Neurological and Appearance-related symptoms in children with Neurofibromatosis type 1 (NF1):

The relationship between NF1 severity and cognitive and behavioural outcomes

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder associated with multiple cutaneous, physical and neurological symptoms. The aim of this study was to validate current NF1 severity scales using PCA, and relating the NF1 severity scale and components to cognitive and behavioural outcomes. Participants were 18 children diagnosed with NF1 aged 8 to 16 years. The PCA showed that NF1 symptoms could be divided into neurological and appearance symptoms. The presence of more neurological symptoms was associated with a lower score on the task Comprehension. More symptoms in the appearance were associated with less assertiveness. A higher total number of NF1 symptoms was negatively related to the scale meta-cognition of the BRIEF, indicating poorer executive functioning in daily life for children with more NF1 symptoms. Also, elevated autistic traits were observed using the SRS, and poorer emotion recognition as measured with the ANT. Together, these results might indicate that children with NF1 share a neuropsychological profile commonly seen in children with ASD, which might be related to neurological symptoms.

Neurological and Appearance-related symptoms in children with Neurofibromatosis type 1 (NF1): The relationship between NF1 severity and cognitive and behavioural outcomes

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder and is one of the most common single gene disorders (Huson & Korf, 2007). NF1 was first described by Von Recklinghausen in the thirteenth century, which is why the disorder became known as Von Recklinghausen's disease (Boyd, Korf, & Theos, 2009). The incidence of NF1 is approximately 1:3000 (Friedman, 1999; Moore & Denckla, 2000; North, 1998) to 1:3500 (Levine, Materek, Abel, O'Donnell, & Cutting, 2006; Theos & Korf, 2006). NF1 is heritable, however, approximately 30 % to 50 % of the cases of NF1 result from spontaneous mutations (Levine et al., 2006). Severity and clinical expression of NF1 is variable, with different degrees of severity even within affected family members and generations (Easton, Ponder, Huson, & Ponder, 1993).

The NF1-gene is located on chromosome 17q11.2, and has the highest rate of new mutations of any known single-gene disorders (Theos & Korf, 2006). The NF1 gene encodes for neurofibromin, which serves as a tumour suppressor (Boyd, Korf, & Theos, 2009). Neurofibromin regulates the activity of the Ras protein, which regulates the signals for cell proliferation and differentiation (Theos & Korf, 2006). When the function of neurofibromin is impaired, regulation of cell proliferation and differentiation is disturbed, leading to uncontrolled cell proliferation (Boyd, Korf, & Theos, 2009). Known abnormalities associated with NF1 can be explained from an inability to regulate development of neural cells (Levine et al., 2006).

The National Institutes of Health established the official diagnostic criteria for NF1 in their Consensus Development Conference Statement on Neurofibromatosis (1988). To diagnose NF1 two or more of the following criteria have to be met:

1. six or more café-au-lait macules over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals.
2. Two or more neurofibromas of any type or one plexiform neurofibroma.
3. Freckling in the axillary or inguinal regions.
4. Optic glioma.
5. Two of more Lisch nodules (iris hamartomas).
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudo-arthrosis.
7. A first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria.

Café-au-lait spots are present in over 99 % of the cases of NF1 and are often the first features to appear in children with NF1, developing between the ages of zero and two years (Huson & Korf, 2007). In the general population, the presence of café-au-lait spots is relatively normal (3 % - 36 %), however, the presence of multiple café au lait spots occurs only in less than 1 % of children and adults in the normal population (Landau & Krafchik, 1999). “Dermal” or “cutaneous” neurofibromas are benign tumours, arising from cell nerve sheaths (Theos & Korf, 2006), and these develop in almost all individuals with NF1 (>99 %) from the age of seven onwards, but mostly prepubertal (Huson & Korf, 2007). The number of neurofibromas that will develop is strongly variable and cannot be predicted. Plexiform neurofibromas, affecting multiple fascicles of a nerve and resulting in subcutaneous swellings, occur in approximately 30 % of the cases and can develop throughout childhood (Huson & Korf, 2007). Freckling in the skinfolds is seen in 67 % of the children with NF1, developing from an age of three to five years old (Huson & Korf, 2007). Freckling often develops in the axilla and groin areas, but also in the neck and sub-mammary regions. A tumour of the optic nerve, an optic glioma, can be seen in approximately 15 % of the children with NF1 using imaging techniques. The optic glioma can increase in size, and can lead to decreased visual acuity and

destruction of continguous structures as a result of extension of the tumour (Listernick, Darling, Greenwald, Strauss, & Charrow, 1995). Also, a relationship between optic glioma involving the optic chiasm and precocious puberty has been found, which is hypothesized to be caused by the lesion affecting hypothalamus, resulting in interference with the hypothalamic-pituitairy-gonadal axis. (Habiby, Silverman, Listernick, & Charrow, 1995). Early puberty most often occurs after the age of six and can present with accelerated linear growth (Boyd, Korf, & Theos, 2009). Lisch nodules are small dome-shaped hyperpigmented macules of the iris (Boyd, Korf, & Theos, 2009). Of the individuals with NF1, 90 % to 95 % develops Lisch nodules (Huson & Korf, 2007). Abnormality of the development of the long bones, most commonly the tibia and fibula, as well as of the sphenoid bone, occurs in approximately 14 % of NF1 cases (DeBella, Szudek, & Friedman, 2000).

Despite not being part of the official diagnostic criteria, a number of other features have been related to NF1. These include macrocephaly (45 %), short stature (31,5 %), scoliosis (±9 %), and malignant tumours (1,5 %) (Huson & Korf, 2007). The cognitive and behavioural phenotype of NF1 can be described using the format of Hachon, Iannuzzi, and Chaix (2011). In their study they describe NF1 at the behavioural level, cognitive level, neurobiological level and genetic level.

At the behavioural level, NF1 is characterized by learning disabilities, which are estimated to be present in 30-65 % of patients (Chabernaud et al., 2009; Hachon et al., 2011; Levine et al., 2006; North, 1998). The overall intelligence level is usually normal in individuals with NF1 (Hachon et al., 2011). In their review, Hachon et al. (2011) conclude from multiple studies that the IQ curve in the NF1 population shows a shift to the left, with the mean IQ of NF1 children being approximately 90, a significantly lower mean IQ than in the general population. Due to this shift of the IQ curve, a higher rate of mental retardation is found in children with NF1, since a larger percentage of the normal distribution for NF1,

approximately 6-7 %, will fall below the IQ value of 70, indicating mental retardation (Hyman, Shores, & North, 2005). There are no indications from recent studies for a significant difference between verbal en performal IQ (Hyman et al., 2005; Hyman, Shores, & North, 2006). Seeing the learning difficulties in the light of intelligence, Hyman and colleagues (2006) conclude that the group of children with NF1 with learning disabilities can be divided into children with general learning difficulties, having both a low general cognitive functioning and academic performance, and children with specific learning disabilities, with a higher general cognitive functioning but poor academic achievement. However, the cognitive profile of children with NF1 has distinct characteristics, which can remain unobserved in studies investigating full-scale IQ scores. According to Hyman and colleagues between 30 %-50 % of individuals with NF1 meet the criteria for Attention Deficit Hyperactivity Disorder (ADHD) (Hyman et al., 2005; North, Hyman, & Barton, 2002). The majority of children with NF1 are diagnosed ADHD inattentive type, lacking the hyperactivity of the combined type (Noll et al., 2007). Huijbregts and De Sonneville (2011) have also found indications of a link between autism and NF1. In their sample, the largest difference between children with NF1 and control children was found for autistic traits. Children with NF1 also have poorer social skills and more social problems than their healthy counterparts, as was found in multiple studies (Barton & North, 2004; Huijbregts & De Sonneville, 2011; Johnson, Saal, Lovell, & Schorry, 1999; Noll et al., 2007). More specifically, Noll et al. (2007) found that children with NF1 displayed less leadership behaviour, and were more sensitive and isolated, but were also more prosocial. Children with NF1 were selected less often as a friend by peers and had less reciprocated friendships. The presence of ADHD is a major risk factor for poor social outcomes and poor social skills (Barton & North, 2004). Children with NF1 also display more behavioural problems in other domains, such as conduct problems and emotional problems (Huijbregts & De Sonneville, 2011; Kayl & Moore III, 2000; Noll et al., 2007).

The behavioural phenotype of children with NF1 can be partly explained by the cognitive phenotype of children with NF1. Multiple attempts have been done to discern a comprehensive cognitive profile of children with NF1 (Hachon et al., 2011; Hyman et al., 2005, 2006; Kayl & Moore III, 2000; Levine et al., 2006; North et al., 2002). Children with NF1 have been found to have an impairment of visuo-spatial skills (Clements-Stephens, Rimrodt, Gaur, & Cutting, 2008; Levine et al., 2006; Schrimsher, Billingsley, Slopis, & Moore III, 2003), language disabilities (Dilts et al., 1996; Hofman, Harris, Bryan, & Denckla, 1994; Joy, Roberts, North, & De Silva, 1995), problems with fine motor coordination and motor speed (Hachon et al., 2011), and problems with executive functioning (Descheemaeker, Ghesquière, Symons, Fryns, & Legius, 2005; Ferner, 2007). More recently, Huijbregts and colleagues found evidence for a specific deficit in social information processing (Huijbregts, Jahja, De Sonneville, De Breij, & Swaab-Barneveld, 2009). Both the bottom-up encoding of social signals as well as the top-down appraisal of social signals was impaired in their group of children with NF1. Social information processing deficits in children with NF1 can explain conduct and peer problems (Huijbregts & De Sonneville, 2011). Recently, the theory has been proposed that the cognitive deficits in children with NF1 can be explained by cognitive control. Cognitive control, involving communication within and between brain areas, is hypothesized to be explanatory of the overall cognitive deficits of children with NF1 (Rowbotham, Pit-ten Cate, Sonuga-Barke, & Huijbregts, 2009). This hypothesis has been confirmed in multiple studies, with children with NF1 showing a cognitive control deficit (Huijbregts & De Sonneville, 2011; Huijbregts, Swaab, & De Sonneville, 2010; Rowbotham et al., 2009). It seems that children with NF1 are able to catch up with respect to more basic cognitive abilities compared to the general population, but that deficits remain evident when they get older for tasks requiring more cognitive control (Huijbregts, Swaab, & De Sonneville, 2010). General cognitive ability, as defined by Huijbregts and De Sonneville

(2011) as a composite score of processing speed, social information processing, and cognitive control, can explain the emotional problems and social responsiveness of children with NF1. In this study, however, autistic traits remained evident, even after control for general cognitive ability. Also, Huijbregts et al. (2010) have found that cognitive control deficits can partly explain social information processing deficits. What can be concluded from these studies is that possibly, a more general deficit underlies the different cognitive profiles seen in children with NF1. This deficit can be further explained at a neurobiological level.

As a result of the disturbed cell proliferation and differentiation, macrocephaly is present in approximately 45 % - 50 % of the cases (Huson & Korf, 2007; Steen et al., 2001). With the use of conventional MRI and MRI T1, a technique more sensitive to subtle structural changes in the brain, brain structures in NF-patients with macrocephaly can be mapped accurately. Macrocephaly in NF1 patients is associated with enlargement of multiple midline brain structures and reduced white matter (Steen et al., 2001). Increases of grey and white matter have been found in multiple studies (Cutting et al., 2002; Greenwood et al., 2005; Moore III, Slopis, Jackson, De Winter, & Leeds, 2000; Steen et al., 2001). Steen et al. (2001) have found that increased white matter is also related to the presence of UBOs, Unidentified Bright Objects, which are bright areas on the MRI image indicating that these specific brain areas have different characteristics than the rest of the brain. DiPaolo and colleagues (1995) hypothesize that these areas consist of cerebral tissue with immature or edematous myelin sheaths, causing these areas to light up in MRI T2-weighted images due to excessive fluid. Studies investigating UBOs report on different numbers of NF1-patients presenting with UBOs, ranging from 43-79 % (Chabernaud et al., 2009), 64 % (Hyman et al., 2003), 60-70 % (Hyman, Gill, Shores, Steinberg, & North, 2007) and 50-74 % (Legius et al., 1995). UBOs have been investigated extensively in combination with cognitive outcomes, but with mixed results. It appears that UBOs in the thalamus are specifically related to cognitive deficits

(Chabernaud et al., 2009; Hyman et al., 2007). The brain abnormalities as described here are in support of the hypothesis by Rowbotham et al. (2009) about cognitive control. Cognitive control is based on functional connectivity, the idea that cognitive operations are performed by networks of brain regions, which are temporally correlated. A synchronous activation of the areas involved in the network is necessary for execution of cognitive operations (Rowbotham et al., 2009). As the thalamus is the part of the brain that coordinates the communication between brain regions (Rowbotham et al., 2009) and white matter and the grey-to-white matter ratio is involved in communication between brain areas, it is plausible that these abnormalities are related to impaired functional connectivity and cognitive control. This conclusion is also drawn by Hachon et al. (2011), who state that connectivity pathology between anterior and posterior cerebral areas is suggested by multiple studies.

Disease severity

As can be concluded from the literature discussed so far, there is major variability between individuals in the phenotype, endophenotype and genotype of NF1. Multiple researchers have tried to create a comprehensive scale to list the NF1 symptoms of individuals and the severity of these symptoms (Ablon, 1996; Huijbregts & De Sonneville, 2011; Noll et al., 2007; Riccardi, 1992; Sebold, Lovell, Hopkin, Noll, & Schorry, 2004). Severity scales include the presence of NF1 symptomatology, cosmetic difficulties, psychological problems, learning difficulties and ADHD status. These can be filled in by caretakers, although a possible lack of knowledge of caretakers, for example about medical issues, might create the need for additional information by a physician. Sebold and colleagues (2004), using an adaptation of the Riccardi scales as an objective measure of severity of the NF1 as rated by clinicians, but also a severity perception scale for parents and adolescents (Perception of Severity of Chronic Illness scale, PSCI), found that the severity as rated by parents and adolescents on the PSCI

was significantly correlated to the severity as indicated by the clinician. Severity was rated by the clinicians on four scales, cutaneous involvement, medical complications, cognitive impairment and behavioural problems. Severity perception of the parents was specifically correlated to medical, cognitive and behavioural problems of the child as rated by the clinician, for the adolescents themselves only cognitive severity perception, indicating cognitive problems such as learning difficulties as rated by the clinician, was significantly correlated to their severity perception, indicating that for adolescents cognitive impairments or learning problems contribute strongly to their perception of disease severity.

However, although the present severity scales are informative, they are lacking in multiple areas. First, most severity scales lack a robust body of psychometric data (Noll et al., 2007). Also, the present scales do not distinguish sufficiently between different features that might differ strongly regarding their impact. For example, cosmetic features, CNS abnormalities and physiological difficulties, but also cognitive impairments as was shown by Sebold and colleagues (2004), may have very different impacts, both qualitatively and regarding their impact on functioning and well-being. Present severity scales do not distinguish between symptoms and outcomes of NF1 either: for example, ADHD and learning disorders have been considered NF1-symptoms (Hyman et al., 2005; North et al., 2002; Noll et al., 2007) but may better be considered outcomes following NF1-specific pathology. Furthermore, despite the evidence for a link between NF1 and autism, no severity scale has yet incorporated autism at all. Also, none of the scales has introduced a weighting of the symptoms, while it seems plausible that some symptoms will have larger impact than others (e.g. malignant tumours versus café-au-lait spots). For research purposes, a better defined scale is necessary to adequately investigate the relationship between severity of NF1 and outcome measures. For clinical purposes, the introduction of a well-designed NF-1 severity

scale is necessary to assess the severity of the NF1 in patients. A severity index can give indications for further treatment, monitoring and support. In the Netherlands, the care system is based on the "need for support" of an individual. A good report on the severity of the NF1 supports the quick and adequate offering of the required support.

Multiple studies have been performed investigating associations between the severity of NF1 and outcome measures. Huijbregts and De Sonneville (2011) found that disease severity, based on all domains except behavioural, psychological and learning problems, was not significantly related to social or behavioural outcomes. Noll et al. (2007) used three separate severity scales. The medical severity scale was only significantly related to attention as reported by fathers. The physical scale was not significantly related to any of the outcome measures, whereas the neurological scale was significantly related to multiple measures of social, emotional and behavioural functioning (peer problems, internalizing and externalizing problems, attention problems, depression and conduct problems). However, as stated previously, this severity scale included outcome features like ADHD and learning problems, so an association with peer problems and attention problems seems obvious. It seems plausible that the results have been confounded, and that no clear statements can be made about the relationship between neurological severity and social and behavioural outcomes without a better defined severity scale.

Current study

In this study, a new NF1 severity scale will be introduced, based on the strengths and limitations of existing scales. The scale will be a questionnaire for parents, but with room to contact the patients' physician for supplementary information. A weighting of symptoms will be included in the scoring system in order to give a more precise representation of the severity of the NF1 in the patients. A first aim of this study is to validate existing NF1-severity scales

using statistical techniques. Existing NF1 severity scales are based on theory, for example the medical, physical, and neurological severity scales (Noll et al., 2007) or the cutaneous, medical, cognitive and behavioural severity scales (Sebold et al., 2004). By investigating the factor structure of the present severity scale, statistical evidence will be given for the division of NF1 severity scales in separate factors. It is hypothesized that a two-factor structure will be found, dividing the symptoms of NF1 into neurological symptoms and cosmetical, physical or cutaneous symptoms like café-au-lait spots or itching. Behavioural problems as investigated with the NF1 severity scale, e.g. ADHD, peer- and social problems etc., are assumed to be a result of cognitive deficits, based on previous results by Huijbregts and De Sonneville (2011), and are not hypothesized to be a separate factor. Since cognitive deficits are related to abnormalities on brain-level (Rowbotham et al., 2009), it is hypothesized that behavioural problems as a result of cognitive deficits will be related to the neurological factor of the NF1 severity scale. However, social- and peer problems may also be caused by cosmetical and physical symptoms, for example due to bullying or exclusion by peers.

A second aim of this study is to relate the NF1 severity factors to cognitive, social, and behavioural outcome measures. Social and behavioural outcomes will be assessed using questionnaires, whereas cognitive functioning will be assessed using clinical testing. Based on the literature on cognitive impairments in children with NF1 (Hachon et al., 2011; Huijbregts & De Sonneville, 2011; Huijbregts et al., 2010; Rowbotham et al., 2009; Huijbregts, et al. 2009), assessments included intelligence, cognitive control and social information processing. Sustained attention was measured in order to assess possible attention deficits, as executive functioning problems have been previously found in children with NF1 (Descheemaeker, Ghesquière, Symons, Fryns, & Legius, 2005; Ferner et al., 2007). Although there are some indications for a relationship between severity of NF1 and social and behavioural outcomes,

no specific relationships have been found. However, most studies report that a possible reason for the lack of a relationship between severity and outcome measures is the severity scale that is used. Therefore, it is hypothesized that the total severity as indicated by the present NF1 severity scale, including weighting of the symptoms, will be related to cognitive, social and behavioural outcomes. Also, it is hypothesized that the severity factors, excluding outcomes as measured by the NF1 severity scale in order to avoid bias, will be specifically related to certain outcome variables. As with the outcomes measured by the NF1 severity scale, it is hypothesized that the cognitive and behavioural outcomes will be most strongly related to the neurological factor. By creating a more valid scale of severity, the relationship between severity and social and behavioural outcomes can be studied more thoroughly.

Method

Participants

Participants of the study were 18 Dutch children and adolescents diagnosed with Neurofibromatosis Type 1 (NF1) (11 boys, 7 girls, mean age 12;8 years, SD 2;4 years, range 8;2-16;7). All participants fulfilled the diagnostic criteria for NF1 specified by the National Institutes of Health Consensus Conference (1988). The participants were recruited through the Dutch Neurofibromatosis Association by means of advertisements in the newsletter and on their website, as well as through a written letter informing eligible participants of the study. Participating families lived in various areas of Holland including rural and urban areas in different regions. Written informed consent was obtained from parents and participants, with parents confirming willingness to participate for children under the age of 18. Ethical approval for the study was granted by Leiden University's education and Child Studies Ethics Committee.

Instruments

Disease severity

Disease severity was measured with a parent questionnaire which was constructed by the research group. The questionnaire was based on existing severity scales by Ablon (1996), Huijbregts and De Sonneville (2011), Noll et al. (2007), and Riccardi (1992). All known symptoms and outcomes of NF1 were included, such as café-au-lait spots, neurofibromas, macrocephaly, malignant tumours, learning problems, ADHD and Autism Spectrum Disorders (ASD) (for the full questionnaire see appendix a). All symptoms are listed in Table 2. A question involving disease severity perception ("Does your child experience his/her symptoms as a burden?") was also added. Questions were constructed hierarchically, parents

first answered whether a symptom was present, and if so, in what amount it was present, e.g. "Does your child have café-au-lait spots? If yes, could you indicate how many?". ADHD and ASD status were asked as diagnosed by a clinician and included medication status, but was also asked in the opinion of the rater (e.g. "In your opinion, does your child display ADHD characteristics?"). Scoring of the symptoms was done by scoring non-presence of a symptom as 1 and presence of the symptom as a 2. A weighting of the symptoms was included for the variables café-au-lait spots, neurofibromas, spinal anomalies, benign tumour, and itch (table 1). The weighting of the symptoms was done by studying the nature of the symptoms. As this NF1 severity scale was newly constructed by the research group, no information can be provided about the reliability or factor structure of the disease severity scale.

Table 1. *Weighted variables.*

Variables	Weighting
Café-au-lait spots	1 = 1-29 café-au-lait spots
	2 = ≥30 café-au-lait spots
Neurofibromas	1 = no neurofibromas
	2 = 1-9 neurofibromas
	3 = ≥10 neurofibromas
	Plexiform neurofibromas = +1
Spinal Anomalies	1 = no spinal anomalies
	2 = spinal anomalies present
	3 = spinal anomalies present and under treatment
Benign tumour	1 = no tumour
	2 = benign tumour present
	3 = benign tumour present and under treatment
Itch	1 = no itch
	2 = itch present
	3 = itch present and treated with medication

Cognitive functioning

WISC-III^{nl}.

Intelligence of the children and adolescents with NF1 was estimated using multiple subtests from the Dutch translation of the Wechsler Intelligence Scale for Children, third edition (WISC-III^{nl}; Wechsler, 2002). The WISC-III^{nl} has been rated sufficient to good by the Dutch test committee (COTAN), with exception of the criteriumvalidity which was rated insufficient. The subtests used were Picture Completion, which measures the ability to observe part-whole relationships, Coding version B, measuring processing speed, Block Design, which measures the ability to observe part-whole relationships and construction abilities, Vocabulary, measuring Word knowledge and verbal fluency, Comprehension, measuring general knowledge and verbal fluency in social situations, and Symbol Search version B, measuring processing speed. Administration and scoring was done in line with the official test manual. Raw scores were transformed into standard scores using age-appropriate norms, with a Mean of 10, SD 3. A higher score indicated a higher better performance on the subtest, giving an indication for a higher total IQ.

ANT.

Three tasks of the Amsterdam Neurological Tasks (ANT; De Sonneville, 1999) were used to assess social information processing, sustained attention and cognitive control respectively. De ANT is a computerized battery for neuropsychological testing of children. Test–retest reliability and construct-, criterion-, and discriminant validity of the ANT are satisfactory, as described by Rowbotham and colleagues (2009). Test administration was done according to the test manual, involving standardized verbal instruction supported by a visual example of the test, a practice session and the test administration. The tasks will be described in more detail below.

Identification of facial emotions.

The task Identification of facial emotions (IFE) examined the ability to recognize emotions from facial expressions. The task consisted of eight parts, each with another target variable. The participants matched faces on a digitalized photograph with the target variable of the specific part by clicking on the 'yes' or 'no' button on the mouse. The target emotions of the eight conditions were respectively happy, sad, angry, fear, surprise, disgust, shame, and contempt. Each trial consisted of 20 trials of the target emotion and 20 trials of a random selection of other emotions, 40 trials in total. Better social information processing was indicated by more accurate answering, as indicated by less incorrect answers, calculated by adding the misses en false alarms of each trial.

Sustained attention dots.

The task Sustained attention dots (SAD) assessed sustained attention. On the screen, participants would see a square with three, four or five dots. Four dots were the target stimulus for which children had to press the 'yes' button on the mouse, when three of five dots appeared the 'no' button had to be pressed. After pushing the button the next stimulus would appear. The test consisted of 600 trials, duration of the task depended on reaction time of the respondent but ranges overall between 15 and 30 minutes. Inhibition of an inaccurate response was calculated by subtracting the mean of the false alarms for low and high dots from the misses of all trials. The result of this calculation, called Bias, is a clean measure of inhibition, since it only measures impulsive inaccurate responses. A combined measure of inhibition and sustained attention was calculated by computing the difference between the Bias measure of the first 120 trials (block 1) and the last 120 trials (Block 5). Better sustained attention was indicated by a lower Bias score for the total test and for the difference between

the first and the fifth block, since this indicated less impulsive errors and a smaller increase of impulsive errors over time.

Memory search two-dimensional objects.

The task Memory search two-dimensional objects (MS2D) examined working memory. The participant had to remember and detect a target object defined by colour and form (e.g. a red circle) from a subset of four objects. In the first condition the participant had to remember one target object, a red circle, and detect it in 48 trials. In the second condition (48 trials), the participant had to remember and detect three objects, a blue triangle, a green square and a yellow cross. When one of the target stimuli was present in the subset of four objects, the participant had to press the 'yes' button, when none of the target stimuli was present the participant pressed the 'no' button. Because of the test construction, cognitive control could be increased in a controlled manner by increasing working memory load and task demands. A better cognitive control is indicated by a smaller increase in the amount of errors in the second task compared to the first task. This was calculated by subtracting the number of misses and false alarms in the first task from the number of misses and false alarms in the second task.

Social Functioning

SSRS.

The Social Skills Rating System (SSRS; Gresham & Elliot, 1990) was used to assess social behaviour. The SSRS assesses two domains, social skills and problem behaviour. Only the domain social skills was used and completed by the parents. The parent form consists of four scales. The Cooperation subscale consists of behaviours such as helping and sharing (e.g. "offers out of his/her own accord to help with tasks"). The Assertion subscale includes initiating behaviours (e.g. "takes part in group activities out of his/her own accord"). The Responsibility subscale consists of items regarding communication with adults and regard for

property or work (e.g. “Discusses unreasonable house rules in an appropriate manner”) and the Self-control subscale consists of behaviours that include self-control in conflict and non-conflict situations (e.g. “Handles criticism in an acceptable manner”). The questionnaire consisted of 38 items, to be rated on a three-point likert scale (1= Never; 2= Sometimes; 3= Very often). A higher total score on the SSRS indicated better social skills in children. The score on the scale can be compared to mean scores of the norm group. Parents completed the SSRS in approximately 10 minutes. Reliability and validity of the SSRS were satisfactory (Diperna & Volpe, 2005).

Behavioural Functioning

SRS.

The Social Responsiveness Scale (SRS; Constantino, 2002) was used to examine autistic traits. The SRS is designed to assess autistic traits, using five scales based on known impairments in children with an ASD. The first scale measures ‘receptive’ social impairments and includes items on awareness of social information (e.g. “is aware of feelings and thoughts of others”). The ‘cognition’ scale represents social information processing (e.g. “gets upset in situations in which a lot is going on”). The ‘expressive’ scale represents the capacity for reciprocal social communication (e.g. “is awkward in taking turns in interaction with peers”). The ‘motivation’ scale assesses social anxiety or avoidance (e.g. “Would rather be alone than with others”). The fifth scale is the scale Autistic Preoccupations (e.g. “Has an unusually limited area of interest”). The total of all scales gives an indication for the severity of autistic spectrum symptoms. A higher total score indicated more severe autistic spectrum symptoms. The SRS was completed by the parents in approximately 15 minutes. It consisted of 65 items rated on a four-point likert scale (1= never true; 2= sometimes true; 3= often true; 4= almost always true). The score on the scale can be interpreted using the interpretation in the manual

of the SRS based on T-scores. Reliability and validity of the SRS are acceptable; an extensive overview of literature on the psychometric properties of the SRS is given by Bölte, Poustka & Constantino (2008).

DEX-K.

The Dysexecutive Questionnaire (DEX; Wilson, Aldermann, Burgess, Emslie, & Evans, 1996) is part of the Behavioral Assessment of the Dysexecutive Syndrome (BADS). The questionnaire measures problems in daily functioning as a result of planning and organisation problems. The DEX-K, the Dutch version of the DEX for children, consists of 20 items, the total score is the sum of the items. Items are rated by parents on a four-point scale (0= Never, 1= Occasionally, 2= Sometimes, 3= Often, 4= Very often). A higher score on the DEX-K indicated greater executive functioning problems. The score on the scale can be compared to mean scores of the norm group. Reliability and validity are considered acceptable (Chamberlain, 2003).

BRIEF.

The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) is a questionnaire assessing executive functioning in home and school environments. The BRIEF consisted of 75 items on eight clinical scales; Inhibition (e.g. “blurts out things impulsively”), Cognitive Flexibility (e.g. “gets upset in new situations”), Emotion Regulation (e.g. “reacts exaggerated to small problems”), Initiating (e.g., “doesn’t start on his/her own), Working Memory (e.g. “has trouble remembering things, even for a couple of minutes”), Planning and Organizing (e.g. “underestimates time needed to get tasks finished”), Orderliness and Neatness (e.g. “leaves playing area messy”), and Behaviour Evaluation (e.g. “doesn’t know his/her own strengths and weaknesses”). The scales form two indexes, Behavioural regulation (Inhibition, Cognitive Flexibility and Emotion Regulation)

and Metacognition (Initiating, Working Memory, Planning and Organizing, Orderliness and neatness, and Behaviour Evaluation). The global executive composite score is the total of all items. Parents answer the items on a three-point likert scale (1= Never; 2= Sometimes; 3= Often). A higher score on the indexes and total score indicates more executive functioning problems. Reliability and validity are acceptable according to the authors (Gioia et al., 2000).

CBCL.

The Child Behavior Checklist 6-18 (CBCL; Achenbach & Rescorla, 2001) is a parent questionnaire assessing behaviour- and emotional problems and skills in children 6-18 years old. The CBCL consists of 113 items to be rated on a three-point likert scale (0= not at all/never; 1= a little/sometimes; 2= clearly/often). The items are divided over 9 syndrome scales: Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints (Internalizing scale), Rule-breaking Behaviour, Aggressive Behaviour (Externalizing scale), Social Problems, Thought Problems, Attention Problems, and other. All items on behaviour together form the Total Problems scale. The items can also be divided over 6 DSM-oriented scales: Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems. A higher score on a scale indicates more problem behaviour on the domain of the scale. Scores can be compared to norm scores for peers.

Procedure

The current study is part of a larger study of NF1 patients and controls on brain functioning in relationship to cognitive and behavioural outcomes by Leiden University. Participants could contact the project leader via e-mail or phone after reading the recruitment advertisement. Supplemental information was then sent by mail, informing the participants more fully about the study and including an informed consent form. If respondents were willing to participate

they were contacted via phone or during the MRI assessment for a home visit, during which the questionnaires were handed to the parents. During the home visit, all cognitive measures were administered with the child in a quiet room. Parents handed back the questionnaires during the home visits. After completion of the study, participating families received a report on the outcomes of the study.

Data-analysis

First, the data were inspected to study the properties of the variables and to check for missings and outliers. Correlations were calculated for the variables of the NF1 severity list to check whether an underlying factor structure might be present. To investigate the factor structure of the NF1 severity scale, a Categorical Principal Component Analysis (CATPCA) was executed. This technique allowed for investigation of principal components in the structure of the NF1 severity scale, including categorical and numeric variables, without an a priori theory. A CATPCA was performed using the variables representing severity of the symptoms in the participants. Behavioural outcomes of the NF1 (speech problems, gross and fine motor problems, learning impairments, ADHD, ASD, psychological problems and social problems), severity perception (whether the NF1 is a burden) and the question whether the NF1 is familial, were left out of the CATPCA in order to get a valid component structure of the objective symptoms involved in severity of NF1. Dichotomous variables, e.g. variables with a yes- or no answer, for example “Does your child have freckling in the groin area, yes or no?”, were considered nominal. Weighted variables were considered numeric. Inspecting the loading plots showed no abnormalities in the quantifications of the variables, indicating that the measurement levels had been set appropriately. The weighted scores were quantified in an ascending manner, with equal distances, indicating that a score of three was indeed higher on the severity scale than a score of two or one.

With use of the CATPCA, quantifications of the variables were computed. The quantifications of the variables were then used to perform a Principal Component Analysis (PCA), which allows for rotation of the components. With the use of orthogonal rotation, the component structure was analyzed for subscales. To assess a possible influence of certain variables on the component structure, biplots were made to visually investigate the relationship between these variables and the component structure. The components have next been saved per participant and the Pearson correlation was calculated between the component scores and scores on the behavioural and cognitive outcome measures.

Results

In Table 2 the symptoms of NF1 as investigated by the NF1 severity scale have been listed, including the percentage of participants presenting with these symptoms. Of the 18 participants, all presented with café-au-lait spots. Malignant tumours, epilepsy, hormonal problems and conduct problems were not present in any of the participants en will therefore be eliminated from further analyses. One child presented with hypertension, however, this was the result of medication, and could not be considered a symptom of NF1, therefore, hypertension will also not be used in further analyses.

Table 2. *Percentage of participants with NF1 presenting with symptoms.*

Symptoms	% with symptoms	Symptoms	% with symptoms
Café-au-lait spots	100%	Spinal anomalies	50%
Neurofibromas	66,7%	Hypertension	5,6%
Plexiform Neurofibromas	27,8%	Hormonal problems	0%
Skinfold Freckling axilla	83,3%	Headache	50%
Skinfold Freckling Groin	77,8%	Itch	16,7%
Optic Glioma	11,1%	Gross motor skills	77,8%
Lisch Nodules	55,6%	Fine motor skills	66,7%
Osseous Lesions	11,1%	Speech Problems	61,1%
First-degree relative with NF1	33,3%	ADHD	33,3%
UBOs	27,8%	ASD	11,1%
Benign tumour	22,3%	Learning Problems	66,7%
Malignant tumour	0%	Social Problems	55,6%
Macrocephaly	55,6%	Conduct Problems	0%
Epilepsy	0%	Psychological Problems	5,6%

In table 3, the mean total severity score and the mean total severity score with weighting are presented, as well as the mean scores on all outcome measures. If the performance can be described in a classification, indicating the performance compared to peers as described in the test manual, the classification of the mean score is added. The mean score on the severity and the weighted severity scale is comparable. The mean scores on the WISC-III^{nl} are average, except for the performance on Block Design, which is weak, children with NF1 perform weaker than the norm group of the WISC-III^{nl} indicating poorer visual-spatial skills. On IFE, the children with NF1 gave most incorrect answers in the sad condition. Children with NF1 appear to have a variable performance on a task assessing social information processing, depending on the type of information that has to be processed. The Bias score of the task SAD is positive, indicating that the participants made more inhibitory errors relative to other errors. The SAD Bias measure over time, incorporating sustained attention is negative, indicating that the participants made less impulsive errors over time, indicating no significant sustained attention problems. The mean score on the cognitive control measure, MS2D, is positive, indicating that children with NF1 made more errors when cognitive control was increased. The mean score on the DEX-K is average compared to the mean score of the norm group (Wilson, Aldermann, Burgess, Emslie, & Evans, 1996). The mean score of the NF1 children on the SRS is higher than average when compared to peers. The mean score (M=65,47), corresponds to a T-score of 60-75, indicating “deficiencies in reciprocal social behaviour that are significant, and are resulting in mild to moderate interference in everyday social interactions” (Constantino, 2002). The NF1 participants display more autistic traits than their peers without NF1. The mean on the SSRS of the NF1 children is above average, the mean score corresponds to a standard score of 84-94 depending on age and gender (Gresham, & Elliott, 1990). The participants display above average social skills compared to peers without NF1. Due to limited availability of the profile scores of the CBCL, scores on the CBCL scales

are compared to the profile score of boys 6-18 years of age (Achenbach, 2001), but not for girls. The mean score on the Withdrawn/Depressed score of the NF1 children is in the borderline clinical range for boys 6-11. For older boys, this score is normal. The score on the Social Problems scale is in the borderline clinical range, indicative of elevated social problems. On the Internalizing scale, the NF1 children score in the borderline to clinical range, indicating elevated internalizing problems compared to boys without NF1. Overall, the participants display more behaviour problems than boys without NF1, indicated by a Total score in the borderline to clinical range.

Correlation NF1 severity scale

The correlation analysis of the data has shown some significant correlations within the NF1 severity scale ($-0{,}64<r<0{,}85$). The fact that only a few significant correlations were found can be explained by the low number of participants and small variations between scores. The correlation matrix gives an indication that the sub domains are related and that an underlying factor structure might be present.

Table 3. *Mean scores on NF1 severity scale and outcome measures including classification.*

Instrument	Mean	SD	Classification
NF1 severity scale total	19,28	1,67	-
NF1 severity scale weighted total	19,56	2,33	-
WISC Picture Completion	9,29	3,04	Average[a]
WISC Block Design	7,18	3,26	Weak[a]
WISC Vocabulary	9,12	3,03	Average[a]
WISC Comprehension	8,35	2,74	Average[a]
WISC Symbol Search	8,88	3,08	Average[a]
WISC Coding	9,82	2,40	Average[a]
IFE happy errors	1,18	1,24	-
IFE sad errors	9,53	6,77	-
IFE angry errors	4,53	2,65	-
IFE fear errors	4,82	4,50	-
IFE disgust errors	4,47	3,61	-
IFE surprise errors	4,59	2,55	-
IFE shame errors	6,00	4,65	-

Instrument	Mean	SD	Classification
BRIEF total	142,94	34,28	-
SRS Total	65,47	25,65	Mild to moderate deficiencies[c]
SSRS Total	46,65	14,94	Above average[d]
CBCL Anxious Depressed	4,56	3,33	Normal[e]
CBCL Withdrawn Depressed	4,44	3,20	Normal-borderline[e]
CBCL Somatic Complaints	3,83	2,18	Normal[e]
CBCL Social Problems	8,00	4,64	Borderline[e]
CBCL Thought Problems	4,61	4,16	Normal[e]
CBCL Attention Problems	8,56	4,80	Normal[e]
CBCL Rule-breaking Behaviour	2,94	1,95	Normal[e]
CBCL aggressive Behaviour	7,78	6,24	Normal[e]
CBCL Other	5,00	2,93	-
CBCL Internalizing Problems	12,83	7,06	Borderline-clinical[e]
CBCL Externalizing Problems	10,72	7,35	Normal[e]
CBCL Total Problems	49,72	26,06	Borderline-clinical[e]

IFE contempt errors	6,24	5,25	-	CBCL Affective Problems	5,50	3,00
SAD Bias	9,82	10,88	-	CBCL Anxiety Problems	3,00	1,88
SAD Bias/SA	-1,59	2,54	-	CBCL Somatic Problems	2,06	1,30
MS2D cognitive control	15,29	6,73	-	CBCL Attention Deficit/Hyperactivity Problems	6,28	3,89
DEX-K total	28,24	16,62	Average[b]	CBCL Oppositional Defiant Problems	3,22	2,34
BRIEF Behaviour regulation index	51,94	16,48	-	CBCL Conduct Problems	3,11	2,56
BRIEF Metacognition index	92,59	19,99	-			

[a]Classification based on M=10 (SD=3) (Wechsler, 2002)

[b]Classification based on M=15,7 (SD=13,6) (Wilson, Aldermann, Burgess, Emslie, & Evans, 1996)

[c]Classification based on M=30,5 (SD=19,7), mean score refers to T-score 60-75 (Constantino, 2002).

[d]Classification based on Standard Score 84-94 depending on age and gender (Gresham, & Elliott, 1990).

[e]Classification based on scoring profile for boys 6-18 years (Achenbach, 2001).

Principal Component Analysis

An exploratory CATPCA was performed, without a fixed set of components. After exploration of component loadings, a two or three-component solution was considered most suitable for the data. A CATPCA including three components was executed, this model accounted for 60 % of the variance in the data, which is acceptable, indicating that more than half of the variance in the data is accounted for by the three components. However, when examining the component solution, no meaningful interpretation could be given for the three components. A two-factor solution explained 44 % of the variance in the data, with the first component explaining 24 %, indicating that all severity measures load on a common factor, and the second component explaining 20 % of the variance. Inspection of the component loadings resulted in a clear segmentation of the data on two dimensions, as presented in figure 1. The symptoms freckling in the axilla and groin area, café-au-lait spots, itch and osseous lesions all load highly on the first dimension. Spinal anomalies and lisch nodules load negatively on the first dimension. The symptoms optic glioma, benign tumour, headache and UBO load highly on the second dimension, macrocephaly loads negatively on the second dimension.

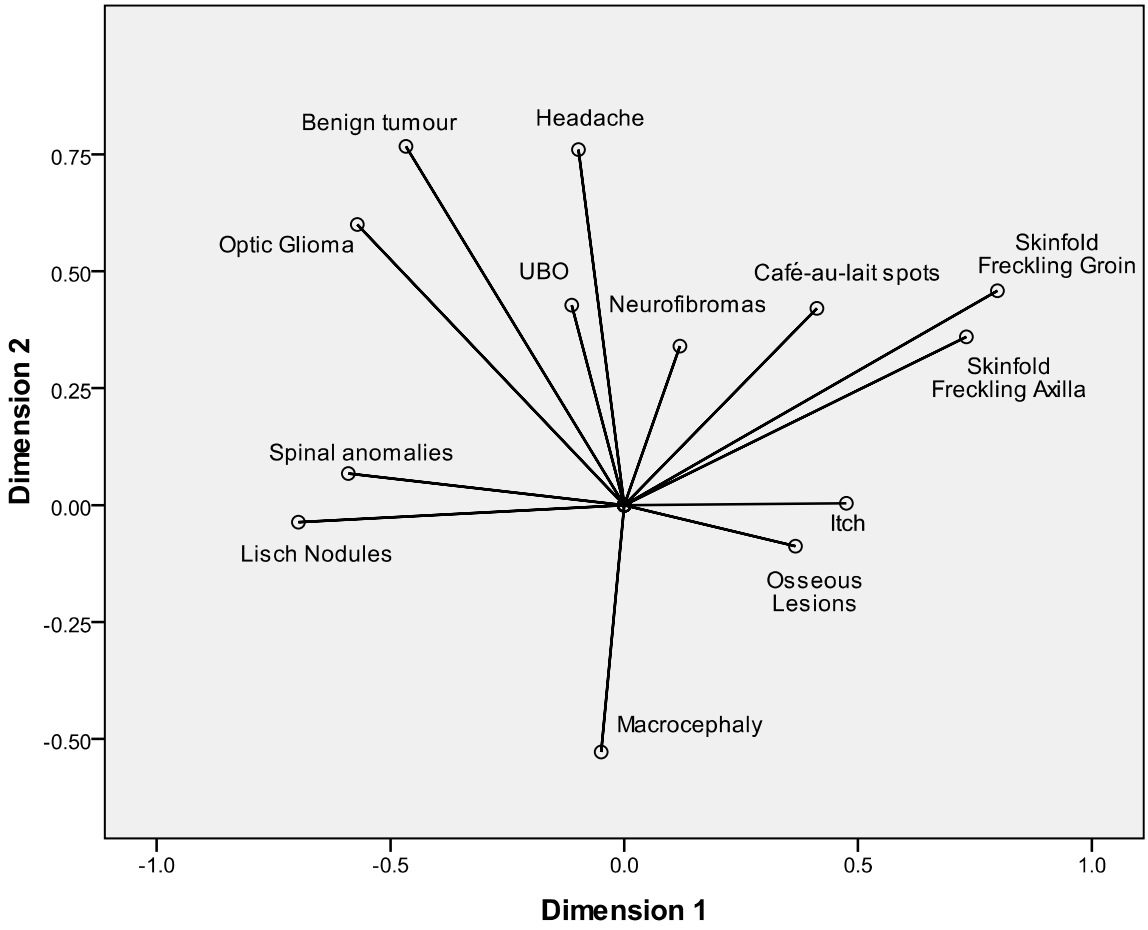

Figure 1. loading plot of NF1 severity scale.

To increase the interpretability of the component solution, the symptom quantifications were inserted in a PCA two-factor solution with orthogonal (varimax) rotation. Inspection of the correlation between the factors using oblique rotation showed that the components were not correlated (r = 0.001). Therefore an orthogonal rotation was done, eliminating influence of component correlations. The component loadings have been listed in table 4, the loadings of the separate components have been outlined.

Table 4. *Component loadings of NF1 severity symptoms on two components.*

	Component	
	1	2
Skinfold Freckling Axilla	,86	,34
Skinfold Freckling Groin	,78	,25
Lisch Nodules	-,70	,06
Spinal Anomalies	-,58	,15
Itch	,47	-,07
Café-au-lait spots	,47	,35
Osseous Lesions	,35	-,13
Benign Tumour	-,35	,83
Headache	,01	,77
Optic Glioma	-,48	,68
Macrocephaly	-,13	-,53
UBOs	-,05	,43
Neurofibromas	,17	,31

The symptoms skinfold freckling in the axilla and groin area, itch, café-au-lait spots and osseous lesions load highly on the first component, lisch nodules and spinal anomalies load negatively on the first component, indicating that children who score high on symptoms like skinfold freckling and café-au-lait spots usually score low on lisch nodules and spinal anomalies. The symptoms benign tumour, headache, optic glioma, and UBOs load highly on the second component, macrocephaly loads negatively on the second component. Neurofibromas load highest on the second component, however, the loading is lower than 0.35, indicating that neurofibromas do not add significantly to either component. Investigating the symptoms involved in each component, the first component represents symptoms which involve appearance and are visible for others. Since lisch nodules and spinal anomalies are often not visible for the naked eye, these load negatively on this component. The second component represents neurological symptoms. However, although macrocephaly also

involves the brain, this symptom does not fit the present component structure. When inspecting the biplot labelling the participants by macrocephaly (figure 2), it is shown that participants with macrocephaly seem to represent a unique group within the present sample, related to almost none of the other variables. Excluding macrocephaly from the component structure however, would expel this symptom from NF1 severity, which cannot be justified based on the data since more than half of the participants presented with macrocephaly. The component structure as was established with the PCA seems the most suitable component structure for the data.

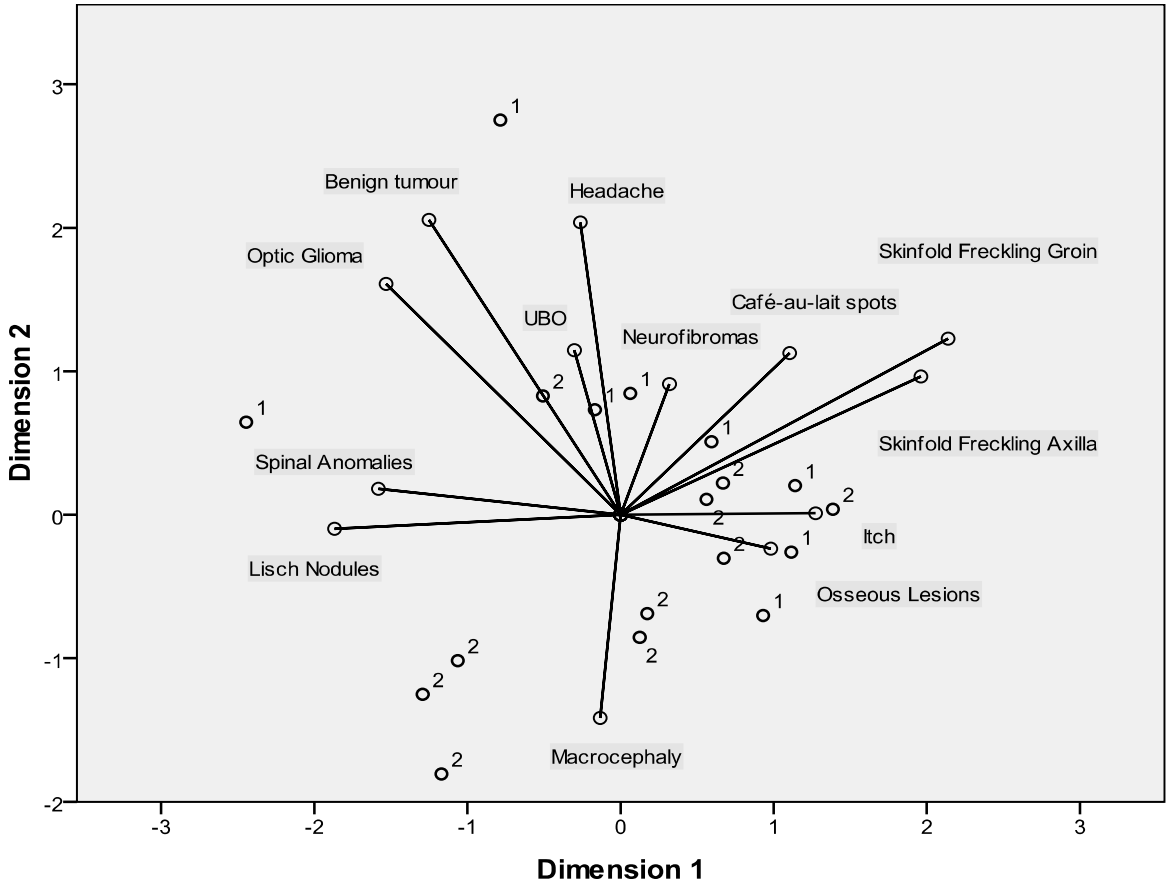

Figure 2. Biplot of component structure including participants labelled by macrocephaly (1=no macrocephaly; 2=macrocephaly).

To investigate the hypothesis whether behavioural severity measures as measured with the NF1 severity scale (speech problems, gross and fine motor problems, learning impairments, ADHD, ASD, psychological problems and social problems), severity perception (whether the NF1 is a burden) and familial NF1 were related to one of the factors, these variables were inserted in the component structure. The component loadings are shown in table 5. Due to the influence of the added variables, some shifts have occurred in the component structure. Spinal anomalies correlates positively with the neurological symptoms optic glioma, UBO, benign tumour and headache. Osseous lesions are negatively related to the neurological component. The second component remains related to visible symptoms, e.g. café-au-lait spots, skinfold freckling in the axilla and groin area and itch. Lisch nodules load negatively on the second component. Component loadings <0.35 are not considered in the component structure, since these variables contribute only marginally to the component structure and cannot be considered meaningful.

Whether the NF1 is familial or not seems to be related to visible symptoms, indicating that people with more NF1 symptoms in their appearance more often have familial NF1. Disease perception, whether the child experiences the NF1 as a burden or not, is most strongly related to symptoms involving the neurological component. The behavioural outcome ADHD is related to the neurological component, children with more neurological symptoms have ADHD more often. Fine motor impairments are negatively related to the neurological component, indicating that fine motor problems occur less when there is more neurological involvement. Speech problems are negatively related to visible symptoms, whereas ASD is positively related to visible symptoms. Children who have more visible symptoms have less speech problems, but more often a diagnosis of ASD. Social problems are not significantly related to either of the components.

Table 5. *Component loadings of NF1 severity symptoms including perception, external and behavioural symptoms on two components.*

	Component	
	1	2
Optic Glioma	0,85	0,12
Benign tumour	0,84	0,21
ADHD	0,63	0,13
Fine motor skills	-0,56	-0,02
UBOs	0,47	-0,02
Headache	0,45	0,29
Spinal anomalies	0,43	-0,33
Osseous Lesions	-0,41	-0,10
Burden	0,38	-0,18
Learning problems	0,33	-0,15
Gross motor skills	-0,27	0,11
Psychological problems	-0,23	0,15
Skinfold Freckling Groin	-0,32	0,70
Café-au-lait spots	0,00	0,68
Speech problems	-0,19	-0,64
Skinfold Freckling Axilla	-0,36	0,54
ASD	-0,14	0,53
Family member	0,34	0,51
Itch	-0,27	0,49
Lisch Nodules	0,44	-0,45
Neurofibromas	0,15	0,33
Macrocephaly	-0,26	-0,30
Social problems	-0,03	-0,28

Relationship between components and outcome measures

The relationship between disease severity and behavioural outcomes has been explored by inserting behavioural symptoms in the component structure of the severity scale To get a

more thorough picture of the relationship between the component structure of the NF1 severity scale and behavioural outcomes, correlations have been computed between the scores of the participants on the components and cognitive and behavioural outcome measures. The component structure as calculated excluding the behavioural outcomes, disease perception and familial NF1, has been used to assess the correlations, in order to avoid bias. The correlations between the component scores and total scale score and the scores on the outcome measures are represented in table 6.

Table 6. *Correlations between components scores and outcome measures.*

	Appearance Component	Sign.	Neurological Component	Sign.	Total scale score	Sign.
WISC Picture Completion	.30	N.S.	-.07	N.S.	.03	N.S.
WISC Block Design	.18	N.S.	-.31	N.S.	-.15	N.S.
WISC Vocabulary	.19	N.S.	-.27	N.S.	-.24	N.S.
WISC Comprehension	.36	N.S.	-.44	.08*	-.14	N.S.
WISC Symbol Search	-.14	N.S.	.56	.02**	.64	.01**
WISC Coding	.04	N.S.	.17	N.S.	.13	N.S.
ANT IFE happy errors	-.19	N.S.	.10	N.S.	-.08	N.S.
ANT IFE sad errors	-.52	.03**	.14	N.S.	-.11	N.S.
ANT IFE angry errors	-.21	N.S.	.25	N.S.	.15	N.S.
ANT IFE fear errors	-.31	N.S.	.20	N.S.	.04	N.S.
ANT IFE disgust errors	.26	N.S.	.05	N.S.	-.26	N.S.
ANT IFE surprise errors	.13	N.S.	-.17	N.S.	-.48	.05**
ANT IFE shame errors	.26	N.S.	-.27	N.S.	-.61	.01**
ANT IFE contempt errors	-.01	N.S.	.03	N.S.	-.30	N.S.
ANT SAD Bias	-.19	N.S.	-.42	.09*	-.46	.06*
ANT SAD Bias/SA	.41	N.S.	.20	N.S.	.20	N.S.
ANT MS2D cognitive control	-.12	N.S.	.20	N.S.	.14	N.S.

Totalscore DEX-K	.14	N.S.	.06	N.S.	-.21	N.S.
Behaviour Regulation index	.22	N.S.	-.12	N.S.	-.07	N.S.
Metacognition index	.10	N.S.	-.28	N.S.	-.47	.06*
BRIEF total	.10	N.S.	-.21	N.S.	-.37	N.S.
SRS Social Awareness	.00	N.S.	.19	N.S.	-.01	N.S.
SRS Social Cognition	-.07	N.S.	.10	N.S.	-.07	N.S.
SRS social Communication	.12	N.S.	.09	N.S.	-.09	N.S.
SRS Social Motivation	.34	N.S.	.26	N.S.	.11	N.S.
SRS Autistic Mannerisms	.19	N.S.	-.19	N.S.	-.38	N.S.
SRS Total	.14	N.S.	.09	N.S.	-.12	N.S.
SSRS Cooperation	-.26	N.S.	.15	N.S.	.23	N.S.
SSRS Assertion	-.60	.01**	-.13	N.S.	.00	N.S.
SSRS Responsibility	-.13	N.S.	-.05	N.S.	.03	N.S.
SSRS Self-Control	-.38	N.S.	.16	N.S.	.21	N.S.
SSRS Total	-.40	N.S.	.06	N.S.	.16	N.S.
CBCL Anxious Depressed	.16	N.S.	.16	N.S.	.18	N.S.
CBCL Withdrawn Depressed	.10	N.S.	-.29	N.S.	-.37	N.S.
CBCL Somatic Complaints	.02	N.S.	.11	N.S.	.15	N.S.
CBCL Social Problems	.21	N.S.	-.16	N.S.	-.10	N.S.
CBCL Thought Problems	-.14	N.S.	-.38	N.S.	-.44	.07*
CBCL Attention Problems	-.03	N.S.	.02	N.S.	-.16	N.S.
CBCL Rule-breaking Behaviour	-.32	N.S.	-.06	N.S.	-.21	N.S.
CBCL aggressive Behaviour	.16	N.S.	-.10	N.S.	-.19	N.S.
CBCL Other	-.18	N.S.	-.15	N.S.	-.12	N.S.
CBCL Internalizing Problems	.13	N.S.	-.02	N.S.	-.04	N.S.
CBCL Externalizing Problems	.05	N.S.	-.10	N.S.	-.21	N.S.
CBCL Total Problems	.04	N.S.	-.14	N.S.	-.20	N.S.
CBCL Affective Problems	.02	N.S.	-.22	N.S.	-.21	N.S.
CBCL Anxiety Problems	-.15	N.S.	.39	N.S.	.24	N.S.
CBCL Somatic Problems	-.29	N.S.	.19	N.S.	.05	N.S.
CBCL Attention Deficit/Hyperactivity Problems	-.05	N.S.	.04	N.S.	.03	N.S.
CBCL Oppositional Defiant Problems	.28	N.S.	-.02	N.S.	-.03	N.S.

CBCL Conduct Problems	-.23	N.S.	-.10	N.S.	-.32	N.S.

**. Correlation is significant at the 0.05 level (2-tailed).
*. Correlation is significant at the 0.10 level (2-tailed).
N.S. = Non-Significant.

The appearance factor is negatively related to IFE sad, the ability to recognize sad facial expressions is weaker when more symptoms affecting the appearance are present. The appearance factor is also negatively related to the Assertion scale of the SSRS, indicating that more visible symptoms are related to less assertive behaviour. The neurological component is negatively related to the score on the task Comprehension of the WISC and the SAD bias measure at the 0.10 level, indicating that more neurological symptoms are related to a weaker ability to apply knowledge in an adaptive manner, and a lower bias score, indicating less impulsive errors. The neurological component is positively related to the task Symbol Search at the 0.05 level, children with more neurological symptoms have higher scores on a task for processing speed. All other correlations are non-significant. Correlations with the full NF1 severity scale are comparable: children with higher full-scale scores have higher scores on the Symbol Search task. The score on the IFE surprise and shame task are negatively related to the full severity scale, indicating that a higher total number of symptoms was related to a more errors in recognizing surprised and ashamed facial expressions. SAD bias was also negatively related to the total severity scale, more NF1 symptoms were related to less impulsive errors on the SAD task. A negative relationship at the 0.10 significance level was found between the total number of symptoms and the Meta-cognition index of the BRIEF, indicating that children with more NF1 symptoms have lower scores on the Meta-cognition index. Also, a negative relationship was found between the total scale score and thought problems as measured by the CBCL (α<0.10), children with more NF1 symptoms often had less thought problems.

Discussion

The current study has investigated the validity of NF1 severity scales with the use of a newly constructed severity scale, and has investigated relationships between this NF1 severity scale and cognitive and behavioural outcomes. The first hypothesis, that a two-factor structure would be found in the NF1 severity scale, has been confirmed. Symptoms of NF1 can be divided into neurological symptoms, affecting the brain and nervous system, and symptoms which affect the appearance, mostly cutaneous symptoms. The variability in the symptoms of NF1 is large, and to date no comprehensive theory to explain the occurrence of a certain combination of symptoms in individuals has been given. Viskochil (2002) gives a thorough explanation of the genetics involved in variable expressivity, stating that multiple genetic mechanisms can lead to random somatic mutations. Following his argument on variable expressivity, it appears that no underlying mechanism for the co-occurrence of symptoms can be given, since random gene mutations can lead to random outcomes. However, considering the fact that neurological symptoms and symptoms in appearance do seem to co-occur respectively, separate underlying mechanisms cannot be excluded and should be studied more specifically.

When including behavioural symptoms in the component structure, it was found that ADHD was related to neurological symptoms, indicating that these often co-occur, as was hypothesized based on the results of Rowbotham et al. (2009). However, no relationship was found between the neurological component and behavioural measures of ADHD, for example a high score on the Attention Problems scale of the CBCL. Although associated with ADHD, cognitive control was not related to the neurological component. The number of impulsive errors made in the sustained attention task was negatively related to the neurological component and the total NF1 symptoms, indicating that more neurological symptoms and more NF1 symptoms were related to less impulsive errors. Since these results are mixed, they

should be interpreted with caution and have to be investigated more thoroughly in future studies. Osseous lesions and fine motor skills were negatively related to the neurological component. Fine motor impairments may results from osseous lesions, which in turn will have their basis in the skeletal system, and will therefore not be strongly related to neurological symptoms. Whether or not NF1 is experienced as a burden by the child is associated with neurological symptoms. Sebold and colleagues (2004) previously showed that adolescents have a more negative severity perception when they experience more cognitive problems. Since ADHD and learning problems are related to neurological symptoms, the present results are in line with the results of Sebold et al. (2004), children with more neurological symptoms, ADHD and/or learning problems more often experience their NF1 as a burden in everyday life. ASD was related to symptoms in the appearance, which stands in contrast to the hypothesis that ASD would be related to neurological symptoms, since ASD is theorized to have a basis in the brain. However, only two children with a diagnosis of ASD participated in the study, of which one had a comorbid diagnosis of ADHD. It seems plausible that the data concerning ASD are not a reliable reflection of the population of children with NF1 and ASD. Speech problems were negatively related to symptoms in appearance, indicating that speech problems probably have another origin than visible symptoms. Inspection of the data showed that multiple parents stated that their children had weak motor skills in the mouth area. Possibly the speech problems are more strongly related to problems with their origin in the skeletomuscular system. Having a family member with NF1 was most strongly related to symptoms in the appearance. In this study, children with a family member with NF1 more often had cutaneous and physical symptoms.

The second hypothesis, that the NF1 severity scale as well as the separate components would be related to outcome measures has been partially confirmed. A number of significant relationships were found, the NF1 children with more symptoms in their appearance showed

significantly less assertive behaviour and a weaker ability to recognize sad facial expressions. It can be theorized that children with many visible symptoms may be more self-conscious, and might therefore be less assertive in social interactions; they wait for the initiative of the other, which will inform them that the other accepts them. Possibly, children with more visible symptoms have experienced negative reactions to their assertive behaviours due to their appearance, therefore conditioning them to show less assertive behaviour. A weaker ability to recognize sad facial expressions cannot be theoretically explained. Possibly, this relationship is a result of specific participant characteristics. It might also be a result of test characteristics, multiple children found especially one person's facial expression hard to identify in the 'sad' condition of the task which might bias the results. Neurological symptoms are negatively related to the task Comprehension, which asks of the participant to use their knowledge adaptively and to express their knowledge in words, which is part of intelligence. A poor performance on the task Comprehension is often seen in children with ASD, since the task requires one to flexibly and adaptively use ones knowledge in social situations. The relationship between neurological symptoms and cognitive functioning confirms the hypothesis that cognitive functioning is related to impairment on brain-level. A significant positive relationship was found between neurological symptoms and overall symptoms and processing speed, indicating that children with more neurological symptoms and overall more symptoms of NF1 had a faster processing speed. The task Symbol Search is a highly structured task, and for example children with ASD do this task relatively well due to the structure offered by the task. Possibly, the mechanisms which lead to a poor performance on the task Comprehension, e.g. inflexibility, difficulty to adapt knowledge to a social situation, is what makes these children good in the Symbol Search task. In line with these results, elevated autistic traits were observed in the participating children, as indicated by an above average score on the SRS. Total number of symptoms was also related to the

Metacognition index of the BRIEF, indicating that children with more NF1 symptoms have more trouble self-managing tasks, monitoring ones performance and to actively solve problems, which are related to executive functioning, which is often impaired in children with ASD and ADHD. Overall NF1 symptoms are related to a weaker ability to recognize surprised and ashamed facial expressions. The recognition of more complex facial expressions is often impaired in children with ASD. These results are in support of previous results by Huijbregts and De Sonneville (2011) who found more autistic traits in their sample of NF1 children. The total number of symptoms was negatively related to thought problems. Thought problems aren't a known behavioural problem in children with NF1 and the negative relationship may be the result of specific sample characteristics. The remaining relations between neurological functioning and cognitive functioning were non-significant. Concluding from these results it is possible that children with NF1 share a neuropsychological profile commonly seen in children with ASD, which might be related to neurological symptoms.

Although these results are promising, they have to be seen in the light of their limitations. The number of participants is small for the analyses that have been executed, rendering the results less reliable. However, in studies involving genetic syndromes small samples are common. When converting the prevalence numbers to the Dutch situation, only approximately 5000 people with NF1 live in The Netherlands, of which only a small part falls in the right age group. Due to recruitment through the Dutch Neurofibromatosis Association, only the families who were a member were contacted, decreasing the number of eligible participants. All in all, the sample of the current study is of reasonable size when considering the limitations of studies involving genetic syndromes. Due to the small sample size relative to the analyses that were done, the reliability of the results is reduced. Possibly, when reanalyzing the data using a bigger sample, or re-analyzing meta-analytically, results will be different, and a more clear picture of the component structure and its relationship to outcome

measures can be found. It is possible a third component referring to skeletomuscular symptoms would be found, since symptoms related to this system now correlate negatively with the found components. Also, the symptom macrocephaly was now negatively related to both components, it was shown that this group of participants showed a different pattern of symptoms than participants without macrocephaly. The results of Steen et al. (2001) would suggest a relationship between neurological symptoms and macrocephaly, since in their study UBOs and macrocephaly were related. However, this could not be confirmed in the present study. More thorough research with more participants can give clarity about the impact of macrocephaly on NF1 symptoms. A second limitation is the fact that a newly constructed NF1 severity scale was used, which has not been tested for its' psychometric properties. No reliability or validity data have been collected, therefore, the questionnaire might not have measured the NF1 severity accurately. However, since the scale was based on existing scales, it does have face validity. Some of the symptoms which were listed in the scale were not present in any of the participants. It is possible that the scale lists symptoms which do not often occur in children with NF1, however, the small variance in the symptoms may also be a result of the small sample of the study. Some symptoms are rarer and may not have been present in the current sample.

Although the results have to be interpreted with caution, they showed only three significant relationships between the NF1 severity scale and cognitive and behavioural outcomes. It appears that severity as measured by a list of present symptoms is not strongly related to outcomes in daily life. Possibly, NF1 symptoms should be inspected for underlying mechanisms, which in turn cause cognitive and behavioural impairments. It might be possible that certain symptoms are related to a cognitive profile which is often seen in children with an ASD, as was suggested previously. A way to study mechanisms which are related to physical symptoms is to use brain imaging techniques. The current study was part of a brain imaging

study which assesses brain functioning while doing cognitive tasks using fMRI. Future results may show a clearer picture of the involvement of brain-level deviations in children with NF1 and cognitive and behavioural outcomes.

The current study has added to the knowledge on NF1 and what factors may account for the mild to severe cognitive and behavioural impairments children with NF1 often face. The results indicate that the presence of ASD or cognitive impairments associated with ASD might be present in children with NF1. It is important to have a clear picture of the specific problems children with NF1 face, in order to give them the best treatment and counselling. For clinicians as well as parents it is important to know the impairments of their child, and treat the child accordingly. Further, no strong relationships were found between NF1 severity as measured with a questionnaire and cognitive and behavioural outcomes. The importance of studies to investigate the cause for cognitive and behavioural problems of children with NF1 must be emphasized, because only when the cause is known, effective treatments can be established, for example through medication. Future studies should therefore aim to establish a clear cognitive profile of children with NF1, and to relate these to underlying mechanisms and behavioural outcomes.

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Appendix

Questionnaire characteristics Neurofibromatosis Type I (NF1)

In this questionnaire you will find questions regarding the different characteristics of NF1 which could be present in your child. Would you please try to answer as thorough and elaborate as possible? All information is important to create an accurate picture of the possible problems your child may face. The answers will be treated anonymous and confidential. If you don't know the answer to a question, would you please verify with the child's treating physician(s)? At the questions with a yes or no answer you may simply strike through the answer which is not applicable.

1) Does your child have café-au-lait spots? Yes/No

If yes, could you indicate how many café-au-lait spots your child

(approximately) has? ……..

2) Does your child have neurofibromas? Yes/No

If yes, could you indicate how many neurofibromas your child

(approximately) has? ……..

Are the neurofibromas on the skin? ……..

Are the neurofibromas plexiform (tangle formation)? ……..

3) Does your child have freckling in the armpit? Yes/No

Does your child have freckling in the groin? Yes/No

4) Does your child have an optic glioma (optic nerve tumour)? Yes/No

Does your child experience problems with sight?

……

5) Does your child have lisch nodules on the eye? Yes/No

6) Does your child have bone abnormalities? You can think of thin and/or

long bones or bones not being able to grow back together.

……

7) Is there a family member with Neurofibromatosis type 1 (NF1)? Yes/No

If yes, could you indicate which family member?

……

8) Does your child have macrocephaly (large head)? Yes/No

If yes, did your child receive treatment for this? Yes/No

9) Does your child have deviations of the spinal column? Yes/No

If yes, could you indicate what kind of deviations?

……

Has your child received treatment for the spinal deviations? Yes/No

10) Are the characteristics of NF1 in your child visible to the outside world in daily life? Yes/No

11) Does your child experience this as a burden? Yes/No

If yes, could you indicate how this expresses itself?

……

12) Does your child have hypertension (high blood pressure)? Yes/No

If yes, does your child use medication for this? Yes/No

If yes, which medication is this? ……..

13) Does your child experience a lot of headache? Yes/No

If yes, has there been pointed to a possible cause of the headache? Yes/No

Could you indicate what cause(s) have been brought forward?

……..

Does your child use medication for headache? Yes/No

If yes, which medication is this? ……

14) Does your child have (a) malignant tumour(s)? Yes/No

If yes, how is your child treated for this (these) tumour(s)?

……

Could you indicate where the tumour(s) is (are) located?

……

15) Does your child have (a) benign tumour(s)? Yes/No

If yes, how is your child treated for this (these) tumour(s)?

……

Could you indicate where the tumour(s) is (are) located?

……

16) Does your child experience itch? Yes/No

If yes, does your child use medication for this? Yes/No

If yes, which medication is this? ……

17) Have hormonal problems been identified in your child? Yes/No

If yes, which hormonal problems are this?

……

Does your child use medication for hormonal problems? Yes/No

If yes, which medication is this? ……..

18) Have Unidentified Bright Objects been identified in your child? Yes/No

If yes, could you indicate how many UBOs have been identified? …….

19) Have speech problems been identified in your child? Yes/No

If yes, which speech problems are these?

……..

Is/was your child treated for speech problems? Yes/No

Does your child experience other speech problems?

……

20) Does your child have gross motor problems

(e.g. walking and swimming)? Yes/No

If yes, which problems with gross motor skills are these?

……..

Is/was your child treated for gross motor problems? Yes/No

21) Does your child have fine motor problems? Yes/No

If yes, which problems with fine motor skills are these?

……..

Is/was your child treated for fine motor problems? Yes/No

22) Has epilepsy been identified in your child? Yes/No

If yes, does your child use medication for this? Yes/No

If yes, which medication is this? ……

23) Have Learning problems been identified in your child? Yes/No

If yes, how do these problems express themselves?

……

Has there ever been investigated what might be underlying

the learning problems? (e.g. problems with memory, interpretation,

problem solving skills)?

……..

Has your child received treatment for learning problems? Yes/No

24) Have psychological problems been identified in your child? Yes/No

If yes, which problems are these?

……..

Has your child received treatment for psychological problems? Yes/No

Does your child use medication for psychological problems? Yes/No

If yes, which medication is this? ……

In your opinion, does your child experience psychological problems? Yes/No

If yes, which psychological problems are these?

……

25) Has ADHD been identified in your child? Yes/No

Is yes, does your child use medication for this? Yes/No

If yes, which medication is this? ……

In your opinion, does your child show ADHD-related behaviours? Yes/No

If yes, which ADHD related behaviours are this?

……..

26) Has there been identified an Autistic Spectrum Disorder (ASD)

in your child? (e.g. autism, Asperger syndrome, PDD-NOS) Yes/No

If yes, which ASD is this? ……

Does your child use medication for an ASD? Yes/No

If yes, which medication is this? ……

In your opinion, does your child show autistic traits? Yes/No

If yes, which autistic traits are these?

…….

27) Has there been identified a behaviour disorder in your child? Yes/No

If yes, which behaviour disorder is this? ……

Does your child use medication for a behaviour disorder? Yes/No

If yes, which medication is this? ……

In your opinion, does your child experience behaviour problems? Yes/No

If yes, which behaviour problems are these?

……

28) Does your child have social problems? Yes/No

If yes, which social problems does your child have? Yes/No

Is your child treated for social problems? Yes/No

29) Does your child experience other specific behaviours or problems?

……

……

Finally, a few questions about the treatment of your child and persons with whom your child has been in contact.

30) Who is the treating physician or treating team of your child (name(s) and hospital)?

…….

…….

31) Who is the general practitioner of your child (name and place)?

…….

…….

32) What is the precise treatment history of your child from the moment the NF1 was identified up till now?

…….

…….

…….

…….

Thank you very much for filling in this questionnaire. If there are any questions which you cannot answer at the moment, but maybe after consulting your doctor you can, please let this know the researcher who brings back your child.