

Neuropsychological correlates of emotional lability in children with ADHD

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Abstract

Background: Emotional lability (EL) is commonly seen in patients with Attention Deficit/Hyperactivity Disorder (ADHD). The reasons for this association are currently unknown. To address this question we examined the relationship between ADHD and EL symptoms, and performance on a range of neuropsychological tasks to clarify whether EL symptoms are predicted by particular cognitive and/or motivational dysfunctions and whether these associations are mediated by the presence of ADHD symptoms.

Methods: A large multi-site sample of 424 carefully diagnosed ADHD cases and 564 unaffected siblings and controls aged 6 to 18 years performed a broad neuropsychological test battery, including a Go/No-Go Task, a warned 4-choice Reaction Time task, the Maudsley Index of Childhood Delay Aversion, and Digit span backwards. Neuropsychological variables were aggregated as indices of processing speed, response variability, executive functions, choice impulsivity and the influence of energetic and/or motivational factors.

EL and ADHD symptoms were regressed on each neuropsychological variable in separate analyses controlling for age, gender and IQ, and, in subsequent regression analyses, for ADHD and EL symptoms respectively.

Results: Neuropsychological variables significantly predicted ADHD and EL symptoms with moderate to low regression coefficients. However, the association between neuropsychological parameters on EL disappeared entirely when the effect of ADHD symptoms was taken into account, revealing that the association between the neuropsychological performance measures and EL is completely mediated statistically by variations in ADHD symptoms. Conversely, neuropsychological effects on ADHD symptoms remained after EL symptom severity was taken into account.

Conclusions: The neuropsychological parameters examined here predict ADHD more strongly than EL. They cannot explain EL symptoms beyond what is already accounted for by ADHD symptom severity. The association between EL and ADHD cannot be explained by these cognitive or motivational deficits. Alternative mechanisms, including overlapping genetic influences (pleiotropic effects), and/or alternative neuropsychological processes need to be considered.

Keywords: ADHD, neuropsychological performance, emotional lability, executive functions, delay aversion

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is frequently accompanied by symptoms of emotional lability (EL)¹ such as irritability, hot temper and sudden unpredictable shifts towards negative emotions (Sobanski et al., 2010; Surman et al., 2011; Biederman et al., 2011). The presence of EL is clinically relevant as it is associated with increased severity of ADHD core symptoms, particularly hyperactivity-impulsivity, elevated rates of comorbid conditions (such as oppositional defiant disorder, depression, anxiety, and substance abuse), more functional impairment and a worse long-term course (Barkley & Fischer, 2010; Hinshaw, 2003; Maedgen & Carlson, 2000; Sobanski et al., 2010; Spencer et al., 2011; Stringaris, Cohen, Pine, & Leibenluft, 2009; Stringaris & Goodman, 2009a).

EL can result from increased bottom-up emotional reactivity and/or reduced top-down emotional regulation skills², implicating possible dysfunctions of various subcortical (e.g. amygdala, hippocampus, and ventral striatum) and/or cortical brain regions or an

altered connectivity between those regions (Meyer-Lindenberg et al., 2006). The amygdala has a strategic role in emotional reactivity by modulating perceptual sensitivity to incoming information and generating an automatic, transient emotional response and subsequent subjective emotional experience, including emotional expressive behaviors and heightened autonomic reactivity. The up- and down-regulation of emotions associated with modulation of neural activity in the amygdala has been shown to be associated with a prefrontal network, including the lateral prefrontal cortex, the anterior cingulate cortex and the orbitofrontal cortex (Wessa & Linke, 2009). An alternative explanation implicated the insula with its rich connections to the ACC and OFC (Craig, 2008).

The causes of the association between ADHD and EL are unknown. Earlier studies indicate that indeed both components of emotion processing, emotional reactivity and regulation skills, might be altered in children with ADHD (Maedgen & Carlson, 2000; Martel, 2009; Melnick & Hinshaw, 2000; Walcott & Landau, 2004). Recently, we showed that EL symptoms are not a mere epiphenomenon of ADHD symptom severity and can only partially be explained by the level of psychiatric comorbidity (Sobanski, et al., 2010). However, the frequent occurrence of EL in patients with ADHD might arise from risk factors or pathophysiological components that influence both ADHD and EL symptoms. Alterations in multiple brain networks and neuropsychological impairments have been implicated in the aetiology of ADHD.

¹Other mood- and emotion-related terms such as emotional dysregulation, deficient emotional self-regulation, affective lability and mood instability have often been used interchangeably in the literature (see: [Skirrow, McLoughlin, Kuntsi, & Asherson \(2009\)](#) for review).

² Most theoretical accounts agree that emotion processing includes different mechanisms and multiple stages. Bottom-up and top-down processes may be inseparable when examined at the behavioral level, but functional imaging, psychophysiological and animal studies show that they are distinguishable at a neural level (Wessa & Linke, 2009). EL symptoms may reflect different underlying etiological mechanisms in the context of different disorders and normal development.

Thus, recent models posit the existence of multiple neurodevelopmental pathways to the disorder and of subgroups of patients with different profiles of neuropsychological dysfunctions (Nigg & Casey, 2005; Sonuga-Barke, 2002). These dysfunctions include a slightly lower general cognitive ability, executive function deficits (e.g. inhibitory control, working memory), reduced processing speed and efficiency (slow and variable reaction times), impulsive preference for immediate rewards, aversion to delay, and regulation skill deficits of psycho-physiological state during periods of under- or over-activation (Willcutt, Sonuga-Barke, Nigg, & Sergeant, 2008). While these neuropsychological alterations and the related brain dysfunctions are not specific to ADHD (Banaschewski et al., 2005), they might nevertheless explain the frequent co-occurrence of ADHD and EL symptoms.

Thus, both sets of symptoms have been suggested to result from executive dysfunctions caused by a primary inhibitory control deficit (Barkley, 2010). Contrary to this hypothesis, previous studies found that behavioural disinhibition predicted only a small amount of variability in emotional regulation in ADHD (Melnick & Hinshaw, 2000; Walcott & Landau, 2004). However, these studies investigated small samples and the contribution of deficits in different domains of executive functioning (e.g., inhibitory control, working memory) to EL have yet to be systematically investigated.

EL and ADHD symptoms might also be influenced by motivational alterations. One of the most robust motivational markers in ADHD is the preference for immediate smaller over delayed larger rewards

in simple choice tasks in ADHD (Luman, Oosterlaan, & Sergeant, 2005; Marco et al., 2009; Paloyelis, Asherson, & Kuntsi, 2009; Sonuga-Barke, 2002; Tripp & Alsop, 2001). This has been argued to result from the combination of an impulsive drive for immediate reward and an emotional aversion to delay (hence: 'delay aversion'; Marco, et al., 2009; Paloyelis, et al., 2009). Because ADHD has been associated with heightened levels of frustration during long and boring tasks (Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2009) and with hyper-activation in the amygdala, when reward is delayed (Plichta et al., 2009), children with ADHD and EL might be characterized by a particularly strong negative emotional response during delay.

According to the cognitive-energetic model, children with ADHD might have particular difficulties in effectively allocating effort to regulate their sub-optimal psycho-physiological states during periods of under- or over-activation, which, for example, might be induced by changes in reward and/or event rates (Sergeant, 2000, 2005). Findings that show that the manipulation of task conditions such as event rate (Kuntsi, Wood, van der Meere, & Asherson, 2009; Sergeant, 2000, 2005; van der Meere, Marzocchi, & De Meo, 2005) or rewards (Kuntsi et al., 2009; Konrad, Gauggel, Manz, & Scholl, 2000; Uebel et al., 2010) or the combination of both factors (Kuntsi et al., 2009, 2010; Andreou et al., 2007) can substantially improve their reaction time performance, are consistent with this model. Psychophysiological under- or over-activation might also lead to increased emotional lability.

Slow and variable reaction times

under slow unrewarded task conditions are two closely related variables that are among the best discriminating variables between ADHD and control samples (Kuntsi, Oosterlaan & Stevenson, 2001; Kuntsi, et al., 2009; Kuntsi et al., 2010). The underlying processes and their relationship to emotion processing are currently unknown but it is feasible that the processes that lead to inconsistent reaction times could reflect general regulatory processes that impact in addition on emotion regulation (discussed in Skirrow et al., 2009). Recent theoretical models, which are not necessarily mutually exclusive, have proposed that increased response variability may reflect momentary attentional lapses, insufficient regulation of arousal, deficient extinction processes, or dysfunctional timing mechanisms (for a review see: Kuntsi & Klein, 2012).

Currently, it is unknown whether the frequent occurrence of EL in children with ADHD might be explained by the presence of particular cognitive and/or motivational dysfunctions. Here we studied the nature of the relationship between ADHD symptoms and EL, with a broad range of neuropsychological performance parameters implicated in ADHD, in a large sample of diagnosed ADHD cases, healthy controls, and siblings of both. Two main questions were addressed. First, whether EL symptoms are predicted by the neuropsychological alterations that have been previously shown to be implicated in ADHD; and second, whether ADHD symptoms explain the relationships between neuropsychological performance parameters and EL or whether there are independent effects of the cognitive

functions on EL. We thus tested the statistical associations between neuropsychological variables and EL, and whether these become attenuated or remain stable when the effect of ADHD symptoms is taken into account.

METHODS

Sample

The sample consisted of 366 ADHD probands and 359 siblings, ascertained as part of the International Multicentre ADHD Genetics project, plus 263 controls including 99 sibling pairs and 65 singletons. MAGE samples were excluded from these analyses if the ADHD, EL and neuropsychological data were not available. All participants were of European descent and aged 6 to 18 years. Probands had a research diagnosis of DSM-IV combined subtype ADHD. Siblings included both affected and unaffected individuals (for a detailed description see Brookes et al., 2006; Chen et al., 2008; Müller et al., 2011a, 2011b). For this analysis we included only one sibling per proband family. Sibling selection was based first on gender and second on nearest age to the index proband. Controls were recruited from primary (ages 6-11 years) and secondary (ages 12-18 years) schools in the UK, Germany, and Spain, aiming for an age and gender match with the clinical sample. Case and control exclusion criteria were IQ < 70, autism spectrum disorders, epilepsy, brain disorders, and genetic/medical disorders that might mimic ADHD (see also: Kuntsi et al., 2010).

The final sample in this study consisted of 988 individuals: 411 were classified as combined subtype ADHD (including 45 affected siblings), 13 siblings who met criteria for the hyperactive-

impulsive or inattentive subtypes, and 564 individuals who were unaffected siblings and controls. Of the 411 individuals with combined-subtype ADHD, 103 had conduct disorder, 269 had oppositional defiant disorder, and 42 had possible mood disorder (excluding bipolar disorder). Ethical approval was obtained from local ethical review boards. Informed written consent was obtained from parents and children, respectively.

Measures

Clinical Symptoms

Diagnosis of ADHD and comorbid disorders according to DSM-IV-criteria were based on the Parental Account of Childhood Symptoms-Revised interview (Chen & Taylor, 2006); a semi-structured, standardized, investigator-based interview, assessing ADHD and other child psychiatric disorders according to DSM-IV, with good inter-rater reliability, predictive and discriminative validity (Taylor, Schachar, Thorley, & Wieselberg, 1986; Chen et al., 2008). Symptom ratings were based on the Conners' Parent and Teachers Rating Scales-Revised (Conners, Sitarenios, Parker, & Epstein, 1998a, 1998b). Mean scores of the parent- and teacher-rated scales for ADHD total symptoms, inattention, hyperactivity/impulsivity, and emotional lability were computed as measures of the corresponding symptom dimensions.

Neuropsychological Tasks

Wechsler Intelligence Scales for Children, Third Edition: The vocabulary, similarities, picture completion, and block design subtests from the WISC-III (Wechsler, 1991) were used to obtain an IQ estimate (Sattler, 1992). Digit span backwards of the WISC-III was included as a measure

of working memory.

The Go/No-Go Task: On each trial, 1 of 2 possible stimuli appeared for 300 milliseconds in the middle of the computer screen. Participants were instructed to respond as quickly as possible only to the "go" stimuli while maintaining a high level of accuracy. The proportion of "go" to "no-go" stimuli was 4:1. There were 3 conditions (slow, fast, and slow-incentive), matched for task duration (Uebel, et al., 2010). The slow condition had an inter-stimulus interval (ISI) of 8 seconds (72 trials). The fast condition had an ISI of 1 second (462 trials). In the incentive condition participants could earn points for correct responses which were exchanged for real prizes after the game. The order of condition presentation varied randomly across participants. Dependent variables were mean reaction time (MRT), standard deviation of individual reaction times (RTV), commission, and omission errors.

The Fast Task: A standard warned 4-choice RT task (72 trials) was the baseline condition (Andreou, et al., 2007; Kuntsi, et al., 2010). At the start of the trial a warning signal (4 empty circles, arranged side by side) appeared on the screen. After 8 seconds (presentation interval for the warning signal), the circle designated as the target signal for that trial was colored in. Participants were asked to press the response key that corresponded in position to the location of the target. After a response, the stimuli disappeared from the screen and a fixed inter-trial interval of 2.5 seconds followed. Speed and accuracy were emphasized equally. If no response occurred within 10 seconds, the trial was terminated.

Comparison conditions with a fast event rate (1 second instead of 8) and incentives followed the baseline condition. During the incentive condition participants could win smiley faces for quick response were exchanged for real prizes after the game (see:Andreou, et al., 2007).

In line with our previous analyses (Kuntsi et al., 2010), neuropsychological variables of the fast task and the Go/No-Go task were aggregated for subsequent analyses. Mean scores were obtained for: MRT and RTV across baseline conditions, as indices of 'processing speed' and 'response variability'; and for omission and commission error rates, as indices of 'attentional lapses' and 'inhibitory dysfunction' on both tasks. Bivariate model-fitting analyses had indicated that the variables that were aggregated as mean scores show a large degree of familial overlap and that these mean scores yield valid measures (Kuntsi et al., 2010).

In addition, we included difference scores in terms of MRT and RTV between the a) fast and slow (baseline) conditions of the Go/No-Go Task, b) slow-incentive and slow (baseline) conditions of the Go/No-Go Task, and c) fast-incentive and slow (baseline) conditions of the Fast task, as measures of performance change across conditions induced by 'energetic' and/or motivational' factors. The latter variables indicate performance dependency on extrinsic factors and thus self-regulation problems of arousal and activation states according to the task requirements.

The Maudsley Index of Childhood Delay Aversion (MIDA):

Participants choose between a smaller, immediate reward (one point involving a 2-second) and a larger delayed reward (two points

involving a 30-second pre-reward delay) under two conditions (Marco, et al., 2009). In the no-post reward-delay condition, choosing the smaller reward led immediately to the next trial, reducing the overall length of task delay; in the post-reward delay condition, choosing the smaller reward led to a delay period of 30 seconds, whereas choosing the large reward led to a delay period of 2 seconds before the next trial (i.e., giving a constant trial length). The variables obtained from the task were the percentage of choices for the smaller, respectively larger reward, for each condition separately, controlling for total number of trials attempted. The percentage of choices of the smaller reward in the no-post-reward delay condition of the MIDA was used as an index of 'choice impulsivity'; the percentage of choices of the smaller reward in the post-reward delay condition was used as an index of 'impulsive drive to immediate reward'; and the difference in percentage of choices of the smaller reward between both the no-post-reward and post-reward delay conditions were computed as an index of 'delay aversion'.

A minimum of a 48-h medication-free period was required prior to testing. Go/no-go data were available from 826, digit span backwards data from 854, fast task data from 823, and MIDA task data from 886 participants. Two of the sites did not administer the go/no-go task, two did not administer the fast task, and there were occasional technical problems with equipment.

Statistical analyses

To analyse the effects of neuropsychological variables on the ADHD score (mean parent and teacher, age and gender standardized, Conners' ADHD score) and EL

score (mean parent and teacher, age and gender standardized Conners' EL score), general linear models (GLM) for correlated observations were applied to account for stochastic dependence of sibling data. For these analyses all variables (except gender) were standardized using the standard deviation of the control group. Thus, coefficients are comparable to beta coefficients. Separate GLM analyses were conducted to investigate the effect of ADHD on EL and the effects of each neuropsychological variable on ADHD and EL. Further, for each neuropsychological variable it was assessed whether the effect on EL remained significant when controlling for ADHD and vice versa.

Results

Background, clinical and neuropsychological variables for probands with ADHD, siblings of probands, and controls are given in Table 1. Correlations between processing speed, respectively response variability (measured as average MRT and RTV across Go/No-go task [slow condition] and Fast task [baseline condition]), and differences in MRT (Δ MRT) and RTV (Δ RTV) between incentive/fast and baseline condition (fast task) were as high as $-.73$ (Δ MRT) and $-.58$ (Δ RTV) for processing speed, respectively $-.71$ (Δ MRT) and $-.78$ (Δ RTV) for reaction time variability. All other correlations (between processing speed and response variability with performance change measures induced by either energetic or motivational factors) were in the range between $-.38$ and $-.68$.

We adopted a mediation model to delineate the degree to which ADHD symptoms might explain the effects of neuropsychological dysfunctions on EL symptoms, i.e., whether the

statistical associations between neuropsychological variables and EL become attenuated or remain stable when the effect of ADHD symptoms are taken into account (Baron & Kenny, 1986). ADHD symptoms were regressed on each neuropsychological variable in separate analyses, controlling for age, gender and IQ (Table 2). All neuropsychological variables significantly predicted ADHD symptoms apart from the 'delay aversion' variable. Standardized regression coefficients (SRC) were moderate ($>.35$ and $<.5$) for MRT and RTV, and omission errors; and low ($>.15$ and $<.35$) for commission errors, digit span backwards, choice impulsivity, impulsive drive for immediate reward, and the effects of event rate and/or incentive change on MRT and RTV except for the effect of incentive change on MRT (Table 2a). Neuropsychological variables also predicted EL symptoms (Table 3), but with substantially lower standardized regression coefficients than found for ADHD symptoms. Coefficients were moderate ($>.35$ and $<.5$) for MRT and low ($>.15$ and $<.35$) for RTV, omission and commission errors, digit span, impulsive drive for immediate reward, and effects of event rate or incentive change on RTV and the combined effect of event rate with incentive change on MRT (Table 3a).

The association between ADHD symptoms and neuropsychological impairments were substantially reduced for all neuropsychological variables, when EL was introduced as an additional covariate into the regression analyses, resulting in low (but statistically significant) coefficients ($>.15$ and $<.35$) for MRT, RTV, omission and commission errors, and event rate plus incentive change on MRT and RTV (Table 2b).

Table 1. Background, Clinical and Neuropsychological Variables

Gender (N; N males; %)	Probands With ADHD			Siblings of Probands			Controls		
	366	325	(88.8)	359	174	(48.5)	263	186	(70.7)
	N	Mean (SD)		N	Mean (SD)		N	Mean (SD)	
Age (years)	366	11.3 (2.6)		359	11.3 (3.0)		263	12.2 (2.5)	
IQ	366	102.8 (15.7)		359	104.1 (13.4)		263	107.6 (13.7)	
Conners' Emotional Lability									
Mean ¹	366	69.1 (10.6)		359	54.7 (10.5)		263	51.2 (8.2)	
Parent ratings	366	69.0 (12.9)		359	53.7 (12.3)		263	52.7 (12.0)	
Teacher ratings	366	69.3 (14.5)		359	55.8 (13.5)		263	49.6 (8.1)	
Conners' DSM-IV ADHD									
Mean ¹	366	75.1 (7.6)		359	55.5 (11.3)		263	51.1 (8.4)	
Parent ratings	366	78.7 (8.5)		359	54.5 (13.4)		263	52.1 (10.4)	
Teacher ratings	366	71.5 (10.2)		359	56.5 (12.6)		263	50.2 (9.1)	
Neuropsychological variables									
MRT ² , ms	142	764.1 (257.4)		155	718.0 (259.6)		215	592.2 (157.8)	
RTV ² , ms	142	374.6 (232.5)		155	285.8 (216.9)		215	179.2 (129.2)	
Omission errors, % ³	288	15.3 (11.3)		291	9.1 (8.8)		234	5.6 (5.4)	
Commission errors, % ³	288	53.3 (18.6)		291	43.5 (19.8)		234	39.4 (18.3)	
Digit span backwards	302	4.6 (1.8)		293	5.1 (2.0)		259	5.6 (2.0)	
Choice impulsivity % ⁴	332	27.5 (32.3)		317	23.8 (29.4)		237	12.6 (22.3)	
IDIR % ⁵	324	15.4 (22.2)		316	12.2 (19.5)		239	6.7 (17.6)	
Delay aversion % ⁶	321	12.2 (24.4)		309	11.3 (25.0)		237	6.0 (19.5)	
<i>Go/no-go task</i>									
MRT (slow condition; ms)	293	649.2 (235.1)		297	590.0 (185.8)		235	501.0 (123.3)	
RTV (slow condition; ms)	293	316.2 (223.3)		297	228.5 (170.8)		235	148.0 (105.9)	
MRT (event rate effect; ms) ⁷	288	-228.7 (195.9)		291	-186.5 (140.2)		234	-141.4 (92.0)	
RTV (event rate effect; ms) ⁷	288	-125.2 (200.3)		291	-81.5 (141.7)		234	-33.2 (100.9)	
MRT (incentive effect; ms) ⁸	153	-43.0 (151.6)		155	-20.5 (115.9)		218	8.4 (73.3)	
RTV (incentive effect; ms) ⁸	153	-91.7 (183.0)		155	-57.5 (145.7)		218	-30.2 (103.7)	
<i>Fast task</i>									
MRT (slow condition; ms)	184	931.4 (354.9)		197	894.9 (409.6)		242	683.4 (216.6)	
RTV (slow condition; ms)	184	461.9 (346.6)		197	369.4 (331.0)		242	209.3 (186.2)	
MRT (event rate + incentive effect; ms) ⁹	179	-282.5 (233.1)		194	-244.8 (209.0)		241	-157.8 (118.0)	
RTV (event rate + incentive effect; ms) ⁹	179	-239.1 (290.3)		194	-156.0 (249.3)		241	-81.9 (144.5)	

Abbreviations: MRT, mean reaction time; RTV, reaction time variability

¹ Mean score (parent- & teacher-rated subscales)

² Mean score (Go/No-go task, slow condition & Fast task, baseline condition)

³ Mean score of error percentage in the Go/no-go task, slow condition & fast condition;

⁴ Percentage of impulsive choices (MIDA task, no-post-delay condition)

⁵ Impulsive drive for immediate reward; percentage of impulsive choices (MIDA task, post-delay condition)

⁶ Difference of percentages of impulsive choices in no-post-delay condition vs. post-delay condition (MIDA task)

⁷ Go/No-go task; fast – slow condition difference

⁸ Go/No-go task; incentive – slow condition difference

⁹ Fast task; incentive/fast - baseline condition difference

Table. 2 Effects of neuropsychological functions on ADHD symptoms, controlling for age, gender, and IQ (A) and for age, gender, IQ, and EL symptoms score (B)

	A				B			
	N	SRC (SE)	t	p	SRC (SE)	t	p	
MRT ¹	512	0.48 (0.06)	8.54	***	0.21 (0.04)	5.24	***	
RTV ¹	512	0.47 (0.05)	10.04	***	0.24 (0.03)	7.42	***	
Omission errors % ²	813	0.39 (0.03)	11.33	***	0.18 (0.02)	7.38	***	
Commission errors % ²	813	0.34 (0.06)	6.11	***	0.19 (0.04)	5.09	***	
Digit span backwards	854	-0.26 (0.07)	-3.92	***	-0.14 (0.04)	-3.16	**	
Choice impulsivity % ³	886	0.15 (0.05)	3.25	**	0.06 (0.03)	2.12	*	
Immediate drive for impulsive reward ⁴	879	0.20 (0.05)	3.70	***	0.08 (0.03)	2.27	*	
Delay aversion ⁵	867	0.04 (0.05)	0.82	ns	0.01 (0.03)	0.34	ns	
MRT (event rate effect; ms) ⁶	813	-0.19 (0.03)	-5.51	***	-0.08 (0.02)	-3.57	***	
RTV (event rate effect; ms) ⁶	813	-0.19 (0.04)	-5.29	***	-0.08 (0.02)	-3.23	**	
MRT (incentive effect; ms) ⁷	526	-0.13 (0.05)	-2.92	**	-0.04 (0.03)	-1.31	ns	
RTV (incentive effect; ms) ⁷	526	-0.19 (0.05)	-3.76	***	-0.07 (0.03)	-2.18	*	
MRT (event rate + incentive effect; ms) ⁸	614	-0.28 (0.04)	-6.86	***	-0.15 (0.03)	-5.44	***	
RTV (event rate + incentive effect; ms) ⁸	614	-0.26 (0.04)	-6.78	***	-0.16 (0.03)	-6.28	***	

Abbreviations: EL, emotional lability; MRT, mean reaction time; RTV, reaction time variability

¹ Mean score (Go/No-go task, slow condition & Fast task, baseline condition);

² Mean score of error percentage in the Go/no-go task, slow condition & fast condition;

³ Percentage of impulsive choices (MIDA task, no-post-delay condition)

⁴ Percentage of impulsive choices (MIDA task, post-delay condition)

⁵ Difference of percentages of impulsive choices in no-post-delay condition vs. post-delay condition (MIDA task)

⁶ Go/No-go task; fast - slow condition difference

⁷ Go/No-go task; incentive - slow condition difference

⁸ Fast task; incentive/fast - baseline condition difference

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

The covariates age, gender and IQ explained 5.4% of EL variance (estimated from a subsample of uncorrelated observations, i. e. no sibling pairs)

However, controlling for ADHD symptom severity in the mediational analysis completely removed the effects of the neuropsychological variables on EL and none of the associations remained significant, except for the combined effect of event rate plus incentive change on RTV (statistically significant, but below .15; Table 3b).

Importantly, the statistical association between ADHD and EL symptoms remained largely the same, whether or not the influence of any particular neuropsychological variables was taken into account (SCR = .71 vs. >.69 for all variables); indicating that the cognitive

dysfunctions included in this study do not explain the association of ADHD with EL.

Discussion

EL symptoms are commonly seen in patients with ADHD (Sobanski et al., 2010; Surman et al., 2011; Biederman et al., 2011) and are clinically relevant, since they predict functional impairment (Maedgen & Carlson, 2000; Melnick & Hinshaw, 2000; Stringaris, et al., 2009; Stringaris & Goodman, 2009b) and poorer adult psychosocial outcomes at 20-year follow-up (Stringaris, et al., 2009; Stringaris & Goodman, 2009a). The specific reasons for the

Table. 3 Effects of neuropsychological functions on EL symptoms, controlling for age, gender, and IQ (A) and for age, gender, IQ, and ADHD symptoms score (B)

	A				B			
	N	SRC (SE)	t	p	SRC (SE)	t	p	
MRT ¹	512	0.36 (0.06)	6.50	***	0.01 (0.04)	0.20	ns	
RTV ¹	512	0.30 (0.05)	6.47	***	-0.05 (0.03)	-1.37	ns	
Omission errors ²	813	0.28 (0.03)	8.47	***	0.00 (0.02)	0.10	ns	
Commission errors ²	813	0.19 (0.05)	3.63	***	-0.05 (0.04)	-1.41	ns	
Digit span backwards	854	-0.15 (0.06)	-2.35	*	0.04 (0.04)	0.97	ns	
Choice impulsivity ³	886	0.11 (0.04)	2.40	*	0.00 (0.03)	-0.14	ns	
Immediate drive for impulsive reward ⁴	879	0.15 (0.05)	3.03	**	0.00 (0.03)	0.15	ns	
Delay aversion ⁵	867	0.03 (0.04)	0.66	ns	0.00 (0.03)	0.13	ns	
MRT (event rate effect; ms) ⁶	813	-0.14 (0.03)	-4.27	***	0.00 (0.02)	-0.06	ns	
RTV (event rate effect; ms) ⁶	813	-0.15 (0.03)	-4.26	***	-0.01 (0.02)	-0.35	ns	
MRT (incentive effect; ms) ⁷	526	-0.12 (0.04)	-2.80	**	-0.02 (0.03)	-0.60	ns	
RTV (incentive effect; ms) ⁷	526	-0.15 (0.05)	-3.14	**	-0.01 (0.03)	-0.20	ns	
MRT (event rate + incentive effect; ms) ⁸	614	-0.17 (0.04)	-4.32	***	0.04 (0.03)	1.43	ns	
RTV (event rate + incentive effect; ms) ⁸	614	-0.13 (0.04)	-3.46	***	0.07 (0.02)	2.68	**	

Abbreviations: EL, emotional lability; MRT, mean reaction time; RTV, reaction time variability

¹ Mean score (Go/No-go task, slow condition & Fast task, baseline condition);

² Mean score of error percentage in the Go/no-go task, slow condition & fast condition;

³ Percentage of impulsive choices (MIDA task, no-post-delay condition)

⁴ Percentage of impulsive choices (MIDA task, post-delay condition)

⁵ Difference of percentages of impulsive choices in no-post-delay condition vs. post-delay condition (MIDA task)

⁶ Go/No-go task; slow-fast condition difference

⁷ Go/No-go task; slow-incentive condition difference

⁸ Fast task; incentive/fast-baseline condition difference

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

The covariates age, gender and IQ explained 5.4% of EL variance (estimated from a subsample of uncorrelated observations, i. e. no sibling pairs)

association with ADHD are not well understood, but could arise from underlying neurobiological processes that influence both sets of symptoms.

The present study addressed two questions: first, whether the neuropsychological impairments previously implicated in ADHD predict EL symptoms; this would indicate that those neuropsychological functions and the related neuronal networks could be functionally involved in emotion. Second, to what extent ADHD symptoms might statistically mediate the relations between neuropsychological dysfunctions and EL symptoms.

Our results confirmed previous analyses of this dataset that found that EL symptoms are associated with ADHD severity (Sobanski, et al., 2010), and that ADHD symptoms are linked to neuropsychological dysfunctions (Andreou, et al., 2007; Kuntsi, et al., 2010; Marco, et al., 2009; Uebel, et al., 2010). ADHD symptoms were predicted by measures of neuropsychological functions, most strongly by processing speed and response variability; followed by measures of executive functions³ (commission

³The correlations of omission errors with RTV (.59), MRT (.51) and digit span backwards (-.38) underlines that omission errors could reflect short lapses of attention. The correlation

and omission errors, digit span backwards) and performance change across conditions induced by energetic and/or motivational factors. The smallest association was with choice impulsivity and there was no association with delay aversion.

EL symptoms were also predicted by neuropsychological variables, in a similar rank order to that found to predict ADHD symptoms, i.e., most strongly by processing speed and response variability, followed by omission errors, and then by commission errors, digit span backwards, variables indicating state regulation problems and choice impulsivity. However, the effects of neuropsychological functioning on EL were substantially lower (small to moderate effect sizes) than on ADHD. This pattern of results is inconsistent with the hypothesis that EL symptoms in ADHD are mainly a consequence of an inhibitory deficit because commission errors, presumably reflecting this deficit, predicted EL to a substantially lesser degree than processing speed and response variability and omission errors (the latter presumably reflecting lapses of attention), and similarly well as measures of working memory and state regulation. The results also argue against a role of either choice impulsivity or delay aversion for EL symptoms. Processing speed and response variability seem to be the best predictors of ADHD and EL symptoms. The substantial correl-

ations of processing speed and response variability with measures of performance change across conditions support the hypothesis that slow processing speed and increased response variability might at least partially reflecting state regulation difficulties (Kuntsi, et al., 2001; Sergeant, 2005).

However, any meaningful influence ($SR > .15$) of neuropsychological parameters on EL disappeared entirely, when the effect of ADHD symptoms was taken into account; revealing that the association between the neuropsychological performance measures and EL is indirect, being statistically completely mediated by ADHD symptoms (Baron & Kenny, 1986). There were, therefore, no direct pathways of any of the neuropsychological functions on EL, independent of the link between neuropsychological dysfunctions and ADHD. Conversely, neuropsychological effects on ADHD symptoms remained after EL symptom severity were accounted for. Furthermore, the strength of the association between ADHD and EL remained similar whether or not the influence of any neuropsychological variable was controlled for (see Figure 1); therefore refuting the hypothesis that these neuropsychological functions might explain the association of ADHD with EL.

Taken together, we found that the neuropsychological parameters investigated here predict ADHD symptoms more strongly than EL symptoms. The influence of these cognitive or motivational processes on EL symptoms is completely accounted for by ADHD, i.e., they are not predicting EL symptoms beyond what is already predicted by ADHD symptom severity. Our results also indicate that neuropsychological

between commission and omission errors reflecting inhibitory dysfunctions (.51) could therefore indicate that attentional processing deficits may cause secondary inhibition deficits and is in line with electrophysiological studies indicating that abnormal inhibitory processing in ADHD is typically preceded by attentional dysfunctions (Banaschewski et al., 2004; Brandeis et al., 1998; McLoughlin et al., 2010)

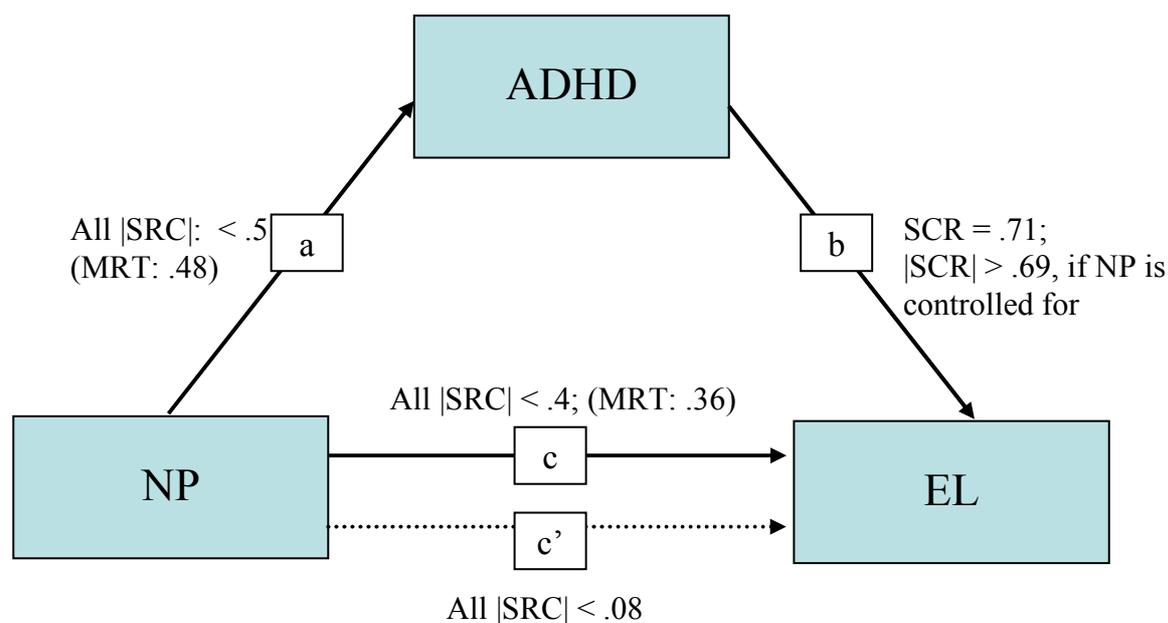


Figure 1 Path diagram showing relations between ADHD symptoms, neuropsychological performance, and EL, controlling for the effects of gender, age and IQ; arrows indicate the directions predicted by the mediation model.

- a) Effect of NP on ADHD symptoms
- b) Effect of ADHD symptoms on EL
- c) Effect of NP on EL
- c') Effect of NP on EL if ADHD symptoms are controlled for

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; EL, emotional lability; NP, neuropsychological performance; MRT, mean reaction time; SRC: standardized regression coefficients; |SRC|: SRC's absolute value

deficits do not explain the association between ADHD and EL. These findings are in line with recent results that neuropsychological deficits do not account for the link between deficient emotional self-regulation and ADHD in adults (Surman et al., in press). Therefore, alternative mechanisms, including overlapping genetic influences (pleiotropic effects) and/or alternative neuropsychological processes not measured in this study, need to be considered as factors explaining the association between ADHD and EL.

The lack of an association between ADHD symptom severity and delay aversion in the current analysis was unexpected, although a general delay aversion tendency has not consistently been reported (Scheres et al., 2006; Paloyelis, et al.,

2009). Our result is not in line with a previous report of significant case-control differences in both impulsive drive for immediate reward and delay aversion in the IMAGE sample, although the effect size in this study was relatively small (Marco, et al., 2009). Various factors might account for this discrepancy, including the use of different samples and analytical approaches. Here we used correlational approaches with dimensional measures of ADHD and a sample including the group of unaffected siblings and probands with sub-threshold symptoms. In the previous analysis, healthy controls were contrasted against diagnosed patients who met DSM-IV criteria for symptoms and impairment.

The study has a number of

strengths: the very large multi-site sample of carefully diagnosed cases, siblings and controls provide strong evidence for the robustness of these effects across a broad age range and different cultural settings, and the use of tasks tapping a broad range of motivational and cognitive factors associated with ADHD. Some limitations should also be considered. The study was conducted in a clinical rather than an epidemiological ADHD sample, which potentially may have increased the associations between ADHD and EL symptoms, and neuropsychological measures. A limitation of the cross-sectional phenotypic design is in the interpretation of these data, since no causal mechanisms can be directly inferred. The association between ADHD, EL and the cognitive variables might all be accounted for by shared etiological (genetic or environmental) factors with no direct causal pathways linking one with the other (Kendler & Neale, 2010). Multivariate genetic model fitting and longitudinal data would be necessary to draw definite causal conclusions on the relationship of ADHD with EL.

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KEY POINTS

- Emotional lability (EL) symptoms are frequently present in patients with ADHD. They are clinically important since they predict psychosocial impairment and poorer outcome.
- The causes for the association are unknown. EL symptoms are not a mere epiphenomenon of ADHD core symptom severity and can only be partially explained by the level of psychiatric comorbidity.
- The neuropsychological alterations implicated in ADHD do predict EL symptoms; processing speed and response variability seem to be the best predictors. However, the association between EL and these cognitive or motivational dysfunctions is less strong than between neuropsychological alterations and ADHD symptoms.
- Neuropsychological dysfunctions are likely not exerting a direct effect on emotion processing; rather, ADHD symptoms seem to mediate these links.

