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Neurological soft signs are associated with attentional dysfunction in children with attention deficit hyperactivity disorder

Mariabernarda Pitzianti^a, Elisa D'Agati^a, Livia Casarelli^a, Marco Pontis^b, Ivo Kaunzinger^c, Klaus W. Lange^c, Oliver Tucha^d, Paolo Curatolo^a and Augusto Pasini^a

^aDepartment of Systems Medicine, Unit of Child Neurology and Psychiatry, "Tor Vergata" University of Rome, Rome, Italy; ^bComprehensive Rehabilitation Center, Ctr Asl 8, Cagliari, Italy; ^cDepartment of Experimental Psychology, University of Regensburg, Regensburg, Germany; ^dDepartment of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, The Netherlands

ABSTRACT

Introduction: Inattention is one of the core symptoms of Attention Deficit Hyperactivity Disorder (ADHD). Most of patients with ADHD show motor impairment, consisting in the persistence of neurological soft signs (NSS). Our aim was to evaluate attentional and motor functioning in an ADHD sample and healthy children (HC) and possible link between attentional dysfunction and motor impairment in ADHD.

Method: Twenty-seven drug-naïve patients with ADHD and 23 HC were tested with a test battery, measuring different aspects of attention. Motor evaluation has provided three primary variables: overflow movements (OM), dysrhythmia and total speed of timed activities.

Results: Compared to HC, patients were impaired in a considerable number of attentional processes and showed a greater number of NSS. Significant correlations between disturbances of attention and motor abnormalities were observed in ADHD group.

Conclusion: Our findings suggest that attentional processes could be involved in the pathophysiology of the NSS and add scientific evidence to the predictive value of NSS as indicators of the severity of functional impairment in ADHD. Given the marked improvement or complete resolution of NSS following treatment with methylphenidate, we suggest that evaluation of NSS is useful to monitor the effectiveness of pharmacological treatment with MPH in ADHD.

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Introduction

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD), a neurodevelopmental disorder with a worldwide prevalence of 5.29% in childhood (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007), is characterised by developmentally inappropriate levels of inattentiveness,

motor hyperactivity and impulsivity. Inattention is one of the core symptoms of ADHD. These children are easily distracted and experience problems in planning, organising and finishing assigned tasks (Curatolo, Paloscia, D'Agati, Moavero, & Pasini, 2009). Neuropsychological assessment revealed that children with ADHD experience difficulties in a variety of functions related to attention, including distractibility, selective and sustained attention in comparison to healthy children (HC) (Borger et al., 1999; Heaton et al., 2001; Lockwood, Marcotte, & Stern, 2001; Perugini, Harvey, Lovejoy, Sandstrom, & Webb, 2000).

Attentional functions

There is empirical evidence that attention represents a multidimensional construct, including several distinct functions, that may be selectively affected by brain dysfunction (Choen, 1993; Pashler, 1998; Posner & Boies, 1971; Posner & Rafal, 1987). Based on the multicomponent model of attention of Posner and colleagues (Posner & Boies, 1971; Posner & Rafal, 1987), Van Zomeren and Brouwer delineated a theoretical framework of attentional functions, including concepts of tonic and phasic alertness, vigilance/sustained attention, selective attention, divided attention and strategy/flexibility (Van Zomeren & Brouwer, 1994). Tonic alertness refers to a relatively stable level of attention which changes slowly according to diurnal physiological variations of the organism, while phasic alertness is the ability to enhance the activation level following a stimulus of high priority. Selective attention is defined as the ability to focus attention. Divided attention requires a simultaneous response to multiple tasks or multiple task demands. The ability to sustain attention enables a subject to direct attention to one or more sources of information over a relatively long and unbroken period of time. This multidimensional model also considers the distinction between aspects of selectivity and intensity made by Kahneman (1973) and the concept of a supervisory attentional control devised by Shallice (1982). Selective attention and divided attention are considered to be aspects of selectivity; instead, alertness and sustained attention are expressions of intensity of attention (Van Zomeren & Brouwer, 1994). Applying the multidimensional model of attention delineated by Van Zomeren and Brouwer, Tucha and colleagues found that children with ADHD suffer from a global deficit of attention, comprising impairments of vigilance, selective attention, focused attention, divided attention and shifting (Tucha et al., 2006a, 2006b, 2009).

Neurological soft signs

Motor ability of children with ADHD is often significantly poorer than it should be based on their age and level of intellectual functioning. Besides the core symptoms, they experience motor impairment and neurological soft signs (NSS) (D'Agati, Casarelli, Pitzianti, & Pasini, 2010; Pasini & D'Agati, 2009; Pasini, D'Agati, Pitzianti, Casarelli, & Curatolo, 2012). NSS are subtle motor, sensory and integrative abnormalities that cannot be related to impairment of a specific brain region and result in considerable sociopsychological dysfunction (Shafer, Shaffer, O'Connor, & Stokman, 1983). Although NSS are commonly observed in children with typical development and reflect the immaturity of the central nervous system, their persistence into later childhood and adolescence suggests

motor dysfunction and could be a “marker” of atypical neurodevelopment (Larson et al., 2007). NSS are mainly represented by overflow movements (OM) and dysrhythmia. OM are defined as co-movements of body parts not specifically needed to efficiently complete a motor task (Larson et al., 2007). There are a number of different forms of OM: associated movements, contralateral motor irradiation and mirror movements. Dysrhythmia is defined as an improper timing and/or rhythm of movement otherwise normal (Cole, Mostofsky, Larson, Denckla, & Mahone, 2008). OM seem to be related to a delay or defect of maturation into the intra-cortical and inter-cortical systems that support automatic inhibition (Mostofsky, Newschaffer, & Denckla, 2003), while dysrhythmia appears to be due to cerebellar dysfunction (Schmahmann, 2004). OM, impaired timing of motor responses and poor motor coordination seem to be the most prominent motor abnormalities in children with ADHD. These could reflect dysfunctions of frontal-striatal-cerebellar networks involved in motor control and white matter abnormalities in motor and pre-motor circuits (D’Agati et al., 2010; Pasini & D’Agati, 2009; Pasini et al., 2012).

Aim of study

The role of attentional processes in motor functioning has already been studied in typically developing school-aged children (Herzog & Durwen, 1992; Lazarus & Todor, 1992; Waber, Mann, & Merola, 1985), while it has not been studied in clinical groups. The aim of our study is to investigate the link between attentional processes and NSS in children with ADHD. In this study we have assessed several components of attention, as suggested by the multicomponent model of Van Zomerén and Brouwer (1994), and we have evaluated NSS by the Physical and Neurological Assessment of Subtle Signs (PANESS) (Denckla, 1985) in patients with ADHD compared with typically developing children. We also investigate the possible correlations between attentional and motor performances in our clinical group.

Methods and materials

Subjects

The study included 50 subjects divided into a clinical group and a control group: 27 patients with ADHD (23 boys, 4 girls) and 23 healthy controls (20 boys, 3 girls) aged 8–15 years with an IQ ≥ 85 . The subjects of the clinical group were consecutive referrals of the Unit of Child Neurology and Psychiatry of “Tor Vergata” University of Rome, Italy. In accordance with the DSM-IV-TR criteria (APA, 2000), the diagnosis of ADHD was based on clinical assessment, observations of children and interviews with parents and children, which were carried out by an experienced child psychiatrist. Both the long version of the Conners’ Parents Rating Scale-Revised (CPRS-R) (Nobile, Alberti, & Zuddas, 2007) and the Conners’ Teachers Rating Scale-Revised (CTRS-R) (Nobile, Alberti, Zuddas, & Conners, 2007) were used to make the diagnosis of ADHD. To keep the sample of children with ADHD as homogenous as possible, only those who met the DSM-IV-TR criteria for ADHD/combined type were included in the study. The interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) was used to exclude

other psychiatric co-morbidities in the ADHD group. The HC were recruited in schools and selected from a pool of subjects who participated voluntarily in the study. None of them had a history of neurological or psychiatric disease or learning disability. Both the long version of the CPRS-R (Nobile, Alberti, & Zuddas, 2007) and the CTRS-R (Nobile, Alberti, Zuddas, & Conners, 2007) were used to exclude the diagnosis of ADHD in all healthy participants. The interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) was used to exclude other psychiatric disorders in the control group. All subjects included in the study had a normal IQ as measured with the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991). At the time of the study, no participants were taking medication known to affect the central nervous system. Prior to the testing, every parent or legal guardian of the subjects included gave written informed consent. In Table 1 characteristics of children with ADHD and healthy controls are summarised.

Evaluation of attentional functioning

All participants were tested with four computerised tasks, measuring different aspects of attention. The tests of attention used were developed and validated for the assessment of attentional deficits in children and adults with cerebral lesions (Zimmermann & Fimm, 1993, 2002). Test procedures were presented on a computer screen. Instructions were given orally. Participants were instructed to perform the computerised tasks as quickly as possible but to maintain a high level of accuracy. In order to familiarise the participants with the tasks, a brief sequence of practice trials preceded each test. Tests were performed only after participants had completed the practice trials without errors. Participants were assessed individually in a quiet room and the examiner was present during the entire assessment.

In the *alertness task*, reaction time is examined under two conditions. The first condition represents a simple reaction time measurement, in which a cross appears on the

Table 1. Results of Z-Test and *t*-test for ADHD and control groups with regard to age, IQ and assessment using CPRS and CTRS.

Number of subjects	ADHD group	Control group	ADHD group vs control group				
	27 (23 boys and 4 girls) Mean $\pm$ SD	23 (20 boys and 3 girls) Mean $\pm$ SD	Z	<i>p</i>	<i>t</i>	<i>p</i>	<i>d</i>
Age (years)	10.11 $\pm$ 1.87	11.22 $\pm$ 2.57	−1.688	.091	−0.037	.971	0.49
TIQ	96.07 $\pm$ 10.12	98.96 $\pm$ 9.21	−0.997	.319	−0.817	.418	0.30
VIQ	96.81 $\pm$ 8.99	98.69 $\pm$ 8.36	−0.873	.383	−0.761	.450	0.22
PIQ	97.07 $\pm$ 9.05	97.60 $\pm$ 8.67	−1.078	.281	0.898	.374	0.05
CPRS-oppositional	62.00 $\pm$ 11.06	51.13 $\pm$ 5.64	−3.822	.001*	4.260	.001*	1.24
CPRS-inattention	75.00 $\pm$ 7.31	52.39 $\pm$ 5.28	−6.050	.001*	12.339	.001*	3.54
CPRS-hyperactivity	71.74 $\pm$ 8.71	53.52 $\pm$ 4.36	−6.059	.001*	9.098	.001*	2.64
CPRS-ADHD-index	75.00 $\pm$ 8.31	53.91 $\pm$ 4.22	−6.050	.001*	11.008	.001*	3.20
CTRS-oppositional	57.18 $\pm$ 6.89	50.30 $\pm$ 6.15	−3.242	.001*	3.699	.001*	1.05
CTRS-inattention	71.89 $\pm$ 6.71	53.35 $\pm$ 4.74	−5.872	.001*	11.092	.001*	3.19
CTRS-hyperactivity	69.92 $\pm$ 9.52	53.52 $\pm$ 4.42	−5.328	.001*	7.568	.001*	2.21
CTRS-ADHD-index	72.55 $\pm$ 7.15	53.73 $\pm$ 4.82	−5.962	.001*	10.707	.001*	3.09

Note: CPRS = Conners' Parents Rating Scale; CTRS = Conners' Teachers Rating Scale.

*Level of significance $p \leq .05$.

monitor at randomly varying intervals and to which the subject has to respond as quickly as possible by pressing a key. Intrinsic alertness is measured in this condition. In a second condition, reaction time is measured in response to a critical stimulus preceded by a cue stimulus presented as warning tone (“phasic arousal” or temporal orientation of attentional focus). Therefore, in the alertness task participants were asked to respond by pressing a button when a visual stimulus appeared on a computer screen. In the first 20 trials, the stimulus appeared on the screen without prior warning (tonic alertness task), while during the second 20 trials, a warning tone preceded the appearance of the stimulus (phasic alertness task). The time span between the warning tone and the appearance of the stimulus was random (Zimmermann & Fimm, 2012). Measures of tonic and phasic alertness are calculated on the basis of the reaction time of the participant. In addition, the variability of reaction time and number of omission errors are measured.

The *incompatibility task* tests the interference tendency in terms of stimulus-reaction incompatibility. For this test, arrows that are directed to the left or the right are presented on the left or right side of a fixation point. Depending on the direction of the arrow, the test person is requested to respond with the right or left hand irrespective of the side on which the arrow is presented. Therefore, in the incompatibility task, arrows pointing to the left or the right were presented briefly on the left or right side of a fixation point in the centre of the computer screen. The participants were requested to press a response button as quickly as possible on the side indicated by the direction of the arrow, independent of the position of the arrow. If the position of the arrow and its orientation accorded (e.g. arrow on the left side of the fixation point pointing to the left side), the trial was classified as a compatible trial while trials in which presentation and orientation were not in accordance (e.g. arrow on the left side of the fixation point pointing to the right side) were classified as incompatible trials. The sequence of trials was random, with about half of the trials compatible and half incompatible (Zimmermann & Fimm, 2012). Reaction time, variability of reaction time and number of commission errors are calculated, providing a measure of selective attention as the capacity to reject irrelevant information.

The *divided attention task* requires participants to process in parallel a visual and an auditory task presented by a computer. In the visual task, a series of matrices was presented in the centre of the computer screen. Each matrix, consisting of a regular array of 16 dots and crosses (4×4), was displayed for 2000 ms. The participant was asked to press the response button as quickly as possible whenever the crosses formed the corners of a square (visual target). In the acoustic task, the participant was requested to listen to a continuous sequence of alternating high and low sounds and to press the response button as quickly as possible when irregularities of the sequence occurred (acoustic target) (Zimmermann & Fimm, 2012). Reaction time for correct responses, variability of reaction time and number of omission errors (lack of response to target stimuli) and number of commission errors (responses to non-target stimuli) are calculated as a measure of divided attention.

In the *sustained attention task*, a sequence of stimuli is presented on the monitor. The stimuli vary in a range of feature dimensions: colour, shape, size and filling. A target stimulus occurs whenever it corresponds in one or the other of two predetermined stimulus dimensions with the preceding stimulus (e.g. the same shape but with different colour,

size and filling). Different levels of difficulty may be selected (e.g. reaction only to “shape” or reaction to “colour and shape”). In order to adapt the difficulty of the task to the performance level of the subjects, reaction only to “shape” was chosen (Zimmermann & Fimm, 2012). Reaction time for correct responses, variability of reaction time, number of omission errors (lack of response to target stimuli) and number of commission errors (responses to non-target stimuli) are calculated as a measure of sustained attention.

Assessment of NSS

For the assessment of NSS, the PANESS (Denckla, 1985) was applied. These evaluations were performed by a child neurologist who underwent training for the reliable application of the PANESS. The examiner was blind to the child’s diagnostic status at the time of assessment and during scoring. The PANESS has been found to have adequate test-retest reliability (Holden, Tarnowski, & Prinz, 1982), inter-rater reliability, internal consistency (Vitiello, Ricciuti, Stoff, Behar, & Denckla, 1989) and sensitivity to age-related changes (Larson et al., 2007) in more current and diverse cohorts. The PANESS measures salient components of motor function, including lateral preference, gaits, balance, motor persistence, coordination, overflow, dysrhythmia and timed movements. Three primary outcome variables were obtained: (1) *total OM* included the total number of abnormal movements for age observed during stressed gaits (i.e. walking on heels, toes or sides of feet), tandem gaits (walking in tandem forward and backward, touching heels to toes) and during timed movements; (2) *total dysrhythmia* included total number of timed the motor examination trials in which the children failed to maintain a steady rhythm throughout the task; (3) *total speed of timed activities* of hands/feet included three repetitive movements and three sequenced movements which were performed bilaterally: toe tapping, alternating heel-toe tapping, repetitive hand patting, hand pronation/supination, repetitive finger tapping and finger sequencing.

Statistical analysis

For the statistical analysis, an alpha level of 0.05 was applied. All statistical analyses were carried out using the Statistical Package for Social Sciences SPSS software (version 17.0, Inc., Chicago, IL, USA). The Mann–Whitney-U test (Z-test) is used to compare differences between the clinical and control groups in regard to the variables collected for each subject enrolled for this study. Moreover, in order to consider the interaction effect of age, the second statistical analysis was conducted using *t*-test for independent samples. Effect sizes for differences between paired observations were computed. Cohen’s *d* was used to calculate the effect size. Cohen’s *d* is defined as the difference between two means divided by a standard deviation of the data. Following Cohen’s (1988) guidelines for interpreting effect sizes, small effects ($d \geq 0.20$), medium effects ($d \geq 0.50$) and large effects ($d \geq 0.8$) were distinguished (Bezeau & Graves, 2001). The Kendall’s rank correlation coefficient or Kendall’s τ is used to find a correlation among multiple independent variables examined. The Kendall’s τ is a non-parametric measure of the statistical dependence among various variables and it is indicative of the strength and direction of the association among various variables measured on at least an ordinal scale.

Results

Comparisons between ADHD group and control group

Age, IQ and Conners' Parents and Teachers Rating Scale

In our study patients and healthy controls did not differ in terms of age ($Z = -1.688$; $p = .091$) and IQ ($Z = -0.997$; $p = .319$). We found significant differences between the ADHD group and the control group with regard to the following ratings: Conners' Parents Rating Scale-Oppositional ($Z = -3.822$; $p < .001$), Conners' Parents Rating Scale-Inattention ($Z = -6.050$; $p < .001$), Conners' Parents Rating Scale-Hyperactivity ($Z = -6.059$; $p < .001$), Conners' Parents Rating Scale-ADHD-Index ($Z = -6.050$; $p < .001$), Conners' Teachers Rating Scale-Oppositional ($Z = -3.242$; $p < .001$), Conners' Teachers Rating Scale-Inattention ($Z = -5.872$; $p < .001$), Conners' Teachers Rating Scale-Hyperactivity ($Z = -5.328$; $p = .001$) and Conners' Teachers Rating Scale-ADHD-Index ($Z = -5.962$; $p < .001$). The t -test confirmed the significant differences between patients with ADHD and HC emerged through the Z-test. In [Table 1](#) results of Z-test and t -test for independent samples are summarised.

Alertness

Comparison between the ADHD group and the control group using Mann-Whitney-U Test revealed no significant differences with regard to reaction time ($Z = -1.149$; $p = .251$) and number of omission errors ($Z = -0.870$; $p = .384$) in the tonic alertness task; however, we found a significant difference between the ADHD group and the control group with regard to variability of reaction time ($Z = -3.018$; $p = .003$). Moreover, the ADHD group did not differ from the control group in reaction time ($Z = -1.052$; $p = .293$) and number of omission errors ($Z = -1.217$; $p = .224$) in the phasic alertness task. A significant difference was found between groups in variability of reaction time ($Z = -2.765$; $p = .006$) of the phasic alertness task. The t -test confirmed the significant differences between patients with ADHD and HC emerged through the Z-test. In [Table 2](#) results of Z-test and t -test for independent samples are summarised.

Selective attention

There was no significant difference between the ADHD group and the control group with regard to reaction time ($Z = -0.244$; $p = .823$) in the incompatibility task, but significant

Table 2. Results of Z-Test and t -test for ADHD and control groups with regard to alertness task.

	ADHD group Mean $\pm$ SD	Control group Mean $\pm$ SD	ADHD group vs control group				
			<i>Z</i>	<i>p</i>	<i>t</i>	<i>P</i>	<i>d</i>
<i>Tonic alertness</i>							
Reaction time in ms	342.33 $\pm$ 125.92	305.78 $\pm$ 87.38	−1.149	.251	1.172	.247	0.96
Variability of reaction time in ms	104.37 $\pm$ 90.66	47.65 $\pm$ 34.35	−3.018	.003*	2.829	.007*	0.83
Number of omission errors	0.11 $\pm$ 0.32	0.04 $\pm$ 0.21	−0.870	.384	0.868	.390	1.39
<i>Phasic alertness</i>							
Reaction time in ms	306.85 $\pm$ 98.46	274.09 $\pm$ 71.78	−1.052	.293	1.323	.192	1.04
Variability of reaction time in ms	82.11 $\pm$ 68.81	38.87 $\pm$ 16.89	−2.765	.006*	2.935	.05*	0.86
Number of omission errors	0.15 $\pm$ 0.36	0.04 $\pm$ 0.21	−1.217	.224	1.223	.227	1.39

*Level of significance $p \leq .05$.

differences in the variability of reaction time ($Z = -4.244$; $p < .001$) as well as the number of omission errors ($Z = -3.755$; $p < .001$) within the same task (see Table 3).

Divided attention

In the *auditory task* we found significant differences between the ADHD group and the control group with regard to reaction time ($Z = -2.735$; $p = .006$), variability of reaction time ($Z = -4.049$; $p < .001$) and number of omission errors ($Z = -6.159$; $p < .001$). Moreover, in the *visual task* we found significant differences between groups with regard to reaction time ($Z = -3.981$; $p < .001$), variability of reaction time ($Z = -4.458$; $p < .001$) and number of omission errors ($Z = -3.857$; $p < .001$). Finally, significant differences between patients with ADHD and HC were observed with regard to total number of commission errors ($Z = -3.705$; $p < .001$) (see Table 3).

Sustained attention

In the sustained attention task the ADHD group did not differ from the control group in reaction time ($Z = -0.710$; $p = .477$), but the patients with ADHD showed a significant higher variability of reaction time ($Z = -3.290$; $p < .001$), as well as increase number of both omission ($Z = -4.332$; $p < .001$) and commission errors ($Z = -4.622$; $p < .001$) when compared to the healthy controls (see Table 3).

Regarding to selective, divided and sustained attention tasks the *t*-test confirmed the significant differences between patients with ADHD and HC emerged through the *Z*-test. In Table 3 results of *Z*-test and *t*-test for independent samples are summarised.

Neurological soft signs

We found significant differences between the ADHD group and the control group with regard to total OM ($Z = -5.460$; $p < .001$), total dysrhythmia ($Z = -5.525$; $p < .001$) and

Table 3. Results of *Z*-Test and *t*-test for ADHD and control groups with regard to different attentional tasks.

Tasks	ADHD group Mean ± SD	Control group Mean ± SD	ADHD group vs control group				
			Z	p	t	p	d
<i>Selective attention</i>							
Reaction time in ms	531.96 ± 145.03	541.04 ± 119.62	−0.244	.823	−0.239	.812	0.07
Variability of reaction time in ms	156.11 ± 62.55	89.30 ± 30.72	−4.244	.001*	4.661	.001*	1.35
Number of omission errors	2.67 ± 4.01	0.17 ± 0.49	−3.744	.001*	2.958	.005*	0.87
<i>Divided attention (auditory task)</i>							
Reaction time in ms	879.85 ± 368.33	664.04 ± 117.68	−2.735	.006*	2.692	.010*	0.79
Variability of reaction time in ms	335.15 ± 274.97	133.35 ± 64.73	−4.049	.001*	3.435	.001*	1.01
Number of omission errors	13.07 ± 4.01	0.35 ± 0.49	−6.159	.001*	15.107	.001*	4.45
<i>Divided attention (visual task)</i>							
Reaction time in ms	1115.30 ± 179.87	881.30 ± 163.99	−3.981	.001*	4.773	.001*	1.36
Variability of reaction time in ms	437.81 ± 181.59	231.04 ± 98.72	−4.458	.001*	4.877	.001*	1.41
Number of omission errors	4.30 ± 2.73	1.52 ± 1.75	−3.857	.001*	4.190	.001*	1.21
<i>Divided attention</i>							
Number of commission errors	9.52 ± 11.45	2.39 ± 3.63	−3.705	.001*	2.862	.006*	0.84
<i>Sustained attention</i>							
Reaction time in ms	688.00 ± 181.86	701.78 ± 129.83	−0.710	.477	−0.303	.763	0.09
Variability of reaction time in ms	235.89 ± 93.55	150.91 ± 78.52	−3.290	.001*	3.443	.001*	0.98
Number of omission errors	22.44 ± 15.10	5.26 ± 6.32	−4.332	.001*	5.084	.001*	1.48
Number of commission errors	22.44 ± 15.10	4.35 ± 5.61	−4.622	.001*	5.428	.001*	1.59

*Level of significance $p \leq .05$.

total speed of timed activities ($Z = -3.583$; $p < .001$). The t -test confirmed the results obtained through the Z -test. In Table 4 results of Z -test and t -test for independent samples are summarised.

Correlations between attentional and motor performances within the clinical group

Regarding *alertness* the correlation analysis according to Kendall showed a significant correlation between the variability of reaction time in the tonic alertness task and total speed of timed activities ($\tau = -0.227$; $p = .05$). Regarding *selective attention* a significant correlation was found between number of omission errors and total dysrhythmia ($\tau = 0.247$; $p = .05$). Regarding *divided attention* significant correlations were observed between total dysrhythmia and number of omission errors in auditory tasks ($\tau = 0.268$; $p = .04$), variability of reaction time in the visual task ($\tau = 0.242$; $p = .05$) and the total number of commission errors ($\tau = 0.288$; $p = .02$). Furthermore, a significant association between the total number of commission errors and total OM, ($\tau = 0.399$; $p < .001$) was observed. Regarding *sustained attention* the correlation analysis according to Kendall revealed significant correlations between reaction time and total speed of timed activities ($\tau = 0.350$; $p < .001$), between number of omission errors and total OM ($\tau = 0.273$; $p = .03$), between number of omission errors and total speed of timed activities ($\tau = 0.260$; $p = .03$), between number of commission errors and total OM ($\tau = 0.273$; $p = .03$), between number of commission errors and total speed of timed activities ($\tau = 0.260$; $p = .03$). In Table 5 results of correlation analysis according to Kendall for ADHD group are summarised.

Discussion

ADHD is a childhood neurodevelopmental disorder, that may persist into adulthood, with deleterious effects on educational and vocational achievement and social adaptation at each developmental stage (Biederman et al., 1996; Weiss & Hechtman, 1993). Disturbances of attention are a core characteristic of children with ADHD (Borger et al., 1999; Heaton et al., 2001; Lockwood et al., 2001; Perugini et al., 2000). The aim of this study was to evaluate attentional function and NSS in a drug-naïve sample of children with ADHD and HC and to elucidate a potential relationship between attentional and motor performances in ADHD. Attentional functioning was assessed according to the multidimensional perspective devised by Van Zomeren and Brouwer (1994). All participants

Table 4. Results of Z -Test and t -test for ADHD and control groups with regard to assessment using PANESS.

	ADHD group Mean ± SD	Control group Mean ± SD	ADHD group vs control group				
			Z	p	t	p	d
<i>Total overflow movements</i>							
Total dysrhythmia	6.63 ± 2.44	1.74 ± 1.89	−5.460	.001*	7.827	.001*	2.24
Total speed of timed activities	6.52 ± 2.17	1.78 ± 1.65	−5.525	.001*	8.556	.001*	2.46
	186.15 ± 26.01	160.74 ± 14.39	−3.583	.001*	4.169	.001*	1.21

*Level of significance $p \leq .05$.

Table 5. Results of correlation analysis according to Kendall for ADHD group.

	Total overflow movements		Total dysrhythmia		Total speed of timed activities	
	τ	p	τ	p	τ	p
<i>Tonic alertness</i>						
Reaction time	0.058	.69	−0.009	.95	−0.135	.33
Variability of reaction time	−0.068	.32	−0.015	.46	−0.227	.05*
Number of omission errors	−0.034	.84	−0.067	.70	0.202	.22
<i>Phasic alertness</i>						
Reaction time	0.133	.36	0.076	.60	0.029	.83
Variability of reaction time	0.083	.28	−0.009	.47	0.060	.33
Number of omission errors	0.084	.63	−0.047	.78	0.095	.56
<i>Selective attention</i>						
Reaction time	0.083	.28	−0.190	.09	−0.172	.10
Variability of reaction time	0.000	.50	−0.051	.36	−0.043	.36
Number of omission errors	−0.017	.46	0.247	.05*	0.193	.09
<i>Divided attention (auditory task)</i>						
Reaction time	0.120	.20	0.087	.27	0.181	.09
Variability of reaction time	0.034	.41	0.094	.26	−0.026	.43
Number of omission errors	−0.017	.46	−0.268	.04*	−0.059	.34
<i>Divided attention (visual task)</i>						
Reaction time	0.117	.21	−0.109	.22	0.052	.35
Variability of reaction time	0.190	.09	0.242	.05*	−0.092	.25
Number of omission errors	0.100	.25	0.038	.40	0.063	.33
<i>Divided attention</i>						
Number of commission errors	0.399	.001*	0.288	.02*	−0.023	.43
<i>Sustained attention</i>						
Reaction time	0.160	.13	0.088	.27	0.350	.001*
Variability of reaction time	0.144	.16	−0.045	.38	0.037	.39
Number of omission errors	0.273	.03*	0.00	.50	0.260	.03*
Number of commission errors	0.273	.03*	0.00	.50	0.260	.03*

*Level of significance $p \leq .05$.

were assessed with a computerised tests battery, which measure different aspects of attention, such as tonic and phasic alertness, selective attention, divided attention and sustained attention.

Attentional dysfunction in ADHD

The present study revealed that, compared to healthy sex- and age-matched children, patients with ADHD were seriously impaired in a considerable number of attentional processes, including alertness, selective attention, divided attention and sustained attention. Therefore, attentional dysfunction observed in these patients involves aspects of both selectivity and intensity of attention. Compared to healthy subjects, children with ADHD displayed an enhanced variability of reaction time in tasks of tonic and phasic alertness, selective attention and sustained attention. Moreover, children with ADHD showed an increased reaction time and an enhanced variability of reaction time in tasks of divided attention. These findings support previous studies showing an increase of reaction time and/or variability of reaction time in measures of alertness (Barkley, 1977; Cohen & Douglas, 1972; Oommen, Kapur, & Shanmugam, 1993; Van der Meere, Vreeling, & Sergeant, 1992), selective attention (Borger & Van der Meere, 2000; Tucha et al., 2006b; Van der Meere & Sergeant, 1998), divided attention (Tucha et al., 2006b) and sustained attention (Borger et al., 1999; Seidel & Joschko, 1990) and extend the results of our former study on attentional and executive functioning in ADHD. In the latter study children with

ADHD showed an impairment on measures of divided and selective attention, response inhibition and working memory compared to healthy peers. Moreover, the ADHD group displayed an increased variability of reaction time in sustained attention tasks compared to the control group (Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007). In our previous study, children with ADHD were markedly impaired in measures of alertness compared to typically developing children and this impairment appears to be due to low levels of arousal (Casagrande et al., 2012). The reaction time is considered a measure of attentional capacity and its variability is a measure of the fluctuation in a subject's efficiency in processing during the course of a continuous task (Van Zomeren & Brouwer, 1994). The reaction time and its variability may be affected by symptoms commonly observed in children with ADHD, including distractibility, deficient self-regulation of motivation and/or impaired perseverance (Barkley, 1998; Solanto, Wender, & Bartell, 1997). Evidence of increased variability of reaction time in ADHD led to the formulation of a mechanistic hypothesis of default network interference. Sonuga-Barke and Castellanos (2007) postulated that deficient regulation of the default network by cognitive and attention networks underlies intrusions in their interplay that manifest as phasic lapses of attention or in impulsive behaviours (Sonuga-Barke & Castellanos, 2007). This hypothesis was supported by several studies that showed abnormalities involving the default network in subjects with ADHD (Cortese et al., 2012; Elton, Alcauter, & Gao, 2014). According to observations of Tucha and colleagues (2006b), the present study showed that in comparison with healthy peers, children with ADHD displayed a significant impairment of accuracy in all tests performed except alertness task. Indeed, a greater number of omission errors in selective attention task and a greater number of omission and commission errors in the divided and sustained attention task were observed in the ADHD group compared to the control group. Omission errors (lack of response to target stimuli) are considered as a measure of inattention; instead, commission errors (responses to non-target stimuli) are a measure of impulsivity (Matier-Sharma, Perachio, Newcorn, Sharma, & Halperin, 1995; Trommer, Hoepfner, Lorber, & Armstrong, 1988). Attentional processes are mediated by cerebral networks, including several cortical and subcortical brain regions. Alertness functions are supported by reticular formation, dorso-lateral prefrontal cortex and inferior parietal cortex (Sturm et al., 1999). Selective attention is related to anterior cingulate gyrus, inferior frontal cortex (left hemisphere) and frontal-thalamic association connections to the reticular nucleus of thalamus (Cabeza & Nyberg, 2000). Divided attention is served by prefrontal cortex (left hemisphere) and anterior cingulate gyrus (Loose, Kaufmann, Auer, & Lange, 2003). Sustained attention is mediated by reticular and intralaminar thalamic nuclei and anterior cingulate gyrus (Cabeza & Nyberg, 2000). Based on our results, it may be hypothesised that all of these cerebral networks are involved in neurobiology of attentional dysfunction in ADHD. This hypothesis is confirmed by structural and functional neuroimaging studies. Indeed, the current body of structural imaging findings provides evidences for a global maturational delay based on reduced grey and white matter volumes and cortical thickness in children with ADHD relative to healthy peers (see review Chandan, 2012). The loci of the reported reductions are in multimodal association cortices such as frontal lobes and its sub-regions, motor and pre-motor cortices, cingulate gyrus, temporal lobes, cerebellum lobes and basal ganglia structures (caudate nucleus, globus pallidus, putamen and ventral striatum). Moreover, there is also evidence for altered maturational courses of selected cerebral regions such

as frontal cortical mantle and caudate nucleus in patients with ADHD relative to healthy controls (see review Chandan, 2012). Findings from functional imaging studies in children with ADHD point to multiple loci of abnormalities, including frontal-striatal-cerebellar networks, parietal-temporal networks, motor and pre-motor circuits and limbic-frontal networks. These brain networks are important for the integrity of executive, attentional, motor and motivational functioning (see review Chandan, 2012). Finally, an increasing number of studies suggests that structural and functional abnormalities in fronto-cortical and fronto-subcortical networks persist into adulthood, despite a relative symptomatic improvement in the adult form of the disorder (see review Cubillo, Halari, Smith, Eric Taylor, & Rubia, 2012).

Motor impairment in ADHD

According to our previous studies (D'Agati et al., 2010; Pasini & D'Agati, 2009; Pasini et al., 2012), the present study revealed that, in comparison to healthy sex- and age-matched children, patients with ADHD performed worse on the PANESS (Denckla, 1985), used to assess motor functioning. Indeed, the ADHD group showed multiple motor abnormalities as compared to the control group. These abnormalities included a greater number of OM, a greater dysrhythmia and a greater motor slowness. These findings are consistent with results of previous investigations, that emphasise the presence of motor dysfunction in children with ADHD. According to these studies, increased OM (Mostofsky et al., 2003; Uslu, Kapci, & Oztup, 2007), impaired timing of motor responses (Rubia et al., 1999), deficits in motor coordination (Waternberg, Waiserberg, Zuk, & Lerman-Sagie, 2007) and deficit in fine motor abilities (Pitcher, Piek, & Hay, 2003) were frequently observed in children with ADHD. Moreover, Meyer and Sagvolden found that children with ADHD performed worse on measure of manual dexterity, motor coordination, movement speed, accuracy and stability of movement in comparison to HC (Meyer & Sagvolden, 2006). OM likely reflects dysfunction within motor and pre-motor circuits that are important for the preparation and execution of motor responses (Cincotta et al., 2002). A functional neuroimaging study showed a smaller extent of activation in the contralateral primary motor cortex in patients with ADHD during performing a simple motor task. It may represent insufficient recruitment of neuronal activity necessary to mobilise transcallosal interhemispheric inhibition (Mostofsky et al., 2006). Dysfunctions in motor and pre-motor circuits, responsible for increased prevalence rate of OM in patients with ADHD, may be due to abnormalities in white matter tracts, including the corpus callosum, important for the effective transfer of transcallosal inhibition (D'Agati et al., 2010; Pasini & D'Agati, 2009). Dysrhythmia may reflect cerebellar dysfunction (Schmahmann, 2004) and slowness of timed activities may be due to functional deficits in frontal-striatal networks, cerebellum and basal ganglia structures (Pasini & D'Agati, 2009).

NSS and attentional dysfunction in ADHD

Given the increased prevalence of NSS in children with ADHD (Denckla & Rudel, 1978; Gillberg, 1998; Rasmussen & Gillberg, 2000; Uslu et al., 2007), it has been hypothesised that these “soft” signs may be indicative of an impaired integrity of attentional processes

and may provide important information about neurobiological bases of ADHD. Therefore, the goal of the present study was to analyse the relationship between attentional processes and motor functioning in the clinical population and particularly in a sample of children with ADHD. Using Kendall's correlation analysis we found significant correlations between disturbances of attentional functioning and motor abnormalities in children with ADHD. Based on our results, deficits of alertness (in terms of increased variability of reaction time) and sustained attention (in terms of an increase of reaction time and number of omission errors) interfere with speed timed activities. Dysfunctions of selective attention (in terms of increased number of omission errors) and divided attention (in terms of increased variability of reaction time in visual tasks and increased number of omission errors in auditory and visual tasks) correlate significantly with dysrhythmia. Impairment of sustained attention (in terms of increased number of omission errors) correlate significantly with OM. Given that selective attention and divided attention are expressions of selectivity and alertness and sustained attention are expressions of intensity of attention (Van Zomeren & Brouwer, 1994), the present study suggest that aspects of intensity are involved in the speed of movement and OM, while aspects of selectivity are involved in the dysrhythmia. Since reaction time, its variability and the number of omission errors are considered a measure of inattention, our findings suggest that there is a link between attentional processes and NSS in children with ADHD. Moreover, our results extend those of a previous study performed by Waber and colleagues in normal school-age children on the role of attentional processes in OM. In this study, in order to investigate the possible link between attentional processes and OM, the authors assessed OM in non-clinical school-aged children, to which were also given a task designed to measure attentiveness to task-relevant or -irrelevant cues. Children who produced high levels of OM were more responsive to task-irrelevant cues (maintained low levels of attention), whereas those produced low levels of OM were more responsive to task-relevant cues (maintained high levels of attention) (Waber et al., 1985). The relationship between reduced attention and increased OM was strengthened by subsequent findings of a reduction but not elimination of OM when participants were asked to inhibit it (Herzog & Durwen, 1992). Moreover, a study by Lazarus and Todor showed that children of all age groups reduced the magnitude of OM when receiving sensory feedback during the task (1992). The significance of mechanisms of attention on OM production is highlighted by a follow-up study performed by Lazarus on OM in young adults with post-acute traumatic left side brain injured. Over three days of training sessions, participants were asked to maintain a percentage of their MVC while involuntary EMG feedback was displayed. Following training, participants were able not only to reduce their overflow but also to maintain this reduction when tested a week later (Lazarus, 1992). Together, these findings that OM may be consciously suppressed emphasise the significance of the attention-OM relationship. In our study, an increased number of commission errors in divided and sustained attention tasks correlate significantly with OM. The commission errors are considered to be a measure of impulsivity, reflecting a general deficit of control in modulating behaviour in response to situational demands and may be affected by impairment of response inhibition (Barkley, 1994, 1997, 1998). This result extends the findings of Mostofsky and colleagues (2003), who observed significant association between OM and response inhibition in children with ADHD, but not in healthy controls, supporting the hypotheses that OM reflect immaturity of cortical systems involved in automatic

inhibition (2003). Finally, based on our data, impulsivity as indicated by an increased number of commission errors in divided and sustained attention interferes with movement speed and is involved in dysrhythmia.

Conclusions

The first strength of our study is the inclusion of a well-defined group of drug-naïve children with ADHD, who were carefully screened for other comorbid psychiatric conditions. The second strength of this study is the inclusion of subjects with normal IQ. Indeed, lower IQ appears to be related to increased NSS in children with ADHD (Fellick, Thompson, Sills, & Hart, 2001). The value of the present results is limited for several reasons. The first limitation of our study is the small sample size, constraining the interpretation of the presented findings. Future studies on a greater sample size will help to expand our knowledge about the role of higher order cognitive mechanisms such as attentional processes in motor functioning and to better understand the link between attentional dysfunction and NSS in clinical populations. The second limitation of this study is the inclusion only of children who met the DSM-IV-TR criteria for ADHD/combined type. So, it was possible to analyse a very homogeneous clinical sample, but it was not possible to study motor and attentional functioning according to the different clinical subtype. Further studies on other clinical subtypes will help to overcome this limitation and in particular future studies should differentiate the motor and attentional functioning according to different subtypes of ADHD. The third limitation of our study is the small number of females in both the clinical group and control group. Therefore, it was not possible to evaluate the effect of gender on motor and attentional performance. Future studies should differentiate the motor and attentional functioning according to the gender. In conclusion, our findings suggest that higher order cognitive mechanisms such as attentional processes could be involved in the pathophysiology of the NSS. Moreover, given the significant correlation between attention deficit and increased number of NSS, our findings add more scientific evidences to the predictive value of NSS as indicators of the severity of functional impairment in children with ADHD and suggest the necessity of including in treatment of patients suffering from ADHD therapeutic measures addressed to their motor development difficulties. It is interesting to note that OM may reflect immaturity and/or dysfunction of the motor/pre-motor circuits involved in motor response inhibition (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Deficits of automatic motor inhibition in patients with ADHD may be due to the volume reduction of these cerebral areas caused by the decrease in their white matter components (Ranta et al., 2009), suggesting a primarily axonal abnormality in patients with ADHD. The persistence of OM in patients with ADHD supports the hypothesis that the brain abnormalities in children suffering from this neuropsychiatric disorder have a developmental origin. Oligodendroglial abnormalities may be due to the dysfunction of a DA system (Sokolov, 2007). MPH treatment produces an increase in DA signalling through multiple actions, including blockade of the DA reuptake transporter, amplification of DA response duration, disinhibition of D2r and amplification of DA tone (Wilens, 2008). These effects could be important because D2r receptors are expressed in oligodendrocyte development and may also regulate the outgrowth of neuronal processes. Indeed, marked improvement or complete resolution of NSS following treatment with methylphenidate (MPH) was described in

patients with ADHD (MPH is the most frequently stimulant drug prescribed in the treatment of children with ADHD) (Lerer & Lerer, 1976). Therefore, we suggest that evaluation of NSS is useful to monitor the effectiveness of pharmacological treatment with MPH in children with ADHD. Finally, in order to evaluate whether the reduction of attentional problems produces a reduction of the NSS, future studies should assess motor and attentional functioning of patients with ADHD at baseline and after treatment. In the future fMRI studies could clarify the link between the attentional and motor dysfunction in patients with ADHD.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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