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Neuropsychological functioning in stimulant-naive boys with hyperkinetic disorder

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ABSTRACT

Background. Although children with hyperkinetic disorder and/or attention deficit hyperactivity disorder (ADHD) show disordered executive neuropsychological functioning, the nature of these changes remains controversial. Additionally, impairments in non-executive neuropsychological functioning have been relatively unexplored. Here, the authors describe the neuropsychological functioning of a sample of stimulant drug-naive boys with hyperkinetic disorder on a battery of neuropsychological tasks sensitive to impairments of both executive and non-executive functions.

Method. Seventy-five stimulant drug-naive boys meeting diagnostic criteria for ICD-10 hyperkinetic disorder were compared with 70 healthy developing controls matched for age but not IQ on computerized tests of neuropsychological functioning from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and a Go/No-Go inhibition task.

Results. Boys with hyperkinetic disorder exhibited impairments on tasks with a prominent executive component – working memory, planning, strategy formation, attentional set-shifting and on a reaction time task. However, they were also impaired on tasks without prominent executive components – pattern and spatial recognition, spatial span, delayed matching to sample and paired associates learning. Contrary to predictions, no impairment was observed on the Go/No-Go inhibition task.

Conclusions. Medication-naive boys with hyperkinetic disorder displayed a broad range of neuropsychological impairments. Deficits were demonstrated on tasks with and without prominent executive components. Impairments were not confined to tasks dependent upon frontostriatal functioning, cannot wholly be explained by deficits in inhibitory control, nor can they be attributed to intelligence or previous exposure to stimulant medication.

INTRODUCTION

Hyperkinetic disorder (ICD-10; WHO, 1992) and attention deficit hyperactivity disorder (DSM-IV; APA, 1994) are characterized by pervasive impaired attention, hyperactivity and impulsivity. These disorders are common, particularly in boys (Swanson *et al.* 1998), with 1 year combined prevalence rates in school-age children of 1·7% for hyperkinetic disorder (Meltzer *et al.* 2000) and between 5 and 10% (Swanson *et al.* 1998) for ADHD. With continuing controversy with respect to nosology, we have adopted the convention suggested by Taylor (1994) and described by Schachar & Tannock (2002) and refer to specific diagnostic terms, such as hyperkinetic disorder (HD) or attention deficit hyperactivity disorder (ADHD) when addressing a particular diagnostic entity and set of criteria. However, we use the acronym AD-HKD when referring to characteristics that are shared by both ADHD and HD.

The impairments associated with AD-HKD are considerable, and core symptoms and associated social, interpersonal, and academic

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problems often persist into adulthood (Klein & Mannuzza, 1991; Hechtman, 1992; Murphy & Barkley, 1996; Barkley *et al.* 2004). Despite considerable study and speculation, the pathophysiology of AD-HKD remains poorly understood (Solanto *et al.* 2001). Converging evidence implicates dysregulation of frontostriatal neural circuits (Castellanos *et al.* 1996*b*; Giedd *et al.* 2001; Rubia *et al.* 2001*b*) and, more specifically, reduced prefrontal dopamine (DA) transmission (Castellanos *et al.* 1996*a*; Pliszka *et al.* 1996; Ernst *et al.* 1998).

Executive neuropsychological functioning (EF) has been used as an umbrella term to describe those functions that mediate 'the ability to maintain an appropriate problem-solving set for attainment of a future goal' (Luria, 1996). EF includes, for example, diverse processes such as response inhibition, planning, working memory, and flexibility of thinking or responding. Performance deficits on executive tasks of working memory have been observed in prefrontal cortex (PFC)-lesioned animals (Goldman-Rakic, 1996) and humans (Owen *et al.* 1990). Similarly, inhibitory control, attentional set-shifting and planning are impaired in patients with frontal lobe resections (Owen *et al.* 1990, 1991; Braun *et al.* 1992). Hence, executive dysfunction might reasonably be predicted in association with the altered frontostriatal functioning reported in AD/HKD. However, no consensus has been derived within the literature concerning EF impairments in AD-HKD (Tannock, 1998; Kempton *et al.* 1999; Castellanos *et al.* 2000). Neuropsychological investigation has undoubtedly been hampered by a lack of clearly defined, specific, sensitive and valid measures of EF other than inhibition (Tannock, 1998) and persistent failure to deploy task batteries sensitive to a broad range of impairments. Other important methodological limitations have included small sample sizes (e.g. Kempton *et al.* 1999), the use of rating scales rather than structured clinical interviews for case definition (e.g. Scheres *et al.* 2001), and the inclusion of children who were either taking, or had recently stopped taking stimulant medication (e.g. Seidman *et al.* 1997; Aman *et al.* 1998). These latter issues are crucial since methylphenidate (MPH), the first-line pharmacological treatment for AD-HKD, significantly enhances various aspects of neuropsychological functioning, including EF (Kempton *et al.* 1999; Mehta *et al.* 2000).

One influential neuropsychological account of AD-HKD emphasizes behavioural impulsiveness and postulates a primary deficit in inhibitory control leading to secondary deficits in other EF (Barkley, 1998). However, no empirical evidence has been provided to support the primacy of inhibition. It is increasingly implausible that AD-HKD could represent the clinical manifestation of a single neuropsychological or neurophysiological abnormality. Recently developed models have, instead, proposed (Castellanos & Tannock, 2002; Sonuga-Barke, 2002) that AD-HKD be viewed as the behavioural consequence of a combination of several risk factors, present to varying degrees in different individuals, with heterogeneity of EF deficits (Pennington & Ozonoff, 1996; Denney & Rapport, 2001). It has further been suggested that only a proportion of those with AD-HKD may demonstrate neuropsychological deficits (Doyle *et al.* 2000; Sonuga-Barke, 2002; Nigg *et al.* 2004). These views are supported by empirical evidence regarding inhibitory function (Rubia *et al.* 2001*b*); working memory and attentional set-shifting (Kempton *et al.* 1999; Tripp *et al.* 2002) and planning ability (Kempton *et al.* 1999). In addition, children with AD-HKD are impaired on tasks with low executive demands, for example a spatial span task (Kempton *et al.* 1999), and on tasks traditionally associated with parietal rather than frontal functioning, such as mental rotation (the Turning task) and visuospatial processing (Aman *et al.* 1998). Similarly, neuroimaging studies in AD-HKD describe abnormalities in several areas of the brain other than the PFC, including the temporal and parietal lobes and the cerebellum (Filipek *et al.* 1997; Castellanos *et al.* 2002). Encouraging an integrative approach that takes these observations in account, Castellanos & Tannock (2002) have proposed four candidate 'endophenotypes' for AD-HKD; delay aversion, deficits in working memory, deficits in time estimation and behavioural inhibition. Compelling empirical evidence for each is awaited.

We have examined the neuropsychological functioning of a large sample of stimulant-naive boys with ICD-10 hyperkinetic disorder (who also met criteria for a diagnosis of DSM-IV

ADHD combined subtype), using tasks from the CANTAB neuropsychological test battery and a computerized Go/No-Go task. The CANTAB battery (Fray & Robbins, 1996) has been extensively validated in both child (Luciana & Nelson, 1998; Hughes *et al.* 1999; Williams *et al.* 2000; Curtis *et al.* 2002) and adult populations (Robbins *et al.* 1994) and has been shown to be differentially sensitive to dysfunction in several brain regions, including frontal, temporal and amygdalo-hippocampal regions (Owen *et al.* 1995). We have previously reported data from the same clinical group on the Spatial Working Memory, Delayed Matching to Sample and Pattern Recognition tasks from the CANTAB battery (Rhodes *et al.* 2004). Having included these data in the correlational and regression analyses that follow, the results are briefly summarized alongside those that represent the present report.

METHOD

Participants

We tested two groups of boys aged between 7 and 15 years. One was an experimental cohort of 75 stimulant-medication-naïve participants with ICD-10 HD, but who also met criteria for DSM-IV ADHD combined subtype (AD-HKD group, mean age 10·8 years). The other contained 70 healthy control boys (Controls, mean age 10·7 years).

AD-HKD group

Participants were recruited from consecutive male out-patient referrals to the Tayside Child and Adolescent psychiatric service using a two-stage screening procedure. Potential participants were first screened using the Child Behaviour Checklist (Achenbach *et al.* 1991) and the Conners' Parent and Teaching Rating Scales (Conners, 1997*a*, *b*). Subjects with a T-score greater than 65 on all subscales of the 27 item Conners' Parent Rating Scale–Revised (S) (CPRS-48) and the Conners' Teacher Rating Scale–Revised (S) (CTRS-28) were interviewed by an experienced child and adolescent psychiatrist using the Kiddie-SADS Present and Lifetime (K-SADS-PL) Version 1.0 semi-structured interview (Kaufman *et al.* 1996, 1997). Each AD-HKD subject met diagnostic criteria on K-SADS interview for both ICD-10 HD, and DSM-IV attention-deficit/hyperactivity disorder, combined type. Although co-morbidity is not formally permitted within the ICD-10 system, the presence of a range of commonly occurring co-morbid conditions; including oppositional defiant disorder, conduct disorder, and anxiety disorder, did not result in exclusion from the study (see Table 1). This was to ensure recruitment representative of the clinical populations seen in routine practice within the UK National Health Service. All co-morbid diagnoses were considered secondary to the primary diagnosis of HD. Five children met criteria for multiple co-morbid diagnoses.

Table 1. *Co-morbid diagnoses in AD-HKD group*

	n	% of sample
Pure hyperkinetic disorder	18	24
Co-morbid diagnoses		
Oppositional defiant disorder (no CD)	31	41·3
Conduct disorder (CD)	21	28
Depressive disorder	3	4
Generalized anxiety disorder	2	2·7
Separation anxiety disorder	3	4
Tic disorder	2	2·7
Social phobia	1	1·3

Controls

Healthy developing boys were recruited from local schools and screened as above. Symptom-free (T-score <60 on all subscales of the CPRS-48, CTRS-28 and CBCL subscale T-scores <60), age-matched participants and their parents were interviewed using the K-SADS-PL to confirm health. A previous or current history of any psychiatric disorder led to exclusion, as did a history of neurological impairment, learning disability, chronic physical illness, sensory or motor impairment, current or previous exposure to prescribed stimulant medication, and abuse of any illegal drugs. The British Picture Vocabulary Scale, second edition (BPVS; Dunn *et al.* 1997) was used to estimate general intellectual ability. The BPVS assesses verbal intelligence and was chosen for its ease of administration and ability to be used with children aged between 3 and 15 years (Dunn *et al.* 1997). Informed written consent to participate in the study was obtained from each child's parent(s)/guardian. The characteristics of both groups are summarized in Table 2.

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Table 2. *Demographic characteristics*

	AD-HKD boys ($n=75$) Mean (S.D.)	Control boys ($n=70$) Mean (S.D.)	p
Age	10·85 (2·46)	10·74 (2·47)	>0·05
BPVS percentile rank	35·43 (27·93)	58·94 (26·25)	<0·001
Conners: parent (T-scores)			
Oppositionality	75·57 (11·38)	45·25 (6·42)	<0·001
Cognitive	72·94 (7·07)	44·16 (3·47)	<0·001
Hyperactive	83·08 (8·88)	46·12 (3·43)	<0·001
ADHD index	77·01 (6·09)	43·96 (3·37)	<0·001
Conners: teachers (T-scores)			
Oppositionality	65·05 (19·52)	49·15 (9·49)	<0·001
Cognitive	62·77 (12·78)	47·66 (7·95)	<0·001
Hyperactive	71·0 (14·34)	47·36 (7·42)	<0·001
ADHD index	72·23 (14·93)	47·79 (8·12)	<0·001

BPVS, British Picture Vocabulary Scale.

Neuropsychological assessment

A total of 10 tasks were used and each subject performed all tasks in the same order. A computer-based Go/No-Go task was used to assess inhibitory control and nine tasks were selected from the three batteries (working memory and planning, visual memory, and attention) of CANTAB (Morris *et al.* 1987). All tasks were presented on a high-resolution colour monitor with CANTAB tasks utilizing a touch-sensitive screen. A scheduled break of approximately 10 minutes was taken midway through the testing session and subjects were informed that they could take further breaks as required. In practice few subjects requested additional breaks.

Go/No-Go

This task assessed the ability to detect and respond to a target stimulus and to inhibit responding to distractor stimuli. A random sequence of 18 letters and numbers (nine of each) were rapidly presented in the centre of a colour computer screen, one by one. Stimuli were presented on screen for 300 ms, with an interstimulus interval of 900 ms. Subjects were instructed to respond to target stimuli (letters) by pressing the space bar as quickly as possible, but not to respond to distractors (numbers). Response contingencies alternated between numbers and letters with two 'switching' and two 'non-switching' blocks. The dependent measures are the mean number of errors for distractors (false positive responses) and reaction time to target stimuli across eight test trials. This version of the Go/No-Go task has not previously been used in the study of neuropsychiatric disorders or psychopharmacological manipulations; however, the test parameters are identical to those previously used, in several studies, to demonstrate impaired inhibitory control in AD-HKD subjects.

CANTAB

Task descriptions and order for presentation of the CANTAB tasks are described in Table 3.

Statistical analysis

All analyses were conducted using SPSS for Windows (v.10) (SPSS Inc., Chicago, IL, USA). As AD-HKD boys tended to score lower on the BPVS percentile rank scores and despite there being no correlation between task performance and BPVS scores on any task, the BPVS percentile rank scores were used as a covariate in all parametric analyses. In addition, a separate analysis of an age- and BPVS-matched subsample was conducted. Data meeting assumptions of normality and homogeneity of variance were analysed using analysis of covariance (ANCOVA) and, thereafter, by determination of simple effects or interactions (Winer *et al.* 1991). All other data were compared using appropriate non-parametric tests (e.g. Mann–Whitney U test). To explore the potential contribution of disordered impulse control on task performance both accuracy measures and reaction times are reported. For analysis of

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Table 3. *Descriptions and order of presentation of CANTAB tasks*

Task	Main outcome measures	Description	References for fuller task description
Working memory and planning battery			
Spatial Span	Span	A test of spatial short-term memory capacity based on the Corsi block-tapping task.	Milner, 1971; Kempton *et al.* 1999
Spatial Working Memory	Between-search errors, Strategy score	A self-ordered search task that assesses working memory for spatial stimuli and requires a subject to use mnemonic information to work towards a goal.	Petrides & Milner, 1982; Kempton *et al.* 1999; Rhodes *et al.* 2004
Stockings of Cambridge	Problems solved in minimum moves	Derived from the 'Tower of Hanoi' task, measuring spatial planning, working memory, and behavioural inhibition.	Shallice, 1982; Kempton *et al.* 1999
Visual memory battery			
Pattern Recognition	Percentage correct	Tests the ability to recognize a previously presented abstract pattern in a forced choice procedure.	Kempton *et al.* 1999
Spatial Recognition	Percentage correct	Tests the ability to recognize the spatial locations of target stimuli.	Kempton *et al.* 1999; Rhodes *et al.* 2004
Delayed Matching to Sample	Percentage correct	Tests the ability to remember the visual features of a complex, abstract, target stimulus and to select from a choice of four patterns after a variable delay.	Kempton *et al.* 1999; Rhodes *et al.* 2004
Paired Associates Learning	Stage reached, total errors, Total trials	Tests the ability to learn the locations of a progressively increasing number of abstract stimuli. The main measures in this task are the number of trials taken to complete the task and the total number of errors across all trials.	Sahakian & Owen, 1992
Attention battery			
Attentional Set-Shifting task/ID-ED	Stage reached	Tests the ability to focus attention on specific attributes of compound stimuli (intradimensional stages) and to shift attention when required to a previously irrelevant stimulus dimension (extradimensional stages).	Kempton *et al.* 1999
Reaction Time	Reaction time, Movement time	Tests reaction and movement times in response to a stimulus under a simple one-choice and a five-choice condition.	Sahakian & Owen, 1992

ID-ED, Intradimensional-extradimensional set-shifting.

performance on the Go/No-Go task, trials were divided into two blocks: Block 1 represented the 'switch' blocks where the task changed from letters to numbers (or vice versa) and Block 2 the 'non-switch' block. Blocks were entered into a repeated-measures ANOVA for analysis. Multiple regression analyses were conducted using a backwards deletion entry method with a probability of F for entry set at 0·05 and removal at 0·10. As each of the neuropsychological tasks is designed to measure a different aspect of functioning, and therefore can be seen as representing a separate experiment, α levels were not adjusted for the main comparative analyses. For the correlational analyses α was adjusted to 0·008 to reflect the multiple comparisons.

RESULTS

All subjects completed each of the tests. Mean performance (raw scores and those adjusted for covariate), statistical comparisons and effect sizes (d) for each task, for both groups, are summarized in Table 4. As the Spatial Working Memory, Pattern Recognition, and Delayed Matching to Sample tasks been previously reported (Rhodes *et al.* 2004), data are only briefly summarized here.

AD-HKD boys showed no impairments on the Go/No-Go task. There was no difference between groups for errors to distractors at either the shift or non-shift block [$F(1, 142) < 1$], or in reaction times to targets [$F(1, 142) = 3{\cdot}1$, $p > 0{\cdot}05$].

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Table 4. *Summary of findings*

Measure	AD-HKD Raw mean (S.D.)	AD-HKD Adjusted mean (S.D.)	Controls Raw mean (S.D.)	Controls Adjusted mean (S.D.)	Sig.	ES raw	ES adj.
Go/No-Go							
Errors for Distractors (Block 1)	2·31 (1·5)	2·4 (1·42)	2·23 (1·35)	2·13 (1·56)	N.S.		
Errors for Distractors (Block 2)	2·21 (1·66)	2·27 (1·59)	1·94 (1·46)	1·88 (1·65)	N.S.		
Reaction time to Targets B1 (log_{10})	2·66 (0·09)	2·66 (0·08)	2·64 (0·08)	2·64 (0·09)	N.S.		
Reaction time to Targets B2 (log_{10})	2·67 (0·09)	2·66 (0·08)	2·64 (0·08)	2·64 (0·09)	N.S.		
Spatial Span							
Span Score	5·08 (1·47)	5·08 (1·26)	5·93 (1·5)	5·94 (1·47)	**	0·57	0·6
Spatial Working Memory							
Total between-search errors	50·71 (19·49)	50·84 (21·0)	35·13 (20·7)	34·99 (21·82)	***	0·77	0·75
Strategy score	36·31 (4·54)	36·32 (5·11)	32·74 (5·17)	32·73 (5·28)	***	0·73	0·70
Stockings of Cambridge							
No. solved in minimum moves	7·13 (2·04)	7·2 (2·11)	8·07 (2·01)	7·99 (2·17)	*	0·46	0·38
Pattern Recognition							
% Correct	0·70	81·29 (11·71)	90·95 (8·37)	90·4 (12·12)	***	0·92	0·89
Spatial Recognition							
% Correct	0·70	68·21 (13·9)	77·64 (13·68)	78·2 (13·8)	***	0·89	0·72
Delayed Matching to Sample							
Simultaneous	90·93 (15·5)	90·77 (12·38)	97·14 (7·03)	97·32 (1·53)	**	0·53	0·52
Delay (0, 4 + 12)	59·38 (18·8)	59·52 (17·84)	75·81 (17·66)	75·66 (17·91)	***	0·91	0·90
Paired Associates Learning							
Stage reached	7·96 (0·26)	7·96 (0·26)	7·97 (0·24)	7·97 (0·25)	N.S.		
Total errors	11·61 (11·5)	11·14 (9·71)	6·71 (7·1)	7·22 (10·39)	**	0·51	0·47
Total trials	12·76 (4·09)	12·61 (4·07)	10·7 (2·93)	10·86 (3·89)	**	0·57	0·58
ID-ED							
Stage reached	7·55 (1·08)	7·5 (1·04)	7·94 (0·97)	7·99 (1·13)	*	0·38	0·46
Reaction Time							
Reaction time latency (5 choice)	2·61 (0·13)	2·62 (0·09)	2·58 (0·11)	2·57 (0·17)	*	0·24	0·71
Movement time latency (5 choice)	2·61 (0·14)	2·63 (0·26)	2·55 (0·34)	2·53 (0·25)	*	0·23	0·39

ID-ED, Intradimensional-extradimensional set-shifting.
* $p<0·05$, ** $p<0·05$, *** $p<0·001$.

There was a significant group difference in performance on the Spatial Span task with AD-HKD boys obtaining a lower Spatial Span score than control boys [$F(1, 142)=9·89$, $p<0·002$, $d=0·6$]. AD-HKD boys also made more between-search errors on the spatial working memory task [$F(1, 142)=18·8$, $p<0·001$, $d=0·75$]. There was a significant interaction between group and difficulty level and *post hoc* tests revealed that AD-HKD boys made more errors at the 8-box stage relative to the 3-, 4- or 6-box stages. AD-HKD boys also had higher (impaired) strategy scores [$F(2, 142)=16·52$, $p<0·001$, $d=0·70$] but there were no differences in within-search errors [$F(1, 142)=1·5$, $p>0·05$].

AD-HKD boys solved fewer problems in the minimum number of moves on the SoC task [$F(1, 142)=4·7$, $p<0·03$, $d=0·38$] but there was no significant difference in the average moves made [$F(1, 141)=3·5$, $p>0·05$] and no significant interaction between group and difficulty level in average moves [$F(2·3, 321)=1·6$, $p>0·05$]. There was no significant overall difference between the two groups with respect to either initial [$F(1, 141)=1·1$, $p>0·05$] or subsequent [$F(1, 141)<1$] thinking times but there was a significant interaction between group and difficulty level [$F(2·5, 349)=3·8$, $p<0·02$] for subsequent but not for initial [$F(1·7, 236)<1$] thinking times. Planned contrasts revealed that controls had longer subsequent thinking times for 5-move problems relative to 3-move problems ($p<0·01$).

AD-HKD boys made fewer correct responses on the Pattern Recognition task ($z=-5·267$, $p<0·001$, $d=0·89$) but latencies for correct responses did not differ. AD-HKD boys had shorter response latencies for incorrect choices.

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However, regression analysis revealed that the latencies for incorrect responses did not predict overall accuracy of responding for the AD-HKD.

AD-HKD boys obtained a lower percentage of correct responses on the Spatial Recognition task [$F(2, 142) = 17{\cdot}4$, $p < 0{\cdot}001$, $d = 0{\cdot}72$]. There was no significant difference in latencies for correct responses [$F(1, 142) = 1{\cdot}07$, $p > 0{\cdot}05$], but AD-HKD boys had shorter latencies to respond when making incorrect choices [$F(1, 141) = 13{\cdot}9$, $p < 0{\cdot}001$]. Again, however, regression analysis revealed that latencies for incorrect responses did not predict overall accuracy of responding for the AD-HKD boys [$F(1, 72) < 1$].

AD-HKD boys demonstrated deficits at both the simultaneous and delay conditions of the Delayed Matching to Sample task. There was a significant interaction between performance accuracy and duration of task delay [$F(2, 284) = 4{\cdot}7$, $p < 0{\cdot}01$] and AD-HKD boys made fewer correct responses with increasing delay, whilst control boys performed equally across all delays. This performance deficit was not explained by differences in response latency on the task.

Groups did not differ as to the Stage Reached on the Paired Associates Learning task [$F(1, 142) < 1$]. AD-HKD boys, however, made more errors [$z = -2{\cdot}9$, $p < 0{\cdot}003$, $d = 0{\cdot}47$] and required more trials [$z = -3{\cdot}7$, $p < 0{\cdot}001$, $d = 0{\cdot}58$].

AD-HKD boys achieved lower stage-reached scores on the Intradimensional-Extradimensional Set-Shifting (ID-ED) attentional set-shifting task [$F(1, 142) = 7{\cdot}0$, $p < 0{\cdot}009$, $d = 0{\cdot}46$]. They made more errors prior to the ED shift stage [$F(1, 142) = 10{\cdot}17$, $p < 0{\cdot}002$]. Fewer AD-HKD boys completed the ED shift stage [$F(1, 142) = 6{\cdot}7$, $p < 0{\cdot}01$], and examination of errors made by boys who did reach the ED Reversal stage (AD-HKD boys, $n = 26$; control boys, $n = 40$), revealed that AD-HKD boys made more errors at this stage [$F(1, 63) = 5{\cdot}4$, $p < 0{\cdot}02$].

Groups differed significantly at the most complex (5-choice) condition of the Reaction Time task. AD-HKD boys were *slower* to respond than controls both in terms of reaction times [$F(1, 133) = 5{\cdot}5$, $p < 0{\cdot}02$, $d = 0{\cdot}71$] and movement times [$F(1, 133) = 3{\cdot}94$, $p < 0{\cdot}05$, $d = 0{\cdot}39$]. Groups did not differ in reaction or movement times at the simple condition (both $F < 1$).

In view of the group differences in BPVS scores a further analysis was conducted on a subset of the sample comprising 47 AD-HKD boys and 47 controls matched for age and BPVS. This broadly confirmed findings for the total group analyses above. Some differences narrowly failed to reach statistical significance [SoC number of problems solved in minimum moves ($F = 3{\cdot}66$, $p = 0{\cdot}059$); total errors on the Paired Associates Learning task ($F = 3{\cdot}33$, $p = 0{\cdot}07$); and stage reached on the ID-ED task ($F = 2{\cdot}87$, $p = 0{\cdot}09$); and movement time latency on the 5-choice condition of the Reaction Time task ($F = 3{\cdot}81$, $p = 0{\cdot}054$). It is likely that these findings simply reflect reduced statistical power due to smaller sample size.

Inter-relationships among tasks

To further examine the role of short-term memory span, strategy, and spatial recognition memory on spatial working memory performance, correlations were conducted between these variables and total between-search errors (BSE) on the Spatial Working Memory task. In view of the multiple comparisons α was adjusted to 0·008. Spatial short-term memory span correlated significantly with BSE for AD-HKD boys ($r = -0{\cdot}473$, $p < 0{\cdot}001$) and control boys ($r = -0{\cdot}533$, $p < 0{\cdot}001$). Strategy score was significantly correlated with total BSE for both AD-HKD boys ($r = 0{\cdot}513$, $p < 0{\cdot}001$) and control boys ($r = 0{\cdot}588$, $p < 0{\cdot}001$). Accuracy on the Spatial Recognition task was also correlated with total BSE for the control ($r = -0{\cdot}351$, $p < 0{\cdot}001$) but not the AD-HKD ($r = -0{\cdot}253$, $p < 0{\cdot}05$) group.

In view of the significant correlations between several task measures and performance on the Spatial Working Memory task, exploratory multiple regression analyses were performed. BSE score was the dependent variable and short-term memory span, strategy score and spatial recognition score were the predictors. Separate analyses, using a backward deletion entry method, were carried out for the AD-HKD boys and the control boys. Spatial span and strategy score were retained in the best fit equation for both groups. For AD-HKD boys these two variables together accounted for approximately 37% of the total variance [$r^2 = 0{\cdot}372$, $F(2, 72) = 21{\cdot}3$, $p < 0{\cdot}001$]. For the control boys, these two variables predicted for

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approximately 49% of the total variance [$r^2 = 0{\cdot}493$, $F(2, 68) = 33{\cdot}0$, $p < 0{\cdot}001$]. Accuracy on the spatial recognition task did not predict performance on the Spatial Working Memory task for either group. There was no evidence of significant multi-co-linearity and the similarities of the values of r^2 and the adjusted r^2 suggest that the models are generalizable. Part correlations indicate that both span and strategy score make independent contributions to BSE score for both the AD-HKD (span $r^2 = 0{\cdot}11$, strategy $r^2 = 0{\cdot}15$) and control (span $r^2 = 0{\cdot}15$, strategy $r^2 = 0{\cdot}21$) groups.

DISCUSSION

These data confirm and extend those published previously (Rhodes *et al*. 2004). AD-HKD boys showed profound impairments of EF in terms of visual working memory, strategy formation, planning, attentional set-shifting and were significantly *slowed* on a reaction time task. Contrary to predictions, inhibitory performance on a Go/No-Go task was unimpaired. Our data suggest that EF impairments cannot be explained on the basis of inhibitory dysfunction. Additionally, profound neuropsychological impairment was evident in aspects of non-executive neuropsychological functioning. AD-HKD boys showed impairments in tasks assessing recognition of patterns and spatial locations, spatial short-term memory span, visual recognition memory, and a spatial delayed response task. Perhaps most importantly, these impairments in executive and non-executive functioning cannot be attributed to exposure to stimulant medications, nor can they be accounted for by differences in verbal intelligence.

Several aspects of the present study design may account for the important differences between these data and those from other studies. Our sample was considerably larger than those previously reported, hence the power to detect differences between AD-HKD boys and healthy boys was increased. One possible consequence of this increased power would be to report statistically significant, but clinically irrelevant, differences between the groups. However, we do not believe this to be the case in the current sample. The effect sizes reported above were all in the medium to strong range and are broadly consistent with those reported in the existing literature (Pennington & Ozonoff, 1996). In addition to meeting DSM-IV criteria for ADHD, the boys in this study also met criteria for the more rigorously defined hyperkinetic disorder as described in ICD-10. Previous studies have, arguably, recruited more homogeneous populations by excluding subjects with co-morbid conditions. Future studies will need to compare neuropsychological functioning across the phenotypic spectrum and to include additional tasks which measure other important processes such as delay aversion and time perception (Castellanos & Tannock, 2002).

EF changes in AD-HKD boys encompass working memory, strategy formation, planning, attentional set-shifting abilities and reaction times. The Spatial Working Memory deficit has previously been described (Rhodes *et al*. 2004). This deficit was negatively correlated with Spatial Span; shorter spans were associated with a greater number of Between Search Errors. Kempton and co-workers (1999) reported similar correlations between these tasks and concluded that impairment was related to a decreased ability to hold multiple elements of spatial information in memory rather than an inability to manipulate this information. Unlike the Kempton study, however, we found impairments in strategy use. Further, strategy use was significantly correlated with between-search error score. Multiple regression analysis confirmed that both Spatial Span and strategy score, along with performance on the Go/No-Go task, correlated significantly with Spatial Working Memory total task variance for both groups. However, in view of the lack of impairments detected on the Go/No-Go task, it is unlikely that inhibition deficits contribute significantly. Thus, the Spatial Working Memory impairment is more likely related to a deficit in spatial short-term memory span and/or strategy formation. Interestingly, performance on the Spatial Recognition task, considered to be an intrinsic component of the Spatial Working Memory task and thus a developmental prerequisite for accurate performance, was not predictive of accuracy on Spatial Working Memory. Thus, recognition impairment does not appear to explain the working memory impairments of the AD-HKD boys.

AD-HKD boys had slower reaction times and were impaired in terms of planning ability and

solved fewer problems in the minimum required moves on the SoC task. SoC performance activates the PFC and connecting areas including the anterior cingulate, striatum, thalamus, and cerebellum (Morris *et al.* 1993; Baker *et al.* 1996; Elliott *et al.* 1997). AD-HKD boys also had lower stage-reached scores on the ID-ED attentional set-shifting task and evident difficulty at the Extra-Dimensional stages. This pattern supports suggestions that frontal lobe functioning is impaired (Owen *et al.* 1991). In particular, these data implicate the anterior frontal lobe (Rogers *et al.* 2000) and support, to an extent, existing dysexecutive models of AD-HKD (Morton & Frith, 1995; Castellanos & Tannock, 2002).

However, in marked contrast to previous studies (e.g. Shue & Douglas, 1992; Iaboni *et al.* 1995; Rubia *et al.* 1999*a*, *b*; 2001*a*, *b*; Castellanos *et al.* 2000), AD-HKD boys performed as well as controls on a Go/No-Go task. One possible criticism of our Go/No-Go task is the relatively high presentation rate of No-Go stimuli (50%). Some positive studies have used lower No-Go rates (e.g. Van der Meere *et al.* 1999, 20%; Rubia *et al.* 2001*a*, 30%) and it is, therefore, possible that the task used in the present study may have been less likely to tax inhibitory processes. However, as several positive studies using a Go/No-Go task have used the same 50% No-Go presentation rate (Shue & Douglas, 1992; Iaboni *et al.* 1995; Castellanos *et al.* 2000) it seems unlikely that differences in this task parameter alone could account for our data. There are, of course, several task parameters that influence performance. We utilized a fast presentation rate with an inter-stimulus interval of 900 ms – a rate which previous studies have shown to be particularly sensitive in detecting impairments in children with AD-HKD (Van der Meere *et al.* 1999). It also seems unlikely that the lack of impairment on the Go/No-Go in our sample was due to sampling differences. Our sample of AD-HKD boys were diagnosed as meeting the more restrictive ICD-10 criteria for HD and were stimulant-medication-naive – both of which factors would probably predict a greater level of impairment. Thus whilst it remains possible that this task is not sensitive to the type of response inhibition that is impaired in AD-HKD, we can see no obvious simple explanations for the absence of inhibitory impairments in our sample. The design could be improved by including other measures of inhibitory ability, such as the Stop Signal Task, and further studies comparing performance on CANTAB tasks with such measures are indicated.

It has been suggested that impairments observed in aspects of EF other than inhibition in AD-HKD are, in fact, secondary to impaired inhibitory responding (Barkley, 1998). Our findings, whilst not ruling out inhibitory dysfunction as a component of AD-HKD, do suggest that inhibitory deficits cannot solely account for the range of executive impairments observed in these children.

Our data do not support earlier conceptualizations of AD-HKD as a dysfunction in a single aspect of EF. They do, however, support the growing literature suggesting impairment across a range of EF (e.g. Kempton *et al.* 1999; Nigg *et al.* 2002; Tripp *et al.* 2002). Development of future models, or refinement of existing models of EF must incorporate the range and complexity of interacting systems involved. Further, our data implicate non-executive neuropsychological impairments as important features of AD-HKD. We have shown impairments on a range of tasks without a prominent executive component. Whilst impairment on the Spatial Recognition task may mirror the performance of frontal lobe damaged patients on this task (Owen *et al.* 1995), the intact performance of lesion patients on Pattern Recognition and Delayed Matching to Sample (Owen *et al.* 1995) differs from our AD-HKD boys. In fact, the performance of AD-HKD boys on these tasks more closely mirrors that of patients with temporal lobe and amygdalo-hippocampal damage. We have, as above, considered the possibility that these deficits may reflect inhibitory dysfunction. AD-HKD boys were more impulsive when responding incorrectly on both tasks. However, latencies for incorrect responding did not predict accuracy of responding on either task. Consequently, as with the EF deficits described above, these impairments are unlikely to be solely ascribable to impaired inhibitory responding.

These deficits in executive and non-executive functioning cannot be accounted for by differences between the two groups with respect to their levels of verbal intelligence. Despite there

being a scheduled break at the mid-point of the testing session and subjects being given the opportunity to take further breaks if required we cannot however rule out the possibility that a proportion of the observed deficit was related to fatigue effects in those tasks carried out later in the testing session.

Our data suggest a potentially important role for the temporal lobes, the amgydala and/or hippocampus in the neuropsychological deficits found with AD-HKD. These are consistent with a recent structural MRI study describing reduced white and gray matter volumes in temporal, parietal, and occipital areas in addition to frontal areas (Castellanos *et al*. 2002). Hence, neuropsychological and structural brain imaging data suggest that AD-HKD is rather more than a 'frontostriatal' disorder of monoaminergic neurocircuitry. Unfortunately, although the current sample is considerably larger than those previously reported in the AD-HKD literature, it is not sufficiently large to conduct a reliable exploratory factor analysis to search for latent variables or fully to explore for heterogeneity. These analyses will be crucial in furthering our understanding of the neuropsychological underpinnings of AD-HKD.

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