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ORIGINAL ARTICLE

Neuropsychological functions among adolescents with persistent, subsyndromal and remitted attention deficit hyperactivity disorder

Y. J. Lin[1,2,3], W. J. Chen[3] and S. S. Gau[1,3,4]*

[1] *Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan*
[2] *Department of Psychiatry, Far Eastern Memorial Hospital, Taipei, Taiwan*
[3] *Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan*
[4] *Department of Psychology, School of Occupational Therapy, Graduate Institute of Clinical Medicine, and Graduate Institute of Brain and Mind Sciences, National Taiwan University, Taipei, Taiwan*

Background. Previous studies have reported mixed results on neuropsychological deficits in attention deficit hyperactivity disorder (ADHD) and only a few studies have focused on adolescents. There is also a debate about whether the executive function (EF) impairments in ADHD are primary deficits or have some contribution from the underlying non-EF processes. The aim of this study was to investigate the impairments in EF and neuropsychological function with relatively low executive demand (low-EF) in adolescents with childhood diagnosis of ADHD as a function of current ADHD status.

Method. Psychiatric diagnostic interviews and computerized neuropsychological tests classified into EF and low-EF tasks were completed by 435 adolescents with a childhood diagnosis of ADHD (300 adolescents classified as persistent ADHD, 109 as subsyndromal ADHD and 26 as remitted ADHD based on the current diagnosis) and 263 typically developing (TD) adolescents.

Results. There were significant EF (spatial working memory, spatial planning and verbal working memory) and low-EF (signal detectability, spatial span and visual recognition memory) impairments in persistent and subsyndromal ADHD. The impairments in EF were independent of low-EF despite significant moderate correlations between any two of these tasks. Adolescents with remitted ADHD showed no deficit in either EF or low-EF.

Conclusions. This study suggests that adolescents with persistent and subsyndromal ADHD have EF and low-EF impairments that might contribute to ADHD independently.

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Key words: Adolescents, attention deficit hyperactivity disorder, neuropsychological functioning, persistence, working memory.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder in childhood that may persist into adolescence and adulthood (Weiss *et al.* 1985; Barkley *et al.* 1990, 2006; Biederman *et al.* 1996). Among the various neuropsychological dysfunctions found in ADHD (Nigg, 2005; Castellanos *et al.* 2006), executive functions (EFs) have been studied most extensively across the lifespan (Seidman, 2006), but with inconsistent results (Sonuga-Barke, 2005). EF is an umbrella term used to describe the 'top-down' cognitive abilities required to maintain problem-solving skills to achieve future goals (Pennington & Ozonoff, 1996). The most evident and consistent EF deficits in ADHD are response inhibition, vigilance, spatial working memory and planning, whereas set-shifting, Stroop interference control and visuospatial orientation of attention are found to be poor candidates for primary neuropsychological deficits in ADHD (Willcutt *et al.* 2005*a*). These subsets of EFs are often correlated with each other, with common shared variance, but may also be independent (Miyake *et al.* 2000), thus administrating multiple executive tasks at the same time may help to achieve an understanding of the nature of impairment and sparing of other EFs in ADHD.

Most executive tasks are complex and involve multi-level processes; for example, arousal, a non-EF ability (Posner & Petersen, 1990; Nigg, 2005), is related to early information processing (Tucker & Williamson, 1984)

* Address for correspondence: S. S. Gau, M.D., Ph.D., Department of Psychiatry, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan.
(Email: gaushufe@ntu.edu.tw)

and working memory involves general intelligence, short-term maintenance memory and executive ability or central executive components (Baddeley, 2003; Sergeant *et al.* 2003). In addition to EF impairments, neuropsychological tasks with relatively low executive demands, such as spatial span and delayed matching to sample (Rhodes *et al.* 2005; Shang & Gau, 2011), have also been found to be impaired in ADHD. However, previous studies investigating EF deficits in ADHD seldom controlled for the 'primary' cognitive process (Castellanos *et al.* 2006) or non-EFs (Pennington & Ozonoff, 1996). Whether impaired performance in EF tasks in ADHD reflects 'pure' executive dysfunction or simply reflects deficits in underlying non-EFs remains elusive (Pennington & Ozonoff, 1996). The few attempts to determine the relationship between multicomponent EFs and ADHD have revealed mixed results. EFs might no longer be related to ADHD after non-EF performance is controlled (Scheres *et al.* 2004). More central executive processing than visuospatial storage ability was reported to account for inattention behavior in ADHD (Kofler *et al.* 2010), but conflicting results also exist (Tillman *et al.* 2011).

During adolescence, the various prefrontal areas continue to develop at different rates, with earlier development of ventromedial areas involved in emotional and instinctual behaviors and later development of prefrontal convexity for higher EFs (Fuster, 2002). Thus, more complex and later developing functions, such as working memory, might be more able to differentiate adolescents with and without active ADHD symptoms than younger children (Tillman *et al.* 2011; Gau & Chiang, 2013). Some studies on adolescents with ADHD have shown significant neuropsychological weakness in inhibition (Toplak *et al.* 2009), interference control, set-shifting (Seidman *et al.* 2005; Martel *et al.* 2007), spatial span, spatial working memory, planning (Gau *et al.* 2009) and verbal working memory (Rogers *et al.* 2011), but contradictory reports also exist for working memory and inhibition (Barkley *et al.* 2001). None of these studies controlled for non-executive functioning involved in EF processes.

Very few studies have specifically evaluated EFs in adolescents who remitted from ADHD (Fischer *et al.* 2005). The improvement in ADHD symptoms during adolescence seems to correspond chronologically to the maturation of the prefrontal cortex and fronto-subcortical networks (Halperin & Schulz, 2006), which are thought to serve EFs (Fuster, 2002). Fischer *et al.* (2005) found inattention, disinhibition and slow reaction time no longer present in remitted ADHD, whereas Biederman *et al.* (2009) reported composite EF deficits independent of ADHD status. Given that EF impairments are associated with poor academic performance (Gropper & Tannock, 2009; Rogers *et al.* 2011) and social adjustment (Clark *et al.* 2002), and symptom remission is not equal to functional recovery (Biederman *et al.* 2000), study of whether remission from ADHD symptoms endorses the normalization of EFs is warranted.

In summary, to date, no study has investigated EFs and non-EFs of adolescents with ADHD and considered their inter-relationships as a function of different ADHD status simultaneously. Our study aimed to investigate various neuropsychological tasks with EF and relatively low-EF to determine the effects of non-EFs in the relationships between EFs and different ADHD status, and to clarify whether single or multiple neuropsychological dysfunctions (EFs and/or non-EFs) lead to ADHD symptoms. We used the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computerized neuropsychological test battery, to test various neuropsychological functions. All the CANTAB tasks are non-verbal and their reliability and validity have been established by previous studies (Luciana, 2003; Gau *et al.* 2009). Seven tasks were chosen and categorized as EF and low-EF tasks (details in the method section), mainly based on the study by Rhodes *et al.* (2005). According to previous studies, we hypothesized that (1) both EF and low-EF are associated with current ADHD, (2) EFs are impaired in persistent/subsyndromal ADHD independent of low-EF, and (3) no or mild neuropsychological deficit is present in remitted ADHD.

Method

Participants

This study included 435 adolescents with childhood diagnosis of ADHD aged 11–16 years (mean age 12.41 ± 1.62 years; male: 72.52%) and 263 typically developing (TD) adolescents (mean age 12.67 ± 1.64 years; male: 58.17%) without lifetime ADHD. The adolescents with ADHD were recruited from the Children's Mental Health Center, Department of Psychiatry, National Taiwan University, Taipei. They had been reported by their parents to have overt ADHD symptoms at a mean age of 4.30 ± 1.74 years and were all clinically diagnosed with ADHD according to DSM-IV diagnostic criteria by board-certified child psychiatrists, and had received out-patient treatments or follow-up in the same center for 3–5 years before the start of this study. Past and current diagnoses of ADHD and other psychiatric disorders were confirmed by interviewing the parents and participants using the Chinese version of the Schedule for Affective Disorders and Schizophrenia for

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School-Aged Children, Epidemiologic Version (K-SADS-E).

The TD adolescents were recruited from the same school districts as the adolescents with ADHD by the teachers and principals rather than from advertisements. They and their parents were interviewed using the K-SADS-E to ensure that they did not have any lifetime diagnosis of ADHD. Participants were excluded if they had a serious medical illness, a full-scale IQ<80, a history of bipolar disorders, psychosis, epilepsy, pervasive developmental disorders or learning disorders. A detailed description of the Chinese K-SADS-E, interviewer training and best estimate of psychiatric diagnoses has been described elsewhere (Gau & Chiang, 2009; Gau *et al.* 2010) and is available upon request.

Persistent, subsyndromal and remitted ADHD

We categorized adolescents with a childhood diagnosis of ADHD that met full DSM-IV diagnostic criteria into (1) adolescents with persistent ADHD if both the adolescents' and their parents' Chinese K-SADS-E interviews of their current symptoms led to the category 'definite', (2) adolescents with subsyndromal ADHD if they had more than three symptoms in either inattention or hyperactivity–impulsivity but did not meet the diagnostic criteria, and (3) adolescents with remitted ADHD if they had $\leqslant$ three symptoms in both inattention and hyperactivity–impulsivity (Biederman *et al.* 2010).

Measures

The CANTAB tests were performed on a personal computer equipped with a touch-sensitive screen and a response key and were administered by trained psychologists. The testing lasted for 90 min with a fixed schedule and order of tasks. Roughly based on the study of Rhodes *et al.* (2005), seven tasks from the CANTAB classified as EF and relatively low-EF tasks were used in this study; however, we defined Reaction Time (RT) and Rapid Visual Information Processing (RVIP) as low-EF tasks because we conceptualized reaction time and A′ in RVIP as components of arousal, as they may be thought of as primary cognitive processes in EFs (Nigg, 2005). Arousal includes the alerting, phasic responding to novel stimuli and signal/noise ratio in attention (Pribram & McGuinness, 1975); reaction time is more likely to be the index of alerting/phasic responding whereas A′ in RVIP is more likely to be the index of the signal/noise ratio of attention in arousal.

EF tasks

Spatial Working Memory (SWM). The SWM task is constructed based on a self-ordered search test (Petrides & Milner, 1982), an adaptation of Olton's radial arm maze (Olton, 1987). Participants are asked to search through the covered box presented on the screen to find the blue token hidden inside. Only one token is hidden in one of the boxes in each trial and the box that is found to have the token inside would not have a token inside again in subsequent trials. The participants have to memorize the boxes that have been opened in each trial and the boxes in which the tokens have been found in the previous trial. This task includes three levels of difficulty (4-, 6- and 8-box levels), and each level includes four tests. Two major indices were presented: (1) strategy utilization: the number of search sequences starting with a novel box in the difficult problems (both 6- and 8-box levels); and (2) between errors: total number of times the participant visits a box that is sure not to have a blue token (i.e. a token inside in a previous trial) in three different levels of difficulty (4-, 6- and 8-box levels).

Stockings of Cambridge (SOC). This task, which assesses spatial planning and is based on the Tower of London task (Shallice, 1982), requires participants to move colored balls to a goal stocking with given orders and locations. At the beginning of each trial, three suspended vertical stockings and three colored balls are presented on the screen. Participants are asked to move the colored balls, one in a single move at a time, between stockings to accomplish a goal position within a specified number of moves in the problem-solving condition, and they are then asked to copy each move by following the identical sequence of moves played back by the computer, based on their use of problem solving in the control condition. The SOC comprises four problem sets (two, three, four and five moves) to reflect increasing demands on planning. Two major indices were used in this study to examine thinking accuracy: (1) problems solved in a specified minimum number of moves; that is, the number of occasions that were successfully completed in the minimum possible number of moves; and (2) mean moves of the five-move task; that is, the number of moves taken in excess of the minimum moves (five) but within the maximum allowed.

Intra-/Extradimensional Set Shift (IED). This task assesses set-shifting by the ability to selectively maintain attention on a specific attribute of compound stimuli across different examples (intradimensional shift) and then to shift attention to a previously irrelevant attribute of stimuli (extradimensional shift) (Luciana & Nelson, 1998). Extradimensional errors were treated as the performance outcome; that is, the number of errors in the extradimensional stages.

Low-EF tasks

RT. This task assessed the alerting stage of arousal of the arousal/activation theory (Pribram & McGuinness, 1975; van der Meere *et al.* 1995) by the reaction time and movement time in response to a stimulus. The participants are asked to press a button on the table and touch the screen while seeing the stimulus presented in the simple circle on the screen. Reaction time (i.e. the time taken to release the button after the stimulus) and movement time (i.e. the time taken to touch the screen after releasing the button pad) were presented.

RVIP. This task, which measures sustained attention capacity, is a 4-min visual continuous performance test (CPT) modified and simplified from Wesnes & Warburton's task. Digits (ranging from 2 to 9) appear one at a time (100 digits/min) in random order. The participants are asked to press a response pad when they note any of three number sequences: 3–5–7, 2–4–6, 4–6–8. 'Total hits' represents the number of occasions upon which the target sequence is correctly responded to. 'Total false alarms' represents the number of times the participant responds outside the response window of a target sequence. Five indices were reported as follows: (1) the probability of hits (h): the total number of hits divided by the sum of total hits and total misses; (2) the probability of false alarms (f): the total number of false alarms divided by the sum of total false alarms and total correct rejections; (3) A′, calculated as $0.5+[(h-f)+(h-f)^2]/[4\,h(1-f)]$: a signal detection measure of sensitivity to the target, regardless of response tendency, which ranges from 0 to 1. A higher score indicates a higher target sensitivity (Sahgal, 1987); (4) B′, calculated as $[(h-h^2)-(f-f^2)]/[(h-h^2)+(f-f^2)]$: a signal detection measure of the strength of trace required to elicit a response, which ranges from −1 to +1. A lower score indicates a higher response tendency (Sahgal, 1987); and (5) mean latency: mean time taken to respond in correct responses.

Spatial Span (SSP). This task measures spatial short-term memory and is the visuospatial analog of the digit span test. Similar to the Corsi blocks task (Milner, 1971), it requires the ability to remember the order of visual stimuli presented. Nine white boxes are presented at fixed locations on the screen. The color of the boxes are changed one after the other in a predetermined sequence. The end of the sequence is indicated by a sound. The participants are asked to point to the boxes on the screen in the order presented previously by the computer. The task begins with a two-box level and then gradually increases up to a maximum nine-box level. There are three sequences at each level. If the participant fails in all three sequences in a particular level, the test terminates. Span length, the longest sequence successfully recalled, is presented. Some studies consider that spatial span is an effortful task and it might be unable to differentiate from spatial working memory, especially when more than four items are recalled (Miyake *et al.* 2001; Klingberg, 2006). However, on comparison with spatial working memory, an even higher EF task, we decided to include spatial span in the relatively low-EF category.

Delayed Matching to Sample (DMS). This task measures visual short-term memory in terms of the ability to remember the arrangements of shape and color of a complex stimulus that consists of four quadrants, with each quadrant being different from another in color and form. Each target stimulus is presented on a touch-sensitive screen for 4.5 s, and then four choice patterns appear under the target stimulus. The target stimulus disappears before the choice patterns show up, with three stimulus onset asynchronies: 0, 4 and 12 s. The number of total correct responses ('total corrects') of all delays is presented.

Procedure

This study was approved by the Research Ethics Committee of National Taiwan University Hospital prior to implementation. Written informed consent was obtained from both parents and children. Using the Chinese version of the K-SADS-E, the parents were interviewed to confirm the DSM-IV ADHD diagnosis in the past and no lifetime ADHD diagnosis for the TD adolescents, and then both participants and their parents were interviewed independently by separate well-trained interviewers for current (past 6 months) psychiatric diagnosis. The participants were then was assessed by the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) for IQ, followed by the CANTAB for neuropsychological functions. Those who took medication were asked to halt medication starting from the day before the assessment, that is at least 24–48 h before the tests.

Statistical analyses

Data analysis was conducted by using SAS version 9.1 (SAS Institute Inc., USA). Because some of the participants were from the same families, we used a linear mixed model to compare IQ and mean scores on neuropsychological performance, and a non-linear mixed model for psychiatric co-morbidity, parents' education and occupational classification and drug use.

Table 1. *Participant characteristics*

Variables	1. Persistent ADHD (*n*=300)	2. Subsyndromal ADHD (*n*=109)	3. Remitted ADHD (*n*=26)	4. TD adolescents (*n*=263)	*F*	Comparison
Current age (years), mean (S.D.)	12.13 (1.55)	12.44 (1.60)	12.69 (2.00)	12.67 (1.64)	5.58*	1<4
Gender, male[a], *n* (%)	248 (82.67)	82 (75.23)	21 (80.77)	153 (58.17)	13.89***	1, 2>4
Intelligence level, mean (S.D.)						
Full-scale IQ	102.96 (11.84)	104.55 (11.28)	105.65 (12.50)	108.09 (10.67)	9.95***	1, 2<4
Performance IQ	103.75 (14.72)	106.81 (13.89)	106.54 (13.52)	107.54 (12.72)	4.19*	1<4
Verbal IQ	102.47 (11.22)	102.64 (10.47)	104.69 (12.19)	107.83 (10.43)	12.79***	1, 2<4
Medication, *n* (%)						
Current[a,b]	175 (58.33)	44 (40.37)	8 (30.77)	–	7.68***	1>2, 3
Ever[a,b]	249 (83.00)	73 (66.97)	15 (57.69)	–	8.87***	1>2, 3
MPH duration (months), mean (S.D.)	20.15 (20.75)	18.40 (19.74)	20.15 (23.82)	–	0.07	
Any psychiatric co-morbidity[a], *n* (%)	209 (69.67)	71 (65.14)	12 (46.15)	89 (31.56)	26.75***	1, 2>4

ADHD, Attention deficit hyperactivity disorder; TD, typically developing; MPH, methylphenidate; S.D., standard deviation. There was no difference in maternal and paternal education and occupation.

[a] SAS proc Glimmix was used for comparison of categorical data.

[b] Comparison of medication was performed only for three ADHD groups.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Neuropsychological tasks were tested by univariate analysis, and then multiple regression analyses adjusted for age, sex, full-scale IQ and any psychiatric co-morbidity. We used the Bonferroni correction method to adjust for multiple comparisons in *post-hoc* analyses.

For the significant tasks in the multiple regression analysis (A′ and B′ in RVIP, simple reaction time in RT, span length in SSP, total corrects in DMS, between errors in SWM, mean moves in SOC and backward digit span), correlations of every two tasks were assessed, and we further tested the effect of spatial working memory, spatial planning and verbal working memory by covarying with other significant low-EF tasks in addition to age, sex, full-scale IQ and psychiatric co-morbidity. The significant level was preselected as $p<0.05$ for comparisons of demographic data, and $p<0.01$ for neuropsychological tasks due to multiple comparisons. The effect sizes (standard difference between two means) were computed using Cohen's d and the adjusted z score by adjustments for age, sex, full-scale IQ and any psychiatric co-morbidity (see Chen *et al.* 1997 for details).

Results

Sample characteristics

The persistent and subsyndromal ADHD groups were younger, had lower full-scale and verbal IQ, more males, and higher psychiatric co-morbidity than the TD adolescent group (Table 1). Adolescents with persistent ADHD were more likely to be currently treated, and to have been treated, with medication for ADHD than the other two ADHD groups (Table 1).

Neuropsychological dysfunctions in persistent, subsyndromal and remitted ADHD

EF tasks

Compared to the TD group, both the persistent and subsyndromal ADHD groups had fewer digits recalled backward, poorer strategy utilization and more between errors in SWM, fewer problems solved in the minimum number of moves (also persistent ADHD *versus* remitted ADHD) and higher mean number of moves in the five-move task (also *versus* remitted ADHD) in SOC, and more extradimensional errors in IED (persistent ADHD *versus* TD only) in univariate analyses (Table 2). Multiple analyses revealed that most of the significance remained except for no group difference in strategy utilization in SWM, problems solved in minimum moves in SOC, and extradimensional errors in IED (Table 2).

Low-EF tasks

In univariate analyses, compared to the TD group, only persistent ADHD had fewer digits recalled

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Table 2. *Comparisons of the neuropsychological functions among persistent, subsyndromal and remitted ADHD and typically developing (TD) adolescents*

Neuropsychological tasks	1. Persistent ADHD (n=300)	2. Subsyndromal ADHD (n=109)	3. Remitted ADHD (n=26)	4. TD adolescents (n=263)	Univariate analysis		Adjusted analysis[a]	
					F	Comparison	F	Comparison
Executive Function Tasks								
Digit Span								
Backward	5.41 (1.69)	5.15 (1.58)	5.96 (1.49)	6.14 (1.48)	14.65***	1, 2<4	6.45***	2<4
Spatial Working Memory (SWM)								
Strategy utilization	34.18 (4.75)	34.37 (4.70)	32.92 (5.04)	32.30 (4.84)	8.84***	1, 2>4	2.06	
Between errors	29.65 (17.36)	29.28 (17.69)	21.35 (11.32)	18.27(13.98)	27.39***	1, 2>4	10.78***	1, 2>4
Stockings of Cambridge (SOS)								
Problems solved in minimum moves	7.62 (2.08)	8.01 (1.83)	8.96 (1.64)	8.64 (1.89)	15.07***	1, 2<4; 1<3	2.05	
Mean moves (five moves)	7.12 (1.44)	7.26 (1.56)	6.03 (1.06)	6.44 (1.29)	17.42***	1, 2>3, 4	7.87***	1, 2>3, 4
Intra-/Extradimensional Set Shift (IED)								
Extradimensional errors	11.99 (10.90)	10.77 (10.27)	8.54 (9.76)	9.33 (9.54)	3.55***	1<4	0.41	
Low Executive Function Tasks								
Digit Span								
Forward	8.23 (0.99)	8.36 (0.90)	8.54 (0.72)	8.51 (0.82)	4.35**	1<4	1.87	
Reaction Time (RT)								
Simple movement time	439.63 (186.64)	438.48 (152.64)	427.51 (178.98)	473.89 (165.74)	2.65		2.23	
Simple reaction time	355.26 (104.76)	354.44 (104.63)	330.25 (47.62)	323.69 (68.46)	6.49***	1, 2>4	4.17**	1, 2>4
Rapid Visual Information Processing (RVIP)								
Probability of hit	0.50 (0.17)	0.50 (0.18)	0.58 (0.21)	0.58 (0.18)	11.49***	1, 2<4	3.58*	
Probability of false alarm	0.03 (0.07)	0.02 (0.06)	0.01 (0.03)	0.01 (0.02)	7.91***	1>4	2.12	
A′ (target sensitivity)	0.86 (0.06)	0.86 (0.05)	0.89 (0.05)	0.89 (0.05)	21.96***	1, 2<4; 1<3	6.56***	1, 2<4
B′ (response tendency)	0.83 (0.21)	0.88 (0.17)	0.92 (0.18)	0.92 (0.11)	15.24***	1<4	5.06**	1<4
Mean latency (ms)	510.86 (141.39)	495.70 (137.37)	469.60 (133.67)	452.00 (108.16)	10.14***	1, 2>4	4.00**	1>4
Spatial Span (SSP)								
Span length	6.69 (1.48)	6.62 (1.51)	6.69 (1.74)	7.38 (1.38)	13.58***	1, 2<4	6.34***	1, 2<4
Delayed Matching to Sample (DMS)								
Total corrects (all delay)	23.16 (3.73)	23.95 (3.74)	25.19 (2.80)	25.74 (2.93)	27.98***	1, 2<4; 1<3	8.58***	1, 2<4

ADHD, Attention deficit hyperactivity disorder.

[a] Controlling for sex, age, full-scale IQ and psychiatric co-morbidity.

Values given as mean (standard deviation).

$p<0.01$ was preselected as the significance level due to multiple comparisons. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

forward, a higher probability of false alarm and a higher response tendency (B′) in RVIP; both persistent and subsyndromal ADHD had longer reaction time, lower probability of hit, lower target sensitivity (A′) (also persistent ADHD *versus* remitted ADHD) and longer mean latency in RVIP, fewer spatial span and fewer total corrects in DMS (also persistent ADHD *versus* remitted ADHD) (Table 2). In multiple analyses, the group differences remained significant for reaction time, target sensitivity (A′) and response tendency (B′) in RVIP, spatial span and total corrects in DMS (Table 2).

Effect of medication on neuropsychological functions

Current medication use was associated with significantly worse performance in response tendency ($F=7.10$, $p=0.01$) in RVIP and between errors in SWM ($F=8.35$, $p=0.006$). After controlling for age, sex, full-scale IQ and any psychiatric co-morbidity, no significant correlation was noted between current medication use and neuropsychological performance.

Effect size

Compared to Cohen's *d*, the magnitude of the adjusted *z* score (adjustment of age, sex, full-scale IQ and any psychiatric co-morbidity) of the three ADHD groups *versus* the TD group decreased in various EF and low-EF tasks (Table 3), suggesting that the effect could be partly explained by full-scale IQ and age. Most of the tasks had medium effect sizes ($d=0.5–0.8$), with the largest effect sizes being seen in SWM and DMS.

Correlations among neuropsychological tasks and independent contribution of EFs to ADHD

Table 4 presents significant moderate correlations between target sensitivity (A′) and other neuropsychological functions, between any two visuospatial tasks and between any two EF tasks. Spatial working memory and spatial planning were significantly impaired in both persistent and subsyndromal ADHD independent of sex, age, full-scale IQ, psychiatric co-morbidity and low-EF tasks (Table 4).

Discussion

As one of the first studies to examine both EF and low-EF in a large-scale sample of adolescents with persistent, subsyndromal and remitted ADHD with well-characterized psychiatric and neuropsychological phenotype assessments, we found that only adolescents with persistent ADHD had poorer verbal working memory and higher proneness to response (B′ in RVIP). We also found that adolescents with persistent and subsyndromal ADHD had lower alerting (simple reaction time) (van der Meere *et al.* 1995) and target sensitivity (A′ in RVIP) of arousal, and poorer spatial short-term memory (SSP), visual recognition memory (total correct in DMS), spatial working memory (between errors in SWM) and spatial planning (mean moves in SOC) than TD adolescents, and EFs, including spatial working memory and spatial planning, remained impaired after controlling for low-EF tasks. The differences in verbal short-term memory, response inhibition (probability of false alarm in RVIP), strategy utilization in SWM, problems solved in minimal moves in SOC and set-shifting between ADHD and TD could be explained by the intelligence level. Adolescents with remitted ADHD had superior spatial planning than those of persistent/subsyndromal ADHD. This study, similar to others (Fischer *et al.* 1990; Seidman *et al.* 1997, 2005; Martel *et al.* 2007; Gau *et al.* 2009), showed that adolescents with persistent ADHD had broad neuropsychological deficits compared to TD adolescents independent of age, sex, full-scale IQ and psychiatric co-morbidity. In general, adolescents with subsyndromal ADHD had impairments comparable with those with persistent ADHD in neuropsychological performance. No neuropsychological impairment was found in adolescents with remitted ADHD. Our findings suggest that improvement in ADHD symptoms to a nonclinical (subsyndromal) level does not endorse the normalization of neuropsychological functions. Subclinical symptoms, especially inattention, might still correlate with executive dysfunctions (Martel *et al.* 2007; Gau & Chiang, 2013).

We did not find impaired target sensitivity (or signal detectability) impairment in remitted ADHD, as reported by Halperin *et al.* (2008), but we did find better spatial planning in remitted than in persistent and subsyndromal ADHD (Halperin & Schulz, 2006). Because of lack of baseline data for neuropsychological functions, we are unable to determine whether better spatial planning at childhood predicts remission, or whether remission follows improvement in spatial planning. More longitudinal studies with broad neuropsychological and neuroimaging assessments are needed to clarify the course of ADHD regarding developmental changes in symptoms and neurocognitive functions. It is possible that persistent planning problems at this developmental stage might contribute to persistent ADHD symptoms. This finding echoes the report that EF problems, reflecting difficulty in prioritizing work and problems in planning ahead, are more specific and persistent in adults with ADHD (Kessler *et al.* 2010).

Our finding that spatial working memory had larger adjusted *z* scores than verbal working memory

Table 3. *Effects of the neuropsychological functions of persistent, subsyndromal and remitted ADHD compared to typically developing (TD) adolescents*

Neuropsychological tasks	Cohen's *d*			Adjusted *z* score		
	Persistent ADHD *v.* TD adolescents	Subsyndromal ADHD *v.* TD adolescents	Remitted ADHD *v.* TD adolescents	Persistent ADHD *v.* TD adolescents	Subsyndromal ADHD *v.* TD adolescents	Remitted ADHD *v.* TD adolescents
Executive Function Tasks						
Digit Span						
Backward	−0.46***	−0.66***	−0.13	−0.26	−0.54***	0.03
Spatial Working Memory (SWM)						
Strategy utilization	0.39***	0.43**	0.13	0.11	0.26	0.02
Between errors	0.71***	0.73***	0.22	0.53***	0.66***	0.12
Stockings of Cambridge (SOS)						
Problems solved in minimum moves	−0.51***	−0.34*	0.17	−0.24	−0.16	0.29
Mean moves (five moves)	0.49***	0.59***	−0.33	0.23**	0.44***	−0.43
Intra-/Extradimensional Set Shift (IED)						
Extradimensional errors	0.26	0.15	−0.08	0.05	0.01	−0.16
Low Executive Function Tasks						
Digit Span						
Forward	−0.31**	−0.18	0.04	−0.18	−0.09	0.13
Reaction Time (RT)						
Simple movement time	−0.19	−0.22	−0.28	−0.29	−0.28	−0.34
Simple reaction time	0.35***	0.38**	0.10	0.41**	0.43**	0.10
Rapid Visual Information Processing (RVIP)						
Probability of hit	−0.45***	−0.45***	−0.01	−0.21	−0.38**	0.02
Probability of false alarm	0.41***	0.31	0.13	0.56 [a]	−0.33 [a]	−0.30[a]
A′ (target sensitivity)	−0.63***	−0.55***	−0.01	−0.46**	−0.47**	0.03
B′ (response tendency)	−0.53***	−0.35	−0.06	−0.68**	−0.32	−0.01
Mean latency (ms)	0.46***	0.37*	0.16	0.48**	0.39	0.19
Spatial Span (SSP)						
Span length	−0.50***	−0.58***	−0.46	−0.31**	−0.45**	−0.50
Delayed Matching to Sample (DMS)						
Total correct (all delays)	−0.78***	−0.56***	−0.18	−0.61***	−0.45**	−0.10

ADHD, Attention deficit hyperactivity disorder.

[a] As the scores of the probability of false alarms in RVIP in all three groups were close to the lower limit of zero, a natural log transformation was used while calculating the adjusted *z* score (Watkins *et al.* 2000).

$p<0.01$ was preselected as the significance level due to multiple comparisons. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, based on univariate analysis for Cohen's *d* and multiple analysis for adjusted *z* scores for each comparison.

Table 4. *Correlation matrix and group comparison of neuropsychological functions*

	Correlation coefficient (*r*)							Group difference[a]	
	I	II	III	IV	V	VI	VII	*F*	Comparison[b]
I. Signal detectability (RVIP A′ target sensitivity)									
II. Response tendency (RVIP B′)	0.47***								
III. Alerting (simple reaction time)	−0.26***	−0.23***							
IV. Spatial span (span length)	0.40***	0.21***	−0.16***						
V. Visual short-term memory (DMS total corrects)	0.48***	0.37***	−0.22***	0.34***					
VI. Spatial working memory (between errors)	−0.46***	−0.28***	0.20***	−0.44***	−0.46***			3.93*	1, 2>4
VII. Spatial planning (SOC mean moves, five moves)	−0.30***	−0.20***	0.09*	−0.22***	−0.31***	0.38***		5.23**	1, 2>3; 2>4
VIII. Verbal sustained attention (digit span, backward)	0.44***	0.23***	−0.08*	0.32***	0.35***	−0.31***	−0.17***	3.29*	2<4

RVIP, Rapid Visual Information Processing; DMS, Delayed Matching to Sample; SOC, Stockings of Cambridge.
[a] Group difference was only calculated in high executive demand tasks by adjusting neuropsychological tasks with relatively low executive demand (I–V), sex, age, full-scale IQ and any psychiatric co-morbidity.
[b] Group comparison: 1. Persistent ADHD, 2. Subsyndromal ADHD, 3. Remitted ADHD, 4. Typically developing adolescents.
For correlation matrix, $p<0.01$ was preselected as the significance level due to multiple comparisons and for group comparison, $p<0.05$ was preselected. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

between adolescents with ADHD and the TD controls is consistent with the conclusion drawn in a previous meta-analysis (Martinussen *et al.* 2005). As suggested by Martinussen *et al.* (2005), it is possible that the verbal tasks were not as difficult as the visual tasks. In addition to deficits in working memory, the significant deficits in visual recognition memory and spatial span in the persistent and subsyndromal ADHD groups also suggest problems with visual/spatial memory in ADHD (Shang & Gau, 2011).

Several studies have found that adolescents with a childhood ADHD diagnosis have a lower IQ than TD adolescents (Frazier *et al.* 2004; Martel *et al.* 2007; Biederman *et al.* 2009). Despite the continuing dispute about IQ (Nigg, 2005; Seidman *et al.* 2005), we put IQ into the analyses to see how much the differences in these tasks would be removed by their covariance with IQ in ADHD (Miller & Chapman, 2001). Persistent and/or subsyndromal ADHD showed deficits in both EF and low-EF tasks except for set-shifting after controlling for full-scale IQ. Our study supports the findings summarized in a meta-analysis and presented in three other studies that the association between ADHD and set-shifting deficits measured by the Wisconsin Card Sorting Test (WCST; Willcutt *et al.* 2005*a*, *b*), CANTAB (Gau *et al.* 2009) and the Trail Making Test, part B (Martel *et al.* 2007) can be explained by intelligence level. Thus, set-shifting may not be a prominent and consistent neuropsychological deficit in ADHD, as shown in autism (Sergeant *et al.* 2002).

In addition to confounding effects from IQ, there is an unresolved debate with regard to whether EF impairments do in fact contribute to ADHD symptoms. After controlling for non-EF tasks and IQ, Scheres *et al.* (2004) found EF to be no longer impaired in boys with ADHD. In addition, spatial short-term memory rather than central executive processing was reported to be the major component in the relationship between inattention and visuospatial working memory (Tillman *et al.* 2011). However, in the trial to determine the correlation between EF and ADHD, we found that spatial working memory and spatial planning remained significantly impaired in the persistent and subsyndromal ADHD groups after controlling for full-scale IQ and low-EF tasks. Furthermore, the effect sizes (adjusted *z* scores) of EF and low-EF tasks are roughly comparable. Thus, our findings are in line with the hypothesis of broad and independent contributions of target sensitivity, alerting, verbal working memory, spatial span, visual short-term memory, spatial working memory and spatial planning to ADHD (Rhodes *et al.* 2005; Wahlstedt *et al.* 2009).

The use of methylphenidate (MPH) was positively associated with the persistence of ADHD in this naturalistic sample but the duration of MPH use was equivalent between the persistent and subsyndromal ADHD groups. Neuropsychological performance, including spatial working memory and response tendency, was worse in the subgroup using medication. If this was not caused by the withdrawal effect of stimulants, it would mean that, in clinical practice, those with severe symptoms or more functional impairments would tend to receive and continue medication (Epstein *et al.* 2006). However, the pharmacological effect of MPH on core neuropsychological processes is still speculative and reports of chronic effects of MPH are inconclusive (Coghill *et al.* 2007). Hence, an investigation into the chronic effects of MPH on neuropsychological function in this population is warranted.

Some methodological limitations in our study should be noted. First, we only conducted one assessment in the follow-up sample. Thus, the trajectory of neuropsychological development of ADHD could not be demonstrated and we were not able to test the correlation of symptom improvement and cognitive improvement with age. Second, the classification of EF and low-EF tasks may be arbitrary although a similar concept has been mentioned in previous studies (Nigg, 2005; Rhodes *et al.* 2005). We tried to explore the latent factors behind these tasks but could only extract one common factor. This is not surprising because the items in the neuropsychological tasks we chose to present here are already very concise, that is, we used only one item to represent a conceptualized neuropsychological function in the final model. In addition, because there are significant diversities in the broad concept of EF and non-EF abilities (Miyake *et al.* 2000), we may be not able to cluster EF and non-EF tasks to one common EF or non-EF factor. Furthermore, limitations of the measures meant that we were unable to match the non-EF tasks to the EF tasks directly, which impedes theory validation. Third, our sample comprised only clinic-based Taiwanese participants, so that generalization of our results to a community sample would be limited. Fourth, we did not include medication in the multiple analysis. Although we asked the participants to withhold their medication for at least 24–48 h to minimize any acute effects of medication, we could not completely rule out an effect of medication. However, withdrawal effects cannot be ruled out, either. Fifth, males were predominant in our ADHD sample, and thus the result may mainly represent the condition in boys. Nevertheless, previous studies have shown that girls have similar neuropsychological impairments to boys (Seidman *et al.* 2005), and the influence of gender proportion should not constitute a major difference. Finally, the small sample size of the remitted ADHD group might diminish the statistical power, although the raw data indicated that the neuropsychological performance between remitted ADHD and controls is similar.

In conclusion, our findings suggest that, despite a decline in symptoms, adolescents with subsyndromal ADHD still have significant impairments in multiple neuropsychological functions with high and low executive demands, but no impairment is found in remitted ADHD. The EF deficits of ADHD are independent of the low-EF tasks examined here. Superior planning ability of remitted ADHD over persistent/subsyndromal ADHD suggests the possibility of a treatment effect of cognitive training (Halperin & Healey, 2011) or a possible predictor of remission. This warrants a longitudinal investigation to further clarify the correlation between the trajectories of behavioral symptoms and the changes in brain function as assessed by neuropsychological functions and structural and functional brain imaging studies.

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Declaration of Interest

None.

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