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Neurological Subtle Signs and cognitive development A study in late childhood and adolescence

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Abstract

Introduction and aim—Neurological subtle signs (NSS) are often observed during the neurological examination of children and tend to disappear with age. Their persistence into late adolescence or young adulthood has been related to psychiatric and neurocognitive disorders. To provide a better understanding of their functional basis a longitudinal correlational study with neurocognitive measurements was performed.

Methods—We conducted multiple regression and correlation analyses of NSS with demographic and cognitive measures on a subset of 341 healthy children (56% males), taking part in a longitudinal dental study. Participants, whose ages ranged between 11–15 years, at first evaluation, undertook yearly, during five years, a 6-item NSS exam (producing a total score ranging between 0–18) and a comprehensive battery of neurocognitive tests. Effects of age, gender, IQ and 7 neurocognitive factors on NSS were analysed.

Results—Over the years, NSS scores correlated consistently with selective attention (Stroop test), motor speed (finger tapping), and visuo-motor speed (pegboard speed).

Discussion—These results suggest that the disappearance of NSS in late childhood and adolescence occurs primarily in parallel with the development of motor and visuo-motor functions and secondarily in relation to higher order functions such as selective attention (Stroop) and executive control (B-A Trails difference).

Introduction

Screening for neurological subtle signs (NSS) is part of the paediatric neurological examination. In that clinical evaluation healthy young children are likely to present a variety of signs described as “dysrhythmia”, “motor overflow” and “clumsiness” (Cole, Mostofsky, Larson, Denckla & Mahone, 2008; Denckla, 1985; Fellick., Thomson, Sills, & Hart, 2001; Peters, Romine & Dykman, 1975) which are usually interpreted as clinical markers of neural immaturity, since they tend to disappear with age. Moreover their rate of extinction is also

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related to gender, being faster in girls than in boys (Cole et al., 2008; Larson, Mostofsky, Goldberg, Cutting, Denckla, & Mahone, 2007; Martins, Lauterbach, Slade, Luis, DeRouen, et al., 2008) in accordance with evidence showing that maturation of the central nervous system and age related peak brain volume does not follow the same pace in boys and girls (Lenroot, Gogtay, Greenstein, Molloy, Wallace et al., 2007).

In addition to that, it is well recognized that NSS tend to persist in children and adolescents with neuro-developmental and neuropsychiatric disorders (Cole et al., 2008; Mostofsky, Newschaffer, & Denckla, 2003; Breslau, Chilcoat, Johnson, Andreski, & Lucia, 2000; Pine, Wasserman, Fried, Paradis & Shaffer, 1997, Chan, McAlonan, Yang, Lin, Shum, et al., 2010, Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002), a finding suggesting that they might be related to cognitive and emotional maturation. Given the potential contribution of NSS for the screening of psychiatric or neuro-behavioural disorders, it is relevant to know how they behave in healthy children by the time they are expected to disappear.

To clarify this issue we assessed motor and coordination NSS functions on a large sample of children for 7 consecutive years as part of a dental study, on the safety of dental treatments with amalgam (DeRouen, Martin, Leroux, Townes, Woods et al., 2006). Evaluation included a standard neurological examination (Lauterbach, Martins, Castro-Caldas, Bernardo, Luís, et al., 2008) and a comprehensive battery of neurocognitive tests (Martins, Castro-Caldas, Townes, Ferreira, Rodrigues, et al., 2005; Townes, Martins, Castro-Caldas, Rosenbaum & Derouen, 2008). The study showed that the use of amalgams in dental treatments was safe concerning the cognitive, neurologic and renal effects when compared with composite. The present article investigates the relationships between motor NSS and other measures of neurocognitive development. The former were assessed during the last five years of the study, when children were moving from late childhood to adolescence and adulthood. Our hypotheses were that: a) that there will be overall negative correlations between NSS and other measures of neurocognitive development, and b) that the disappearance of NSS during adolescence will be particularly associated with both fine motor development and the refinement of executive functions. In addition, we were interested in how closely each of the individual NSS signs would correlate with neurocognitive factors.

Methods

Participants

Participants were a subset of 341 children taken from a larger sample of 507 attending a public school system, who were 8.0 to 11.9 years of age at the onset of the study. Since the primary endpoints of this study were focused on the safety of dental treatments, the inclusion criteria were the following: 1) having at least one carious lesion in a permanent tooth, 2) no previous exposure to amalgam treatments, 3) urinary mercury level less than 10 u/L at baseline, 4) blood lead level less than 15u/dL, 5) IQ equal to or greater than 67 as obtained on the Comprehensive Test of Nonverbal Intelligence (CTONI) (Hammill, Pearson & Wiederholt, 1997) and no interfering health condition. At baseline 54.9% of participants were male, 70.6% were Caucasian, 28.4% Afro-Portuguese and 1% Asian-Portuguese. The mean age was 10.1 years (range 8.0–11.9) and mean IQ was 85.10 (range 67–118) (13). The lower IQ boundary of 67, on the CTONI (based on USA norms) was chosen, as a selection criterion, because of clinical experience suggesting that the CTONI underestimates intelligence in non-US populations by up to one standard deviation (Martins et al., 2005) and the fact that the CTONI IQ is known to underestimate fluid intelligence (Lassiter, Harrison, Matthews, Bell, & The Citadel, 2001). Though truncated at the lower end, the CTONI IQ at baseline was otherwise normally distributed with a mean of 85.10 (SD=9.96).

At the onset of the study participants were randomly assigned to receive either dental amalgam for posterior restorations or composite only restorations. With Institutional Review Board and parental or guardian approval, neurological examinations including neurological hard signs and subtle signs, and neurocognitive (NC) assessments were obtained prior to the onset of treatment (baseline) and annually for 7 subsequent follow-up years. Since no differences were found between the two treatment groups on any of the measures studied, namely on the standard neurological exam or cognitive tests (DeRouen et al, 2006; Lauterbach et al, 2008) it was possible to assemble all cases into a single corpus of data for further analysis.

Systematic and scored examination for Neurological Subtle Signs (NSS) was introduced in follow-up year 3 (children's ages ranging from 11 to 15 years) and continued through follow-up year 7. These examinations will be referred to here as NSS1 (corresponding to the 3rd follow-up year of the study) through NSS5 (performed in the 7th follow-up year of the study). Participants included in the present analysis were those who completed both examination (scored NSS and neurocognitive assessment in each follow-up year). The sample varies in each year of study because there were children who did not complete both exams every year. The children's ages, gender and ethnicity per study year are shown in Table 1.

Procedures

Neurological examinations were conducted by two qualified neurologists (IPM and ML) taking part in the study. In addition to the standard neurological examination aimed to detect "hard signs", six neurological subtle signs directed at aspects of fine motor development, coordination and balance were sought, adapted from the scale designed by Peters et al. (1975). These items were selected from the original 80-item test, with the following criteria: a) NSS signs (44/80) that differentiated children with learning disabilities from normal controls in the study of Peters et al. b) NSS that correlated with cognitive development, as demonstrated in a previous study performed in healthy Portuguese school children (Martins & Fernandes, 2003) (a subset of 18 out of the 44) and c) the six NSS that have proved to be reliable and easy "to transform in scales that summarize performance on related tasks" (Pine et al., 1996). In fact, according to some authors (Pine et al., 1996; Berninger & Rutberg, 1992;) the inter rater reliability (IRR) for the assessment of motor signs is higher than for sensory signs. Berninger & Rutberg reported an excellent IRR for their set of 16 tasks; the 10 finger tasks reached an inter class correlation coefficient (ICC) of .94 and the 6 motor overflow tasks reached an ICC of 0,78. In the study of Pine et al, 11 motor tasks were scored on four continuous scales, regarding smoothness, accuracy, slowness and movements. The ICC for IRR was at least .87 for any single tasks and the overall IRR was excellent with an ICC of .95. The internal consistency of all tasks was good, with an internal consistency coefficient of .86 (Cronbach's alpha) During this exam the child is asked to perform six tasks during which 6 items (underlined here) are observed and scored: Tandem gait (walk a straight line heel-to-toe, keeping the balance), Motor persistence (stand still with eyes closed and keep the arms outstretched in front, for about one minute); Fine motor control tested by finger-tapping (fast index- thumb finger taps), diadochokinesia (alternating pronation-supination hand pats) and finger-thumb (fast and sequential touching each finger to the thumb, beginning with the fifth finger), during which behavior is scored for Mirror movements, Synkinesias and Clumsiness. Finally, the degree of Restlessness/Hyperactivity during all the examination is scored. Items were scored as follows: 0 (normal or absent NSS), 1 (subtle, minor or inconsistent mirror or adventitious movements or minor imprecision; initial difficulty in gait that is overcome in a couple of steps); 2 (mirror or adventitious movements of small amplitude or not present all the time; moderate clumsiness in one or two tasks; initial difficulty in gait but the child manages to walk on line with

effort) and 3 (exuberant signs; evident clumsiness; the child has difficulty making isolated finger movements while immobilizing the other fingers, tasks are poorly planned or performed in slow movements with hesitations and errors; child drops off line, in gait). Scores were summed up producing a total NSS score that ranged from 0 to 18 points, the highest corresponding to a worse performance (a detailed description of the procedures in Lauterbach et al., 2008).

A battery of neurocognitive tests was administered at baseline and annually. Tests administered and methods of scoring and monitoring the integrity of the data have been described elsewhere (Martins et al., 2005; Townes et al., 2008). In an earlier report (Townes et al., 2008) the 19 individual neurocognitive tests were subjected to a series of factor analyses, which revealed a stable structure of seven factors across the eight year period of the study. This enabled seven factor scores to be generated based on a reduced number of tests.

The seven factors (and the tests measuring them) are as follows: 1) Divided Attention (Trails A and B); 2) Selective Attention (Stroop Test, Portuguese version which construct validity has proved similar to the original English version in another study (Martins et al., in press)); 3) Visual Learning and Recall (WRAML Test); 4) Motor Speed (Finger Tapping with Dominant and Non-Dominant Hands); 5) Visual-Motor Speed (Pegs Dominant and Non-Dominant); 6) Verbal Learning and Recall (Rey Auditory Learning Test); and 7) Working Memory (Digit Span and Finger Windows). The above were the tests examined in NSS1. During the subsequent four study years (NSS2 – NSS5) some of the child versions of the tests were replaced by their adult forms or by adult equivalents, as follows: The Adult Trails Test (A&B) replaced the intermediate version; and the WMS-R Visual Reproductions and Delayed Recall Tests replaced the WRAML Visual Learning and Recall Tests. In terms of the factors, Working Memory during NSS2 – NSS5 was measured by a single test, the adult Digit Span from the WAIS-III battery.

Despite these changes to the actual tests in NSS years 2–5, the previous factor analytic study had shown that the factor structure remained constant over this five year period (Townes et al., 2008).

Statistical Analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 15.0. A series of standard Multiple Regression Analyses (MRA's) were carried out for each of the five years of NSS examinations. Since the NSS total score had a J-shaped distribution in each of the five years, a square root transformation was performed. The dependent variable was therefore the square root transformed NSS score in each year. Three sets of independent predictor variables were used: demographic variables (age and gender), the NIQ measure of overall intelligence from the CTONI which had been administered in the baseline year of the wider study and the 7 neurocognitive factors identified in the previously reported factor-analytic study (Townes et al., 2008). Standard MRA's were used rather than Hierarchical Regression Analyses as we had no clear a priori prediction as to the order of relative contribution of the two sets of independent factors.

Point biserial correlations were also carried out between the presence/absence of four of the NSS signs (mirror movement, synkinesia, clumsy finger & motor impersistence) and the 3 neurocognitive factors which proved to be significant predictors in the above analysis (motor speed, visuo-motor and selective attention), to determine the specific pattern of relationships between them in each year. This was not possible with the other two NSS signs (clumsy balance and hyperactivity) as the frequency of occurrence was below 5% or less. Finally, we carried out point biserial correlations between the four NSS signs in each year

and a specific measure of executive control - TMT B-A (Lesak, 1995; Sanchez-Cubillo, Perianez, Adrover-Roig, Rodriguez-Sanchez, Rios-Lago et al., 2009). This measure removes the motor component (i.e. movement time), therefore providing a pure index of shifting ability, thinking/decision time.

No values were calculated for the motor impersistence score in NSS 5 because the frequency of occurrence was less than 5 per cent.

Results

The results of the MRA's are presented in Table 2. The upper section of the table shows the standardized coefficients (*betas*) associated with each of the 10 predictor variables in NSS years 1 to 5.

The first result of note is that the *betas* for the two demographic variables (age and gender) were statistically significant in the first three years (NSS 1–3) but not in NSS 4–5. This mirrors the findings of the previous report in the same cohort (Martins et al., 2008) in which younger males were found to have consistently higher NSS scores than older males or younger/older females in the first three years; after which their scores decrease to comparable levels in the latter two years when they reach average ages of 14–16 (see Table 1).

The second main result concerns the predictive value of neurocognitive factors. The first point of note is that NIQ was a significant predictor in the NSS 1 analysis but not in any of the subsequent years. Moreover, the NSS1 result is likely to be a pure confound due to its relationships with the other predictive variables, for two reasons. First, the Pearson correlation between the NSS transformed score and NIQ was not significant ($r = 0.05$, $p > .05$); and, secondly, when the subjects were divided into three subgroups on the basis of their NIQ scores (below average, average and above average IQ) no significant differences were found on the transformed NSS scores ($df.2,338$; $F=0.33$, $p=NS$).

By contrast with NIQ, three of the seven factors were regularly predictive of NSS as evidenced by significant *betas*. The most consistent were 'visual-motor' performance and 'motor speed' which, in tandem, were present in all five study years. Poorer 'visual-motor' performance (pegboard score, reflecting accuracy and speed), and slower 'motor speed' (finger tapping speed) were associated with higher NSS scores. The third factor, present in the first three of the five study years, was 'selective attention', which corresponds to the performance on the Stroop test. Lower scores on this factor were associated with higher NSS scores. The lower section of Table 2 presents the Model Summary data. In all years, the model was supported. In particular, the demographic and neurocognitive factors predicted NSS scores significantly, as shown by the statistically significant 'F' values. Conservatively, the predictive variables shown by the Adjusted R^2 accounted for between 6% (NSS4) and 19% (NSS1) of the variance in NSS scores.

Finally, in all cases the Durbin-Watson test values were close to 2.0, indicating a lack of autocorrelation among residuals, a basic requirement underlying multiple regression analysis.

The point biserial correlations between four individual NSS and three of the neurocognitive factors (Motor Speed, Visuo-Motor Speed and Selective Attention) plus the specific executive control index (TMT B-A) are shown in Table 3, together with the percentage of subjects presenting with each of the signs in each year.

Altogether a total of 76 correlations were computed between the 4 NSS signs and the 4 neurocognitive measures in the five NSS years, of which 35 (i.e. 46%) were statistically significant at the 5% level of significance or less. This is well in excess of the 3 or 4 we would expect to be significant by chance alone. Thus, there is strong support for an association between NSS signs and these specific neurocognitive factors overall.

When we turn to the 4 individual NSS signs, there is a marked variation between them in terms of their associations with the neurocognitive factors. For Mirror Movements, only 4 out of 20 correlations (20%) were significant; and for Synkinesias, only 6 out of 20 (30%). By contrast, for Motor Impersistence, 10 out of 16 (63%) were significant; and for Clumsy Finger, 15 out of 20 (75%) were statistically significant.

Discussion

The present study shows that there is a negative correlation between the number and severity of motor neurological subtle signs, as measured by NSS total score, and the performance in some cognitive and behavioural domains. This correlation is consistently significant across a period of five years that ranges from late childhood to adolescence, when these subtle motor signs are vanishing. It also shows that gender explains part of the variance of NSS score, particularly during the first years of the study when children were younger, and that boys display higher scores than girls during the early stages of adolescence corroborating our previous findings (Martins et al., 2008) of a different pace of fine motor maturation related to gender.

Intelligence, as measured by CTONI NIQ scores taken in the baseline year, were not found to be predictive of NSS scores in this study. Rather it was some of the more specific aspects of cognitive function which were related to, and predictive of, NSS signs.

As expected, NSS were correlated with tests of fine motor abilities like “motor speed” and “visuo-motor speed”. Yet, in addition to that, they were associated with different measures of executive functions such as selective attention assessed by the Stroop Test, that relies heavily on inhibitory control and to a far lesser extent with the Trails-Difference (TMT B-A), a measure of divided attention, task-set switching ability or cognitive flexibility (Sanchez-Cubillo et al., 2009). Both inhibitory control and switching are measures of executive control, a group of functions subserved by higher cortical centres namely the late developing prefrontal cortex (Egner & Hirsch 2005; Loose, Kaufmann, Auer & Lange 2003). A similar result was found in a cross sectional study of normally developing young Chinese children (below the 11th anniversary), in whom different NSS measures were related to different tests of executive function like the Stroop interference score, number of Wisconsin card sorting test – WCST (Chan et al., 2010) categories completed, number of WCST perseverative errors and verbal fluency.

The neural basis of NSS has been a source of controversy. To our knowledge this is the first evidence of a developmental association between NSS and cognitive measures, demonstrated on a longitudinal study of healthy children, evaluated by a large range of neurobehavioral measures. The consistent association along development between the improvement of fine motor control and some cognitive functions known to be related to cognitive control and monitoring and related to the frontal lobes, suggests that their maturation may share mechanism or neural circuits.

Alternative explanations, such that the observed association could be due to a similar trend in cerebral maturation or a learning effect, are refuted by the fact that the neurocognitive factors correlate differentially with the demographic factors and NSS. In fact, girls improve their NSS score earlier in life than boys (Martins et al., 2008) which is against a simple

practice effect since both were exposed to the same extent to the neuropsychological tests. Moreover, if NSS and cognitive domains co-varied simply as a result of overall neural development, one should expect a correlation between NSS and any other developing cognitive abilities, which did not occur. For example the factors called verbal and visual memory and learning did not correlate consistently with NSS, although they also improved with age (Townes et al., 2008).

These results point to our first hypothesis, that there is a negative association between specific measures of cognitive development and NSS. Different types of evidence support this hypothesis.

The first concerns the commonality of processes involved in the disappearance of NSS and the performance of executive tasks. While disappearance of NSS consists in a progressive suppression of unnecessary movements that interfere with fine motor performance, the Stroop test requires inhibition of an automatic behavior in favor of an incongruent response, and in task shifting it is necessary to suppress and disengage from a previous set up to redirect attention to a new one. Therefore, “inhibition”, either motor or behavioral, is required to all.

The second point concerns the neuroanatomical basis of inhibition and the relation between the maturation of those structures and the evolution of NSS. Functional brain imaging studies have consistently shown that the Stroop task is associated to an activation of the prefrontal cortex (PFC), namely the anterior cingulate cortex (ACC) but also the parietal cortices and the striatum (Peterson, Skudlarski, Gatenby, Zhang, Anderson et al., 1999; Adleman, Menon, Blasey, White, Warsofsky et al, 2002), while another study demonstrated that transcranial inhibition of the mesial frontal lobe (supplementary motor area, SMA) impairs switching ability (Rushworth, Hadland, Paus & Sipila, 2002). Those PFC areas are part of the frontostriatal loops that support self regulation in general, and inhibition in particular. Those circuits connect the prefrontal cortex to the striatum, and from there follow a chain of projections to the globus pallidus, substantia nigra and thalamus, which closes the loop by projecting back to the cortex. There are at least five parallel frontostriatal loops subserved by different regions of the PFC. Two of them are involved in motivation and reward and engage the orbito frontal cortex (OFC) and ACC, while the other three (involving the supplementary motor area, the frontal eye fields and the dorsolateral prefrontal cortex), support motor learning and stimulus response (Alexander, DeLong & Strick, 1986).

Compared to the rest of the cortex, the PFC matures relatively late and its fastest growth occurs between 8 and 14 years of age (Kanemura, Aihara, Aoki, Araki, & Nakazawa, 2003), the period of time during which the NSS disappear. It is also known that maturation of those regions, namely the ACC which has been associated to motor inhibition (Wang, Maia, Marsh, Colibazzi, Gerber et al., 2011), has been related to the development of self-regulation (Marsh, Zhu, Schultz, Quackenbush, Royal, et al., 2006; Posner & Rothbart, 1998; Posner, Rothbart, Sheese, & Tang, 2007).

The third evidence concerns the gender differences observed in the evolution of NSS which are quite similar to the gender effect found of the maturation of those loops, namely in the caudate and OFC, two components of the OFC/ACC loops (Sowell, Trauner, Gamst & Jernigan, 2002).

Finally, neuropsychiatric disorders that have been associated to an impaired inhibitory control or frontostriatal dysfunction, such as obsessive compulsive disorder (OCD)(Maia, Cooney & Peterson 2008), Tourette syndrome (Marsh R, Maia TV & Peterson BS), attention deficit hyperactivity disorder (ADHD) (Barkley, 1997; Nigg, 2001) have been

associated to the persistence of NSS (Mostofsky et al 2003; Chan et al., 2010; Mitterschiffthaler, Ettinger, Mehta, Mataix-Cols & Williams, 2006; Menzies, Chamberlain, Laird, Thelen, Sahakian et al., 2008).

The correlation between executive functions and NSS during childhood and adolescence, the parallel paths in development between NSS and maturation of frontostriatal systems, their similar variance with gender and the persistence of NSS in the disorders of those specific systems, support our argument that the disappearance of NSS during adolescence might be a rough signature of the maturation of the frontal-striatal systems that support motor and executive control.

The progressive disappearance of NSS with age was demonstrated by a decrease in their number and severity. In a previous report (Lauterbach et al., 2008) this tendency was found in all subtle signs of the battery but was more evident in clumsiness, motor impersistence, mirror movements and synkinesias than in hyperactivity/restlessness, because the latter were infrequent in this age group. Visuo-motor and motor speed correlated with most signs as expected, since they also require rapid and accurate movements. However, among neurocognitive factors, those related to executive functions also correlated with NSS, namely selective attention and, to a lesser extent, switching ability (Egner & Hirsch 2005; Loose et al., 2003). Thus, the disappearance of clumsiness and synkinesias may depend on the ability to inhibit a connected network possibly through the maturation of the structures involved in top down control of motor behaviour (Loose et al., 2003).

In terms of individual NSS signs, it is clumsy finger and motor impersistence which show the strongest associations with neurocognitive factors during the study. This suggests the tentative hypothesis that focused attention, the ability to maintain a verbal command on line and to inhibit associated movements are more dependent on higher cortical functions such as executive control than other NSS that are possibly more reliant on inter-hemispheric inhibition or visuo motor or cerebellar control.

We acknowledge limitations to this study, namely the fact that the scoring of NSS only began on the third year of the study (not allowing an extrapolation of results to younger age groups) and that a number of participants were lost to follow up or did not complete all the evaluations, which might eventually introduce a bias in selection. It would be interesting to perform a similar study starting at a younger age and including a more comprehensive battery of executive functions tests, namely a behavioural assessment. The screening for NSS is simple, rapid and inexpensive and can be performed in schools or in primary care, by trained physicians. More studies are necessary to demonstrate if their screening is valuable in clinical and epidemiological settings and to determine their specificity and sensitivity as early indicators of neurobehavioral disorders.

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References

1. Adleman NE, Menon V, Blasey CM, White CD, Warsofsky IS, Glover GH, Reiss AL. A developmental fMRI study of the Stroop color-word task. *NeuroImage*. 2002; 16(1):61–75.10.1006/nimg.2001.1046 [PubMed: 11969318]

2. Alexander G, DeLong M, Strick P. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual review of neuroscience*. 1986; 9:357–381.10.1146/annurev.ne.09.030186.002041
3. Barkley R. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological bulletin*. 1997; 121(1):65–94.10.1037/0033-2909.121.1.65 [PubMed: 9000892]
4. Berninger V, Rutberg J. Relationship of finger function to beginning writing: application to diagnosis of writing disabilities. *Developmental medicine and child neurology*. 1992; 34:198–215.10.1111/j.1469-8749.1992.tb14993.x [PubMed: 1559600]
5. Breslau N, Chilcoat HD, Johnson EO, Andreski P, Lucia VC. Neurologic soft signs and low birthweight: their association and neuropsychiatric implications. *Biological Psychiatry*. 2000; 47:71–79.10.1016/S0006-3223(99)00131-6 [PubMed: 10650451]
6. Chan RCK, McAlonan GM, Yang B, Lin L, Shum D, Manschreck TC. Prevalence of Neurological Soft Signs and Their Neuropsychological Correlates in Typically Developing Chinese Children and Chinese Children With ADHD. *Developmental Neuropsychology*. 2010; 35(6):698–711.10.1080/87565641.2010.508552 [PubMed: 21038161]
7. Cole WR, Mostofsky SH, Gidley Larson JC, Denckla MB, Mahone EM. Age-related changes in motor subtle signs among girls and boys with ADHD. *Neurology*. 2008; 71:1514–1520.10.1212/01.wnl.0000334275.57734.5f [PubMed: 18981373]
8. Crawford T, Bennett D, Lekwuwa G, Shaanak S, Deakin J. Cognition and the inhibitory control of saccades in Schizophrenia and Parkinson's disease. *Progress in brain research*. 2002; 140:449–466.10.1016/S0079-6123(02)40068-4 [PubMed: 12508608]
9. Denckla MB. Revised neurological examination for subtle signs. *Psychopharmacological Bulletin*. 1985; 21:773–779.
10. DeRouen TA, Martin MD, Leroux BG, Townes BD, Woods JS, Leitão J, et al. Neurobehavioral effects of dental amalgam in children: A randomized clinical trial. *Journal of American Medical Association*. 2006; 295:1784–1792.10.1001/jama.295.15.1784
11. Egner T, Hirsch J. The neural correlates and functional integration of cognitive control in a Stroop task. *Neuroimage*. 2005; 24:539–547.10.1016/j.neuroimage.2004.09.007 [PubMed: 15627596]
12. Fellick JM, Thomson APJ, Sills J, Hart CA. Neurological soft signs in mainstream pupils. *Archives of Disease in Childhood*. 2001; 85:371–374.10.1136/adc.85.5.371 [PubMed: 11668095]
13. Garvey MA, Ziemann U, Bartko JJ, Denckla MB, Barker CA, Wassermann EM. Cortical correlates of neuromotor development in healthy children. *Clinical Neurophysiology*. 2003; 114:1662–1670.10.1016/S1388-2457(03)00130-5 [PubMed: 12948795]
14. Halsband U, Lange RK. Motor learning in man: A review of functional and clinical studies. *Journal of Physiology – Paris*. 2006; 99:414–424.10.1016/j.jphysparis.2006.03.007
15. Hammill, DD.; Pearson, NA.; Wiederholt, JL. C-TONI Comprehensive Test of Nonverbal Intelligence – Manual. Austin, Texas: Pro-Ed; 1997.
16. Kanemura H, Aihara M, Aoki S, Araki T, Nakazawa S. Development of the prefrontal lobe in infants and children: a three-dimensional magnetic resonance volumetric study. *Brain and Development*. 2003; 25(3):195–199.10.1016/S0387-7604(02)00214-0 [PubMed: 12689699]
17. Larson J, Mostofsky SH, Goldberg MC, Cutting LE, Denckla MB, Mahone EM. Effects of gender and age on motor exam in developing children. *Developmental Neuropsychology*. 2007; 32:543–562.10.1080/87565640701361013 [PubMed: 17650993]
18. Lassiter KS, Harrison TK, Matthews TD, Bell NL. The Citadel. The validity of the Comprehensive Test of Nonverbal Intelligence as a measure of fluid intelligence. *Assessment*. 2001; 88:95–103. [PubMed: 11310730]
19. Lauterbach M, Martins IP, Castro-Caldas A, Bernardo M, Luís H, Amaral H, et al. Neurological outcomes in children with/without mercury exposure from amalgam: seven years of observation in a randomized trial. *Journal of the American Dental Association*. 2008; 139:138–45. <http://jada.ada.org/cgi/collection/restoratives>. [PubMed: 18245680]
20. Lenroot RK, Gogtay N, Greenstein DK, Molloy E, Wallace GL, Vaituzis AC, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage*. 2007; 36:1065–1073.10.1016/j.neuroimage.2007.03.053 [PubMed: 17513132]

21. Lezak, MD. Executive functions and motor performance. In: Lesak, MD., editor. *Neuropsychological assessment*. 3. New York: Oxford University Press; 1995. p. 650-685.
22. Loose R, Kaufmann C, Auer DP, Lange KW. Human prefrontal and sensory cortical activity during divided attention tasks. *Human brain mapping*. 2003; 18:249–259.10.1002/hbm.10082 [PubMed: 12632463]
23. Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. *Development and psychopathology*. 2008; 20(4):1251–83.10.1017/S0954579408000606 [PubMed: 18838041]
24. Marsh R, Ph D, Maia TV, Peterson BS. Functional Disturbances Within Frontostriatal Circuits Across Multiple Childhood Psychopathologies. *Brain*. 2009; 166(6):664–674.10.1176/appi.ajp.2009.0809135
25. Marsh R, Zhu H, Schultz RT, Quackenbush G, Royal J, Skudlarski P, Peterson BS. A Developmental fMRI Study of Self-Regulatory Control. *Human brain mapping*. 2006; 27(11):848–863.10.1002/hbm.20225 [PubMed: 16421886]
26. Martins I, Maruta C, Silva C, Rodrigues P, Chester C, Ginó S, Freitas V, et al. The effect of education on age related changes in three cognitive domains: a cross-sectional study in primary care. *Applied Neuropsychology*. (in press).
27. Martins I, Fernandes T. Avaliação cognitiva e neurológica numa população recém-escolarizada. *Psychologica*. 2003; 34:187–214.
28. Martins IP, Castro-Caldas A, Townes B, Ferreira G, Rodrigues P, Marques S, et al. Age and Sex Differences in Neurobehavioral Performances: A Study of Portuguese Elementary School Children. *International Journal of Neuroscience*. 2005; 115:1687–1709.10.1080/00207450590958556 [PubMed: 16287634]
29. Martins IP, Lauterbach M, Slade P, Luis H, DeRouen T, Martin M, et al. A Longitudinal Study of Neurological Soft Signs from Late Childhood into Early Adulthood. *Developmental medicine and child neurology*. 2008; 50:602–607.10.1111/j.1469-8749c.2008.03043.x [PubMed: 18754898]
30. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neuroscience and Biobehavioral Review*. 2008; 32:525–549.10.1016/j.neubiorev.2007.09.005
31. Mitterschiffthaler MT, Ettinger U, Mehta MA, Mataix-Cols D, Williams S. Applications of functional magnetic resonance imaging in psychiatry. *Journal of Magnetic Resonance Imaging*. 2006; 23:851–861.10.1002/jmri.20590 [PubMed: 16652410]
32. Mostofsky SH, Newschaffer CJ, Denckla MB. Overflow movements predict impaired response inhibition in children with ADHD. *Perceptual and Motor Skills*. 2003; 97:1315–1331.10.2466/pms.2003.97.3f.1315 [PubMed: 15002876]
33. Nigg J. Is ADHD a disinhibitory disorder. *Psychological bulletin*. 2001; 127(5):571–598.10.1037/0033-2909.127.5.571 [PubMed: 11548968]
34. Peters JE, Romine JS, Dykman RA. A special neurological examination of children with learning disabilities. *Developmental medicine and child neurology*. 1975; 17:63–78.10.1111/j.1469-8749.1975.tb04959.x [PubMed: 1123123]
35. Peterson BS, Skudlarski P, Gatenby JC, Zhang H, Anderson aW, Gore JC. An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Biological psychiatry*. 1999; 45(10):1237–58.10.1016/S0006-3223(99)00056-6 [PubMed: 10349031]
36. Pine D, Scott M, Busner C, Davies M, Fried J, Parides M, Shaffer D. Psychometrics of neurological soft signs. *Journal of American Academy of Child and Adolescent Psychiatry*. 1996; 15(4):509–515. <http://dx.doi.org/10.1097/00004583-199604000-00017>.
37. Pine DS, Wasserman GA, Fried JE, Paradis M, Shaffer D. Neurological Soft signs: One year stability and relationship to psychiatric symptoms in boys. *Journal of the American Child and Adolescent Psychiatry*. 1997; 36:1579–1586.10.1016/S0890-8567(09)66568-0
38. Posner MI, Rothbart MK. Attention, self-regulation and consciousness. *Philosophical transactions of the Royal Society of London Series B, Biological sciences*. 1998; 353(1377):1915–27.10.1098/rstb.1998.0344

39. Posner MI, Rothbart MK, Sheese BE, Tang Y. The anterior cingulate gyrus and the mechanism of self-regulation. *Cognitive, affective & behavioral neuroscience*. 2007; 7(4):391–5.10.3758/CABN.7.4.391
40. Rushworth MF, Hadland KA, Paus T, Sipila PK. Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. *Journal of Neurophysiology*. 2002; 87:2577–92.10.1152/jn.00812.2001 [PubMed: 11976394]
41. Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, Rodriguez-Sanchez JM, Rios-Lago M, Tirapu J, Barcelo F. Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuo-motor abilities. *Journal of the International Neuropsychological Society*. 2009; 15:438–450.10.1017/S1355617709090626 [PubMed: 19402930]
42. Sowell ER, Trauner Da, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental medicine and child neurology*. 2002; 44(1):4–16.10.1111/j.1469-8749.2002.tb00253.x/ [PubMed: 11811649]
43. Townes BD, Martins IP, Castro-Caldas A, Rosenbaum G, Derouen T. Repeated test scores on neurobehavioral measures over an eight year period in a sample of Portuguese children. *International Journal of Neurosciences*. 2008; 118:79–93.10.1080/00207450601042102
44. Townes BD, Rosenbaum G, Martin M, Martins IP. A longitudinal factor analytic study of children's neurocognitive abilities. *International Journal of Neurosciences*. 2008; 118:1009–1023.10.1080/00207450701768895
45. Wang Z, Maia TV, Marsh R, Colibazzi T, Gerber A, Peterson BS. The Neural Circuits That Generate Tics in Tourette's Syndrome. *American Journal of Psychiatry*. 2011; 168:1326–1337.10.1176/appi.ajp.2011.09111692 [PubMed: 21955933]

Table 1

Demographics of participants examined each year in current report

Variables	Follow-Up Year						
	Year 3 (NSS 1)	Year 4 (NSS 2)	Year 5 (NSS 3)	Year 6 (NSS 4)	Year 7 (NSS 5)		
N	341	388	392	290	278		
Age:							
Mean	13.11	14.05	14.99	15.98	16.99		
SD	0.96	0.97	0.96	0.95	1.00		
Range	11–15.3	12–16	12.8–17.3	13.8–17.9	14.8–19.5		
Gender:							
Male	191	214	211	158	150		
%	56%	55%	54%	55%	54%		
Female	150	174	181	132	128		
%	44%	45%	46%	45%	46%		
Ethnicity:							
White	248	267	284	194	194		
%	73%	69%	72%	67%	70%		
Non-White	93	121	108	96	84		
%	27%	31%	28%	33%	30%		

Table 2
Standard Multiple Regression Analyses of Demographic and Neurocognitive Factors on square root transformed NSS scores

	NSS Year				
	NSS1	NSS2	NSS3	NSS4	NSS5
N	328	381	384	281	275
Predictor Variables:					
Gender	-.28 ^{***}	-.15 ^{**}	-.20 ^{***}	-.08	-.12
Age	-.13 [*]	-.20 ^{***}	-.17 ^{**}	.02	.09
NIQ	.13 [*]	.09	.04	.03	.06
Verbal Learning	.04	.06	.03	.13 [*]	.12
Visual Learning	.10	-.05	-.06	.03	-.01
Motor Speed	-.11	-.15 [*]	-.03	-.05	-.26 ^{**}
Visuo-Motor	-.18 ^{**}	-.07	-.05	-.19 ^{**}	-.23 ^{**}
Selective Att.	-.13 [*]	-.14 [*]	-.15 [*]	-.05	-.02
Sustained Att.	.00	-.05	-.06	.06	.03
Working Memory	-.05	-.06	-.02	-.04	-.09
Model Summary:					
Multiple R	.47	.39	.34	.28	.41
Adjusted R ²	.19	.13	.09	.04	.14
Model 'F'	8.87 ^{***}	6.62 ^{***}	4.87 ^{***}	2.26 [*]	5.47 ^{***}
Durbin-Watson	2.13	1.89	1.85	1.80	2.11

* = <.05

** = <.01

*** = <.001

Table 3

Biserial Correlations between Individual NSS and Neurocognitive Factors

NSS Year	%Present	Motor Speed	Visual Motor	Selective Attention	B-A TMT
NSS 1:					
Mirror Mov.	34%	-.10	-.12*	-.05	.08
Synkinesia.	45%	-.12*	-.20**	-.14**	.10
Clumsy Finger	27%	-.23**	-.28**	-.30**	.13*
Mot. Impersist.	21%	-.16**	-.06	-.09	-.01
NSS 2:					
Mirror Mov.	27%	-.05	.04	-.05	.05
Synkinesia	36%	-.08	-.11*	-.10	.10
Clumsy Finger	12%	-.17**	-.25**	-.27**	.23**
Mot. Impersist.	13%	-.23**	-.24**	-.15**	.15**
NSS 3:					
Mirror Mov.	27%	-.04	-.08	-.10	.09
Synkinesia	30%	-.01	-.10	-.10	-.01
Clumsy Finger	15%	-.12*	-.14**	-.17**	.09
Mot. Impersist.	9%	-.09	-.13*	-.12*	.08
NSS 4:					
Mirror Mov.	22%	-.01	-.08	-.06	.01
Synkinesia	21%	-.09	-.12*	-.08	.01
Clumsy Finger	11%	-.04	-.13*	-.04	.04
Mot. Impersist.	5%	-.16**	-.22**	-.20**	.11
NSS 5:					
Mirror Mov.	19%	-.14*	-.18**	-.13*	.09
Synkinesia	11%	-.06	-.16**	-.02	-.03
Clumsy Finger	10%	-.21**	-.20**	-.24**	.01
Mot. Impersist.	3%	-	-	-	-

*
=<.05

10<=

Mirror Mov. = Mirror Movement; Mot. Impersist. = Motor Impersistence; B-A=specific executive control index