Pathophysiology of NSS in ADHD

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Abstract
Attention deficit/hyperactivity disorder (ADHD) is the behavioural disorder most commonly diagnosed in childhood. In addition to the main symptoms of inattention, impulsiveness and hyperactivity, neurological soft signs (NSS) are often associated with ADHD. NSS are discrete motor and sensory disorders that cannot be linked to specific cerebral lesions. We review all the scientific contributions on NSS in ADHD. The conclusions support the presence of an alteration in the neural networks for motor control inhibition, at the base of the pathophysiology of NSS in children with ADHD, as well as a possible central role of dopamine in these neural circuits.

Key words: ADHD, NSS, control inhibition, neural networks, dopamine

Introduction
Neurological soft signs (NSS) have been described as non-normative performance on a neurological examination of motor and sensory functioning in the absence of a focal lesion (Shafer et al. 1983). Some examples of NSS include difficulty in the fluid execution of rapid alternating movements such as pronation and supination of the hand (dysdiadochokinesia), motor slowness, dysgraphesthesias (Schonfeld et al. 1989), and difficulty in sequencing complex motor tasks. The origin of NSS is unknown. Nichols and Chen (1981) found that only a small number of many possible perinatal complications discriminated children diagnosed as having soft signs from normal controls. NSS have been found to be associated with IQ deficits, hyperactivity and learning disorders (Nichols and Chen 1981). These neurological abnormalities have longitudinal stability and are positively correlated with poor functional outcome in adulthood (Pine et al. 1996). Several investigators found positive correlations between neurological soft signs and increased risk of psychiatric disorders, such as depression and ADHD (Rasmussen and Gillberg 2000), and a strong association between NSS and ADHD (Denckla and Rudel 1978; Gillberg 1998). Shaffer et al. (1985) reported that adolescents with early soft signs had significantly lower IQs and were more likely to have a psychiatric disorder characterized by anxiety, withdrawal and affective disorders (Shaffer et al. 1985) as well as schizophrenia in adulthood (Leask et al. 2002). During the past 32 years, a number of standardized neurological test instruments have been used in research and clinical practice to identify and quantify NSS. One of the first was the Physical and Neurological Examination for Soft Signs (PANESS) (Guy 1976). Then, Touwen and Prechtl developed the Examination of the Child with Minor Neurological Dysfunction (Touwen and Prechtl 1970) as a quantitative examination for children with possible minor neurological dysfunction (MND), often referred to as “soft signs” (Touwen and Sporrel 1979). In clinical practice, The Revised Neurological Examination for Subtle Signs (NESS, Denckla 1985) is sensitive to soft developmental changes and to revealing soft motor deficits in central nervous system development. Denckla proposed a clear distinction between “soft signs” that, although soft, are abnormal at any age and those that would be normal if found in a younger child. In fact, motor ability and neuroanatomical structures show substantial growth, elaboration and myelination during early childhood (Denckla 1985). Although it is common to observe soft signs in typically developing younger children, persistence of soft signs into later childhood and adolescence suggests motor dysfunction and could
be a marker for atypical neurological development (Larson et al. 2007). NSS are variable and their presence alone should not be considered either diagnostic or the unique basis for explaining complex behavioural and neurological diseases (Dijkhoorn et al. 1987).

NSS and ADHD

Attention deficit/hyperactivity disorder (ADHD) is the behavioural disorder most commonly diagnosed in childhood. It usually manifests before a child reaches 7 years of age and consists of a persistent pattern of inattentiveness, impulsiveness and/or hyperactivity. Besides the “core” symptoms, the motor ability of ADHD children is often significantly poorer than it should be based on their age and level of intellectual functioning. Gillberg and Rasmussen (2000) examined the longer-term outcome of 55 subjects, aged 22 years, affected by ADHD, particularly when combined with developmental coordination disorder (DCD), previously referred to as attention deficit disorder (ADD) or minimal brain dysfunction (MBD), at initial workup at 7 years of age. In this context, MBD requires the presence of both attentional deficit and signs of either fine-motor, gross-motor or visual perception/conceptualization dysfunction. None of the subjects had received stimulant treatment. They were compared with 46 age-matched subjects not affected by such diagnoses. In the ADHD/DCD group 58% had a poor outcome characterized by remaining symptoms of ADHD, antisocial personality disorder, alcohol abuse, criminal offending, reading disorders, and low educational level compared with 13% in the control group. The authors determined that increased NSS were very useful as a screening tool for psychopathology, and diagnosis of ADHD (Rasmussen and Gillberg 2000). Dickstein et al. (2005) studied NSS in 17 children with ADHD and in 20 normal controls (NC) with no significant group differences in hand or foot lateral preference. They found that subjects with ADHD were slower than NC on repetitive motor tasks (Dickstein et al. 2005), consistent with some previous studies reporting that children with ADHD had impaired repetitive motor responses (Rubia et al. 1999b; Epstein et al. 2003). Uslu et al. (2007) underlined that certain factors investigated by the Neurological Examination for Subtle Signs (NESS), such as speed of movement, dysrhythmia and overflow with timed movements, provide important information that could increase our understanding of the neurobiological bases of ADHD and the clinical implications of neurological soft signs. They studied a group of 30 children with ADHD using the NESS and found an increase in overflow movements in children with ADHD. This could indicate a deficit in cortical inhibitory functions, which is a cardinal neurophysiological feature of ADHD (Uslu et al. 2007). This was also underlined in a study by Mostofsky et al. (2003) in which 42 children with ADHD showed significantly more overflow movements than 30 NC, predicting performance on measures of motor response inhibition (Mostofsky et al. 2003). At the same time, dysrhythmia and slowed speed of movement are associated with functional deficits in the cerebellum and basal ganglia (Kandel 2000). Mostofsky et al. (2003) also underlined a significant effect of sex on the association between ADHD and Total Overflow movements; in fact, in boys the presence of ADHD is associated with significantly more overflow movements than in girls, and the number of movements is higher in children with the full syndrome of impulsive, hyperactive and inattentive symptoms (Mostofsky et al. 2003).

NSS and clinical subtypes of ADHD

Meyer and Sagvolden (2006) studied 528 South African children (264 with symptoms of ADHD and 264 normal controls) of both genders, divided in two age groups, 6–9 and 10–13 years, who were assessed using the following tests: the Grooved Pegboard, which measures manual dexterity, complex coordination and movement speed; the Maze Coordination Task, which measures complex coordination, goal-directed fine movements, accuracy and stability of movement; and the Finger Tapping Test, which is a sample measure of finger movement and speed (Meyer and Sagvolden 2006). All tasks were performed with both hands. Problems in motor control were found primarily in children between 6 and 9 years of age. In fact, motor speed and accuracy on both repetitive and sequential tasks increased with age in healthy children (Denckla 1973), confirming that in order for an examination to be useful it must be standardized for different ages. This study also shows that in children with ADHD motor control problems are independent from cultural differences (in fact, they are detected in Europe and Africa as well as in other countries) and are not related to hand preference. Compared with children who had no mental disorders, all ADHD clinical subtypes (C, combined; I, predominantly inattentive; HI, predominantly hyperactive/impulsive) performed worse on the Grooved Pegboard and Motor Coordination Task than on the Finger Tapping Test. This result replicates the findings of a European study (Seidman et al. 1997). The impairment was most severe in the ADHD-C subtypes and less severe in the ADHD-I and HI subtypes in both
genders, with slight differences in performance between hands. Pitcher et al. (2003) found that type and degree of movement difficulty differed between subtypes and that males with ADHD-I and ADHD-C had significantly poorer fine motor ability \( (P < 0.001) \) than control children (Pitcher et al. 2003). In a preceding study they showed that boys in the ADHD-I subtypes had great difficulty with timing and force output and showed greater variability in motor outcomes (Pitcher et al. 2002). Thus, it is likely that poor fine motor skills make greater demands on sustained attention. Furthermore, there is a strong association between inattention and movement difficulties, as greater inattention is predictive of greater difficulty in motor coordination (Pitcher et al. 2003). These findings indicate the need for increased recognition of the clinical and research implications of the relationship between ADHD and motor dysfunction (Pitcher et al. 2002).

The “network inhibition hypothesis” at the base of the pathophysiology of NSS In ADHD

The neuroanatomical basis of NSS remains poorly understood, and it has yet to be established whether the disorder is due to specific or to diffuse brain abnormalities (Dazzan and Murray 2002). The excessive overflow movements in children with ADHD appear to reflect immaturity of the neural networks involved in inhibitory control (Mostofsky et al. 2003). Houk and Wise (1995) described the interconnections and the role of the basal ganglia, the cerebellum and the cerebral cortex in planning and controlling action (Houk and Wise 1995). Using blood oxygen level-dependent functional magnetic resonance imaging, Cao et al. (2006) showed decreased regional homogeneity in the frontal-striatal-cerebellar circuits, consistent with the hypothesis of abnormal frontal-striatal-cerebellar networks in boys with ADHD (Cao et al. 2006).

Role of cerebral cortex in inhibitory control

The neural mechanisms underlying habituated motor responding and motor response inhibition in children with ADHD, were studied by comparing fMRI activation during a Go/No go task in 25 children with ADHD and 25 typically developing (TD) children, aged 8-13 years. Increased intrasubject variability (ISV), measured in response time, is reported in children with ADHD across various tasks. For TD children, increased pre-supplementary motor area (pre-SMA) activation during No/Go events was associated with less ISV, while the reverse was true in ADHD children for whom increased pre-SMA activation was associated with more ISV. In contrast, ADHD patients with less ISV showed greater prefrontal activation. These data suggest a functional anomaly of the pre-SMA in ADHD and the recruitment of prefrontal circuits as a compensatory mechanism by which some children with ADHD are able to achieve more consistent performance despite abnormalities in pre-SMA activation (Suskauer et al. 2008a). The pre-SMA area is connected to the anterior prefrontal areas (Dum and Strick 1991) and striatal projections from the pre-SMA largely extend to the caudate nucleus and the middle and rostral putamen (Lehericy et al. 2004). Anatomic imaging studies of children with ADHD reported localized anomalies in pre-SMA area, including reduced volume (Mostofsky et al. 2002) and thickness when compared with control children (Shaw et al. 2006). This area plays an important role in motor planning and switching from automatic to voluntary controlled actions (Hoshi and Tanji 2004). A possible explanation is that abnormality in the pre-SMA circuits is central to impaired response inhibition in ADHD, regardless of task demand (Suskauer et al. 2008b).

Role of basal ganglia in inhibitory control

Deficits in repetitive motor tasks, documented in children with ADHD (Dickstein et al. 2005), provide further evidence of dysfunctional dopaminergic circuits in cortical and basal ganglia structures that result in the inability to regulate motor excitation and inhibition in the pathophysiology of ADHD (Casey et al. 1997; Durston et al. 2003). Schulz et al. (2005) examined inhibitory control in adolescents with ADHD during childhood using fMRI with the Stimulus and Response Conflict Tasks. They found positive correlations between prefrontal and basal ganglia activation and ADHD symptom intensity (ratings). This evidence suggests that difficulty with inhibitory control may represent a core deficit in ADHD and raises the possibility that the increased frontostriatal activation normalizes with the concomitantly remission of symptomatology (Schulz et al. 2005).

Role of cerebellum in inhibitory control

Another region in the brain showing deviance associated with ADHD is the cerebellum. This is true when it is measured algorithmically as a single unit and when its different components are considered (Castellanos et al. 2002), and even more when the posterior cerebellar vermis is measured (Mostofsky et al. 1998; Castellanos et al. 2001). In
fact, in the cerebellum of males with ADHD the size of the posterior vermis is significantly decreased; further, within the posterior vermis the inferior posterior lobe (lobules VIII-X) is involved in this reduction, whereas the superior posterior lobe (lobules VI/VII) is not (Mostofsky et al. 1998). The dopamine membrane transporter (DAT) is a specific marker of DA axons (Ciliax et al. 1995) and the cerebellar vermis contains selective dopamine-transporter-like immunoreactive axons. Further, within the vermis labelled axons were present only in portions of a subset of lobules. In lobules II, III and IV, DAT-IR axons were found primarily in the depths of the intracentral and preculminate fissures and to a lesser degree in the more external folia of these lobules. In lobules VIIIA and VIIIB, DAT-IR axons were present in both the external and the internal folia, but the density of immunoreactive axons was greater in the internal folia (Melchitzky and Lewis 2000). Another fMRI study demonstrated that the reduced volume of the inferior posterior cerebellar hemispheres is correlated with a poor clinical outcome in patients with ADHD (Mackie et al. 2007). Thus, both the cerebellar vermis and the cerebellar posterior lobe have an important function in motor control (Ito 1984).

In an fMRI study, Sakai et al. (2000) showed some of the interactions between the pre-SMA area and the posterior lobe of the cerebellum. The authors found that the pre-SMA area was selectively active in response selection, whereas the cerebellar posterior lobe was selectively active in timing adjustment, and that the primary motor cortex received connections from both the pre-SMA and the cerebellum (Sakai et al. 2000). Both the basal ganglia and the cerebellum have recurrent connections with the prefrontal cortex, which is the site of high-level information processing because of its activity related to working memory, action planning and decision-making. The activity of the cortical neurons could be the result of the recurrent dynamics of the cortico-basal ganglia and the cortico-cerebellar networks to provide common representations of the cerebellum and the basal ganglia working together (Doya 2000) (see Figure 1).

In ADHD, inborn developmental abnormality of the brain-impaired function of neurocircuitries is important for attention and for the motor system. Exploration of the cerebellum’s influence on cortico-striatal-thalamo-cortical (CSTC) circuits (Alexander et al. 1986), which determine the choice, the initiation and the performance of complex motor and cognitive responses (Graybiel 1998), seems very promising for clarifying the pathophysiology of ADHD.

Animal models and the “network inhibition hypothesis” of NSS in ADHD

Animal models are helpful in medical research since they have simpler nervous systems, more easily interpretable behaviours, more homogeneous genetics, a more easily controlled environment, and a greater variety of interventions available (Sagvolden et al. 2008). In the literature, there are no investigations on neurological soft signs in animal models of ADHD, but some interesting findings are useful to clarify the pathophysiology of NSS in ADHD. There is a variety of commonly used animal models for ADHD: e.g., the spontaneously hypertensive rats (SHR), the dopamine transporter knockout and knockdown (DAT KO and DAT KD) mice, and the Coloboma mice. Irrespective of the genetic determinants of each of these models, these animal models show possible impairments of response inhibition as being related directly to abnormal catecholamine function in the prefrontal cortex and/or basal ganglia. (Groman et al. 2008). SHR are a selectively bred line originating from normotensive Wistar-Kyoto (WKY) rats and display many characteristics that resemble ADHD symptoms, such as hyperactivity and inattention (Sagvolden 2000). Dopamine release is decreased in SHR prefrontal cortex and norepinephrine concentrations are elevated (Russell et al. 2000a). The noradrenergic system appears to be hyperactive as a result of impaired alpha-2A adrenoceptor regulation (Russell et al. 2005). Russell et al. (2000) investigated possible long-term effects of methylphenidate treatment on dopaminergic function in striatal slices of

![Figure 1. Principal neural networks involved in inhibitory control.](image-url)
SHR compared to their WKY control rats, suggesting that presynaptic mechanisms controlling dopamine release had been altered in SHR rats (Russell et al. 2000b). Effective ADHD treatments, including methylphenidate, amphetamine and atomoxetine, reduce impulsive behaviour, probably by enhancing response inhibition, in rats (Navarra et al. 2008). Some studies evaluate both cognitive and motor function of DA-depleted rats after intracerebral neonatal microinjections of 6-hydroxydopamine (6-OHDA). This experimental model, in developing rats, is strikingly similar to the clinical syndrome of MBD (Shaywitz et al. 1976; Archer et al. 1988). Animal models provide us with important findings in order to understand the anatomic bases of motor learning and motor control. Recent anatomical studies proposed a cerebellar and basal ganglia interaction, based on the identification of a disynaptic pathway originating from cerebellum and projecting to the striatum via the thalamus (Ichinohe et al. 2000). Rossi et al. (2008) studied striatal long-term depression (LTD), a crucial form of synaptic plasticity involved in motor learning after cerebellar lesions in rats. Authors showed that the cerebellum controls striatal synaptic transmission in general, and synaptic plasticity in particular, supporting the notion that the two structures operate in conjunction during motor learning (Rossi et al. 2008).

**NSS and pharmacological treatments**

**Effect of methylphenidate on NSS in patients with ADHD**

Lerer and Lerer (1976) published the first study about the effect of methylphenidate (MPH) on NSS in patients with ADHD. These authors found that out of 40 children with three or more NSS, 29 showed marked improvement or complete resolution of NSS following a 60-day treatment with MPH. They also underlined that administration of the placebo did not appreciably change the neurological status of 20 hyperactive children and that behavioural improvement, which was studied by means of Conners’ Abbreviated Teacher Rating Scale, did not always correspond to resolution of the abnormal neurological signs (Lerer and Lerer 1976). Rubia et al. (2003) demonstrated the effectiveness of persistent administration of methylphenidate on deficits in motor timing in ADHD children and extended the use of methylphenidate from the domain of attentional and inhibitory functions to the domain of executive motor timing (Rubia et al. 2003).

Motor system excitability can be investigated in vivo by means of single and paired pulse transcranial magnetic stimulation (TMS). Moll et al. (2000) studied motor system excitability in 18 drug-naive ADHD children, aged 8–12 years, compared with 18 age-matched healthy children using the TMS. They provided evidence of inhibitory deficits within the motor cortex of ADHD children and of an enhancement of inhibitory mechanisms in this brain region after the oral intake of 10 mg of methylphenidate (Moll et al. 2000). Deficits in repetitive motor tasks provide further evidence that dysfunctional dopaminergic circuits in cortical and basal ganglia structures cause the inability to regulate motor excitation and inhibition in the pathophysiology of ADHD (Casey et al. 1997; Durston et al. 2003).

**Conclusion**

Multiple abnormalities of the motor system have been identified in some children with ADHD including persistence of overflow movements (Denckla and Rudel 1978), impaired timing of motor responses (Rubia et al. 1999a) and deficits in fine motor abilities (Pitcher et al. 2003). The presence of excessive overflow movements in children with ADHD appears to reflect immaturity of the neural networks involved in inhibitory control (Mostofsky et al. 2003). This review analyzes all the scientific contributions on NSS in ADHD (see Table I) and supports the evidence of a “network inhibition hypothesis” at the base of the pathophysiology of NSS in ADHD, where the interconnections between

<table>
<thead>
<tr>
<th>Reference</th>
<th>ADHD</th>
<th>Controls</th>
<th>Mean age</th>
<th>Evaluation scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitcher et al. 2003</td>
<td>104</td>
<td>39</td>
<td>10 years</td>
<td>Movement Assessment Battery for Children (MABC) and the Purdue Pegboard Test</td>
</tr>
<tr>
<td>Mostofsky et al. 2003</td>
<td>42</td>
<td>30</td>
<td>9.8 years</td>
<td>The Physical and Neurological Examination for Soft Signs, Conflicting motor response task, Contralateral response task</td>
</tr>
<tr>
<td>Dickstein et al. 2005</td>
<td>17</td>
<td>20</td>
<td>10.6 years</td>
<td>The Revised Physical and Neurological Examination for Soft Signs</td>
</tr>
<tr>
<td>Meyer and Sagvolden 2006</td>
<td>264</td>
<td>264</td>
<td>6–13 years</td>
<td>The Grooved Pegboard, the Maze Coordination Task and the Finger Tapping Test</td>
</tr>
<tr>
<td>Uslu et al. 2007</td>
<td>30</td>
<td>74</td>
<td>9.20 years</td>
<td>Neurological Examination for Soft Signs (NESS)</td>
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</table>
basal ganglia, cerebellum and cerebral cortex have a central role in the inhibition of voluntary movements. The finding of selectively containing dopamine transporter-like immunoreactive axons in the cerebellar vermis (Melchitzky and Lewis 2000) suggests that dopamine has a central role; this is also supported by the effect of methylphenidate on NSS, documented in the articles cited above. The importance of the dopamine function in the genesis of NSS derives from evidence that deficits in repetitive motor tasks are due to dysfunctional dopaminergic circuits in cortical and basal ganglia structures. Dysfunction of the nigro-striatal dopamine branch causes several NSS associated with ADHD, including impaired force and timing regulation of muscle groups, and symptoms include poor motor control (Kadesjo and Gillberg 1999). The finding of slowed speed of movement in repetitive motor tasks is connected to functional deficits in the cerebellum and basal ganglia. NSS are spontaneously present in drug-naïve children with ADHD. This evidence supports the possibility of a dopamine dysfunction prior to the administration of drugs also because of marked improvement or complete resolution of NSS in children with ADHD after treatment with MPH (Lerer and Lerer 1976).

More studies are needed to assess the sensory and motor soft signs associated with ADHD and to integrate clinical evidence with neuroimaging findings and neuropsychological dysfunction. Direct investigation of the cortical processes leading to motor overflow may provide a more complete understanding of the pathological relevance of motor overflow and NSS in general (Hoy et al. 2008). The comparability of future studies can be improved by using the same structured rating scale for NSS; moreover, a useful examination must be standardized for different ages. In an attempt to elucidate the role of NSS in children with ADHD, it is crucial that repeated neurological assessment be included in the medical examination of drug-naïve and treated children with ADHD.

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Statement of Interest

The authors disclose any commercial or other associations that might pose a conflict of interest in connection with the submitted article.


