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Developmental changes of neuropsychological functioning in individuals with and without childhood ADHD from early adolescence to young adulthood: a 7-year follow-up study

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Abstract

Background. Our knowledge about the developmental change of neuropsychological functioning in attention-deficit/hyperactivity disorder (ADHD) is limited. This prospective longitudinal study examined the changes in neuropsychological functions and their associations with the changes of ADHD symptoms across the developmental stages from early adolescence to young adulthood.

Methods. We followed up 53 individuals diagnosed with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) ADHD during childhood (mean age 12.77 years at time 1, 19.81 years at time 2) and 50 non-ADHD controls (mean age 12.80 years at time 1, 19.36 years at time 2) with repeated psychiatric interviews at two time points to confirm ADHD and other psychiatric diagnoses. Neuropsychological functions with high- and low-executive demands, measured by the Cambridge Neuropsychological Testing Automated Battery (CANTAB) at two time points, were compared.

Results. Both groups showed improvements in all neuropsychological tasks except reaction time in the ADHD group. Despite having a greater improvement in spatial working memory (SWM) than controls, individuals with ADHD still performed worse in various neuropsychological tasks than controls at follow-up. Better baseline intra-dimension/extra-dimension shift and parental occupation predicted fewer ADHD symptoms at follow-up independent of baseline ADHD symptoms. The degree of ADHD symptom reduction was not significantly linearly correlated to the magnitude of neuropsychological function improvement.

Conclusion. Individuals with ADHD and controls had parallel developments in neuropsychological functioning, except a catch-up in SWM in ADHD. Almost all neuropsychological functions herein were still impaired in ADHD at late adolescence/young adulthood. There may be a threshold (i.e. non-linear) relationship between neuropsychological functioning and ADHD symptoms.

Introduction

Symptoms of childhood-onset attention-deficit/hyperactivity disorder (ADHD) often decline with age, particularly hyperactivity symptoms (Faraone *et al.*, 2006; Gau *et al.*, 2010*a*). However, 30–80% of children with ADHD continue to suffer from the ADHD-related impairments as they enter late adolescence and adulthood (van Lieshout *et al.*, 2016). The age-dependent development of ADHD symptoms is not a universal process; instead, it is highly variable between individuals (Lahey *et al.*, 2016). Differential developmental courses of ADHD symptoms bring different impacts on several life domains (Sasser *et al.*, 2016).

Many efforts have been made to investigate the influence of genetic risk, brain structure and activities, neurocognitive functioning, behavioral and environmental factors on the developmental course of ADHD (van Lieshout *et al.*, 2013). For behavioral and environmental factors, higher childhood symptoms of ADHD, greater functional impairment, a higher level of aggressiveness or more oppositional/conduct problems during preschooler age (Lahey *et al.*, 2016), lower socioeconomic status (Cheung *et al.*, 2015; Lahey *et al.*, 2016), more psychiatric comorbidity and maternal psychopathology (Biederman *et al.*, 2011) were found to predict the persistence of ADHD diagnosis or symptoms at follow-up. To date, the link between these behavioral/environmental predictors and the developmental course of ADHD remains unclear (van Lieshout *et al.*, 2013).

Longitudinal structural neuroimaging studies suggested that ADHD might be a problem of maturational lag (Shaw *et al.*, 2007) with a delay for 3–5 years for different brain regions, and the developmental trajectories of brain volumes between individuals with ADHD and controls

were roughly parallel (Castellanos and Tannock, 2002). It was suggested that the 'normalization' of some brain regions, e.g. the right parietal cortex (Shaw *et al.*, 2006), or 'compensatory maturation' of some brain regions, e.g. prefrontal, cerebellar, and thalamic circuitry (Proal *et al.*, 2011), might compensate for neurocognitive deficits in individuals with ADHD who showed more behavioral improvements and had better outcomes. The role of neuropsychological functioning in the association between brain functions and ADHD symptoms is still inconclusive (Coghill *et al.*, 2014*a*).

Some neuropsychological functions are consistently found to be impaired in individuals with ADHD across the lifespan (Seidman, 2006) and their unaffected relatives (Gau and Huang, 2014; Lin *et al.*, 2015). Neuropsychological functioning is therefore suggested as an endophenotype and a useful proxy to understand ADHD (Castellanos and Tannock, 2002). For example, Sahakian and coworkers have suggested that deficits in sustained attention are a core cognitive feature and an endophenotype in ADHD (del Campo *et al.*, 2013; Pironti *et al.*, 2014). Based on the observation that the development of the prefrontal cortex roughly paralleled the decline of ADHD symptoms, Halperin and Schulz (2006) hypothesized that with age, executive functions subserved by the prefrontal cortex and the interconnected brain regions might compensate for the core non-executive deficits of ADHD and result in improvements of ADHD symptoms. In support, Halperin *et al.* (2008) reported that adults with persistent ADHD had both executive and non-executive deficits, while adults with remitted ADHD had only non-executive deficits in a cross-sectional study. Against the hypothesis of Halperin *et al.* (2008), Cheung *et al.* (2016) suggested that preparation-vigilance but not working memory was the marker of remission. However, these two studies lacked the developmental longitudinal study design; hence, it is possible that the ADHD non-persisters may have better neuropsychological functioning than persisters at the baseline. Longitudinal data of neuropsychological functions and ADHD symptoms are needed to elucidate the role of neuropsychological functions in the developmental change of ADHD symptoms.

Only a few studies have examined the relationships between developmental changes in ADHD symptoms and the neuropsychological functioning. Two studies showed no linear associations between changes in ADHD symptoms and some specific executive functions, including sustained attention (Vaughn *et al.*, 2011), spatial planning, spatial working memory (SWM), and set shifting (Coghill *et al.*, 2014*a*). Another two studies demonstrated a linear association between changes in ADHD symptoms and changes in overall neuropsychological functioning in children during early childhood (Rajendran *et al.*, 2013) and in girls from childhood to young adulthood (Miller *et al.*, 2013). The mixed results call for more data covering broader domains of various neuropsychological functions in a longitudinal design.

There is no consistent evidence that any specific neuropsychological domain might predict the developmental trajectories of ADHD symptoms (van Lieshout *et al.*, 2013). Some follow-up studies from childhood to adolescence or young adulthood found that better baseline set-shifting (Coghill *et al.*, 2014*a*) and global executive functions (Miller and Hinshaw, 2010) predicted a greater reduction of clinical ADHD symptoms; others reported reaction time variability (Sjowall *et al.*, 2017) and SWM (van Lieshout *et al.*, 2017) predicted later ADHD symptom severity after adjusting for baseline ADHD symptoms. Few studies examined the predicting effects of neuropsychological functioning and other demographic factors on the ADHD outcome within the same study. Cheung *et al.* (2015) found that baseline ADHD symptoms, socioeconomic status, and IQ were the predictors of ADHD symptoms in late adolescence. In their study, cognitive functions did not play a significant role in predicting ADHD outcome. Another study reported that neither baseline socioeconomic status nor baseline neuropsychological functions anticipated the change of ADHD symptoms (Rajendran *et al.*, 2013), despite their high correlation with baseline ADHD symptoms.

Due to the limited and inconsistent results about the developmental changes of neuropsychological functions and their relationship with ADHD symptom changes, the current study had three specific aims. First, this study investigated whether the development of neuropsychological functioning of adolescents with ADHD was different from those without ADHD and to explore whether neuropsychological functions showed the pattern of persistent impairment, maturational lag, deterioration, or catch-up in adolescents with ADHD. Second, we investigated the associations between the changes in ADHD symptoms and the changes in various neuropsychological functions with high- and low-executive demands from early adolescence to young adulthood. Third, we explored the neuropsychological functions and demographic characteristics at baseline (early adolescence) predicting the ADHD symptoms at follow-up (late adolescence/early adulthood) independent of baseline ADHD symptoms in the ADHD group. We expected that baseline neuropsychological functions and parental education and/or occupation would predict the severity of ADHD symptoms at follow-up.

Methods

Participants and procedure

We reassessed the neuropsychological functioning of part of participants of our previous study (Gau *et al.*, 2009), which conducted around 5–10 years (mean ± standard deviation 85.17 ± 22.97 months) (time 1) before the current study (time 2). At time 1, 95 participants with ADHD, 107 controls, and their parents agreed to attend the future re-assessment and signed the informed consent. Among them, we successfully recruited 56 subjects with ADHD and 50 controls for the re-assessment within the research time frame at time 2. The reasons that participants with ADHD and controls did not complete the second assessments were because they were either out of Taipei or they had busy school or work schedules in 2014–2015 during the study period. Three participants with ADHD who did not complete all measurements were excluded. Finally, a total of 53 (55.8%) participants with a clinical diagnosis of ADHD according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnostic criteria and 50 typically developing controls (42.7%) without a lifetime diagnosis of ADHD entered and completed the current follow-up study.

At time 1, adolescents with ADHD, aged 10–16 years, were recruited from an outpatient clinic in the National Taiwan University Hospital, Taipei, Taiwan. The typically developing community controls of the same age range were recruited from the schools at the similar school districts as the ADHD group with the help of school principals and teachers. All the participants first received a formal psychiatric diagnostic interview by the corresponding author. Thereafter, they and their parents received interviews of the Chinese version of Kiddie–Schedule

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Affective Disorders and Schizophrenia – Epidemiological Version (K-SADS-E) (Gau *et al.*, 2005; Gau *et al.*, 2010*b*) by trained interviewers to confirm their ADHD status and other psychiatric disorders based on the DSM-IV symptom and impairment criteria at time 1 and time 2. The symptoms of ADHD were collected from the comprehensive assessment of the participant's interviews at the two time points by ADHD supplement of the K-SADS-E. Participants who took medication were asked to report the symptoms when the effect of medication had worn off. The interviewers at time 2 were blind to the diagnosis of the participants at time 1. The details of the interviewer training are described in the supplementary material and elsewhere (Gau *et al.*, 2010*a*; Lin *et al.*, 2016).

The participants received intelligence assessment by using the Wechsler Intelligence Scales for Children-Third Edition (WISC-III) at time 1 and neuropsychological tests by the Cambridge Neuropsychological Testing Automated Battery (CANTAB) (www.cambridgecognition.com) (Sahakian and Owen, 1992) at both time 1 and time 2. Participants were asked to hold medication for ADHD at least 48 h before the CANTAB assessment. Participants were excluded if they had any systemic medical illness such as cardiovascular disease, learning disability, autism spectrum disorder, or full-scale intelligence quotient (FIQ) <80 at time 1. The Research Ethics Committee of the National Taiwan University Hospital, Taiwan (IRB ID, 2010003087R; ClinicalTrials.gov number, NCT01247610) approved this study before its implementation.

Comparison of study variables of participants followed and not followed

There was no significant difference between participants who were successfully followed and not followed in sex, age, ADHD symptoms, IQ, medication history, psychopathology, neuropsychological functions, parental age, and education at time 1 in either the ADHD group or the control group with the following exceptions. Participants with ADHD followed in this study were less likely to use medication and more likely to have any psychiatric comorbidity than those not followed (online Supplementary Table S1). Compared to controls not followed, controls followed in this study had worse performance in spatial planning [Stocking of Cambridge (SOC)] (online Supplementary Table S2). Therefore, the difference of the neuropsychological functioning between individuals with ADHD and controls at time 1 in this study might not be as significant as the original sample.

Neuropsychological assessment

CANTAB. Six tasks of the CANTAB were selected and described in Table 1.

Statistical analysis

We used SAS 9.3 to conduct the data analyses (SAS Institute Inc., Cary, NC, USA). The cross-sectional comparison of basic data and neuropsychological functions of the ADHD and control groups at time 1 and time 2 were performed by analysis of variance for continuous variables and χ^2/Fisher's exact test for categorical variables. The effect sizes (the standard difference between two means) were computed using Cohen's *d* (Cohen, 1988).

For longitudinal data, we performed paired *t* test to compare symptom changes between time 1 and time 2 at each group and repeated-measures linear mixed model to evaluate the group × time interactions (time as a within-subject factor and group as a between-subject factor). We tested whether time 1 neuropsychological functions could predict time 2 ADHD symptoms in the correlation matrix controlling the effects of age, sex, time 1 ADHD symptoms, and duration of follow-up. Besides, we tested whether changes in neuropsychological functions could predict changes in ADHD symptoms in the linear regression model adjusting for age, sex, and duration of follow-up. The influences of FIQ and the presence of any psychiatric condition on the models were tested by adding these two covariates separately in the majority of statistical models.

We further identified predictors for time 2 neuropsychological functions using the following procedures. Time 1 neuropsychological functions which showed significant or marginal associations (raw *p* values <0.05) with time 2 ADHD symptoms, as well as time 1 symptoms, FIQ, any current psychiatric comorbid condition, pariticipant's and parental educational level (i.e. junior high school or below, senior high school, college or above), parental occupation (professional, technical, others), time 2 age, sex, duration of ADHD medication treatment, and duration of follow-up (in months) between two time points were included into the stepwise linear regression model to identify the variables significantly predicting time 2 ADHD symptoms. Duration of follow-up and time 2 age were included in the statistical models because we assumed that they might influence time 2 ADHD symptom severity (van Lieshout *et al.*, 2017). FIQ, parental educational level, and occupation were controlled in the model because these variables were related to later ADHD outcome (Cheung *et al.*, 2015; Lahey *et al.*, 2016). We used the significance level of 0.05 as a criterion for variables to enter the model and used adjusted R^2 as the model selection criterion.

We addressed the multiple comparison problems by using the Benjamini–Hochberg procedure (Benjamini and Hochberg, 1995), which was performed by using the SAS software. We presented the adjusted *p* value adjusting for the false discovery rate (maximum false discovery = 0.05) and set the significance level of adjusted *p* value as 0.05. For the models with results of extremely small *p* value, i.e. $p < 0.0001$, in almost all the tests, we did not present the adjusted *p* value because the probability of true null hypotheses among these rejected results is very low (Glickman *et al.*, 2014).

Results

Basic data

The clinical data of the participants are presented in Table 2. There was no significant group difference in sex, age, duration of follow-up, and educational levels. The symptoms of inattention and hyperactivity/impulsivity and psychiatric comorbidities were significantly higher, and IQ was significantly lower in the ADHD group than the control group at baseline. Of 53 participants with ADHD, 47 (88.68%) were ever treated with methylphenidate, and 21 and two currently used methylphenidate and atomoxetine at time 2, respectively. There was no group difference in parental ages, educational levels, and occupations.

Changes in ADHD symptoms

There was a significant decrease in inattention and hyperactivity/impulsivity symptoms in the ADHD group with a larger effect

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Table 1. Neuropsychological tasks and the corresponding functions

Neuropsychological tasks	Functions measured	Descriptions
Low EF demand		
Reaction time		
Simple reaction time Five-choice reaction time	Alertness	This task assesses alerting stage of arousal (including stages of alerting, phasic responding, and signal/noise ratio enhancing) in arousal/activation theory (Pribram and McGuinness, 1975), by recording the reaction time in response to a stimulus with minimal influence by the movement speed. The participants are asked to press a button on the table and touch the screen while seeing the stimulus presented in the simple circle (simple-choice) or one of five circles (five-choice) on the screen. The task lasts for 3 min. Reaction time (i.e. the mean of time taken to release the button after the presence of the stimulus) of the simple-choice and five-choice tasks was presented.
Rapid visual information processing (RVP)		
Probability of hit	Sustained attention	This task, a 7 min visual continuous performance test (CPT) modified, is used to measure sustained attention capacity. Digits (ranging from 2 to 9) appear one at a time (100 digits per minute) in a random order. The participants are asked to press a response pad when they noted any of three number sequences: 3–5–7, 2–4–6, 4–6–8. Three indices were reported: (1) probability of hits (h): total hits divided by the sum of total hits and total misses; (2) A': sensitivity to the target, regardless of response tendency, which ranges from 0 to 1, calculated as $A' = 0.5 + [(h-f) + (h-f)2]/[4 \times h \times (1-f)]$, and higher score indicating higher sensitivity of signal/noise discrimination of arousal (f: probability of false alarm, i.e. total false alarms divided by the sum of total false alarms and total correct rejections).
A'	Signal detectability (signal/noise discrimination)	
Spatial span		
Span length	Spatial short-term memory	This task is the visuospatial analog of the digit span test and lasts for 5 min. Similar to the Corsi blocks task, it requires the ability to remember the order of visual stimuli presented. There are nine white boxes presented in 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 as previously presented on the screen. The task begins with a level of two-box then gradually up to a level of nine-box. If the participant fails in all the three sequences in a particular level, the test terminates. One index was presented: (1) span length, the longest sequence successfully recalled.
High EF demand		
Spatial working memory (SWM)		
Strategy utilization	Strategy usage	It takes 4 min to complete the task. Participants are asked to search through the covered box presented on the screen to find the blue token hidden inside. Only one single token is hidden in one of the boxes in each trial and the box that had been found to have the token inside would not have a token again in the subsequent trials. The SWM includes three difficulty levels (four-, six-, and eight-box), each included four tests. Two indices were presented: (1) strategy utilization: the number of search sequences starting with a novel box in both six- and eight-box; (2) Between errors: total times the participant opens a box without a blue token because of ever having a token inside in previous trial across three difficulty levels.
Between errors	Spatial working memory	
Intra-dimension/extra-dimension shift (IED)		
Completed stages Extra-dimensional shift errors	Set shifting	This task assesses set-shifting, the ability to learn new problem, and shift to a new strategy from the feedback. It takes 7 min to complete the task. There are two artificial dimensions: white line and color-filled shapes. Simple followed by compound (combination of line and shape) stimuli are presented and the participant has to select which stimulus is right by the feedback. When the participant reaches the criterion (six consecutive correct responses) at a given stage, the task progresses to the next stage and the stimuli/rules change. If the participant fails to reach 50 trials at any stage, the test terminates. There are nine stages. During stages 1–7, the participant has to selectively maintain attention on the rule based on the color-shape dimension, i.e. intra-dimensional shift, and then at stages 8 and 9, the participant has to shift attention to the rule based on the white line dimension, i.e. extra-dimensional shift (Luciana and Nelson, 1998). Two indices were presented: (1) completed stage: the number of stages that were completed; (2) extra-dimensional shift errors: the number of errors in the extra-dimensional stages.

(*Continued*)

Table 1. (*Continued.*)

Neuropsychological tasks	Functions measured	Descriptions
Stocking of Cambridge (SOC)		
Problems solved in minimum moves Mean move, five-move problems	Spatial planning	This task assesses spatial planning based on the Tower of London and takes 10 min. 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 then they are asked to copy each move by following the identical sequence of moves played back by the computer, based on their employment of problem solving in the control condition. The SOC comprises of four problem sets (two, three, four, and five moves) to reflect increasing demands on planning. Two major indices were presented to tap the thinking accuracy: (1) problems solved in minimum moves: the number of occasions which were successfully completed in the minimum possible number of moves; (2) mean moves of the five-move task: the mean of the number of moves taken in excess of minimum moves (five moves) but within the maximum allowed.

EF = executive function.

size in the decrease of hyperactivity/impulsivity symptoms (paired $t = -5.49$, $p < 0.001$, $d = -1.01$) than that of inattention symptoms (paired $t = -3.33$, $p = 0.002$, $d = -0.47$). On the other hand, we found a significant increase in inattention symptoms in the control group (paired $t = 2.33$, $p = 0.023$, $d = 0.33$).

Comparison and changes of neuropsychological functions

Cognitive alertness (reaction time)

Longer reaction time in the simple task (Fig. 1*a*) and five-choice task (Fig. 1*b*) in ADHD participants than controls was noted only at time 2 but not at time 1. Both groups showed no significant change overtime in the simple task (Fig. 1*a*). For the five-choice task, there was a significant decrease in reaction time in the control group but not the ADHD group (Table 3). The repeated-measures linear mixed model showed no group difference in the magnitude of the slope of reaction time changes (group × time interaction) (Fig. 1*a*, *b*, more details of statistics in online Supplementary Table S3).

Sustained attention (rapid visual information processing)

Participants with ADHD had a lower probability of hit and A' (signal detectability) at both two time points than controls (Fig. 1*c*, *d*). Both the ADHD and control groups had significant improvements in these two indices from time 1 to time 2 (Table 3). The repeated-measures linear mixed model showed a significant main effect of time and group (only in A', $p < 0.05$) without significant group difference in the slope of changes in the two rapid visual information processing indices (Fig. 1*c*, *d*, online Supplementary Table S3).

Short-term spatial memory (spatial span)

Participants with ADHD had a significantly shorter spatial span length at both time points than controls (Fig. 1*e*). Both the ADHD and control groups showed a significant increase of spatial span lengths from time 1 to time 2. There was no group difference in the slope of changes of spatial span length (Fig. 1*e*, online Supplementary Table S3).

Spatial working memory

Compared to the control group, the ADHD group had significantly more SWM between errors at time 1 and time 2 and used more strategies to complete the tasks at time 1 (Fig. 1*f*, *g*). Both groups showed a significant improvement in strategy utilization and between errors from time 1 to time 2 (Table 3) with significant greater magnitude of reduction slopes in both indices in ADHD than controls (Fig. 1*f*, *g*, online Supplementary Table S3).

Set-shifting (intra-dimension/extra-dimension shift)

There was no significant group difference in the number of completed stages at time 1 and time 2, and extra-dimensional shift errors at time 1. Participants with ADHD showed significantly more extra-dimensional shift errors at time 2 than controls. Both indices had significant improvements from time 1 to time 2 in both groups. There was no significant group difference in the slope of changes in both indices (Fig. 1*h*, *i*, online Supplementary Table S3).

Spatial planning (SOC)

Compared to the controls, participants with ADHD needed more moves to solve the five-move problems at time 1 and time 2 (Fig. 1*j*), and they solved fewer problems in minimal moves at time 1 without group difference at time 2 (Fig. 1*k*). These two

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Table 2. Demographic and clinical data

	ADHD ($n = 53$)		Control ($n = 50$)		ADHD–Control $F_{(1104)}$ statistics	
Mean (s.d.)	Time 1	Time 2	Time 1	Time 2	Time 1	Time 2
Male, *n* (%)	42 (79.25)		35 (70.00)		$\chi^2_{(1)} = 1.17$	
Age, years	12.77 (1.60)	19.81 (2.39)	12.80 (1.60)	19.36 (1.40)	−0.25	1.60
(age range)	(10–16)	(16–24)	(10–16)	(17–23)		
Duration of follow-up, months		85.17 (22.97)		79.69 (9.13)		2.50
Education						
College and above		34 (65.38)		39 (78)		$\chi^2_{(1)} = 1.99$
Senior high school and below		18 (34.62)		11 (22)		
ADHD symptom count (self-report)						
Inattention	5.90 (2.46)	4.60 (2.60)	0.27 (0.69)	0.60 (1.23)	271.62***	100.43***
Hyperactivity/impulsivity	4.66 (2.56)	2.20 (2.33)	0.25 (0.64)	0.18 (0.56)	132.0***	35.87***
Intelligence quotient (IQ)						
Full IQ	103.82 (11.44)	–	112.90 (9.10)	–	21.26***	–
Verbal IQ	103.43 (12.10)	–	113.42 (8.59)	–	26.28***	–
Performance IQ	104.41 (11.95)	–	110.60 (11.90)	–	6.70*	–
ADHD medication history						
Ever use, *n* (%)	45 (84.91)	47 (88.68)	–	–		
Current use, *n* (%)	23 (43.40)	23 (43.40)	–	–		
Duration, months	18.79 (21.94)	58.80 (36.72)	–	–		
Current any psychiatric comorbidity	41 (77.36)	32 (64.00)	18 (36.00)	4 (8.00)	Fisher's test $p < 0.0001$	Fisher's test $p < 0.0001$
Paternal age	46.02 (5.67)		46.78 (4.10)		1.91	
Maternal age	42.86 (4.42)		44.45 (3.81)		1.34	
Parental education						
College and above	34 (66.67)		41 (83.67)		Fisher's test $p = 0.18$	
Senior high school	14 (27.45)		7 (14.29)			
Junior high school and below	3 (5.88)		1 (2.04)			
Parental occupation						
Professional	8 (16)		9 (18.75)		Fisher's test $p = 0.80$	
Technical	40 (80)		46 (75)			
Others	2 (4)		3 (6.25)			

s.d., standard deviation; ADHD, attention deficit/hyperactivity disorder.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

indices showed significant improvements from time 1 to time 2 for both groups (Table 3). There was no significant group difference in the slope of changes in both indices (Fig. 1*j*, *k*, online Supplementary Table S3).

The correlation matrix of FIQ at time 1, ADHD symptoms, and all neuropsychological functions at the two time points is presented in online Supplementary Table S4. After further controlling for any psychiatric comorbidity, the significance of group differences (ADHD–control) of neuropsychological functions vanished only in the tasks with high-executive demands, i.e. SWM, intra-dimension/extra-dimension shift (IED), and SOC, at time 2. After controlling for any psychiatric comorbidity and FIQ as well, the significance of group differences decreased almost in all the neuropsychological tasks at time 1 and time 2 (online Supplementary Table S5).

Association between time 1 neuropsychological functions and the changes of neuropsychological functions

Poorer time 1 performance predicted more improvements between time 1 and time 2 in all neuropsychological tasks in the whole sample (online Supplementary Table S6 and S6-1) as well as in the ADHD group (online Supplementary Table S7 and S7-1) after adjusting for time 1 age, sex, duration of follow-up, and FIQ (all $p < 0.001$), suggesting that there may be

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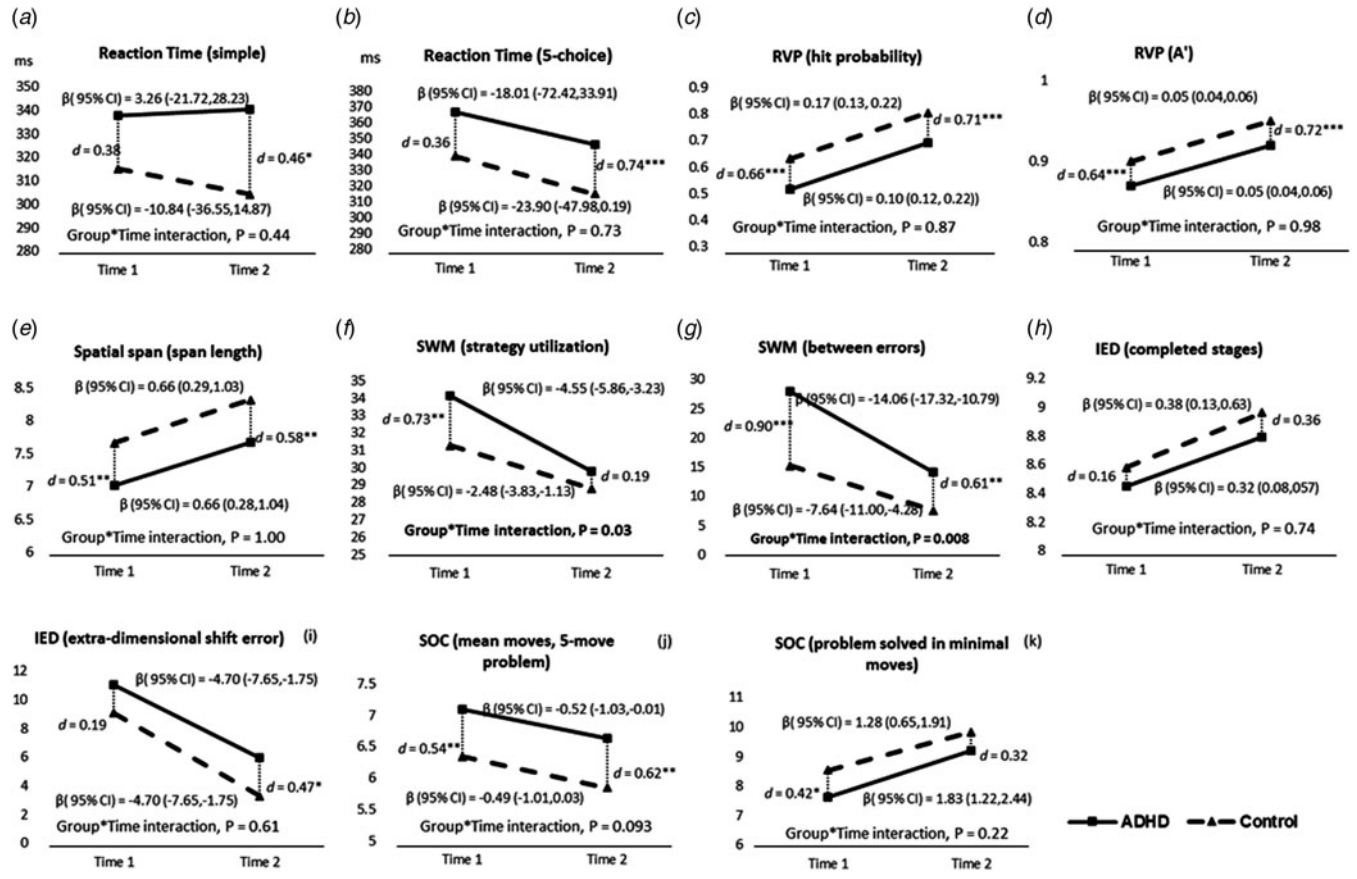

Fig. 1. Developmental changes of neuropsychological functions of ADHD and controls from early adolescence to late adolescence/young adulthood. Note: RVP, rapid visual information processing; SWM, spatial working memory; IED, intra-dimension/extra-dimension shift; SOC, Stocking of Cambridge; β, slope of the change of the neuropsychological function; CI, confidence interval. Group difference: d = Cohen's d; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

a catch-up in individuals with poorer performance at baseline, probably due to brain maturation.

Association between neuropsychological functions and ADHD symptoms in the ADHD group

There was no significant association between changes of neuropsychological functions and changes of inattention or hyperactivity/impulsivity symptoms after adjusting for time 1 age, sex, and/or FIQ as well as the presence of psychiatric comorbidity in the whole sample (online Supplementary Table S8 and S8-1) and the ADHD group (online Supplementary Table S9 and S9-1) (all $p >$ 0.05 if adjusting for multiple comparison).

Predictors of time 2 ADHD symptoms in the ADHD group

Time 1 SWM, IED, and SOC had significant associations with time 2 overall ADHD symptoms [SWM: β (S.E.) = 0.10 (0.04), $F = 6.16$, $p = 0.01$, adjusted $p = 0.06$; IED completed stages: β (S.E.) = −2.35 (0.71), $F = 11.08$, $p = 0.003$, adjusted $p = 0.02$; IED extra-dimensional shift errors: β (S.E.) = 0.15 (0.06), $F = 2.17$, $p = 0.02$, adjusted $p = 0.06$] and hyperactive/impulsive symptoms [SWM: β (S.E.) = 0.05 (0.02), $F = 5.10$, $p = 0.02$, adjusted $p = 0.09$; IED completed stages: β (S.E.) = −1.29 (0.39), $F = 11.23$, $p = 0.004$, adjusted $p = 0.02$; IED extra-dimensional shift errors: β (S.E.) = 0.09 (0.03), $F = 8.65$, $p = 0.01$, adjusted $p = 0.03$; SOC strategy utilization: β (S.E.) = −0.29 (0.14), $F = 4.38$, $p = 0.05$, adjusted $p = 0.09$; SOC mean move of five-move task: β (S.E.) = 0.48 (0.21), $F = 4.98$, $p = 0.02$, adjusted $p = 0.09$] after controlling for time 1 age, sex, duration of follow-up, and same dimension of ADHD symptoms at time 1 (online Supplementary Table S10). While adding the psychiatric comorbidity or FIQ into the predictive models, the significance of the results remained similar (online Supplementary Table S10).

In the ADHD sample (Table 4), time 1 IED completed stages, and parental occupation accounted for 38% of the variance in time 2 overall ADHD symptoms. Time 1 inattentive symptoms, IED completed stages, and SWM between errors explained 33% of the variance of time 2 inattentive symptoms (Table 4). Time 1 IED, SOC mean moves of the five-move task, and parental occupation accounted for 49% of variance in time 2 hyperactive/impulsive symptoms (Table 4).

Discussion

As one of few longitudinal follow-up studies examining the developmental changes of neuropsychological functions assessed by the CANTAB in individuals with and without ADHD, this study had the following important findings. First, both ADHD symptoms and neuropsychological functions improved with age, but young adults with ADHD continued to perform poorer than controls not only at time 1 but also at time 2. Second, the developmental changes of neuropsychological functions of ADHD and controls were parallel, except SWM, in which individuals with ADHD showed a larger magnitude of improvement

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Table 3. Changes of neuropsychological functions from adolescence to young adulthood for the ADHD and control groups

	ADHD ($n = 53$)						Control ($n = 50$)					
			Time 2–Time 1						Time 2–Time 1			
Mean (s.d.)	Time 1	Time 2	Cohen *d*	*t* (52)[#]	Raw *p* value	Adjusted *p* value	Time 1	Time 2	Cohen *d*	*t* (49)[#]	Raw *p* value	Adjusted *p* value
Reaction time												
Simple	336.98 (51.53)	340.23 (100.46)	0.03	0.21	0.84	0.84	315.11 (66.99)	304.28 (38.97)	−0.20	−1.28	0.21	0.21
Five-choice	364.10 (93.36)	346.09 (44.75)	−0.28	−1.22	0.23	0.25	338.95 (50.55)	315.05 (38.68)	−0.53	−3.11	0.003	0.004
Rapid visual information processing												
Probability of hit	0.52 (0.18)	0.69 (0.16)	1.00	7.79	<0.0001	0.0002	0.63 (0.16)	0.81 (0.15)	1.16	6.36	<0.0001	0.0003
A' (signal detectability)	0.87 (0.05)	0.92 (0.04)	1.09	8.36	<0.0001	0.0002	0.9 (0.05)	0.95 (0.04)	1.10	6.38	<0.0001	0.0003
Spatial span												
Span length	7.00 (1.29)	7.67 (1.30)	0.50	3.20	0.002	0.004	7.66 (1.21)	8.32 (0.89)	0.62	3.67	0.0006	0.001
Spatial working memory												
Strategy utilization	34.42 (4.00)	29.80 (5.45)	−0.89	−6.94	<0.0001	0.0002	31.26 (5.25)	28.78 (5.38)	−0.47	−3.44	0.0012	0.002
Between errors	28.40 (15.19)	14.15 (12.76)	−0.97	−7.99	<0.0001	0.0002	15.2 (12.7)	7.56 (8.15)	−0.71	−4.82	<0.0001	0.0003
Intra-dimension/extra-dimension shift												
Completed stages	8.47 (0.82)	8.79 (0.60)	0.48	2.50	0.02	0.03	8.58 (0.78)	8.96 (0.28)	0.64	3.14	0.0028	0.004
Extradimensional shift errors	10.66 (10.55)	5.96 (7.40)	−0.55	−3.03	0.004	0.006	9.08 (9.94)	3.28 (3.01)	−0.79	−3.98	0.0002	0.0004
Stocking of Cambridge												
Problems solved in minimum moves	7.53 (2.37)	9.19 (2.27)	0.67	4.39	<0.0001	0.0002	8.54 (1.91)	9.82 (1.56)	0.73	4.77	<0.0001	0.0003
Mean moves (Five-move problem)	7.16 (1.53)	6.64 (1.47)	−0.31	−1.94	0.059	0.072	6.34 (1.28)	5.85 (1.04)	−0.42	−2.11	0.04	0.04

#Paired *t* test. Adjusted *p* value is the value adjusted for the false discovery rate (maximum = 0.05) from the raw *p* value.

Table 4. Predictors of time 2 ADHD symptoms in the ADHD group

Outcome/predictors	*b* (S.E.)	*β*	*t*-value	*p*	R^2	ΔR^2
Overall ADHD symptoms						
Intercept	20.51 (6.42)		2.94	0.005		
IED, completed stages	−2.56 (0.64)	−0.49	−3.65	0.0007	0.26	0.26
Parental occupation	3.09 (1.55)	0.26	2.79	0.008	0.38	0.12
Inattentive symptoms						
Intercept	9.85 (3.87)		2.55	0.02		
IED, completed stages	−1.03 (0.42)	−0.34	−2.46	0.02	0.17	0.17
Time 1 inattention symptoms	0.35 (0.14)	0.33	2.42	0.02	0.26	0.09
SWM, between errors	0.05 (0.02)	0.27	2.03	0.05	0.33	0.07
Hyperactive/impulsive symptoms						
Intercept	8.58 (3.24)		4.05	0.0002		
IED, completed stages	−1.64 (0.35)	−0.58	−4.59	<0.0001	0.24	0.24
SOC, mean move (five-move problem)	0.64 (0.19)	0.37	2.91	0.006	0.44	0.10
Parental occupation	1.58 (0.25)	0.74	2.13	0.04	0.49	0.05

ADHD symptoms, SWM between errors, IED completed stage and extra-dimensional shift errors, SOC mean moves of the five-move task, FIQ, ADHD symptoms, parental occupation, parental educational level and any psychiatric disorder at time 1, time 2 age, sex, duration of ADHD medication treatment, and duration of follow-up between two evaluations (months) were put into the stepwise linear regression. SWM, spatial working memory; IED, intra-dimension/extra-dimension shift; SOC, Stocking of Cambridge; parental occupation, a highest parental job level, the 'professional' group as the reference group.

than controls. Third, there was no significant linear correlation between changes of ADHD symptoms and changes of neuropsychological functions. Fourth, for individuals with ADHD, time 1 set-shifting (IED), SWM, and spatial planning (SOC) predicted time 2 ADHD symptoms severity independent of baseline ADHD symptoms, sex, age, and duration of follow-up. Lastly, better baseline set-shifting, SWM, and spatial planning and parental occupation as professional predicted fewer ADHD symptoms at follow-up based on the model selection.

Similar to other longitudinal studies (Faraone *et al.*, 2006), we found that with age, there was a significant decline of ADHD symptoms, especially hyperactive/impulsive symptoms (Gau *et al.*, 2010*a*). Consistent with the hypothesis of maturational lag, our data showed that neuropsychological functions, except cognitive alertness (reaction time), demonstrated parallel improvements with age for both the ADHD and control groups with persistently poorer performance in young adults with ADHD than controls. Converging data suggest that ADHD is characterized by a delay but not a deviance in brain development based on the observation that the behavioral presentations of children with ADHD often like their younger typically developing counterparts, including activity level, behavioral regulation ability, neurocognitive performance, speech development and quantitative electroencephalographic presentation [see review, El-Sayed *et al.* (2003)]. Neuroimaging studies showed that children with ADHD had a similar ordered sequence of brain maturation as typically developing children, i.e. primary sensorimotor cortex prior to high-order association areas, but had a lag of years in attaining the peak of cortical thickness (Shaw *et al.*, 2007). Also, there was a fixed and non-progressive rate of cortical thinning (Shaw *et al.*, 2013) and persistent smaller brain volume (Castellanos *et al.*, 2002) in individuals with ADHD, especially those with persistent diagnosis (Shaw *et al.*, 2013). In other words, the gap of neuropsychological functions between individuals with ADHD and controls did not enlarge from early adolescence to late adolescence/early adulthood.

Although roughly parallel with the typically developing youth, the brain development of individuals with ADHD was found to have a differential delay in maturation over different brain regions (Shaw *et al.*, 2007; Shaw *et al.*, 2012). We found a tendency of the development of SWM of individuals with ADHD to converge toward controls from early adolescence to young adulthood. The significant convergence might imply a delayed but rapid catch-up of this ability through the developmental stage of adolescence in ADHD, coincident with the delayed, vigorous development of the frontal area during this period (Halperin and Schulz, 2006). The anterior frontal gyri, especially the right side, subserving visuospatial working memory (Chase *et al.*, 2008), were demonstrated to be the brain region with the most marked delay in ADHD (Shaw *et al.*, 2012). Because there was no such a catch-up in spatial short-term memory, it was more likely that the central executive component, rather than spatial sketchpad component, accounted for the rapid improvement of ADHD in SWM during early to late adolescence. Nevertheless, young adults with ADHD consistently showed a significant deficit in SWM. This ability might catch up but be still impaired. On the other hand, the most simple task, the simple reaction time task, showed almost no improvement in both ADHD and controls, implying that this ability reaches a plateau before adolescence (Luciana and Nelson, 1998).

Our finding that FIQ shared a significant part of variance contributing to the group differences in neuropsychological functions might be explained by the high correlations among ADHD, FIQ, and neuropsychological functions. Putting IQ into analysis would diminish the associations between ADHD and neuropsychological deficits (Miller *et al.*, 2013) because IQ tests and neuropsychological tasks might share some common indirect measures of brain functions which were related to ADHD. Therefore, our discussions still focused on the neuropsychological deficits of ADHD without controlling for FIQ. Some influences of the psychiatric comorbidity on group differences in CANTAB

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performance might be explained by the small sample size and the high proportion of the psychiatric comorbidity in ADHD. Although IQ and the psychiatric comorbidity were reported to influence the outcome of ADHD (Uchida *et al.*, 2018), neither IQ nor the psychiatric comorbidity had a significant influence on the association between changes of ADHD symptoms and changes of neuropsychological functioning, or prediction of neuropsychological functions to time 2 ADHD symptoms in the ADHD group.

Consistent with previous studies (Cheung *et al.*, 2015; Lahey *et al.*, 2016), we found that parental occupation and baseline set-shifting ability (Coghill *et al.*, 2014*a*) predicted time 2 ADHD symptoms, especially hyperactive/impulsive symptoms. Parents having a professional occupation, compared with non-profession/non-technical occupation, implying a higher socio-economic status, was a protective factor for adolescents with ADHD (Cheung *et al.*, 2015). This result again highlights the importance of environmental factors, especially the family influence, in the outcome of ADHD in addition to the inherent executive abilities. In contrast to the finding of Cheung *et al.*, we found the parental occupation explained more variance than IQ, possibly because we included neuropsychological functions in the model selection which shared the variance of the association between ADHD and IQ.

Although there was no significant linear relationship between the changes of ADHD symptoms and changes of neuropsychological functioning, we could not rule out the possibility that there was a 'threshold effect' of neuropsychological functioning in ADHD symptoms, i.e. when individuals' neuropsychological functioning reaching the normal developing level or maturation, the ADHD symptoms would remit. Because this study focused on the dimensional approach and the sample size was small, we did not divide the ADHD group into subgroups of normal or impaired neuropsychological functioning nor subgroups of persistent ADHD or non-persistent ADHD at time 2. Further longitudinal studies with large samples would be helpful in elucidating the existence of a non-linear relationship between ADHD symptoms and neuropsychological functions.

There are some conflicts with regards to the definition of 'core neuropsychological deficits' and 'epiphenomenon' of ADHD. Miller *et al.* (2013) suggested that the neuropsychological deficits with developmental trajectories unrelated to ADHD symptom changes were the core deficits, otherwise were the epiphenomenal deficits (Carr *et al.*, 2006). In contrast, Coghill *et al.* (2014*a*) suggested that because of the lack of linear relationship between developmental changes in neuropsychological functions and ADHD symptoms, neuropsychological deficits were phenotypes co-occurring with ADHD symptoms at the same level of analysis in the causal model, the concept closer to epiphenomena. By the definition of Walters and Owen (2007), the only difference between the endophenotype (core deficits) and the epiphenomenon is that the former lies in the middle of the pathway from genes to the target phenotypes, which is state-independent, and the later shares the same genes with the target phenotypes but is not within the pathway. The confusion comes from the developmental nature of ADHD symptomatology and neuropsychological functioning. The definitions of trait vs. state-dependent factors suitable for the mental illness with significant wax and wane might not be ideal for a developmental disorder with a gradual change of symptoms and without substantial short-term fluctuations like ADHD. Artificially, methylphenidate causes acute and transient phenotypical changes, and also improves several high- and low-executive neuropsychological functions (Coghill *et al.*, 2014*b*), but the changes might not be linear or prominent (Coghill *et al.*, 2007). On the other hand, there might be different sets of genetic and environmental factors contributing to the baseline condition and the developmental course of ADHD (Pingault *et al.*, 2015). In other words, there might be different mechanisms underpinning the cause and recovery of ADHD (Halperin and Schulz, 2006). While investigating the causal model of ADHD, factors associated with pathogenesis and developmental course might have to be addressed separately (Kuntsi *et al.*, 2010). The longitudinal familial genetic studies would be more informative to identify endophenotypes in the pathway from genes to ADHD phenotypes (Gau and Shang, 2010; Kuntsi *et al.*, 2014).

There are some limitations in this study. First, we used the clinical sample, and thus our results cannot be generalized to the community population. Second, the sample sizes for both groups may be too small to detect the differences and changes. Third, more than half of the participants were currently or ever medicated for ADHD, so we could not rule out the effect of long-term ADHD medication use (mostly methylphenidate) on the changes of ADHD symptoms and neuropsychological functioning. Neveretheless, Saville *et al.* (2015) ever reported no influences of medication use on the development of ADHD symptoms. Fourth, although we asked the participants who currently took medication for ADHD to hold medication for at least 24 h, we cannot rule out the possible withdrawal effect of methylphenidate and the therapeutic effect of atomoxetine (only two participants currently used). Fifth, we intended to do dimensional-based analysis and the sample size was small, so we did not divide individuals with ADHD into persisters/remitters or groups of normal/impaired neuropsychological functioning. Use of the dimensional approach to evaluating the development of ADHD would be informative given that ADHD symptoms exist in a continuum in the population (Kuntsi *et al.*, 2010; Cheung *et al.*, 2016). For categorical analysis, a larger size of the sample to accord with the strict definition of persisters and remitters in combination with functional impairment would be necessary. Finally, we discuss group differrencs in neuropsychological functions mainly focusing on the results without controlling for the influence of FIQ.

In conclusion, there were parallel improvements of several neuropsychological functions with high- and low-executive demands in individuals with and without ADHD from early to late adolescence/young adulthood. Young adults with ADHD showed a fixed delay in arousal, signal detectability, spatial span, set-shifting, and spatial planning but had a 'catch-up' in SWM, especially the central executive component. Till late adolescence/early adulthood, ADHD showed deficits in almost all these neuropsychological functions. There might be different determinants of the cause and the developmental change of ADHD (Halperin and Schulz, 2006; Pingault *et al.*, 2015). Executive functions at baseline and parental occupation might influence the persistence of ADHD symptoms, especially hyperactive/impulsive symptoms, during adolescence. The predicters for persisting ADHD symptoms can be used for designing the specific strategies to offset the adverse outcome of ADHD at adulthood. To elucidate the causal relationship of neuropsychological functioning, ADHD symptoms and the mutual relationship of their developmental changes requires large-scale longitudinal familial genetic studies.

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