Editor's Choice

Relationship between cognitive dysfunction, gait, and motor impairment in children and adolescents with neurofibromatosis type 1

JOEL A CHAMPION[1] | KRISTY J ROSE[2] | JONATHAN M PAYNE[1,2] | JOSHUA BURNS[1,2,3] | KATHRYN N NORTH[1,2,4]

1 Discipline of Paediatrics and Child Health, Faculty of Medicine, University of Sydney, Sydney, NSW; **2** Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Sydney, NSW; **3** Arthritis and Musculoskeletal Research Group, Faculty of Health Sciences, University of Sydney, Sydney, NSW; **4** Murdoch Childrens Research Institute, The Royal Children's Hospital, Melbourne, Vic., Australia.

Correspondence to Kathryn N North, Murdoch Childrens Research Institute, The Royal Children's Hospital, Flemington Road, Parkville, Vic., 3052, Australia.
E-mail: kathryn.north@mcri.edu.au

This article is commented on by Johnson on page 415 of this issue.

PUBLICATION DATA
Accepted for publication 6th November 2013.
Published online 4th January 2014.

ABBREVIATIONS

BOT-2	Bruininks–Oseretsky Test of Motor Proficiency, 2nd Edition
BRIEF	Behavior Rating Inventory of Executive Function
CANTAB	Cambridge Neuropsychological Test Automated Battery
FSIQ	Full Scale intelligence quotient
NF1	Neurofibromatosis type 1
SWM	Spatial working memory

AIM Motor skill impairment and cognitive dysfunction are commonly reported features of neurofibromatosis type 1 (NF1). We characterized and determined the relationship between motor impairment, gait variables, and cognitive function in children and adolescents with NF1.

METHOD Motor function, gait, and neurocognitive abilities were assessed in 46 children and adolescents with NF1 (26 males, 20 females; age range 7–17y; mean age 11y 1mo, SD 3y 2mo). Tests to establish correlations between neurocognitive, motor, and gait variables were performed.

RESULTS Compared with normative data, 28/39 of our NF1 cohort demonstrated impaired performance for balance and upper limb coordination and 16/38 for running speed and agility. Gait data revealed a strategy to preserve balance at the expense of velocity, with the unexpected exception of a tendency for reduced base of support. Neurocognitive testing confirmed mean IQ in the low average range (86.0) and deficits in spatial working memory and strategy generation. Significant correlations between a number of neurocognitive measures and motor abilities and gait were identified. The largest associations were between gait width and spatial working memory (r=0.594) and running speed and agility with strategy generation (r=0.549).

INTERPRETATION We have identified a relationship between balance, running speed and agility, gait, and cognition in children with NF1. Findings suggest a shared abnormal neurodevelopmental process underlying some cognitive and motor abilities in NF1. Results are discussed within the context of evidence highlighting abnormal dopamine-mediated corticostriatal circuitry in NF1.

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic condition with a birth incidence of 1 in 2700 individuals.[1] Caused by a mutation in the gene encoding neurofibromin on chromosome 17q11.2, NF1 is characterized by a diverse range of cutaneous, neurological, and neoplastic manifestations, including café-au-lait macules, skinfold freckling, neurofibromas, and optic pathway tumours.[2] Skeletal anomalies have also been documented, including scoliosis, tibial dysplasia/pseudoarthrosis, and sphenoid wing dysplasia. Neurocognitive impairment is also well documented in children with NF1.[3,4] Although intelligence tends to be only mildly affected, specific impairments on measures of attention, executive function, language, and visual perception are common. Given the frequency and severity of cognitive deficits, it is not surprising that up to 70% of children with NF1 underachieve at school, with formal learning disability estimated to be present in approximately 50% of children.[5]

There is an emerging body of evidence demonstrating motor impairment as a common feature of NF1 in childhood.[4,6,7] Early research in this area documented problems with manual dexterity, balance, and ball skills, with 32% of children exhibiting severe impairment of coordination skills.[8] More recently, Johnson et al. compared children with NF1 with normative data on the Bruininks Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2).[6] Children with NF1 displayed significantly impaired motor skills across a number of domains; the largest effect sizes were observed for measures of balance, upper limb coordination, and running speed and agility. With regard to fine motor skills, Hyman et al. reported impaired performance on the grooved pegboard task and reported a correlation

 DOI: 10.1111/dmcn.12361

between motor speed and non-verbal intellectual skills.[4] Associations have also been reported between fine motor, maths/premaths skills, and focal areas of hyperintensity on T2-weighted cerebral images.[7]

Reduced motor competency may contribute to a range of poor outcomes for children with NF1. Gross motor skill impairments, for example, have been shown to predict a range of social, emotional, behavioural, and academic problems in children with developmental coordination disorder, all of which are common features of the NF1 phenotype.[3,9,10] Relationships have also been demonstrated between motor coordination and neurocognitive performance in normative samples[11] and clinical cohorts.[12] Children with delayed gross motor skills, for example, are at a higher risk of impairment in attention, self-regulation, language, and scholastic achievement. A number of recent studies have highlighted a specific relationship between motor difficulties and executive functioning impairments, including working memory.[12–14] This relationship is intriguing given that particular brain regions, such as the cerebellum and prefrontal cortex, are associated with cognitive and motor problems, suggesting a common mechanism.[15] It is possible that common, domain-general, neurocognitive mechanisms are involved in the cognitive and motor impairments observed in NF1. To date, however, these relationships have not been examined.

Despite the recognition of poor motor coordination in children with NF1, there have been no studies that specifically analyse gait in children with the condition. Gait abnormalities have been reported in a number of developmental conditions, including attention-deficit–hyperactivity disorder (ADHD),[16,17] which is comorbid in approximately 40% of children with NF1.[4] Converging data suggest that ADHD symptoms and executive impairments may be secondary to abnormalities in frontostriatal-cerebellar circuits,[18] which are also crucial for posture and gait control.[19,20]

The current study had two primary aims. The first was to examine motor proficiency and gait in children and adolescents with NF1. The second was to establish the relationship between gross motor skills and gait with cognition, especially executive function. A better understanding of the relationship between these parameters may provide a basis for more effective early interventions.

What this paper adds

- This paper characterises the nature of motor impairment in children and adolescents with NF1.
- Novel associations between motor impairment, gait, and neurocognitive measures in children with NF1 are presented.
- Data suggest a common pathogenic pathway affecting aspects of motor and cognitive impairment in NF1.

METHOD

Participants

Forty-six children and adolescents aged 7 to 17 years with a diagnosis of NF1 were recruited on a sequential basis from the Neurogenetics Clinic at The Children's Hospital at Westmead, Australia. Participants with NF1 fulfilled the diagnostic criteria specified by the National Institutes of Health Consensus Conference.[21] Clinic demographics have been previously described.[22]

Children were excluded if they had diagnosed intracranial pathology (other than asymptomatic optic gliomas), recent orthopaedic surgery (<6mo), tibial dysplasia, significant visual or auditory impairment, or were unable to speak English. So as not to confound performance on neurocognitive testing, children taking stimulant medication for ADHD (n=8) ceased medication on the day of the assessment.

Procedure and materials

Before assessment, a medical history of all participants was obtained from their parent(s)/legal guardians. In addition, the medical file of the participants was reviewed.

Motor skills were assessed using the BOT-2, a well-validated movement assessment tool that is frequently used to assess movement disorders in childhood and has been shown to be reliable and sensitive in children from the general population and those with an intellectual disability.[23,24] Subtests of balance, upper limb coordination, and running speed and agility were assessed as these have been shown to yield the largest effect sizes from age-matched normative data in a previous study of children with NF1.[6] Subdomain raw scores were converted to scaled scores using normative age- and sex-specific data from the BOT-2 manual.

Gait was assessed using the GAITRite (CIR Systems Inc., Haverton, PA, USA) electronic instrumented walkway in our paediatric gait analysis laboratory.[25] The GAITRite is a 420cm length mat, which has 16 128 sensors at a resolution of 1/cm^2 and a sample rate of 80 Hz. The reliability and validity of the GAITRite has been well established in children.[26–28] Children were instructed to walk down the mat at their own pace. The following temporospatial gait parameters were recorded and averaged by the GAITRite software: velocity (cm/s), cadence (steps/min), step time (s), step length (cm), stride length (cm), base of support (cm), and single and double support percentage of gait cycle (%GC). Adequate space at either end of the walkway ensured that the children were recorded at their self-selected speed, so acceleration and deceleration did not occur during the trial. Three trials were recorded for each child and averaged for analysis using GAITRite software, version 3.8.

Cognitive assessment was conducted individually in a quiet, well-lit room and was completed in one session. Rest breaks were provided as necessary. Intellectual function was assessed using the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV), which provided four index scores (Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed) and a Full Scale IQ (FSIQ). Two participants, aged 17 years, completed the Wechsler Adult Intelligence Scale, 3rd Edition rather

than the WISC-IV because of age restrictions of the WISC-IV.

Spatial working memory was assessed using the Spatial Working Memory (SWM) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB).[29] Detailed descriptions of this measure have been reported elsewhere.[30] SWM is a self-ordered task that assesses participants' ability to retain and manipulate spatial information in immediate memory. The two SWM outcome measures reported in this study are (1) between search errors, representing the total number of errors made during the task, and (2) a strategy score, reflecting the degree to which searches are conducted in a systematic manner. SWM has been validated in a number of different patient groups, including NF1.[30] Impaired strategy scores have been selectively associated with frontal lobe damage, and reduced working memory performance has been reported after damage to frontal and temporal cortex.[31,32] Normative scores for CANTAB tasks were obtained from age-matched data provided with the CANTAB software. Before SWM was completed, participants were administered a motor coordination screening task from the CANTAB to assess whether they were capable of using the touch screen apparatus. All participants completed this task adequately.

In order to examine the relationship between motor abilities and behavioural aspects of executive functions, parents/legal guardians of participants completed the Behavior Rating Inventory of Executive Function (BRIEF) – Parent Version.[33] The BRIEF allows for a broad assessment of executive function in a real-world context. Although the questionnaire provides eight distinct clinical scales, to minimize the risk of type I error, we have only reported the two indices (Behavioral Regulation Index, Metacognitive Index) and the composite score, which incorporates all eight clinical scales (Global Executive Composite). The clinical validity of the BRIEF has been supported in a variety of diagnostic groups, including ADHD,[34] autism spectrum disorder,[35] and NF1.[22]

Written informed consent was obtained from all participants before assessment. The study was approved by the human research ethics committee of the Sydney Children's Hospitals Network and the University of Sydney.

Statistical analysis

Data were analysed with the Statistical Package for Social Sciences, version 21 (IBM SPSS Statistics, IBM Corp., NY, USA). Normality of data distribution was assessed using Shapiro Wilk and Kolmogorov Smirnov tests. Median and interquartile range have been reported for data that were not normally distributed. Raw data from the balance, running speed and agility and upper limb coordination domains from the BOT-2 were converted to scaled scores using normative data from the test manual, and submitted to one sample Student's *t*-tests to explore differences from normative reference values. Gait variables were converted to z-scores based on normative age-matched data.[36–38] The *p* values were then calculated using one sample Student's *t*-tests (two-tailed). Gait variables of participants aged 16 and 17 were presented as raw data but could not be included in the correlation analysis as there were no GAITRite normative data available for these ages. As intraclass correlation coefficients (ICCs) between left and right gait parameters were high, the mean of the left and right side were calculated and used for analysis: base of support, (ICC=0.961, paired *t*-test p=0.203), step length (ICC=0.972, paired *t*-test p=0.999), step time (ICC=0.923, paired *t*-test p=0.683), stride length (ICC=0.993, paired *t*-test p=0.425).

Neurocognitive data were scaled and one sample Student's *t*-tests (two-tailed) were used to determine whether the children with NF1 were significantly different from the normative data. A one sample Wilcoxon signed-rank test was used when the data were non-parametric. Pearson's rank correlation coefficients were calculated to investigate the relationship between motor function, gait, and executive function when both variables were continuous and the assumption of normality was met. When the data were not normally distributed (for the SWM Strategy variable only), Spearman's rank correlation coefficients were conducted. Only the global executive composite from the BRIEF, FSIQ, working memory index, and perceptual reasoning index scores from the WISC-IV were included to limit the number of correlations performed. Missing values were not included in the correlation analysis. To control for type 1 error, the level of significance was set at 0.01.

RESULTS

Our sample consisted of 46 children (20 females, 26 males), aged 7 to 17 years (mean age 11y 1mo, SD 3y 2mo; mean height 144.4cm, SD 17.4cm). Of these, 39 were assessed using the BOT-2 subdomains of upper limb coordination and balance. Thirty-eight children were assessed on the running speed and agility domain. One child was unable to complete this domain because of a prior appointment.

BOT-2 normalized scores are shown in Table I and were significantly lower than age-matched normative reference values. The majority of the study participants displayed at least 'below average' performance, with 28/39 falling below the 17th centile for balance and upper limb coordination and 16/38 falling below the 17th centile for running speed and agility. No study participant performed at an 'above average' level (i.e. >84th centile) in the running speed and agility or upper limb coordination domains,

Table I: BOT-2 normalized scores

Motor domain	Mean	SD	*p*
Balance	9.03	4.72	<0.001
Running speed and agility	11.54	3.67	<0.001
Upper limb coordination	10.07	4.31	<0.001

One sample *t*-test. Mean 15 (SD 5). BOT-2, Bruininks Oseretsky Test of Motor Proficiency, 2nd Edition.

and only 2/39 performed above average for the balance domain.

Table II shows raw gait parameters of 39 children with NF1. Changes in gait with increasing age were similar to those of typically developing children, with increases in velocity, step length, stride length, and step time, and decreases in cadence. Norm-derived z-scores for children with NF1 are shown in Table III. Compared with normative reference values, children with NF1 demonstrated significantly decreased velocity, cadence, stride length, single support (%GC), and base of support. Significantly increased step time, and double support (%GC) were also observed.

Neurocognitive data are shown in Table IV. One sample Student's *t*-tests revealed that children with NF1 performed at levels significantly below ($p<0.001$) normative data on all IQ variables and SWM between search errors. One sample Wilcoxon signed-rank test revealed that SWM strategy scores, which were not normally distributed, were significantly poorer than normative data. Parent ratings of NF1 participants' functional executive skills showed significantly more behavioural executive difficulties than expected from the normative data. This was evident on the Behavioural Regulation Index and Metacognition Index as well as the Global Executive Composite.

Relationships between motor and neurocognitive function

Correlations between motor and cognitive variables revealed a number of significant associations. As shown in Table V, poorer balance skills were significantly associated with a reduced perceptual reasoning index ($r=0.493$, $p<0.01$) and working memory index ($r=0.425$, $p<0.01$). Reduced running speed and agility was significantly associated with a poorer SWM strategy score (rho=0.549, $p<0.01$), working memory index ($r=0.447$, $p<0.01$), and perceptual reasoning index ($r=0.454$, $p<0.01$).

Of the gait variables, increasing base of support (i.e. gait width) was significantly associated with decreased SWM between search errors ($r=-0.594$, $p<0.01$) and strategy ($r=-0.462$, $p<0.01$) scores. Reduced step length (rho=0.404, $p<0.01$) was significantly associated with poorer SWM strategy.

DISCUSSION

The aims of this study were to examine motor proficiency and gait in children with NF1 and to examine the relationship between motor proficiency and gait with neurocognitive outcomes. As expected, children with NF1 demonstrated impairments in gross motor skills when compared with age-matched normative data, with 28/39 exhibiting impaired balance and upper limb coordination and 16/38 showing impaired running speed and agility. The degree of impairment identified in our cohort is similar to that found in two previous studies of gross motor proficiency, in which 76 to 81% of children with NF1 were reported as displaying at least below average motor skills.[6,8]

This is the first study, to our knowledge, to report on gait parameters in children with NF1. Age-related changes in gait were similar to those described in typically developing children, with increasing velocity, step time, step and stride length with decreasing cadence.[27] However, there were spatiotemporal gait variables that showed significant variations from those reported in typically developing children.[37,39] Children with NF1 demonstrated statistically significant reductions in velocity, cadence, stride length and single support (%GC), and an increased double support (%GC) and step time, although the mean z-score may not be clinically significant as all but the double and single support (%GC) parameters were within 1 SD of normative reference values. Such changes are consistent with a cautious walking strategy to preserve balance at the expense of velocity.[40] An unexpected finding, however, was the tendency towards a narrowed base of support (i.e. gait width), which requires increased frontal plane stability and is not typically a compensation for impaired balance.[41] However, base of support is a measure that should be treated with caution as it has been shown to exhibit lower repeatability than other spatiotemporal measures.[26]

Table II: Raw gait data for children with neurofibromatosis type 1 (NF1) by age

	Age, y									
	7–8		9–10		11–12		1–14		15–17	
n	11		9		5		6		8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Velocity (cm/s)	104.9	17.2	112.4	16.2	112.2	13.4	115.2	18.6	108.7	15.9
Cadence (steps/min)	124.8	10.8	119.4	11.3	115.5	9.3	106.5	8.8	103.5	7.4
Step length (cm)	54.4	7.1	60.0	13.6	70.3	27.6	71.9	13.0	66.7	12.3
Stride length (cm)	100.6	11.3	112.8	8.2	119.1	8.3	129.5	14.0	126.3	15.9
Base of support (cm)	5.6	1.7	8.1	2.4	6.1	2.5	6.1	3.4	7.9	4.8
Step time (s)	0.48	0.05	0.51	0.05	0.52	0.04	0.57	0.05	0.58	0.04
Single support (%GC)	40.1	1.6	39.9	1.4	40.4	1.7	39.8	1.5	38.0	1.4
Double support (%GC)	19.3	2.5	19.4	2.4	23.1	9.5	20.5	3.2	23.3	2.8

%GC, percentage of gait cycle.

This study is consistent with previously published research, reporting that children with NF1 demonstrate impairments on measures of intelligence,[4] spatial working memory,[30] and parent reports of functional executive behaviours.[22] To the best of our knowledge, this is the first study to report on the associations between cognitive functioning and gross motor skills in NF1. Moderate-to-large correlations were identified between a number of cognitive and motor abilities. Running speed and agility displayed the greatest associations with neurocognitive variables, including the strategy score from the spatial working memory task, the working memory index, and the perceptual reasoning index. There were also significant associations between balance and the perceptual reasoning index and working memory index. Taken together, these associations suggest that children with NF1 and neurocognitive impairments – particularly working memory and non-verbal reasoning deficits – are more likely to experience reduced motor abilities. Relationships between working memory and motor abilities have been reported in children with developmental coordination disorder,[12,14] raising the possibility of shared abnormal neurodevelopmental processes underlying these abilities in children with NF1.

Significant associations were also identified between neurocognitive variables and the base of support (spatial working memory, strategy) and step length (strategy) measures of gait. There are a number of possible explanations for the association between gait and neurocognitive variables. One suggests the possibility of cerebellar dysfunction, a brain structure shown to be important in motor coordination, balance, and cognition, particularly executive functions.[15] However, the observed tendency of children with NF1 to have a narrower base of support is inconsistent with an impaired cerebellar mechanism.[42] An alternate hypothesis could be that abnormalities within the corticostriatal network, a circuit that intimately links regions of frontal cortex to striatal structures via the thalamus and globus pallidus,[43] contributes to the association between executive and motor impairments. Although it is well established that executive functions, such as working memory, are mediated by corticostriatal circuitry, recent data from *Nf1* mice models (*Nf1*±strain with GFAP+ cell bi-allelic *Nf1* gene inactivation) have established a mechanistic connection between *NF1* gene expression and decreased dopamine levels in the striatum, thus strengthening this hypothesis.[44] Interestingly, our cohort of children with NF1 demonstrated a similar gait profile to that seen in early Parkinson disease; a disease associated with decreased dorsal striatal dopamine levels and gait abnormalities which are characterized by a shorter step length and longer step time, reduced cadence and base of support and increased double support time.[45] Although identifying

Table III: Gait descriptives for children with neurofibromatosis type 1 (NF1) 7–15 years of age

Gait variable	Mean z-score	SD	*p*
Velocity	−1.00	0.94	<0.001
Cadence	−0.82	0.99	<0.001
Step time	0.94	1.03	<0.001
Step length	0.02	2.41	0.121
Stride length	−0.88	0.72	<0.001
Base of support	−0.65	1.06	0.001
Single support (%GC)	−1.38	1.11	<0.001
Double support (%GC)	1.12	1.92	0.002

Mean z-scores compared with normative reference values using a one sample *t*-test. %GC, percentage of gait cycle.

Table IV: Mean neurocognitive data compared with normative reference values using a one sample *t*-test (unless noted)

Variable	Mean	SD	*p*
FSIQ[a]	86.00	11.71	<0.001
VCI[a]	89.03	12.32	<0.001
PRI[a]	84.44	18.80	<0.001
WMI[a]	85.11	10.67	<0.001
PSI[a]	92.37	11.15	<0.001
SWM BSE[b]	−0.501	1.06	0.004
SWM strategy[b,c]	−0.640	1.09	0.005
BRI[d]	59.61	13.38	<0.001
MCI[d]	63.24	12.11	<0.001
GEC[d]	62.76	12.47	<0.001

[a]Standard score, mean 100, SD 15; [b]z-score, mean 0, SD 1; [c]Median (IQR) reported. Wilcoxon sign-ranked test; [d]*t*-score, mean 50, SD 10. FSIQ, Full Scale IQ; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index; SWM, spatial working memory; BSE, between search error; BRI, behavioral regulation index; MCI, metacognition index; GEC, global executive composite.

Table V: Pearson's rank correlation coefficients between standardized scores for motor skills, gait, and neurocognitive measures

Tests	FSIQ	PRI	WMI	SWM BSE	SWM strategy[a]	GEC
Motor skills						
Balance	0.308	0.493[b]	0.425[b]	0.357	0.270	−0.147
Running, speed and agility[c]	0.376	0.454[b]	0.447[b]	0.281	0.549[b]	−0.338
Upper limb coordination	0.248	0.322	0.419	0.112	0.049	−0.124
Gait						
Base of support	−0.409	−0.068	−0.099	−0.594[b]	−0.462[b]	0.285
Step length	0.326	0.245	0.242	0.222	0.404[b]	0.098
Double support time	−0.350	−0.188	−0.187	−0.296	−0.405	−0.079

$n = 39$ for all motor skills correlations and $n = 37$ for all gait correlations unless otherwise indicated. [a]Spearman's rank correlations; [b]$p < 0.01$; [c]$n = 38$. FSIQ, Full Scale IQ; PRI, perceptual reasoning index; WMI, working memory index; SWM BSE, spatial working memory between search errors; SWM strategy, spatial working memory strategy score; GEC, global executive composite.

the cause of the combined motor/cognitive deficits in NF1 is beyond the scope of this study, these findings add support to the body of evidence demonstrating comorbidity of motor and cognitive deficits in developmental disorders.

The present study is not without limitation and we acknowledge that the simultaneous recruitment of an age-matched healthy comparison group would have allowed for a more thorough investigation of gait in the entire NF1 cohort and should be considered for future research investigating gait in NF1. The size of our cohort also restricted the number of associations we could investigate between cognition and motor function.

In conclusion, we have demonstrated motor and gait impairments in children and adolescents with NF1. Considering that motor skill impairment can cause a multitude of problems including engagement in school and sporting activities and impaired processing and perceptual abilities, future research should focus on interventions to improve deficits in this area. We have additionally identified a relationship between neurocognitive performance and running speed and agility, balance and gait in children with NF1. This relationship raises the possibility of a common pathogenic pathway caused by abnormalities of dopamine-mediated corticostriatal circuitry. We plan to further explore the interdependency in motor and cognitive outcomes using functional magnetic resonance imaging, and to examine neurocognitive and motor response to pharmacological manipulation of the dopaminergic pathway.

ACKNOWLEDGEMENTS

This study was funded by the Sherman Fellowship in Neurofibromatosis 1 Research Australia, awarded to Dr Payne.

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

REFERENCES

1. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet A* 2010; **152A**: 327–32.
2. Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL. Neurofibromatosis type 1 revisited. *Pediatrics* 2009; **123**: 124–33.
3. Lehtonen A, Howie E, Trump D, Huson SM. Behaviour in children with neurofibromatosis type 1: cognition, executive function, attention, emotion, and social competence. *Dev Med Child Neurol* 2012; **55**: 111–25.
4. Hyman SL, Shores EA, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology* 2005; **65**: 1037–44.
5. Hyman SL, Shores EA, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention–deficit–hyperactivity disorder. *Dev Med Child Neurol* 2006; **48**: 973–7.
6. Johnson BA, MacWilliams BA, Carey JC, Viskochil DH, D'Astous JL, Stevenson DA. Motor proficiency in children with neurofibromatosis type 1. *Pediatr Phys Ther* 2010; **22**: 344–8.
7. Soucy EA, Gao F, Gutmann DH, Dunn C. Developmental delays in children with neurofibromatosis type 1. *J Child Neurol* 2012; **27**: 641–4.
8. North K, Joy P, Yuille D, Cocks N, Hutchins P. Cognitive function and academic performance in children with neurofibromatosis type 1. *Dev Med Child Neurol* 1995; **37**: 427–36.
9. Skinner RA, Piek JP. Psychosocial implications of poor motor coordination in children and adolescents. *Hum Mov Sci* 2001; **20**: 73–94.
10. Kanioglou A, Tsorbatzoudis H, Barkoukis V. Socialization and behavioral problems of elementary school pupils with developmental coordination disorder. *Percept Motor Skills* 2005; **101**: 163–73.
11. Roebers CM, Kauer M. Motor and cognitive control in a normative sample. *Dev Sci* 2009; **12**: 175–81.
12. Michel E, Roethlisberger M, Neuenschwander R, Roebers CM. Development of cognitive skills in children with motor coordination impairments at 12–month follow-up. *Child Neuropsychol* 2011; **17**: 151–72.
13. Alloway TP, Temple KJ. A comparison of working memory skills and learning in children with Developmental Coordination Disorder and moderate learning difficulties. *Appl Cognitive Psych* 2007; **21**: 473–87.
14. Alloway TP. Working memory, reading, and mathematical skills in children with developmental coordination disorder. *J Exp Child Psychol* 2007; **96**: 20–36.
15. Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Dev* 2000; **71**: 44–56.
16. Buderath P, Gärtner K, Frings M, et al. Postural and gait performance in children with attention deficit/hyperactivity disorder. *Gait Posture* 2009; **29**: 249–54.
17. Leitner Y, Barak R, Giladi N, et al. Gait in attention deficit hyperactivity disorder. *J Neurol* 2007; **254**: 1330–8.
18. Giedd JN, Blumenthal J, Molloy E, Castellanos FX. Brain imaging of attention deficit/hyperactivity disorder. *Ann N Y Acad Sci* 2001; **931**: 33–49.
19. Timmann D, Diener HC. Coordination and ataxia. In: Goetz CG, Pappert EJ, editors. Textbook of Clinical Neurology. Orlando: Sanders, 2003: 299–315.
20. Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov Disord* 1998; **13**: 428–37.
21. Neurofibromatosis Conference Statement. *Arch Neurol* 1988; **45**: 575–8.
22. Payne JM, Hyman SL, Shores EA, North KN. Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. *Child Neuropsychol* 2011; **17**: 313–29.
23. Bruininks RH, Bruininks BD. Bruininks-Oseretsky Test of Motor Proficiency. 2nd edn. Minneapolis: NCS Pearson, 2005.
24. Wuang YP, Su CY. Reliability and responsiveness of the Bruininks-Oseretsky Test of Motor Proficiency-Second Edition in children with intellectual disability. *Res Dev Disabil* 2009; **30**: 847–55.
25. Burns J, Ryan MM, Ouvrier RA. Evolution of foot and ankle manifestations in children with CMT1A. *Muscle Nerve* 2009; **39**: 158–66.
26. Thorpe DE, Dusing SC, Moore CG. Repeatability of temporospatial gait measures in children using the GAITRite electronic walkway. *Arch Phys Med Rehabil* 2005; **86**: 2342–6.
27. Dusing SC, Thorpe DE. A normative sample of temporal and spatial gait parameters in children using the GAITRite electronic walkway. *Gait Posture* 2007; **25**: 135–9.
28. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. *Gait Posture* 2003; **17**: 68–74.
29. Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lesions in man. *Neuropsychologia* 1990; **28**: 1021–34.
30. Payne JM, Arnold SS, Pride NA, North KN. Does attention-deficit–hyperactivity disorder exacerbate executive dysfunction in children with neurofibromatosis type 1? *Dev Med Child Neurol* 2012; **34**: 898–904.
31. Owen AM, Morris RG, Sahakian BJ, Polkey CE, Robbins TW. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain* 1996; **119**: 1597–615.
32. Robbins TW. Dissociating executive functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci* 1996; **351**: 1463–70.
33. Gioia G, Isquith P, Guy S, Kenworthy L. Behavior Rating Inventory of Executive Function-Professional Manual. Odessa, FL: Psychological Assessment Resources, 2005.
34. Shuster J, Toplak ME. Executive and motivational inhibition: associations with self-report measures related to inhibition. *Conscious Cogn* 2009; **18**: 471–80.

35. Gilotty L, Kenworthy L, Sirian L, Black DO, Wagner AE. Adaptive skills and executive function in autism spectrum disorders. *Child Neuropsychol* 2002; **8**: 241–8.
36. Lythgo N, Wilson C, Galea M. Basic gait and symmetry measures for primary school-aged children and young adults whilst walking barefoot and with shoes. *Gait Posture* 2009; **30**: 502–6.
37. Lythgo N, Wilson C, Galea M. Basic gait and symmetry measures for primary school-aged children and young adults. II: walking at slow, free and fast speed. *Gait Posture* 2011; **33**: 29–35.
38. Bladen M, Alderson L, Khair K, Liesner R, Green J, Main E. Can early subclinical gait changes in children with haemophilia be identified using the GAITRite walkway. *Haemophilia* 2007; **13**: 542–7.
39. Rinehart NJ, Tonge BJ, Iansek R, et al. Gait function in newly diagnosed children with autism: cerebellar and basal ganglia related motor disorder. *Dev Med Child Neurol* 2006; **48**: 819–24.
40. Benedetti MG, Piperno R, Simoncini L, Bonato P, Tonini A, Giannini S. Bait abnormalities in minimally impaired multiple sclerosis patients. *Mult Scler* 1999; **5**: 363–8.
41. Kelly VE, Schrager MA, Price R, Ferrucci L, Shumway-Cook A. Age-associated effects of a concurrent cognitive task on gait speed and stability during narrow-base walking. *J Gerontol A Biol Sci Med Sci* 2008; **63**: 1329–34.
42. Mochizuki H, Ugawa Y. Cerebellar ataxic gait. *Brain Nerve* 2010; **62**: 1203–10.
43. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; **9**: 357–81.
44. Brown JA, Emnett RJ, White CR, et al. Reduced striatal dopamine underlies the attention system dysfunction in neurofibromatosis-1 mutant mice. *Hum Mol Genet* 2010; **19**: 4515–28.
45. Nelson AJ, Zwick D, Brody S, et al. The validity of the GaitRite and the Functional Ambulation Performance scoring system in the analysis of Parkinson gait. *NeuroRehabilitation* 2002; **17**: 255–62.