Beyond the Dual Pathway Model: Evidence for the Dissociation of Timing, Inhibitory, and Delay-Related Impairments in Attention-Deficit/Hyperactivity Disorder

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Objective: The dual pathway model explains neuro-psychological heterogeneity in Attention Deficit/Hyperactivity Disorder (ADHD) in terms of dissociable cognitive and motivational deficits each affecting some but not other patients. We explore whether deficits in temporal processing might constitute a third dissociable neuropsychological component of ADHD. **Method:** Nine tasks designed to tap three domains (inhibitory control, delay aversion and temporal processing) were administered to ADHD probands (n=71; ages 6 to 17 years), their siblings (n=71; 65 unaffected by ADHD) and a group of non-ADHD controls (n=50). IQ and working memory were measured. **Results:** Temporal processing, inhibitory control and delay-related deficits represented independent neuropsychological components. ADHD children differed from controls on all factors. For ADHD patients, the co-occurrence of inhibitory, temporal processing and delay-related deficits was no greater than expected by chance with substantial groups of patients showing only one problem. Domain-specific patterns of familial co-segregation provided evidence for the validity of neuropsychological subgroupings. **Conclusion:** The current results illustrate the neuropsychological heterogeneity in ADHD and initial support for a triple pathway model. The findings need to be replicated in larger samples. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(4):345–355. **Key words:** ADHD, delay aversion, heterogeneity, inhibitory control, timing

Neuropsychological studies of attention deficit/hyperactivity disorder (ADHD) implicate a broad range of processes.[1] These include executive dysfunction (EDF),[2] for example, inhibitory[3] and working memory (WM)[4] deficits, and nonexecutive deficits, for example, perception,[5] memory,[6] timing,[7] and alterations in motivational processes.[8] However, even the most robust neuropsychological effects are only moderate in size (e.g., 0.3 to 0.6, Cohen's *d*; 2) and fall short of the level required for diagnosis.[9] For example, Nigg et al.[10] found only 30% of patients with deficits on at least three tasks in a large EF battery. This pattern of limited associations across distinct domains highlights the neuropsychological heterogeneity in ADHD.[11] The dual pathway model[12-14] explains this heterogeneity as two, more or less independent, patterns of deficit, each affecting some ADHD patients: one grounded in dorsal fronto-striatal dysregulation mediated by inhibitory based EDF (I-EDF), and the other underpinned by ventral fronto-striatal circuits and linked to altered signaling of delayed rewards and delay aversion (DAv[11,15]). Clinical and preclinical studies provide support for this model,[16-20] although not all studies do.[21] However many patients appear unaffected by either DAv or I-EDF.[17] To our knowledge, this article is the first to explore whether temporal processing deficits (TPD) in ADHD represent a dissociable third neuropsychological "pathway." This is biologically plausible, as magnetic resonance imaging (MRI) suggests that although TPD may share neural components (i.e., basal ganglia[22,23]) with I-EDF and DAv, it is also distinctive in some ways (i.e., cerebellum[24]). This is clinically plausible, as ADHD children have shown TPD across a range of timing tasks.[25-31] Results regarding motor timing are less consistent.[29,32-34] Functional MRI (fMRI) confirms alterations within key components of temporal processing circuits in ADHD.[35]

ADHD involves a complex causal structure,

with both genetic and environmental factors implicated.[10,36,37] Where they mediate genetic effects, neuropsychological deficits (i.e., endophenotypes[38,39]) will be correlated within families and levels of deficits in unaffected family members will be intermediate between their ADHD relatives and unrelated controls. Furthermore, if different endophenotypes mediate specific pathways these familial effects should "breed true"—e.g., siblings of ADHD children with I-EDF should also show I-EDF. Evidence of familial correlation and co-segregation has been reported for I-EDF,[40,41] TPD,[28,42,43] and DAv.[15] Here we explore this further.

We adopted a multivariate methodology with three tasks chosen for each neuropsychological domain to improve measurement reliability and allow the underlying latent structure of neuropsychological deficits to be explored. Performance on the I-EDF tasks (i.e., Stop Signal, Go-No-Go, and a Stroop-like response interference tasks) is intercorrelated and associated with ADHD.[3] For DAv tasks (i.e., Maudsley Index of Delay Aversion; Delayed Frustration Task; Delayed Reaction Time Task), correlations are smaller.[44] For TPD, we assessed time discrimination, reproduction and motor synchronization.[45,25] Our battery also included a simple measure of WM (i.e., WISC digit span). Previous reports suggest that TPD implicates WM problems,[25] although Carelli et al. did not substantiate this,[46] and that I-EDF and WM are closely associated processes,[47] although readers are also referred to Engelhartd et al.[48]

We predicted the following: (a) neuropsychological domains would form independent principal components; (b) there would be significant case–control differences in each domain; (c) subgroups of ADHD individuals would be affected by only one deficit; (d) there would be domain-specific familial effects, i.e., that neuropsychological deficits "would breed" true; and (e) neuropsychological domains would show distinctive patterns of associations in terms of: IQ and oppositional defiant disorder (ODD). Literacy was included because of the possibility of a common role for the cerebellum in reading disorder and ADHD in children with TPD,[49] although this was not substantiated by Ramus et al.[50]

METHOD

Participants

Seventy-one families with an ADHD child participated in the Southampton arm of IMAGE.[51] Seventy-one ADHD probands with a combined type diagnosis (mean [*M*] = 12.03 years, *SD* = 2.34 years), 65 unaffected siblings (*M* = 11.46 years, *SD* = 3.19 years) and 50 non-ADHD controls (*M* = 12.15 years, *SD* = 2.25 years) were included in the key analyses. Six siblings had ADHD and were excluded from the case–control and familiality analyses. Cases (between 6 and 17 years of age) with an existing full clinical diagnosis of ADHD were included in IMAGE if they also fulfilled criteria for a research diagnosis (see below) and had an IQ of at least 70. Patients were excluded if they had a history of clinically significant depression and anxiety or other major mental health problems (e.g., autism, epilepsy). Oppositional defiant disorder (ODD) or obsessive-compulsive disorder (OCD) was not an exclusion criteria. The research diagnostic protocol is described in detail elsewhere.[51] Probands and those siblings with *T* scores > 63 on the Conners' ADHD subscales were administered the Parental Account of Childhood Symptoms (PACS),[52] a semi-structured clinical interview (interrater reliability 0.79 to 0.96).[53] A standardized algorithm was applied to derive the 18 DSM-IV ADHD items. To receive a research diagnosis, children had to do the following: 1) have sufficient PACS symptoms, 2) meet the PACS criteria for impairment, and 3) display at least one symptom in both the hyperactive/impulsive and inattentive domains (i.e., a rating of 2 or 3) on the Conners. Control children attended local schools. Parent and teacher versions of the SDQ[53] confirmed that 15 of the 65 controls initially recruited, scored above the borderline cut-offs for hyperactivity/impulsivity and were excluded. This left a preponderance of female controls (gender $\chi^2(1) = 9.37$, $p < .01$). Table 1 reports the background and clinical characteristics for the three groups.

Tasks and Measures

For more detailed descriptions, readers are referred to Bitsakou et al.[3,44]

I-EDF Tasks.

Stop-Signal Task.[54] On six blocks (the first two blocks were practice) of 32 trials, participants responded to "go" stimuli by pressing a response button and inhibited their response when an auditory stop signal was presented (25% of trials). The go task consisted of "X" and "O." presented in the center of the screen for 1,000 ms (ISI 2,500 ms). The interval between the go signal and stop tone varied to ensure approximately a 50% success rate. The stop signal reaction time (SSRT) was estimated by subtracting the mean stop signal latency from the mean correct go response time in each block.

Go/No-Go task (GNG). On 100 trials, participants responded as fast and accurately as they could to "go" stimuli by pressing the left or right computer mouse button indicating the direction of a green left- or right-pointing arrow, respectively, and inhibited their response when a double-headed arrow ("no-go" stimulus) was presented (25% of trials). The probability of

TABLE 1 Sample and Clinical Characteristics of Attention-Deficit/Hyperactivity Disorder (ADHD) Probands, Their Unaffected Siblings, and Typical Control Cases by Age

	ADHD probands		Unaffected Siblings		Controls			
	6–12 Years	13–17 Years	6–12 Years	13–17 Years	6–12 Years	13–17 Years	Status *F*	*P*
	N = 48	N = 23	N = 40	N = 25	N = 29	N = 21		
Male %	85.4	82.6	55	48	58.6	76.2	16.40[e]	<.001[c]
Age	10.69 (1.41)	14.81 (1.09)	9.45 (2.23)	14.68 (1.22)	10.90 (2.12)	13.89 (0.83)	1.16	.31
WISC-III	*N* = 48	*N* = 23	*N* = 40	*N* = 25	*N* = 29	*N* = 21		
Vocabulary	8.77 (2.85)	8.61 (2.33)	9.00 (2.78)	8.68 (2.61)	10.31 (3.56)	9.14 (3.30)	2.30	.10
Block design	9.42 (2.79)	9.13 (1.91)	9.85 (3.15)	9.40 (2.21)	10.97 (2.32)	9.81 (2.80)	2.85	.06
Full	94.60 (13.66)	93.21 (9.53)	96.51 (14.42)	94.24 (11.45)	103.91 (14.31)	96.85 (15.74)	3.90	<.05[b]
TOWRE	*N* = 46	*N* = 22	*N* = 38	*N* = 23	*N* = 24	*N* = 21		
Total	96.22 (21.40)	88.45 (17.13)	100.61 (20.76)	99.61 (21.93)	108.25 (16.81)	96.29 (14.32)	3.91	<.02[b]
Parent SDQ	*N* = 48	*N* = 23	*N* = 40	*N* = 25	*N* = 29	*N* = 21		
Hyperactivity	8.31 (1.74)	8.26 (2.05)	3.13 (3.05)	2.20 (2.04)	2.14 (1.72)	1.76 (1.64)	164.45	<.001[c]
Total	23.27 (6.55)	20.61 (5.68)	10.53 (8.71)	8.64 (7.59)	6.66 (4.79)	6.00 (3.91)	101.04	<.001[c,d]
Teacher SDQ	*N* = 38	*N* = 18	*N* = 36	*N* = 16	*N* = 24	*N* = 13		
Hyperactivity	6.74 (2.86)	6.94 (2.36)	3.11 (2.42)	4.50 (2.73)	1.29 (1.51)	1.46 (1.05)	63.82	<.001[c,d]
Total	14.61 (7.27)	15.56 (7.26)	6.64 (5.48)	11.31 (8.17)	3.63 (3.62)	3.69 (2.68)	38.79	<.001[c,d]
Parent Conners	*N* = 48	*N* = 23	*N* = 39	*N* = 24	N/A[a]	N/A[a]		
Hyperactivity	83.31 (9.21)	83.39 (10.33)	55.59 (14.82)	54.29 (12.57)			191.45	<.001
Inattention	73.48 (8.47)	75.13 (9.14)	53.08 (12.80)	51.13 (8.20)			158.19	<.001
Total	80.50 (7.95)	82.35 (8.89)	54.59 (14.41)	52.58 (10.64)			213.85	<.001
Teacher Conners	*N* = 40	*N* = 19	*N* = 35	*N* = 18	N/A[a]	N/A[a]		
Hyperactivity	63.53 (14.82)	68.32 (17.47)	49.80 (6.46)	60.17 (14.22)			20.67	<.001
Inattention	61.20 (13.55)	70.32 (13.35)	52.29 (8.90)	59.00 (8.52)			17.67	<.001
Total	63.33 (14.58)	71.95 (13.55)	51.46 (7.42)	60.61 (10.83)			23.44	<.001

Note: SDQ = Strengths and Difficulties Questionnaire; TOWRE = Test Of Word Reading Efficiency; WISC = Wechsler Intelligence Scales for Children.

[a] *Typical controls did not complete parent and teacher Conners' questionnaire.*

[b] *ADHD probands were significantly different from controls.*

[c] *ADHD probands were significantly different from siblings and controls.*

[d] *Siblings were significantly different from controls.*

[e] χ^2

a correct inhibition was the main index of the GNG task.

Modified Stroop Task (MStroop[55]). One hundred trials of congruent or incongruent stimuli were presented. Congruent stimuli (75% of trial) were green left- or right-pointing arrows, and participants had to press a left or right computer mouse button indicating the direction of the green arrows. Incongruent stimuli (25% of trials) were red, left- or right-pointing arrows, and participants had to press the opposite mouse button to that indicated by the red arrows. Probability of inhibitions on the incongruent trials was the dependent variable (MStroop).

DAv tasks.

Maudsley's Index of Childhood Delay Aversion (MIDA[56]). This is a game-like, computer-based, choice delay task.[12] Individuals choose to either wait for 2 seconds and shoot one spaceship (one point) or to wait for 30 seconds to shoot two spaceships (two points). There was no post-reward delay period. There were 15 trials. Children were told that they would get either one or two rewards based on their performance, although the specific cut-off was not revealed. Rewards were stationary items chosen by participants at the end of the session. The percentage of large delayed choices made is the dependent variable (MIDA).

Delay Frustration (DeFT[57]). A series of simple math questions (55 trials) were presented on a computer. Participants selected from four possible answers by pressing buttons on a box. On most trials response was immediately followed by the next trial. On a minority of trials, access to the next question was delayed by 20 seconds (8 trials). On eight distractor trials, the delay period varied from 3 to 10 seconds. The mean total duration of responding per second of delay in the 20 second trials was the dependent variable. For the present analysis, we used responses during the first 10 second, as analysis showed that participants' responses during these two periods may be reflect different processes (i.e., early responses frustration and later responses persistence).

Delay Reaction Time (DRT[58]). On 12 trials and four practice trials, a stimulus (either a left or a right green arrow) appeared on the center of the computer screen for either 3 or 20 seconds. The screen then turned blank, and the participants responded as quickly and accurately as possible to the disappearance of the stimulus, by pressing the left or right mouse button. A DRT index was calculated by subtracting the mean RT score for the two delay levels of the DRT task from the RT on a simple RT condition with no delay, as described in Bitsakou et al.[44]

TPD Tasks.

Tapping.[45] This is an auditory computerized task. An auditory tone was presented every 1,200 ms, and the child had to tap along at the same pace by pressing a response button (15 cued trials). In 41 uncued trials, in which the tone was not present, the child was asked to continue tapping at the previously cued rate. The main index of the task is the variability of tapping on uncued trials, calculated as the within-subject standard deviation.

Duration Discrimination.[25] Participants were presented with two unfilled intervals (target and comparison), each defined by two brief tones (50 ms; 1,000 Hz) at the beginning and end. The target interval of 400 milliseconds was randomly presented as either the first or second duration. The comparison interval was always longer than 400 milliseconds and was adjusted up or down in 10-millisecond increments depending upon the accuracy of the participant's responses. The target and comparison interval were separated by 800 milliseconds and the inter-trial interval was 1,000 milliseconds. Participants were instructed to press the left button on a response box if they thought that the first tone was longer and the right button of a response box if they thought the that second tone was longer. An up–down transformed-response adaptive procedure was used to track 80% accuracy.[59] The procedure stopped after six reversals of direction. The average of the last five reversal values was the dependent measure.[25]

Time anticipation.[45] In this game-like task, participants anticipated when a visual stimulus would reappear. The child beamed oxygen over to a spaceship to save the crew. In block 1 the anticipation interval was 400 milliseconds and in block 2 it was 2,000 milliseconds . In each block the ally spaceship was visible for the first 10 trials, and for the remaining 16 trials participants were asked to press a button to anticipate when it would arrive (i.e., 400 or 2,000 ms). The participant was given feedback after every trial. The mean percentage of total early responses (i.e., made before the ally arrived) was the dependent measure.

Other measures.

Working memory. Forward and backward digit span subscales from the WISC-III[60] were administered. The level at which the participant failed to correctly repeat numbers on two consecutive trials at one level of difficulty was the dependent measure.

IQ. The vocabulary and block design subtests from the WISC-III[61] were used to estimate full-scale IQ.[62]

Reading. The TOWRE test of word reading efficiency[61] was administered. The combined score from the two subscales (sight word efficiency and phonetic decoding efficiency) was used as a reading ability index.

Procedure

Children with ADHD were off medication at least 48 hours before testing. Probands and siblings were tested by different researchers. Full testing took between 2 to 2.5 hours. The tasks within each neuropsychological domain (e.g., MIDA, DeFT and DRT for DAv) were administered in the same order. The three

TABLE 2 Correlations Among Putative Inhibitory Control, Delay Aversion, Temporal Processing, and Working Memory Indices (Age Adjusted)

		1	2	3	4	5	6	7	8	9
Delay-related measures										
1	MIDA									
2	DeFT	0.01								
3	DRT	−0.18*	0.17*							
Inhibitory control measures										
4	SSRT	−0.11	0.08	0.05						
5	GNG	−0.01	−0.21**	−0.08	−0.29***					
6	MStroop	0.20**	−0.22**	−0.12	−0.19**	0.56***				
Temporal processing measures										
7	Tapping	−0.05	0.01	−0.02	0.14*	−0.07	−0.16*			
8	Discrimination	−0.14	0.18*	0.08	0.20*	−0.16*	−0.13	0.23**		
9	Anticipation	−0.04	0.12	0.19*	0.03	−0.14	−0.14	0.15*	0.26**	
Working memory measures										
10	Digit span	0.13	0.07	−0.16*	−0.09	0.03	0.14*	−0.15*	−0.23**	−0.13

Note: DeFT = delay frustration task; DRT = delay reaction time; GNG = go-no-go; MIDA = Maudsley's Index of Delay Aversion; MStroop = modified stroop; SSRT = stop signal reaction time.

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

neuropsychological constructs (i.e., DAv, I-EDF, TPD) were presented in counterbalanced order. Children rested during short breaks. The experimenter remained with each child throughout the task. At the end of the session, all children received a £5 voucher for participation in addition to any MIDA rewards. Ethical approval was received from the University of Southampton, School of Psychology ethics committee and the local National Health Service medical ethics committee. Participants and parents gave written informed consent.

Data Analysis

Principal components factor analysis was used to examine the structure of associations between the tasks. We chose an exploratory over a confirmatory approach because this was the first analysis of its kind in the literature. To maximize statistical power and to allow a common metric by which controls, probands and siblings could be compared all participants were included. Given the correlation between age and performance (eight of nine were significant; $r > -0.24$), test scores were age adjusted using standard regression procedures. Factor scores (item to factor loadings as weightings) were calculated and used to estimate case–control differences using analysis of variance (ANOVA). We checked whether case–control differences were due to group differences in IQ and ODD. The number of ADHD patients (including affected siblings) with a deficit in each of the neuropsychological domains identified in the factor analysis was calculated using cut-offs based on the lowest 10% of scores in the control group (11). We then examined the frequency with which individuals showed one and not another types of deficit. The association between these neuropsychological groupings in the ADHD and comorbid psychiatric problems, IQ, and literacy was examined using multiple regression. Familiality was examined through intersibling correlations and comparisons of 1) probands, unaffected siblings, and controls, and 2) unaffected siblings of probands with and without domain-specific deficit.

RESULTS

Correlations were in general larger within domains (mean $r = 0.22$) than between domains (mean $r = 0.11$) (Table 2). Correlation between putative I-EDF and TPD measures were moderate. Correlations between putative DAv measures were weak and nonspecific. WM was associated with TPD measures and DRT and MStroop. For the principal components analysis there were four factors with Eigenvalues greater than 1 (Table 3). Component 1 (17.25% variance) had high loadings for SSRT, GNG and MStroop only (factor labeled Inhibition). Component 2 (14.68%) had high loadings for TPD items and WM (factor labeled Timing). Components 3 and 4 both implicated delay-related tasks. Component 3 appeared to tap the negative effect of imposed delay (12.95% of the variance) and was associated with poorer DRT performance, increased DeFT responding, and premature responding during time anticipation. A preference for the large

TABLE 3 Component Structure of Inhibitory Control, Delay Aversion, and Temporal Processing Measures

Construct	Measures	Component Inhibition	Timing	Delay-Negative	Delay-Positive
Inhibitory Control	SSRT	**−0.56**	0.21	−0.20	−0.10
	GNG	**0.81**	−0.03	−0.22	−0.08
	MStroop	**0.77**	−0.05	−0.18	0.18
Temporal Processing	Tapping	−0.16	**0.68**	−0.16	0.06
	Discrimination	−0.11	**0.66**	0.20	−0.05
	Anticipation	0.05	**0.51**	**0.52**	−0.06
Delay aversion	MIDA	0.16	0.003	0.09	**0.76**
	DRT	0.02	−0.06	**0.56**	**−0.58**
	DeFT	−0.25	−0.01	**0.70**	0.17
Working memory	Digit span	0.000	**−0.48**	0.08	**0.49**
	Eigenvalue	1.72	1.46	1.29	1.26
	% Variance	17.25	14.68	12.95	12.68

Note: Figures in bold indicate factor loadings greater than 0.4. DeFT = delay frustration task; DRT = delay reaction time; GNG = go-no-go; MIDA = Maudsley's Index of Delay Aversion; MStroop = modified stroop; SSRT = stop signal reaction time.

delayed reward (MIDA), reduced DRT, and better WM loaded on a fourth component (2.68% of the variance), suggesting the productive use of delay. Given their differential loadings, these components were labeled Delay-Negative and Delay-Positive, respectively.

Children with ADHD had poorer scores on all components (Table 4). No gender effects were found. The effects sizes (Cohen's d) were 0.76 for Inhibition; 0.79 for Delay-Negative; 0.67 for Timing, and 0.51 for Delay Positive. Effects remained significant controlling for IQ (Inhibition: $F(1,116) = 17.53$, $p < .001$; Delay Negative: $F(1,116) = 6.67$, $p < .05$; Delay Positive: $F(1,116) = 4.18$, $p < .05$) except for Timing ($F(1,116) = 3.60$, $p = .06$). The presence of ODD had no effect (Inhibition: $F(1,67) = 3.24$, $p = .07$; Timing: $F(1,67) = 0.30$, $p = .86$; Delay-Negative: $F(1,67) = 0.07$, $p = .78$; Delay-Positive: $F(1,67) = 0.001$, $p = .99$).

Figure 1 presents a Venn diagram showing the proportion of ADHD individuals who met threshold for deficits in the Timing, Inhibition, and the Delay domains. To simplify the presentation of this categorical data, we added those who met threshold for Delay-Positive and Delay-Negative and included them in one group. Of the individuals, 71% displayed some neuropsychological deficit. Timing was the most common deficit and Inhibition the least common. Overlap between the different deficits was uncommon and never greater than expected by chance (Inhibition and Delay, $\chi^2 = 0.14$; $p = .91$; Inhibition and Timing, $\chi^2 = 2.75$; $p = .10$; Timing and Delay, $\chi^2 = 1.00$; $p = .32$), with more than 70% of those affected showing just one deficit. Inhibition showed the smallest proportion of "pure" cases (31% vs. 56% for Timing and 60% for any Delay). The three deficit categories were introduced as predictors into multiple regression models with IQ, ODD, and literacy as outcomes. Delay deficits were associated with IQ ($\beta = -0.28$; $p = .012$) and literacy ($\beta = -0.33$; $p = .002$), whereas Timing was significantly associated with literacy only ($\beta = -0.40$; $p < 0.001$). When IQ was added as a predictor, the effects of Delay ($\beta = -0.17$; $p = .11$) but not Timing on literacy ($\beta = -0.30$; $p = .004$) were significantly reduced. Inhibition was associated with neither cognitive outcomes ($p > .3$). No deficit predicted the presence of comorbid ODD ($p > .3$).

The unaffected sibling scores were intermediate between probands and controls scores (Table 4). Probands and siblings were impaired compared with controls on Timing, Delay-Negative and Delay Positive. For Inhibition, probands were more impaired than both unaffected siblings and controls. In contrast, proband–sibling correlations were significant only for Inhibition ($r = 0.31$, $p = .01$) and Timing ($r = 0.34$, $p = .005$; Delay-Negative, $r = -0.08$, $p = .48$; Delay-Positive; $r = 0.009$, $p = .94$). Multiple regressions with proband scores in the four domains as the predictor and sibling scores in each domain as the outcome (forward stepwise procedure) showed that these associations were homotypic in nature; i.e., sibling domain scores were specifically predicted only by probands' scores for Inhibition ($R^2 = 0.09$; $F(1,63) = 6.94$; $p < .05$) and Timing ($R^2 =$

TABLE 4 Inhibition, Timing and Delay-Related Factor Scores: Comparison Between ADHD Probands Versus Unaffected Siblings Versus Control Cases

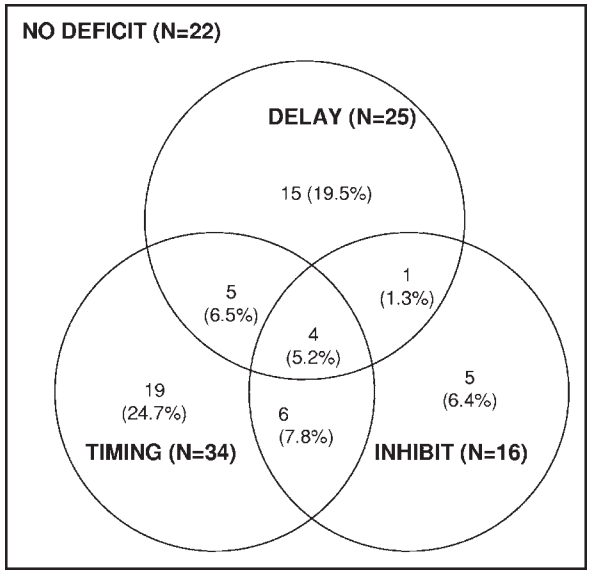
	ADHD Probands		Unaffected Siblings		Controls		ANOVA ADHD vs. Controls			ANOVA ADHD vs. Siblings vs. Controls				Trends (*p*)	
	Male *N* = 60	Female *N* = 11	Male *N* = 34	Female *N* = 31	Male *N* = 33	Female *N* = 17	Status (S)	Gender (G)	S × G	S	G	S × G	Post hoc[a]	Linear	Quadratic
Inhibition	−0.29 (0.97)	−0.46 (1.08)	0.32 (1.15)	−0.28 (0.90)	0.22 (1.03)	0.83 (0.81)	$F_{(1,117)}$ 17.74***	$F_{(1,117)}$ 1.00	$F_{(1,117)}$ 3.24	$F_{(2,180)}$ 9.47***	$F_{(1,180)}$ 0.53	$F_{(2,180)}$ 2.28	1 > 2, 3	.000	.845
Timing	0.30 (1.20)	−0.20 (0.82)	0.15 (1.04)	−0.10 (0.87)	−0.32 (0.61)	−0.55 (0.55)	$F_{(1,117)}$ 5.30*	$F_{(1,117)}$ 3.03	$F_{(1,117)}$ 0.42	$F_{(2,180)}$ 3.85*	$F_{(1,180)}$ 4.19*	$F_{(2,180)}$ 0.26	1, 2 > 3	.001	.407
DN	0.30 (1.11)	0.006 (0.87)	0.12 (0.85)	0.04 (0.93)	−0.40 (0.59)	−0.47 (0.57)	$F_{(1,117)}$ 8.71**	$F_{(1,117)}$ 0.84	$F_{(1,117)}$ 0.32	$F_{(2,180)}$ 4.62*	$F_{(1,180)}$ 4.03*	$F_{(2,180)}$ 1.06	1, 2 > 3	.000	.440
DP	−0.03 (0.93)	−0.32 (0.92)	0.05 (1.06)	−0.37 (0.92)	0.37 (0.90)	0.46 (0.90)	$F_{(1,117)}$ 8.51**	$F_{(1,117)}$ 0.23	$F_{(1,117)}$ 0.86	$F_{(2,180)}$ 5.93**	$F_{(1,180)}$ 1.71	$F_{(2,180)}$ 1.03	1, 2 > 3	.007	.035

Note: ADHD = attention-deficit/hyperactivity disorder; ANOVA = analysis of variance; DN = delay negative; DP = delay positive; 1 = proband; 2 = Sibling; 3 = control.

[a]*Group[s] on the left of the symbol (>) had worse performance.*

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

FIGURE 1 Proportion of Attention-Deficit/Hyperactivity Disorder cases (N = 77) with inhibiton, timing, and delay-related problems and their degree of co-occurrence.



0.11; $F(1,63) = 8.46$; $p < .01$), respectively. Furthermore, siblings of probands with Inhibition deficits were more impaired on Inhibition themselves than siblings of probands without Inhibition deficits ($t(63) = 2.71$, $p < .01$) but showed no other deficits (Timing; $t(63) = 0.04$, $p = .96$; Delay-Negative; $t(63) = -1.21$, $p = .23$; Delay Negative $t(63) = 0.36$, $p = .71$; Table 5). Likewise, siblings whose probands had Timing deficits had higher levels of these themselves ($t(63) = -2.17$, $p < .05$) but not Inhibition, Delay-Negative or Delay Positive ($t(63) = 0.14$, $p = .88$; $t(63) = -0.46$, $p = .64$; $t(63) = -.025$, $p = .80$ respectively). No specific familial effects were evident for the delay factors (Table 5).

DISCUSSION

ADHD is neuropsychologically heterogeneous, with different individuals affected to different degrees in different domains.[12,21] These results extend and refine the dual pathway model of ADHD heterogeneity.[12-14] To our knowledge, our data provide the first evidence that Timing, Inhibition, and Delay deficits in ADHD are dissociable from each other and that substantial subgroups of patients are affected in only one domain. The results therefore run counter to a recent suggestion that timing deficits may be the

TABLE 5 Specificity of Familial Effects: Comparison Between Siblings of Probands With and Without Neuropsychological Impairment in Each Domain

	Siblings of Probands without Inhibition Problems		Siblings of Probands with Inhibition Problems				
Factor score	**Mean**	**SD**	**Mean**	**SD**	***df***	***t***	***p***
Inhibition	**0.21**	**0.84**	**−0.54**	**0.86**	**63**	**2.71**	**.009**
Timing	0.03	1.00	0.02	0.80	63	0.04	.96
Delay negative	−0.04	0.92	0.39	1.67	63	−1.21	.23
Delay positive	−0.13	0.98	−0.25	1.17	63	0.36	.71
	Siblings of Probands without Timing Problems		**Siblings of Probands with Timing Problems**				
Factor score	**Mean**	**SD**	**Mean**	**SD**	***df***	***t***	***p***
Inhibition	0.10	0.95	0.06	0.82	63	0.14	.88
Timing	**−0.20**	**0.85**	**0.29**	**1.02**	**63**	**−2.17**	**.03**
Delay negative	−0.02	1.35	0.09	0.68	63	−0.46	.64
Delay positive	−0.18	1.02	−0.11	1.01	63	−0.25	.80
	Siblings of Probands without DN Problems		**Siblings of Probands with DN Problems**				
Factor score	**Mean**	**SD**	**Mean**	**SD**	***df***	***t***	***p***
Inhibition	−0.07	0.87	0.35	0.87	63	−1.88	.06
Timing	0.06	1.01	−0.01	0.89	63	0.33	.73
Delay negative	**−0.003**	**1.21**	**0.09**	**0.82**	**63**	**−0.34**	**.73**
Delay positive	−0.21	1.02	−0.03	1.01	63	−0.68	.49
	Siblings of Probands without DP Problems		**Siblings of Probands with DP Problems**				
Factor score	**Mean**	**SD**	**Mean**	**SD**	***df***	***t***	***p***
Inhibition	0.02	0.86	0.49	1.05	63	−1.38	.17
Timing	0.05	1.00	−0.08	0.70	63	0.36	.71
Delay negative	0.06	1.09	−0.17	1.02	63	0.58	.56
Delay positive	**−0.09**	**1.02**	**−0.54**	**0.85**	**63**	**1.16**	**.24**

Note: *Bold figures highlight the results in terms of the same specific deficit displayed by probands and siblings. DP = delay positive; DN = delay negative.*

underlying core of the diverse range of problems seen in ADHD.[35] The strongest evidence for familial effects came for Inhibition[40,63-67] and Timing.[28,41-43] Indeed siblings of probands with impairment in one of these domain also tended only to have problems in these domains, indicating that Inhibition and Timing deficits in ADHD breed true. Consistent with the previous inconsistent literature,[63,68,69] evidence was much weaker for the familial basis of the Delay components: Whereas levels of sibling impairment were intermediate between controls and probands, sibling correlations were weak and there was no evidence of cosegregation. Finally, there was a degree of domain specific association. Timing was associated with reading problems. Delay problems were associated with low IQ and reading problems, although reading effects were mediated by IQ.

Our findings challenge the delay aversion model[70] in which delay-related processes in ADHD are seen as a single overarching construct. In fact, in the present study, two components were found. The first associated with negative performance in the face of imposed delay (i.e., DRT and DeFT), including time anticipation.

The second was associated with performance that depended on a commitment to wait for a desired outcome or persist in a task even when this was not imposed (e.g., MIDA and working memory). Clearly much more work is required to establish these as separate components. Our prior analysis of performance on the "DAv" tasks[44] supported a DAv single factor consisting of loosely associated test scores. When set alongside tasks tapping other domains, it becomes clear that the situation is more complex than originally thought.

The current study had a number of limitations. First, the sample used was small for the examination of subgroups; in the future, much larger studies using measures from multiple domains are required to replicate these findings. The current analysis should be seen as exploratory and illustrative. Second, measurement of working memory and intelligence was limited.

From a clinical perspective highlighting the neuropsychological heterogeneity of ADHD encourages us to explore 1) the possibility of the existence of neuropsychological subtypes and 2) the significance of specific neuropsychological deficits as both moderators of treatment effects and novel putative treatment targets.

In terms of the first point, assuming that such subtypes can be replicated in larger samples and validated using clinical outcomes, the current results would provide some support for the establishment of neuropsychological subtypes in ADHD with distinctions drawn between, for instance, Inhibitory and Timing ADHD subtypes. In terms of the second point, recent studies suggest that cognitive training on executive tasks may have efficacy as a treatment for ADHD.[71] The current results highlight the possibility that such training will be more effective if it is targeted and tailored for children with problems in the executive domain (e.g., I-EDF), whereas training that strengthens temporal processing or delay-related functions might be more effective for patients with these types of deficits. &

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