal analysis can give a better account in depicting the developmental nature of attention and inhibition and the associated electrophysiological performance.

As previous findings suggest that EEG analysis particularly that involving frontality are still developing till adolescents, therefore breaking the group according to smaller age brackets is desirable but then imply the need for a bigger sample.

As there are always many more ASD boys than girls, so the control group is nevertheless loaded with boys also, in such case, results and understandings obtained on the normal group should not be regarded as a fair representation of that age population.

Some also debate that a simple Go/NoGo task does not really account for sustained attention unless the test is really long and the changes of performance level over the course of test is measured. However, it will be increasingly difficult to do the

EEG acquisition successfully with longer test period.

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Table 1:

Demographic characteristics of the normal controls (NC) and children with Autism Spectrum Disorder (ASD) groups

Variable	NC (n = 20)	ASD (n =20)
Mean Age in Years	9.80 (1.884)	10.75 (2.074)
TONI-III - Deviation Quotient	110.7 (17.84)	101.4 (16.83)
Gender - Male : Female	18:2	19:1
Handedness - Right : Left	19:1	19:1
Mean scores in CARS	--	31.98 (3.31)

Note: Standard deviations are in parentheses.

TONI-III, Test of Nonverbal Intelligence, 3rd ed.

CARS, Childhood Autism Rating Scale; the dash indicates that the CARS was not administered to NC.

Table 2

Mean performance on the neuropsychological tests of normal controls (NC) and children with Autism Spectrum Disorder (ASD)

Measure	NC (n = 20)	ASD (n =20)	t-value	Partial Eta Squared
BRIEF				
Behavioural Regulation	47.60 (10.26)	61.11 (8.33)	-4.500****	354 (L)
HKLLT				
Random- False Alarm	.35 (.59)	4.05 (5.82)	-2.761**	.178 (L)
Blocked –False Alarm	.57 (.76)	4.08 (5.92)	-2.042**	.169 (L)
OR				
False Alarm	.05 (.22)	3.41 (3.43)	-4.035***	.355 (L)
DS	12.79 (1.85)	10.17 (2.62)	2.977**	.270 (L)
Forward				

Note: Standard deviations are in parentheses

S= small effect size; M=medium effect size; L= large effect size

*p<.05; **p<.01. *** p<.005, ****p<.001

Table 3:

Correlations between performances in Go/NoGo paradigm and other neuropsychological measures:

	%Correct Hit	%Correct NoHit	BRI	Random-FA	Blocked-FA	OR	DS
Go/NoGo							
%Correct Hit	1.00						
%Correct No-Hit	.587**	1.00					
BRIEF							
BRI	-.301	-.318*	1.00				
HKLLT							
Random FA	-.693****	-.384*	.408*	1.00			
Blocked –FA	-.855****	-.459*	.416*	-.660****	1.00		
OR							
False Alarm	-.602****	-.427**	.406*	.610****	.717****	1.00	
DS	.510***	.408*	-.594***	.709****	-.660****	-.633***	1.00

Note: FA=False Alarm

*p<.05; **p<.01. *** p<.005, ****p<.001

Table 4:

Mean scores on Go/NoGo task of normal controls (NC) and children with Autism Spectrum Disorder (ASD)

Variable	NC (n = 20)	ASD (n =20)	Partial Eta Squared
Go condition – % Correct Hit	97.60 (2.39)	90.36 (12.01) *	.155 (L)
NoGo condition - % Correct No-Hit	81.30 (11.41)	71.17 (18.89) *	.100 (M)
Reaction time (msec)	374.67 (61.78)	425.24 (145.0)	.051 (S)

Note: Standard deviations are in parentheses

S= small effect size; M=medium effect size; L= large effect size

*p<.05

Table 5

Correlations between relative theta powers (anterior region), and attention/ inhibition indices after controlling age and IQ:

Measure (N=40)	Relative theta – Go condition	Relative theta – NoGo condition
BRIEF		
Behavioural Regulation	-.485 *	-.532 **
HKLLT		
Random –False Alarm	-.498 *	-.174
Blocked –False Alarm	-.500 *	-.214
OR		
False Alarm	-.566 *	-.613 ***
DS	.566**	.571**

Note *p<.05;

**p<.01

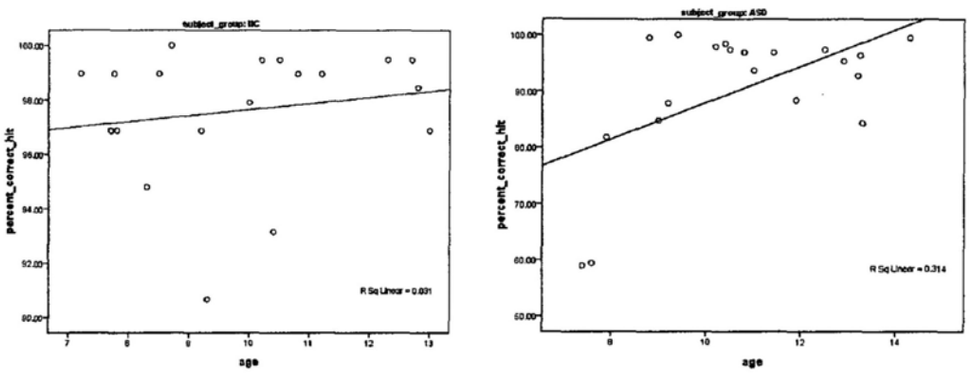
***p<.005

Figure 1:

Scatterplots showing the relationship between % Correct Hits and (a) Age and (b) IQ by Group at Go condition: performance correlated with both age and IQ for ASD group but not for the NC group

NC Group **ASD Group**

(a) with age:



(b) with IQ:

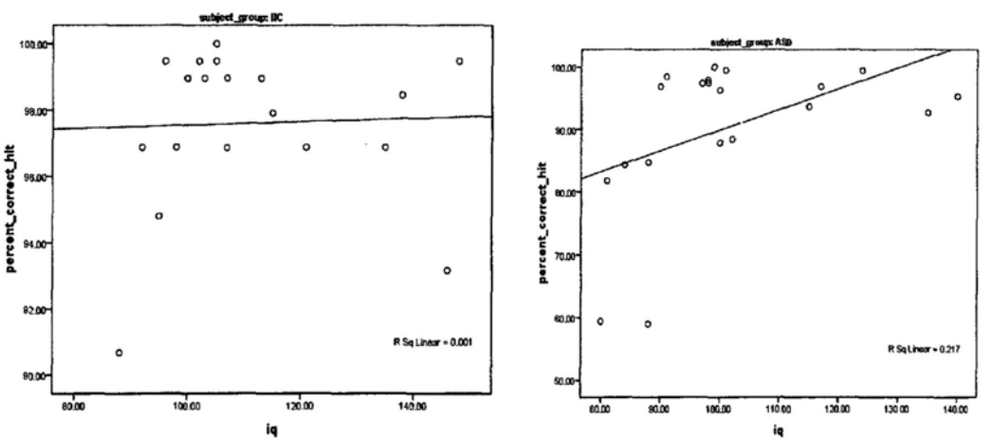
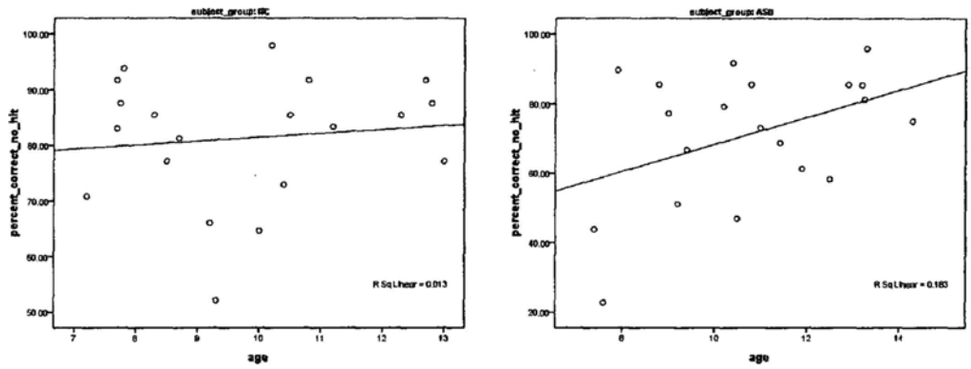


Figure 2:

Scatterplots showing the relationship between % Correct No-Hits and (a) Age and (b) IQ by Group at NoGo condition: performance correlated with age for ASD group but not for the NC group

NC Group **ASD Group**

(a) with age:



(b) with IQ:

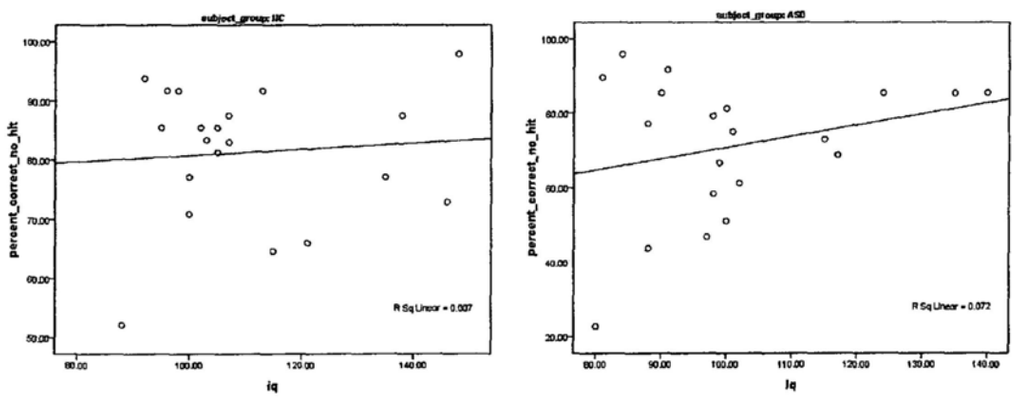


Figure 3:

Topographic maps demonstrating the mean values of relative theta power, with the frontal regions at the top of each map, are shown for normal children (NC), and children with autistic spectrum disorder (ASD) during (a) Go and (b) No-Go conditions.

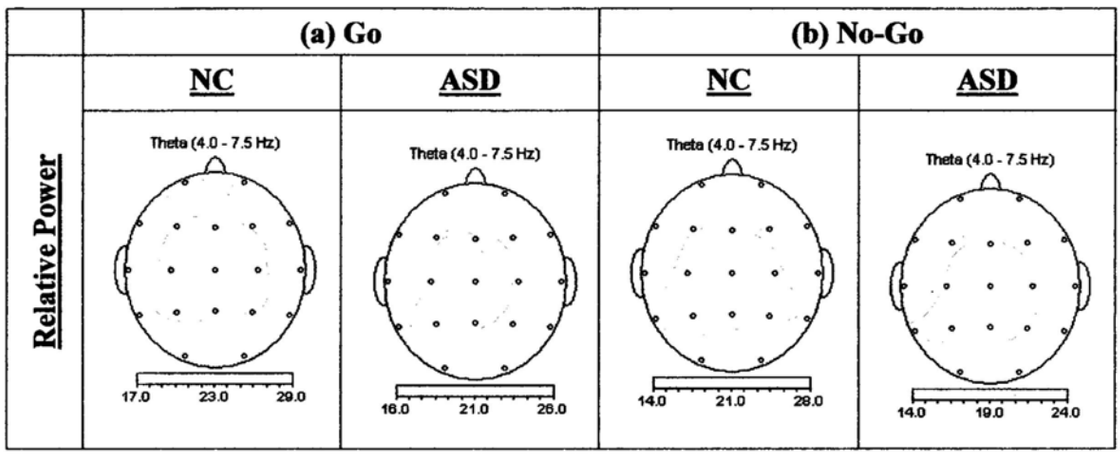
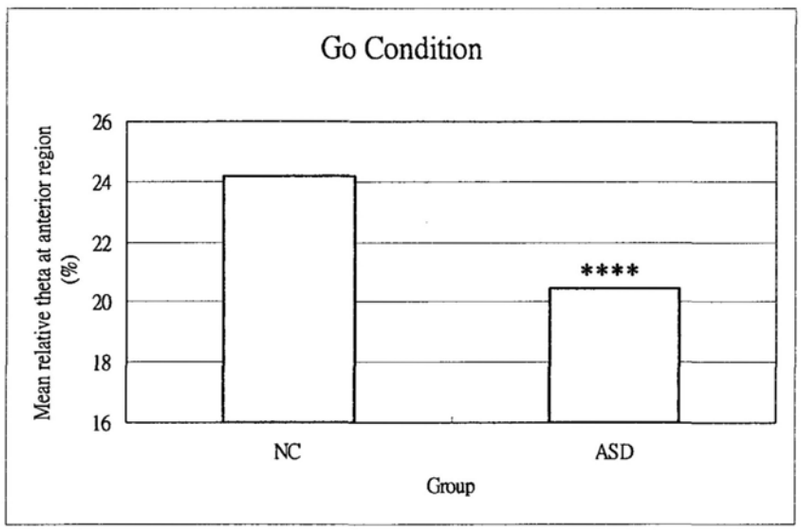
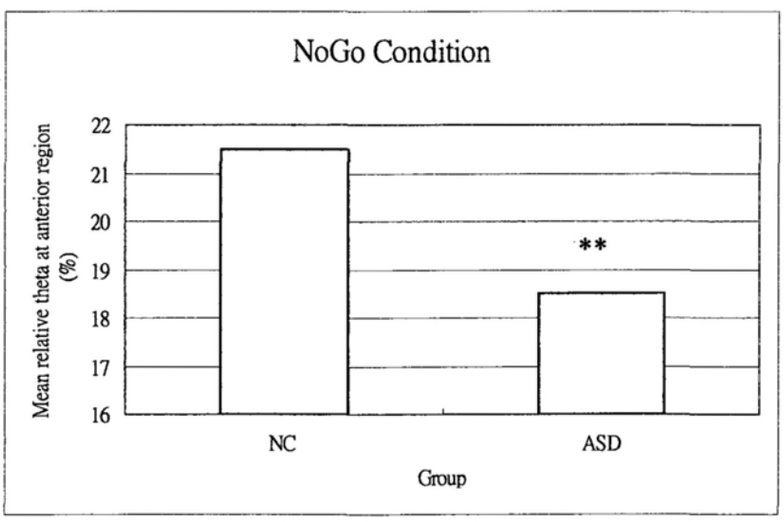


Figure 4:

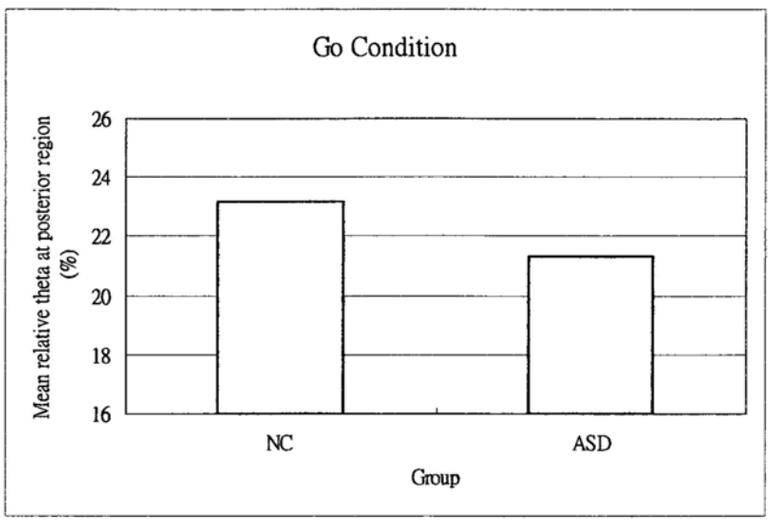
Magnitude of relative theta power across the 2 conditions (Go, NoGo) of normal controls (NC) and children with autism spectrum disorder (ASD) at (a) anterior region and (b) posterior region. ASD showed significantly lower theta activation than NC at anterior region across all the 3 conditions, $p<.01$ but not at posterior region. $*p<.05$, $**p<.01$, $***p<.005$, $****p<.001$

(a) Anterior Region





(b) Posterior Region



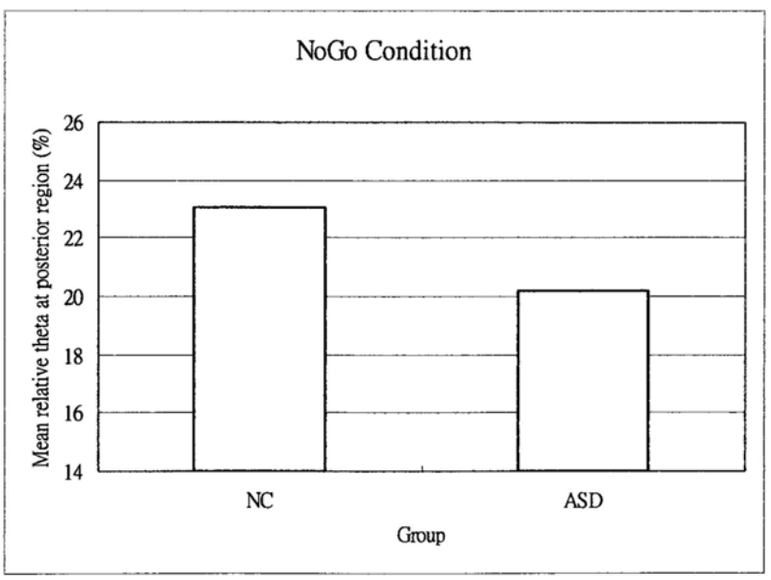
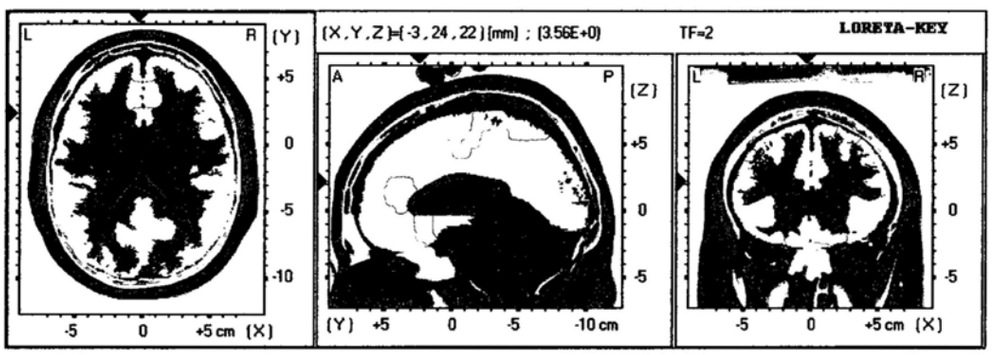


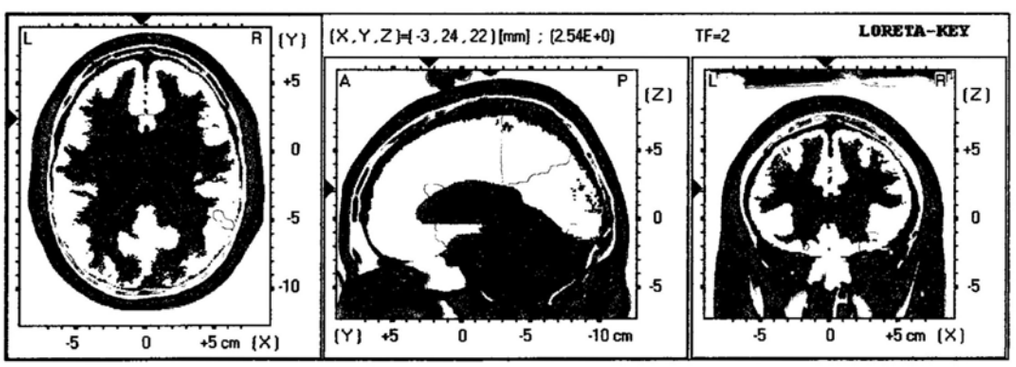
Figure 5:

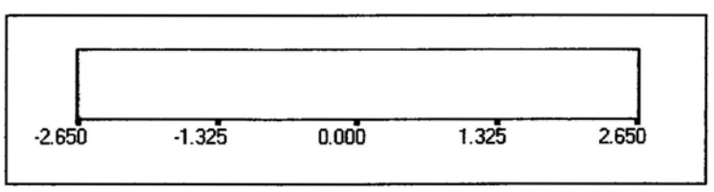
Graphical representation of the LORETA *t*-statistics illustrating the difference in theta activity between NA group and ASD group during (A) during Go Condition and (B) during NoGo condition. Red color indicates the location of significantly reduced electrical activity in the brain of the ASD children as compared to the NC group (left, axial; middle, sagittal; right, coronary slice through the reference brain). Black arrows indicate the center of the difference in activation in the ACC (Brodmann area 24).

(A) During Go condition



(B) During NoGo Condition





t-test