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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Abstract

Objectives: 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 sub-groupings.

Conclusion: The current results illustrate the neuropsychological heterogeneity in ADHD and initial support for a triple pathway model. The findings need to replicated in larger samples.

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]) e.g, inhibitory [3] and working memory (WM [4]) deficits), non-executive deficits (e.g. 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. .3 to .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), the other underpinned by ventral fronto-striatal circuits and linked to altered signalling of delayed rewards, manifest as delay aversion (DAv [11,15]). Clinical and pre-clinical studies provide support for this model [16-20] (but see [21]). However many patients appear unaffected by either DAv or I-EDF. [17] This paper is the first to explore whether temporal processing deficits (TPD) in ADHD represent a dissociable third neuropsychological 'pathway'. This is biologically plausible as 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]). It is clinically plausible as ADHD children have shown TPD across a range of timing tasks. [25-31] Results on motor timing are less consistent. [29, 32-34] fMRI confirms alterations within key components of temporal processing circuits in ADHD. [35]

ADHD has a complex causal structure with both genetic and environmental factors implicated. [36,37,10] 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 inter-correlated 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] (but see [46]) and I-EDF and WM are closely associated processes [47] (but see [48]).

We predicted; (a) that neuropsychological domain will form independent principal components; (b) significant case-control differences in each domain; (c) sub-groups of ADHD individuals affected by only one deficit; (d) domain specific familial effects – neuropsychological deficits will breed true and; (e) neuropsychological domains will 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] (but see [50]).

Methods

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 (*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 (aged between 6 and 17 years) 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). ODD or CD was not an exclusion criteria. The research diagnostic protocol is described in detail elsewhere (see [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 (inter-rater reliability ranging from .79 to .96) [53] A standardized algorithm was applied to derive the 18 DSM-IV ADHD items. To receive a research diagnosis, children had to; (i) have sufficient PACS symptoms, (ii) meet the PACS criteria for impairment and (iii) 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 females controls (gender $\chi^2(1) = 9.37$, $p < .01$). Table 1 reports the background and clinical characteristics for the three groups. .

Insert Table 1 about here

Tasks & Measures

For more detailed descriptions see Bitsakou et al. [3,44]

A) I-EDF tasks

i) Stop-Signal Task [54] : On six blocks (the first 2 blocks were practice) of 32 trials participants responded to 'go' stimuli by pressing a response button and inhibited their response when a auditory stop signal was presented (25% of trials). The go task consisted of "X" and "O", presented in the centre of the screen for 1000ms (ISI 2500ms). 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.

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

iii) Modified Stroop Task (MStroop [55]). 100 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).

B) DAv tasks

i) 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 (1 point) or to wait for 30 seconds to shoot two spaceships (2 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).

ii) 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 seconds as analysis showed that participants' responses during these two periods may be reflect different processes (i.e. early responses frustration and later responses persistence).

iii) Delay Reaction Time (DRT [58]): On 12 trials (and 4 practice trials) a stimulus (either a left or a right green arrow) appeared on the centre 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 (see [44] for details).

C) TPD tasks

i) Tapping [45]: This is an auditory computerised task. An auditory tone was presented every 1200 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.

ii) Duration Discrimination [25]: Participants were presented with two unfilled intervals (target and comparison), each defined by two brief tones (50ms, 1000Hz) at the beginning and end. The target interval of 400ms was randomly presented as either the first or second duration. The comparison interval was always longer than 400ms and was adjusted up or down in 10ms increments depending upon the accuracy of the participant's responses. The target and comparison interval were separated by 800 ms and the inter-trial interval was 1000 ms. Participants were instructed to press the left button on a response box if they thought the first tone was longer and the right button of a response box if they thought the second tone was longer. An up-down-transformed-response adaptive procedure was used to track 80% accuracy. [59] The procedure stopped after 6 reversals of direction. The average of the last 5 reversal values was the dependent measure. [25]

iii) 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 400ms and in the block 2 it was 2000ms.

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 2000ms). 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 sub-scales (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 1/2 hours. The tasks within each neuropsychological domain (e.g., MIDA, DeFT and DRT for DAv) were administered in the same order. The three 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 NHS medical ethics committee. Participants and parents gave written informed consent.

Analytical strategy

(i) 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 allow a common metric by which controls, probands and siblings could be compared all participants were included. Given the correlation between age and performance (8 out of 9 were significant; r > -.24), test scores were age-adjusted using standard regression procedures.

(ii) Factor scores (item to factor loadings as weightings) were calculated and used to estimate case-control differences using ANOVA. We checked whether case-control differences were due to group differences in IQ and ODD.

(iii) 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 percent of scores in the control group (11). We then examined the frequency with which individuals showed one and not another types of deficit.

(iv) The association between these neuropsychological groupings in the ADHD and comorbid psychiatric problems, IQ and literacy was examined using multiple regression.

(v) Familiality was examined through inter-sibling correlations and comparisons of; (i) probands, unaffected siblings and controls and (ii) unaffected siblings of probands with and without domain specific deficit.

Insert Table 2 and Table 3 about here

Results

Correlations (Table 2) were in general larger within domains (Mean *r* =.22) than between domains (Mean *r* =.11). Correlation between putative I-EDF and TPD measures were moderate. Correlations between putative DAv measures were weak and non-specific. WM was associated with TPD measures and DRT and MStroop. For the principle components analysis there were four factors with eigen values greater than one (Table 3). Component one (17.25% variance) had high loadings for SSRT, GNG and MStroop only (factor labelled *Inhibition*). Component two (14.68%) had high loadings for TPD items and WM (factor labelled *Timing*). The third and fourth components both implicated delay-related tasks. Component three 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 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 labelled *Delay-Negative* and *Delay-Positive* respectively.

Insert Table 4 about here

Children with ADHD had poorer scores on all components (Table 4). No gender or effects were found. The effects sizes (Cohen's d) were .76 for Inhibition; .79 for Delay-Negative; .67 for Timing and .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: $F(1,67) = 0.001$, $p=.99$).

Insert Figure 1 about here

Figure 1 presents a Venn diagram showing the proportion of ADHD cases who met threshold for deficits in the Timing, Inhibition and the Delay domains. In order 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. Seventy one percent of cases displayed some neuropsychological deficit. Timing was the most common deficit and Inhibition the least. 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 over 70 percent of those affected showing just one deficit. Inhibition showed the smallest proportion of 'pure' cases (31% compared to 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 ($\beta=-.28$; $p=.012$) and literacy ($\beta=-.33$; $p=.002$) while Timing was significantly associated with literacy only ($\beta=-.40$; $p<0.001$). When IQ was added as a predictor the effects of Delay ($\beta=-.17$; $p=.11$) but not Timing on literacy ($\beta=-.30$; $p=.004$) 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 to controls on Timing, Delay-Negative and Delay Positive. For Inhibition probands were more impaired than both unaffected siblings and controls. Trends analysis suggested that siblings' were intermediate relative to ADHD probands and control cases except for Delay-Positive. In contrast proband-sibling correlations were significant only for Inhibition (r=.31, p=.01) and Timing (r=.34, p=.005; Delay-Negative- r=-.08, p=.48; Delay-Positive; r=.009, p=.94). Multiple regressions with proband scores in the four domains as the predictor and sibling scores on 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 =.09; F(1,63)=6.94; p<.05) and Timing (R^2 =.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).

Insert Table 5 about here

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] Our data provides the first evidence that Timing, Inhibition and Delay deficits in ADHD are dissociable from each other and that substantial sub-groups of patients are affected in only one domain. The results therefore run counter to a recent suggestion that timing deficits may be the underlying core of the diverse range of problems seen in ADHD. [35] The strongest evidence for familial effects came for Inhibition [63-67,40] and Timing. [41-43,28] Indeed siblings of probands with impairment in one of these domain also tended also to have problems in these domains: Inhibition and Timing deficits in ADHD breed true. Consistent with the previous inconsistent literature [68,69,63] evidence was much weaker for the familial basis of the Delay components: While levels of sibling impairment were intermediate between controls and probands, sibling correlations were weak and there was no evidence of co-segregation. 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 - though 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 sub-groups and in 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; (i) the possibility of the existence of neuropsychological subtypes and (ii) the significance of specific neuropsychological deficits as both moderators of treatment effects and novel putative treatment targets. In terms of (i), assuming they can be replicated in larger samples and validated using clinical outcomes the current results would provide some support for the establishment of neuropsychological sub-types in ADHD with distinctions drawn between, for instance, Inhibitory and Timing ADHD subtypes. In terms of (ii), 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), while training that strengthens temporal processing or delay-related functions might be more effective for patients with these types of deficits.

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Table 1: Sample and clinical characteristics of 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 (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

Table 2: Correlations between 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	*.01*								
3	DRT	*-.18**	*.17**							
Inhibitory control measures										
4	SSRT	-.11	.08	.05						
5	GNG	-.01	-.21**	-.08	*-.29****					
6	MStroop	.20**	-.22**	-.12	*-.19***	*.56****				
Temporal processing measures										
7	Tapping	-.05	.01	-.02	.14*	-.07	-.16*			
8	Discrimination	-.14	.18*	.08	.20*	-.16*	-.13	*.23***		
9	Anticipation	-.04	.12	.19*	.03	-.14	-.14	*.15**	*.26***	
Working memory measures										
10	Digit Span	.13	.07	-.16*	-.09	.03	.14*	-.15*	-.23**	-.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.

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	**-.56**	.21	-.20	-.10
	GNGI	**.81**	-.03	-.22	-.08
	MStroop	**.77**	-.05	-.18	.18
Temporal Processing	Tapping	-.16	**.68**	-.16	.06
	Discrimination	-.11	**.66**	.20	-.05
	Anticipation	.05	**.51**	**.52**	-.06
Delay Aversion	MIDA	.16	.003	.09	**.76**
	DRT	.02	-.06	**.56**	**-.58**
	DeFT	-.25	-.01	**.70**	.17
Working Memory	Digit Span	.000	**-.48**	.08	**.49**
	Eigenvalue	1.72	1.46	1.29	1.26
	% Variance	17.25	14.68	12.95	12.68

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.

Table 4: Inhibition, Timing and Delay-related factor scores comparison between ADHD probands vs. unaffected siblings vs. control cases

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

Note: DN = Delay Negative; DP = Delay Positive; S.D. = Standard Deviation; 1 = Proband; 2 = Sibling; 3 = Control

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

[a] > indicates that the group(s) on the left of the symbol had worse performance

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*	*S.D.*	*Mean*	*S.D.*	*df*	*t-value*	*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*	*S.D.*	*Mean*	*S.D.*	*df*	*t-value*	*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*	*S.D.*	*Mean*	*S.D.*	*df*	*t-value*	*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*	*S.D.*	*Mean*	*S.D.*	*df*	*t-value*	*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: DP = Delay Positive; DN = Delay Negative; S.D.=Standard Deviation;

Figure 1: The proportion of ADHD cases (N=77) with Inhibiton, Timing and delay-related problems and their degree of co-occurrence.