Neurofibromatosis Type 1 – Cognitive Profile and the Role of Attention Deficit for Cognitive Development

DISSERTATION

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Abstract

Background: Neurofibromatosis type 1 (NF1) is a rare genetic disorder with a long list of cognitive symptoms. One of the core difficulties in the cognitive area is attention deficit, culminating frequently in the diagnosis of Attention deficit hyperactivity disorder (ADHD). Given that each of the two diseases by themselves are associated with impaired cognitive functioning, the comorbidity of ADHD in NF1 may be a specific risk factor for major impairments in the affected patients. The goal of this work was to identify characteristics of the cognitive profile(s) of NF1 with and without ADHD and to distinguish attention dysfunctions in NF1 from those in neurotypical ADHD. Furthermore, this work investigated the role of attention deficit in the intellectual development of children with NF1.

Methods: 111 children with NF1 and/or ADHD (53 $NF1^{ADHD}$, 28 $NF1^{only}$, 30 $ADHD^{only}$), aged between 6 and 12 years, performed an extensive neuropsychological test battery at three times within two years. Standardized assessments regarding intelligence, memory, attention functions, executive functions, and quality of life were performed in a time interval of 12 months.

Results: Firstly, the cognitive characteristics of children with $NF1^{ADHD}$ differ markedly from those of children with $NF1^{only}$. Comorbid ADHD in NF1 was associated with lower intellectual ability, more attention problems, executive dysfunctions, and lower quality of life. Additionally, certain attention dysfunctions differed between NF1 and neurotypical ADHD. Secondly, attention functions correlated with intellectual functioning in the short and long term and predicted them in NF1. However, intellectual functioning in children with NF1 was not modified by changes in attention over the term of the research project.

Conclusions: [1] The NF1 patient group of this research project can be divided into two distinct subgroups regarding their cognitive profile: one group with almost unimpaired cognitive functioning ($NF1^{only}$) and one group with affected cognitive functioning ($NF1^{ADHD}$). [2] Certain attention dysfunctions in NF1 might rather be associated with the NF1-condition, than merely be the result of comorbid ADHD. [3] Attention functions are dimensionally and causally linked to intellectual development in NF1.

Zusammenfassung

Hintergrund: Neurofibromatose Typ 1 (NF1) ist eine seltene genetische Erkrankung, die mit einer Reihe an kognitiven Symptomen einhergeht. Zu den häufigsten kognitiven Beeinträchtigungen zählen Aufmerksamkeitsprobleme bis hin zur Diagnose einer Aufmerksamkeitsdefizit-/ Hyperaktivitätsstörung (ADHS). Da sowohl NF1 als auch ADHS an sich mit beeinträchtigten kognitiven Funktionen assoziiert sind, ist anzunehmen, dass eine komorbide ADHS bei NF1 einen entscheidenden Risikofaktor für schwere kognitive Beeinträchtigungen darstellt. Ziel der vorliegenden Doktorarbeit war es, die kognitiven Profile von NF1 mit und ohne ADHS zu charakterisieren und Unterschiede bezüglich spezieller Aufmerksamkeitsdefizite zwischen ADHS bei NF1 und neurotypischer ADHS herauszuarbeiten. Zudem wurde die Rolle von Aufmerksamkeitsproblemen in der intellektuellen Entwicklung von Kindern mit NF1 untersucht.

Methoden: 111 Kinder mit NF1 und/oder ADHD (53 $NF1^{ADHD}$, 28 $NF1^{only}$, 30 $ADHD^{only}$) im Alter von 6-12 Jahren wurden mit einer neuropsychologischen Testbatterie untersucht. Zu drei Zeitpunkten innerhalb von 2 Jahren wurden Untersuchungen bezüglich Intelligenz, Gedächtnis, Aufmerksamkeit, Exekutivfunktionen und Lebensqualität durchgeführt.

Ergebnisse: $NF1^{ADHD}$ und $NF1^{only}$ unterschieden sich stark in ihrem kognitiven Profil. Eine komorbide ADHS bei NF1 war mit niedrigeren intellektuellen Fähigkeiten, mehr Aufmerksamkeitsproblemen, exekutiven Dysfunktionen und niedrigerer Lebensqualität verbunden. Zudem ergaben sich Unterschiede in bestimmten Aufmerksamkeitsdefiziten bei NF1 im Vergleich zu neurotypischer ADHS. Aufmerksamkeitsfunktionen korrelierten kurz- und langfristig mit intellektuellen Fähigkeiten und konnten diese bei NF1 vorhersagen.

Schlussfolgerung: [1] Es bestehen zwei voneinander abgrenzbare kognitive Profile innerhalb der NF1-Population, mit einer nahezu unbeeinträchtigten Gruppe ($NF1^{only}$) und einer Gruppe ($NF1^{ADHD}$) mit starken kognitiven Beeinträchtigungen. [2] Bestimmte Aufmerksamkeitsdefizite scheinen eher mit NF1 an sich assoziiert zu sein als mit einer komorbiden ADHS. [3] Die Aufmerksamkeit steht in einer dimensionalen und kausalen Verbindung zur intellektuellen Entwicklung bei NF1.

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Contents

Contributions

Statement about Workshare

The present thesis originated in the context of a large research project about children with Neurofibromatosis type 1 (NF1). The study was conceptualized by Prof. Dr. Karen Lidzba and Prof. Dr. Victor-Felix Mautner. Prof. Lidzba obtained funding, gave methodological advise and supervised the research project. Neuropediatric examinations were conducted by Prof. Mautner and Dr. Karin Haas-Lude. Patient recruitment, clinical interviews and neuropsychological assessments were conducted by Sofia Granström and Magdalena Heimgärtner or by student assistants under supervision of Sofia Granström and Magdalena Heimgärtner. Data analyses were conducted by Magdalena Heimgärtner. The thesis was exclusively written by Magdalena Heimgärtner.

Publications

"Attention deficit predicts intellectual functioning in children with Neurofibromatosis Type 1" (Heimgärtner et al., 2019). Parts of the results presented in Chapter 3 are published in the International Journal of Pediatrics. This concerns data about intelligence, attention and executive functions, as well as demographic data. Text segments of Chapter 1, Chapter 3 and Chapter 5 of the thesis resemble text segments or correspond to text segments of the article. Magdalena Heimgärtner is the first and principle author of the article. She contributed to data acquisition, conducted data analyses and data interpretation, and wrote the manuscript. Her co-authors contributed with conceptualizing the study, obtaining funding, data acquisition, and reviewing the manuscript.

"Motor dysfunction in NF1: Mediated by attention deficit or inherent to the disorder?" (Haas-Lude et al., 2018). Parts of the results presented in Chap-

ter 3 are used in the article for describing the study population. This concerns data about intelligence, attention and demographic data. The article is cited in Chapter 1 of the thesis. Karin Haas-Lude and Magdalena Heimgärtner share the joint first authorship. They contributed equally to the manuscript. Additionally, Magdalena Heimgärtner contributed to data acquisition and conducted data analyses.

"Exekutive Dysfunktion bei Neurofibromatose Typ 1: Welche Rolle spielt ADHS?" (Denkinger, Heimgärtner, Mautner, & Lidzba, 2018). Parts of the results presented in Chapter 3 are used in the article. This concerns data about intelligence, attention, executive functions and demographic data. The article is cited in Chapter 1 of the thesis. Magdalena Heimgärtner is the second author of the article. She contributed to conceptualizing the study, data acquisition, data interpretation, and revised the manuscript.

"Attention Deficit in Neurofibromatosis Type 1: Part of the Neurocognitive Profile or Comorbidity?" (Schulze, Granström, Mautner, & Lidzba, 2014). Magdalena Heimgärtner (nee Schulze) presented parts of the data as poster on the 2014 conference of the German Society of Pediatric Neurology.

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Table 1.2 is reprinted from "Guidelines for the Diagnosis and Management of Individuals with Neurofibromatosis 1", Journal of Medical Genetics (Ferner et al., 2007)[1] with permission from BMJ Publishing Group Ltd.

Figure 1.3 is adapted from "Assessment and Development of Executive Function (EF) During Childhood", Child Neuropsychology (Anderson, 2002)[2] with permission from Taylor & Francis Group (`https://www.tandfonline.com/`).

[1] `https://doi.org/10.1136/jmg.2006.045906`
[2] `https://doi.org/10.1076/chin.8.2.71.8724`

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ANCOVA	Univariate Analysis of Covariance
ANOVA	Univariate Analysis of Variance
API	Attention Performance Index
ASD	Autism Spectrum Disorder
BRIEF	*Behavior Rating Inventory of Executive Function®*
CBCL	*Child Behavior Checklist*
Conners-3	*Conners Skalen zu Aufmerksamkeit und Verhalten - 3®*
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5th edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders - 4th edition, Text Revision
Disyps-KJ	*Diagnostik-System für psychische Störungen im Kindes- und Jugendalter*
GEC	Global Executive Composite
ICD-10	International Classification of Diseases - 10th edition
Kiddo-Kindl	*Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern*
MPNST	Malignant Peripheral Nerve Sheath Tumor
MANCOVA	Multivariate Analysis of Covariance

MANOVA	Multivariate Analysis of Variance
MPH	Methylphenidate
NF1	Neurofibromatosis type 1
QoL	Quality of Life
Ras	Rat sarcoma
SES	Socio-Economic Status
T.O.V.A.	*Test of Variables of Attention*®
VLMT	*Verbaler Lern- und Merkfähigkeitstest*
WISC-IV	*Wechsler Intelligence Scale for Children IV*

1. Theoretical Background

1.1. Neurofibromatosis Type 1

1.1.1. Disease Characterization and Pathophysiology

Neurofibromatosis type 1 (NF1), also called Recklinghausen's disease, is an autosomal dominant single-gene disorder, affecting skin and nervous system. With an incidence rate of one in 2600 to 3000 individuals (Friedman, 1999; Lammert, Friedman, Kluwe, & Mautner, 2005), NF1 is one of the most frequent of rare genetic disorders. There are no known differences in the incidence of NF1 regarding ethnic groups or gender (Friedman, 1999). Approximately half of the cases of NF1 are caused by an inherited defect of the NF1-gene, while the remainder is caused by de-novo mutations (Friedman, 1999). Characteristic clinical features of NF1 include café-au-lait spots on skin, dermic neurofibroma and/or plexiform neurofibroma, freckling in the axillary or inguinal regions, Lisch nodules, typical bone lesions, and a first degree relative with NF1 (National Institutes of Health, 1988). NF1 is diagnosed by clinical diagnostics of observable symptoms and/or by molecular genetic tests. For the diagnosis of NF1, the patient needs to present at least two of the clinical features mentioned above. All diagnostic criteria and additional common clinical manifestations of NF1 are listed in Table 1.1 and Table 1.2.

NF1 results from a heterozygous mutation in the NF1-gene and is located on chromosome 17 (17q11.2). The NF1-gene encodes for the cytoplasmic protein Neurofibromin, which takes part in Ras GTPase activation. Ras GTPase down-regulates the Ras (Rat sarcoma) protein family, which is involved in cellular signal transduction associated with cell proliferation and differentiation. Therefore, a lack of Neurofibromin leads to increased Ras GTPase and to decreased inhibitory control of cell growth, consequently increasing the risk for tumorigenesis (Kehrer-Sawatzki & Mautner, 2009). Especially nerve cell and

Table 1.1.

Diagnostic criteria for NF1 (National Institutes of Health, 1988)

	Diagnostic criterion
1	Six or more café-au-lait skin macules over 5 mm in prepubertal individuals and over 15 mm in postpubertal individuals
2	Two or more neurofibromas of any type or one plexiform neurofibroma
3	Axillary or inguinal freckling
4	Two or more Lisch nodules
5	Optic glioma
6	Bone lesion with sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis
7	A first-degree relative (parent, sibling, or offspring) that meets NIH criteria
The diagnosis of NF1 requires at least two out of seven NIH criteria.	

nerve sheath tumors are very common in NF1 and can lead to severe complications, if they occur in the central nervous system. Typically, tumors caused by NF1 are benign, but there are special types of tumors that are tending to grow malign. The most prominent malign tumor in NF1 is the Malignant Peripheral Nerve Sheath Tumor (MPNST). The lifetime risk to develop a MPNST reaches 8 to 13% for patients with NF1 and most of these tumors are resistent against chemo- or radiotherapy (Kehrer-Sawatzki & Mautner, 2009). Since there is no causal treatment for NF1 so far, early diagnostics of symptoms and comorbidities, especially MPNSTs or other space-occupying tumors, are crucial for the further course and potential cure.

Although NF1 manifests with complete penetrance, the clinical severity and phenotype of the disorder are highly variable, indicating that other factors than the mutation of the gene alone add to the specific clinical phenotype (Kehrer-Sawatzki & Mautner, 2009). However, until now it remains unclear which factors contribute.

Table 1.2.

Frequency and age of onset of major clinical manifestations of neurofibromatosis 1 (Ferner et al., 2007).

Clinical manifestation	Frequency (%)	Age of onset
Café au lait patches	>99	Birth to 12 years
Skin-fold freckling	85	3 years to adolescence
Lisch nodules	90–95	>3 years
Cutaneous neurofibromas	>99	>7 years (usually late adolescence)
Plexiform neurofibromas	30 (visible) – 50 (on imaging)	Birth to 18 years
Disfiguring facial plexiform neurofibromas	3–5	Birth to 5 years
Malignant peripheral nerve sheath tumor	2–5 (8–13% lifetime risk)	5–75 years
Scoliosis	10	Birth to 18 years
Scoliosis requiring surgery	5	Birth to 18 years
Pseudarthrosis of tibia	2	Birth to 3 years
Renal artery stenosis	2	Lifelong
Phaeochromocytoma	2	>10 years
Severe cognitive impairment (IQ <70)	4–8	Birth
Learning problems	30–60	Birth
Epilepsy	6–7	Lifelong
Optic pathway glioma	15 (only 5% symptomatic)	Birth to 7 years (up to 30 years)
Cerebral gliomas	2–3	Lifelong
Sphenoid wing dysplasia	<1	Congenital
Aqueduct stenosis	1.5	Lifelong

1.1.2. Structural Brain Abnormalities in NF1

The widespread spectrum and the variability in presence and severity of cognitive impairments suggest that more than just one factor is responsible for the genesis of the cognitive profile of NF1 (Diggs-Andrews et al., 2012). Aside from underlying molecular features (Diggs-Andrews et al., 2012), structural abnormalities of the brain are discussed as causal factors (De Winter, Moore, Slopis, Ater, & Copeland, 1999; Schrimsher, Billingsley, Slopis, & Moore, 2003).

Patients with NF1 present a long list of structural brain abnormalities such as symptomatic and asymptomatic opticus glioma (Kehrer-Sawatzki & Mautner, 2009), brain tumors, macrocephaly with higher volumes of white matter (Payne, Moharir, Webster, & North, 2010), enlargement of the corpus callosum (Cutting, Cooper, et al., 2002; Kayl, Moore, Slopis, Jackson, & Leeds, 2000; Payne et al., 2010), or unidentified bright objects (UBO, also: T2 weighed MRI hyperintensities) (Payne, Barton, Shores, & North, 2013). However, cognitive deficits were observed in NF1 even in the absence of tumors or macrocephaly (Ferner, Hughes, & Weinman, 1996), and data on the association between UBOs and cognitive deficits remains inconclusive (Cutting et al., 2000; Hyman et al., 2003; Hyman, Gill, Shores, Steinberg, & North, 2007). General cognitive impairment has consistently been associated with UBOs in NF1, and in a longitudinal design, Payne et al. (2013) found functional improvement of cognitive deficits, when UBOs dissolved over the years. In contrast, the cognitive profile of patients without UBOs was stable, albeit impaired (Payne et al., 2013).

Functional MRI studies discovered abnormal network structures in the brain of NF1 patients with reduced long-range anterior-posterior connectivity that correlated with intelligence and internalizing symptoms (Tomson et al., 2015). In task-based fMRI studies with visuo-spatial and spatial working memory tasks, researchers found a general pattern of increased short-range and decreased long-range connectivity and reduced activation in frontal regions (Billingsley et al., 2004; Shilyansky, Lee, & Silva, 2010).

1.1.3. Molecular Abnormalities in NF1

Animal research on molecular abnormalities in NF1 reveals that the deficiency of neurofibromin caused by mutations in the NF1 gene not only leads to increased tumor genesis, as mentioned above, but also seems to be involved in

different cognitive impairments. Neurofibromin is expressed in all organ systems of the body, but plays a particularly important role in the nervous system (Gutmann, Geist, Wright, & Snider, 1995). It acts as an inhibitor in the Ras signaling pathway. Overly active Ras signaling can provoke an abnormally high GABA-release, which consecutively leads to increased GABA-mediated inhibition, decreased cell growth, and reduced synaptic plasticity (see Figure 1.1) (Ismail, Fatemi, & Johnston, 2017; Oliveira & Yasuda, 2014; Diggs-Andrews & Gutmann, 2013; Costa & Silva, 2002). Animal models of NF1 suggest abnormal Ras-dependent functioning of the prefrontal cortex, striatum and hippocampus, leading to deficits in attention, memory and visuo-spatial learning (Costa et al., 2002).

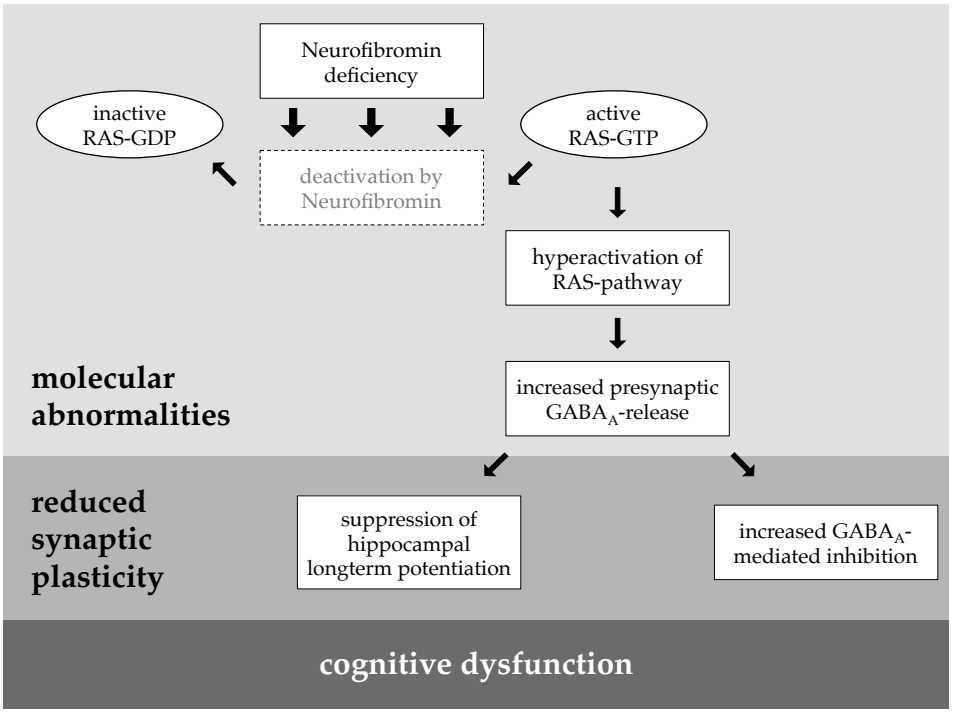

Figure 1.1. Neurofibromin deficiency leads to reduced synaptic plasticity and is associated with cognitive dysfunction in NF1.

Pathological Ras-pathway activity seems to be linked to cognitive dysfunction in patients with NF1. Research on influencing synaptic plasticity through medication suggests that the HMG-CoA reductase inhibitors simvastatin and lovastatin have the potential to directly affect the Ras signaling pathway (Krab,

de Goede-Bolder, et al., 2008; Li et al., 2005). Therefore, it was hypothesized that treatment with simvastatin or lovastatin would influence GABA-mediated intracortical inhibition and would lead to an amelioration of cognitive functions in NF1. Krab, de Goede-Bolder, et al. (2008) conducted a major study, during which a 12-week simvastatin treatment was tested against placebo in children with NF1. Against their expectations, the authors did not observe a significant difference between the simvastatin and placebo groups on cognitive functions after the treatment. In contrast, a study investigating the effect of lovastatin in adult patients revealed that a 4-day treatment with 200 mg lovastatin significantly decreased intracortical inhibition and significantly increased synaptic plasticity and phasic alertness (Mainberger et al., 2013). However, another lovastatin study conducted by Payne et al. (2016) could not confirm the positive effect of lovastatin on cognitive functions. After 16 weeks of treatment with lovastatin (40 mg/day), no improvement of visuo-spatial learning and attention could be found in children with NF1 (Payne et al., 2016).

Additional to Ras-dependent signaling alterations, more recent studies suggest that neurofibromin deficiencies lead to reduced dopamine signaling, which may be responsible for impairments in learning and memory (Diggs-Andrews et al., 2012; Wolman et al., 2014), and even more so for attention problems in NF1 (Diggs-Andrews & Gutmann, 2013). In a mouse model, Brown and colleagues could trace back attention defects in NF1-mutant mice to reduced dopamine levels and reduced postsynaptic dopamine signaling in the striatum. Striatal dopamine levels could be normalized by dopamine-elevating drugs (e.g. methylphenidate), accompanied by an amelioration of attention performance (Brown et al., 2010).

1.1.4. Neuropsychological and Developmental Difficulties

Besides a wide range of physical complications (Friedman & Birch, 1997), NF1 is considered to cause a variety of cognitive dysfunctions (Hyman, Shores, & North, 2005; North, Joy, Yuille, Cocks, & Hutchins, 1995). The vast majority of NF1 patients experiences moderate to severe impairment in at least one area of cognitive functioning (North, Hyman, & Barton, 2002). Figure 1.2 illustrates the profile of NF1 and includes the most prominent impairments, without claiming to be a complete list of the symptoms.

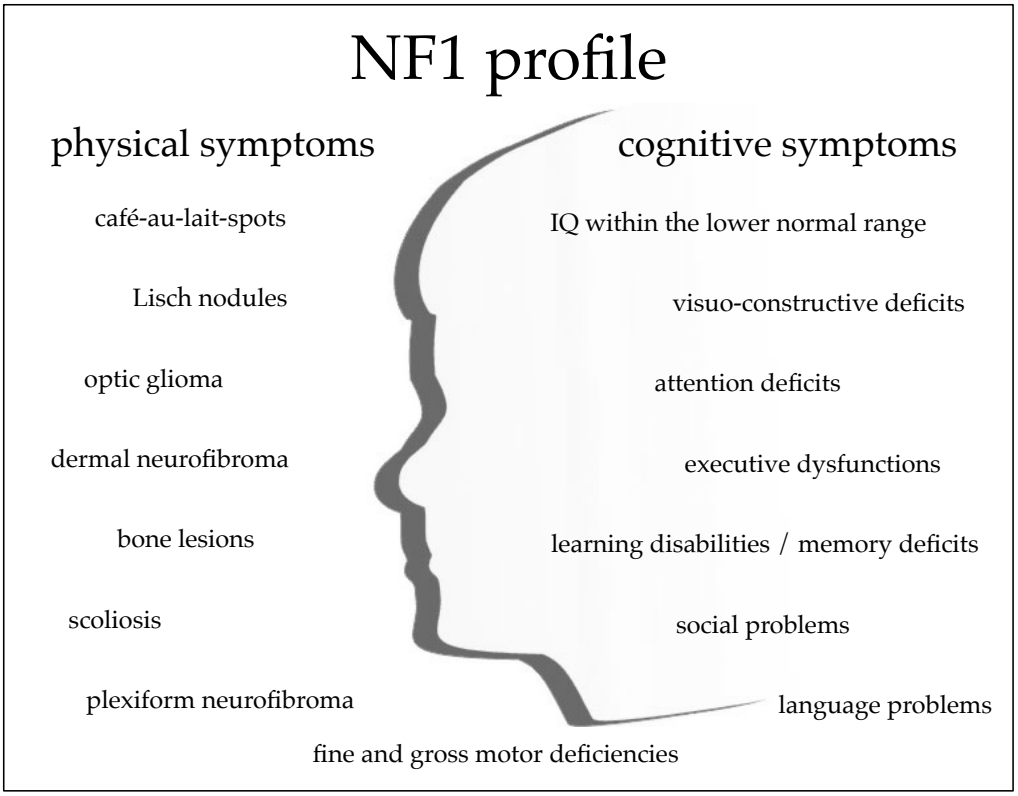

Figure 1.2. Physical and cognitive profile of NF1.

Intelligence

Mean intelligence quotients of patients with NF1 have been repeatedly located in the lower normal range (Ferner et al., 1996; North et al., 2002) and NF1 patients are reported to score significantly lower in intelligence tests than healthy (sibling-) controls (Hachon, Iannuzzi, & Chaix, 2011; Hyman et al., 2005). Hyman, Arthur, and North (2006) found in their study that 10% of children with NF1 fall over two standard deviations below and 20% fall between one to two standard deviations below their healthy siblings with their general intellectual ability. Karmiloff-Smith (2008) strongly believes that genetic mutations tend to affect low-level cognitive processes that will have diverse, cascading effects on different domains as development proceeds over time. In view of this assumption, it seems reasonable that the NF1-gene mutation should lead to a high number of patients with severe cognitive dysfunction and mental retardation. However, the prevalence of mental retardation seems to be just slightly

increased in NF1 (about 4-8%), which distinguishes NF1 from other genetic disorders like Fragile-X-Syndrome (Brewer, Moore, & Hiscock, 1997).

The intelligence profile of NF1 patients measured with the Wechsler Intelligence Scale for Children (WISC-IV) often presents with strengths in verbal comprehension, but weaknesses in visuo-spatial abilities, working memory and processing speed (Lidzba, Granström, Lindenau, & Mautner, 2012; Potvin, Hardy, & Walsh, 2015).

Learning disabilities

In the context of NF1 research, a distinction is made between specific and general learning disabilities. Specific learning disabilities are defined as poor performance in one or more specific didactic domain with an intelligence score in the normal range, whereas general learning disabilities are defined as poor performance in one or more specific didactic domain with an intelligence score below 85. According to a study by Hyman et al. (2006), about 30 to 60% of NF1 patients exhibit specific and general learning disabilities. Other authors found an even higher prevalence. Krab, Aarsen, et al. (2008) found a prevalence of specific and general learning disabilities of 39% in the NF1 patient group. Only 22% of their patients had no learning disability and only 10% of the children with NF1 had no problems in any aspect of school functioning. In the study by Krab, Aarsen, et al. (2008), impairment in school functioning was assessed in 4 domains of school performance (technical and comprehensive reading, spelling and mathematics) and in 6 domains of cognitive skills (intelligence, memory, language, visual-spatial skills, executive skills and attention). Children with NF1 showed impairment in all 4 domains of school performance and in all cognitive skills. Academic underachievement in children with NF1 has also been reported by Pride, Payne, and North (2012), who assessed intelligence, academic achievement, attention functions and executive functions. The NF1 group performed significantly poorer than the healthy control group on the majority of academic and cognitive measures, but especially attention problems and executive dysfunctions seemed to undermine academic achievement in children with NF1 (Pride et al., 2012).

Attention and executive dysfunctions

About 30-50% of NF1 patients manifest attention problems (Hyman et al., 2005; Templer, Titus, & Gutmann, 2012) and an even higher number of patients display executive dysfunctions (Payne, Hyman, Shores, & North, 2011). A study by Mautner and colleagues revealed that 73% of children with NF1 had at least light attention problems and 33% of them presented very serious attention dysfunctions (Mautner et al., 2010).

Executive functions play a central role when it comes to learning processes and they are important for the handling of many everyday situations. Problems with executive functions have been identified in patients with NF1 independently from IQ (Galasso et al., 2014; Plasschaert et al., 2016) and could be observed by professionals in laboratory test situations as well as in daily living by parents and teachers (Casnar & Klein-Tasman, 2017; Payne et al., 2011). Executive dysfunctions were found in the NF1 population concerning cognitive flexibility (Zöller, Rembeck, & Bäckman, 1997; Roy et al., 2014), response inhibition (Payne et al., 2011), working memory (Payne, Arnold, Pride, & North, 2012; Casnar & Klein-Tasman, 2017), planning (Roy et al., 2010; Galasso et al., 2014; Gilboa, Rosenblum, Fattal-Valevski, Toledano-Alhadef, & Josman, 2014), organization (Payne et al., 2011), and processing speed (Lidzba et al., 2012; Potvin et al., 2015). Difficulties in executive skills can continue into adulthood in patients with NF1 (Zöller et al., 1997) and are suggested to be related to academic underachievement (Gilboa et al., 2014; Janke et al., 2014). Whether and to what extent executive dysfunctions in NF1 depend on the occurrence of a comorbid Attention Deficit Hyperactivity Disorder (ADHD) is disputed so far (Potvin et al., 2015; Payne et al., 2012; Roy et al., 2010). However, in a small study by our own research group, we found that children with NF1 plus comorbid ADHD were affected in executive functioning compared to population norms, while children with NF1 without comorbid ADHD showed no dysfunctions (Denkinger et al., 2018).

Visuo-spatial disabilities

Visuo-spatial disabilities are consistently reported in parients with NF1 (Zöller et al., 1997; Krab, de Goede-Bolder, et al., 2008; Schrimsher et al., 2003). Schrimsher et al. (2003) could predict the NF1 diagnostic status against healthy con-

trols in up to 90% of NF1 patients with a combination of visual-spatial/motor tasks. The most robust indicator of NF1 was an impairment in the Judgement of Line Orientation Test. Payne et al. (2013) found significantly poorer visuo-spatial learning in children with NF1 compared to healthy controls using the Paired Associates Learning (PAL) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Memory problems

Problems with short-term, long-term and working memory were found for both the verbal/auditive domain and the visual-spatial domain (Descheemaeker, Plasschaert, Frijns, & Legius, 2013; Krab, de Goede-Bolder, et al., 2008; Payne et al., 2012; Billingsley, Slopis, Swank, Jackson, & Moore, 2003; Hofman, Harris, Bryan, & Denckla, 1994). Descheemaeker and colleagues investigated adult NF1 patients and compared their performance in auditory short- and long-term memory (task: Auditory Verbal Learning Test) as well as visual-spatial short- and long-term memory (task: Complex Figure of Rey) to matched controls. NF1 patients showed impairment in all tested memory domains and scored significantly below the control group (Descheemaeker et al., 2013). In children with NF1, Payne and colleagues demonstrated severe dysfunctions in visual-spatial short-term memory (task: PAL, CANTAB) and in working memory (task: working memory index, WISC-IV) even after controlling for confounders like full-scale IQ, sustained attention and visuo-spatial disabilities (Payne et al., 2012). In contrast to these findings stands a study by Hyman et al. (2005), who assessed verbal learning and verbal delayed memory (task: California Verbal Learning Test for Children) as well as visual learning and visual delayed memory (task: Continuos Visual Memory Test) and found no memory impairment in any modality in children with NF1, compared to healthy sibling-controls. Comparing standard scores, they even found stronger memory skills than general intellectual functioning in their patient group. The authors explained their unusual findings with the application of a standardized verbal memory test, the abstract nature of the visual task and the inclusion of a control for perceptual discrimination difficulties.

Impaired language acquisition and language skills

Language impairments are also very common among patients with NF1 (Alivuotila et al., 2010; Brei, Klein-Tasman, Schwarz, & Casnar, 2014). Alivoutila and colleagues investigated speech characteristics in children and adolescents as well as adult patients with NF1. They found deviations in phonation and articulation in 94% of the patients compared to 50% in healthy controls. The most typical speech issue among patients with NF1 was difficulty to regulate pitch, resulting in monotone speech, and nasal voice. Also very common were fluency problems including slurred speech, labored or sloppy articulation, deletion and reduction of sounds and syllables. The authors believe that these issues can have great negative social consequences. Brei et al. (2014) found difficulties in core language skills in more than one third of preschool-aged NF1 patients. Areas of particular difficulties were Receptive Language (33.3%), Language Structure (28.6%) and Expressive Language (28.6%), all measured with the Clinical Evaluation of Language Fundamentals – Preschool 2 (CELF-P2; Wiig et al. 2004). These lab-measured difficulties also seemed to relate to everyday communication and social interaction (Brei et al., 2014).

Emotional and social difficulties

Many patients with NF1 demonstrate emotional and social difficulties, which include challenges in forming friendships, rejection by their peers or teasing, poorer social skills in general, and both internalizing and externalizing problems (Barton & North, 2004; Huijbregts & de Sonneville, 2011). Social cognition, such as understanding paradoxical sarcasm or the capacity to recognize emotion seems to be significantly impaired in adult NF1 patients compared to healthy controls and these deficits were associated with decreased grey matter volume in the right superior temporal gyrus in a study by Pride et al. (2014). Also, children with NF1 exhibited problems in functional communication as well as weaker adaptive behavior compared to same-aged peers (Klein-Tasman et al., 2014, 2013). It is suggested that general cognitive disabilities like difficulties in processing speed, cognitive control and social information processing account for emotional problems in patients with NF1, because adaptive functioning in complex social situations seems to require good communication between many cognitive operations (Huijbregts & de Sonneville, 2011). Fur-

thermore, there is an increased incidence of autistic traits in patients with NF1 (Plasschaert et al., 2015). Walsh et al. (2013) found a clinically relevant symptomatology for Autism Spectrum Disorder (ASD) in about 40% of children with NF1. Garg and colleagues found an even higher prevalence of ASD symptomatology in the Social Responsiveness Scale (SRS): 29.4% of children with NF1 exhibited symptoms in the severe clinical range and a further 26.6% exhibited symptoms in the mild to moderate range (Garg et al., 2013).

Quality of Life

Like in other chronic diseases, research consistently reports lower global Quality of Life (QoL) in children and adolescents with NF1 compared to healthy children (Vranceanu, Merker, Park, & Plotkin, 2015; Garwood et al., 2012; Krab et al., 2009). For example, Cipolletta, Spina, and Spoto (2018) found that children with NF1 rated their QoL in the Pediatric Quality of Life Inventory as significantly lower than healthy controls on all scales (physical health, emotional state, social life, school activities, and global score), while parents rated their children's QoL as significantly poorer on only two of the four subscales (emotional state and social life) and on the global score. In general, however, QoL in NF1 is rated as poorer in parent proxy-reports than in children's reports (Vranceanu et al., 2015).

Some authors started the attempt to identify factors that influence QoL in NF1. According to these authors, the familial type of NF1, parental education, and good family relationships/cohesion should have a positive effect on QoL (Vranceanu et al., 2015; Oostenbrink et al., 2007; Graf, Landolt, Mori, & Boltshauser, 2006), while male sex, perceived disease severity, presence of plexiform neurofibromas, more disease complications, greater pain interference, orthopedic problems, socioemotional problems, cognitive dysfunctions, and learning disabilities were negatively correlated with QoL (Vranceanu et al., 2015; Wolters et al., 2015; Wolkenstein et al., 2009; Oostenbrink et al., 2007; Graf et al., 2006). Disease visibility was not associated with QoL in parent proxy-reports, but it was a significant negative predictor for QoL by child report (Vranceanu et al., 2015). Pain alone has no influence on QoL in NF1 (Vranceanu et al., 2015), but when pain is combined with complications it impacts QoL.

Motor dysfunction

Motor dysfunction is a common comorbidity of very different neuro-developmental disorders, including NF1. Impairments in patients with NF1 affect gross motor function, including hypotonia and hampered motor coordination, gait, balance as well as fine motor function (Haas-Lude et al., 2018; Johnson et al., 2010; Krab, de Goede-Bolder, et al., 2008) and muscle strength (Stevenson et al., 2012; Souza, Passos, Guedes, Rezende, & Rodrigues, 2009). The large number of prescriptions for physiotherapy or occupational therapy in children with NF1 is an indicator for the great burden that these motor deficits mean to NF1 patients (Krab, de Goede-Bolder, et al., 2008).

1.2. NF1 and Attention Deficit Hyperactivity Disorder

It is well known that, regarding their cognitive profile, patients with NF1 do not represent a homogeneous group (Kayl & Moore, 2000). There seem to be some combinations of cognitive dysfunctions which have more impact than others. Especially Attention Deficit Hyperactivity Disorder (ADHD) appears to increase the risk for a number of cognitive comorbidities (Pride et al., 2012; Lidzba et al., 2012; Koth, Cutting, & Denckla, 2000; Hyman et al., 2006). Lidzba et al. (2012) and colleagues as well as other authors (Koth et al., 2000) found that patients with NF1 and additional attention deficit score significantly lower in intelligence tests and have more specific learning disabilities than children with NF1 without clinically relevant attention problems (Hyman et al., 2006). In addition to unspecific attention problems, up to 50% of all NF1 patients present ADHD-like symptoms to an extent that they fulfill the diagnostic criteria for ADHD (Hyman et al., 2005; Kayl & Moore, 2000; Koth et al., 2000; Mautner, Kluwe, Thakker, & Leark, 2002) according to the Diagnostic and Statistical Manual of Mental Disorders - 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000). The prevalence of ADHD is about ten times higher in the NF1 patient group than in the general population (Mautner et al., 2002), where ADHD is already the most prevalent psychiatric disorder in childhood, affecting 3-5% of all children (American Psychiatric Association, 2000). With the introduction of the Diagnostic and Statistical Manual of Mental Dis-

orders - 5th edition (DSM-5), it must be assumed that the prevalence of ADHD in the general population is even increasing, since the diagnostic criteria have been extended (American Psychiatric Association, 2013).

1.2.1. General Characteristics of ADHD – Disease Characterization and Comorbidities

ADHD in general is characterized by a plurality of symptoms in the categories inattention, hyperactivity, disruptive behavior and impulsivity, all being developmentally inappropriate for the child's age (American Psychiatric Association, 2000). Children with ADHD often have trouble to act appropriate to the situation and attract negative attention. Because they have basic problems to regulate their behavior, they are often regarded as "agitators", defiant or lazy. Negative social interactions with family members, friends and teachers, as well as academic difficulties lead to decreased self-esteem, lower life satisfaction, and a variety of psychiatric comorbidities (Becker, Roessner, Breuer, Dopfner, & Rothenberger, 2011).

In Germany, ADHD is diagnosed according to the diagnostic criteria of the International Classification of Diseases - 10th edition (ICD-10) (World Health Organization, 2004), whereas in international research contexts, ADHD is usually diagnosed with the diagnostic criteria of the DSM-IV-TR (American Psychiatric Association, 2000) or since May 2013 the DSM-5 (American Psychiatric Association, 2013). In this thesis, we used the diagnostic criteria of the DSM-IV-TR. All clinical symptoms are listed in Table 1.3. In the DSM-IV-TR, three main subtypes of ADHD are classified: the inattentive subtype, the combined subtype and the hyperactive-impulsive subtype. Children have to present at least six symptoms of the categories inattention and/or hyperactivity/impulsivity to fulfill the diagnostic criteria. Symptoms have to be observed in different situations of daily life and have to be stable over at least six months. According to the DSM-IV-TR, symptoms have to be present prior to seven years of age, which was changed to twelve years of age in the DSM-5.

The gender distribution of ADHD in childhood is uneven with approximately three affected boys to one affected girl (Cuffe, Moore, & McKeown, 2005; Dulcan, 1997). One reason for the higher prevalence among boys could be that they more often annoy by externalizing behavior problems and therefore get

Table 1.3.

Diagnostic criteria for ADHD as described in the DSM-IV-TR (American Psychiatric Association, 2000)

A. Either 1 or 2:	
1. Symptoms of Inattention: Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.	
a	often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
b	often has difficulty sustaining attention in tasks or play activities
c	often does not seem to listen when spoken to directly
d	often does not follow through on instructions and fails to finish school work, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
e	often has difficulty organizing tasks and activities
f	often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school work or homework)
g	often loses things necessary for tasks and activities (toys, school assignments, pencils, books, or tools)
h	is often easily distracted by extraneous stimuli
i	is often forgetful in daily activities
2. Symptoms of Hyperactivity and Impulsivity: Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.	
	Hyperactivity:
a	often fidgets with hands or feet or squirms in seat
b	often leaves seat in classroom or in other situations in which remaining seated is expected
c	often runs or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feeling of restlessness)
d	often difficulty playing or engaging in leisure activities quietly
e	often "on the go" or often acts as if "driven by motor"
f	often talks excessively
	Impulsivity:
g	often blurts out answers before questions have been completed
h	often has difficulty awaiting turn
i	often interrupts or intrudes on others (eg., butts into conversations or games)
B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before 7 years of age	
C. Some impairment from the symptoms is present in two or more settings (eg., at school [or work] and at home)	
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning	
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (eg., Mood Disorder, Anxiety Disorder, Dissociative Disorders, or a Personality Disorder)	

diagnosed more often, while girls with ADHD rather tend to develop the more unremarkable inattentive subtype of ADHD and more often exhibit depressive symptoms (Biederman et al., 2002; Muller et al., 2011). Patients with the inattentive subtype of ADHD often attract attention very late, because they do not exhibit as many behavior problems in situations of daily living and can sometimes compensate their deficits with their intellectual abilities.

The course and severity of clinical symptoms of ADHD vary over time and the smooth transitions between normative behavior and clinically relevant problem behavior sometimes complicate diagnostics. The diagnosis of a clinically relevant disease often depends on the extent of developmental risks that are caused by the symptoms and the clinically relevant psychosocial impairment (Banaschewski & Dopfner, 2014).

At the end of the last century, it was believed that ADHD was a children's disease, which would disappear in the course of adolescence, but current studies provide increasing evidence for its continuation into adulthood for between 15% to 65% of affected individuals (Faraone, Biederman, & Mick, 2006). Muller et al. (2011) found that 4 to 6% of patients with childhood ADHD still experience serious ADHD-symptoms in adulthood. The prevalence of ADHD in the general adult population is 2.5% (Katzman, Bilkey, Chokka, Fallu, & Klassen, 2017). However, it is possible to reduce ADHD symptomatology by learning strategies to cope with these deficits.

Patients with ADHD are at a high risk for additional psychiatric comorbidities. Jensen and colleagues found that 70% of children with ADHD aged between 7 and 9 years had at least one additional psychiatric disorder (P. S. Jensen et al., 2001). Very common are oppositional defiant disorder (40%), conduct disorder (14%), anxiety (33.5%), tics (11%), mood disorders like depression (3.8%) and specific learning disorders (Muller et al., 2011). Also very common in patients with ADHD are traits and symptoms of ASD with 15-25% (Kotte et al., 2013; Antshel, Zhang-James, Wagner, Ledesma, & Faraone, 2016). Since clinicians are permitted to make an ASD diagnosis in the context of ADHD, 12.4% of ADHD patients have an ASD diagnosis (C. M. Jensen & Steinhausen, 2015). In earlier versions of the DSM, this was not acceptable, but with the introduction of the DSM-5 it is allowed (Antshel et al., 2016).

1.2.2. Etiology of ADHD with and without NF1

Although the definition of ADHD without NF1 ($ADHD^{only}$) is based on behavior, it is increasingly recognized that the neurocognitive components of $ADHD^{only}$, which are based on impairments of the central nervous system, can not be ignored (American Psychiatric Association, 2013). There is increasing evidence, that $ADHD^{only}$ might be a result of a disturbed self-regulation with a high involvement of executive dysfunctions (e.g. dysfunctions in the areas cognitive control, impulse control and working memory) (Barkley, 1997; Gawrilow, Schmitt, & Rauch, 2010). Additionally, $ADHD^{only}$ is associated with a disturbance of the reward system, which interferes with the ability to be self-motivating (Gawrilow et al., 2010). Some authors are also convinced that $ADHD^{only}$ is a result of disturbances in neuronal control circuits (Biederman & Faraone, 2005; Cortese, 2012b). Biederman and Faraone (2005) hypothesized that the polygenetic factors provoke abnormalities in brain structures and a dysregulation of neurotransmitters (dopamine and noradrenalin) in the basal ganglia. While noradrenalin is known to be important for attentional processes, dopamine influences impulse/drive and motivation.

In the etiology of $ADHD^{only}$, genetic factors seem to explain a high percentage (up to 80%) of phenotype variance (Burt, 2009; Thapar, Cooper, Eyre, & Langley, 2013), but the pathophysiology is a very complex pattern of gene to gene, to environment, to epigenetic interactions (Thapar et al., 2013; Banaschewski & Dopfner, 2014). Twin and family studies indicate that the heredity of $ADHD^{only}$ adds up to 70-80% (Biederman & Faraone, 2005; Cortese, 2012a). Environmental factors that seem to have a great influence on the manifestation of $ADHD^{only}$ are prenatal exposure to harmful substances like alcohol (Pagnin, Zamboni Grecco, & Furtado, 2018) or nicotine (Schwenke et al., 2018), as well as infections and complications during pregnancy (Millichap, 2008). Also, the exposure to environmental containments like lead or polychlorinated biphenyl (PCB) during childhood seems to be associated with an increased incidence of $ADHD^{only}$ (Eubig, Aguiar, & Schantz, 2010). Furthermore, negative social constructions and dysfunctional family systems can aggravate symptoms of $ADHD^{only}$. Disturbed behavior of a child provokes negative reactions, which leads to an increase of disturbed behavior and to more negative reactions, creating a vicious circle (American Psychiatric Association, 2013; Gawrilow et al., 2010).

Although the etiology of ADHD symptoms in NF1 ($NF1^{ADHD}$) still remains unclear (Payne et al., 2010), at least genetic factors are likely to differ from those in $ADHD^{only}$: The incidence of attention problems is far higher in NF1 patients than in their healthy siblings or parents (Koth et al., 2000), and the typical gender ratio of three boys to one girl in $ADHD^{only}$ seems to face a balanced gender ratio in the NF1 population (Hyman et al., 2005).

A closer look at the underlying neural mechanisms reveals both, similarities and differences between $NF1^{ADHD}$ and $ADHD^{only}$: According to current hypotheses, disturbances in the catecholaminergic metabolism in fronto-striatal brain structures play a role in the genesis of both $ADHD^{only}$ and $NF1^{ADHD}$ (Diggs-Andrews & Gutmann, 2013; Brown et al., 2010; Cantwell, 1996). But additionally, $ADHD^{only}$ has been associated with a reduction of brain volume, especially in the left-sided prefrontal cortex (Cantwell, 1996), anomalies in white matter microstructure in the fronto-striatal system (Cantwell, 1996; Frodl & Skokauskas, 2012), anomalous hemispheric asymmetries (Silk et al., 2016), and structural changes in limbic regions such as the amygdala (Frodl & Skokauskas, 2012). Up to date, there is no evidence for such alterations in $NF1^{ADHD}$.

In NF1, attention deficit could be traced back to reduced dopamine levels in the striatum in a mouse model (Brown et al., 2010). Brown and colleagues observed an altered dopaminergic metabolism in the striatum and showed a normalization of reduced striatal levels of dopamine by methylphenidate, accompanied by an improvement of attention performance (Brown et al., 2010). So far, there are still many uncertainties regarding the etiology of ADHD in patients with NF1, but given the high incidence, it does not seem to be an independent comorbidity.

1.2.3. ADHD and Cognitive Development of Children with and without NF1

Intelligence and learning disabilities

Cognitive deficits and secondary impairments of $NF1^{ADHD}$ resemble those of $ADHD^{only}$. Similar to patients with $ADHD^{only}$, NF1 patients with ADHD score significantly lower in intelligence tests than healthy (sibling-) controls (Biederman et al., 2009; Frazier, Demaree, & Youngstrom, 2004; Pride et al., 2012), and show lower IQ scores than NF1 patients without ADHD ($NF1^{only}$) (Koth et

al., 2000; Lidzba et al., 2012; Pride et al., 2012). For ADHD^{only}, meta-analyses found significantly lower overall cognitive abilities and lower levels of overall achievement compared to healthy controls (Frazier et al., 2004; Frazier, Youngstrom, Glutting, & Watkins, 2007). Learning disabilities, repeated grades and placement in special classes were observed more often in children with ADHD^{only} than in healthy children (Biederman et al., 2009). In NF1, patients with NF1^{ADHD} also display more specific learning disabilities and academic underachievement than patients with NF1^{only} (Hachon et al., 2011; Payne et al., 2012).

The course and profile of cognitive impairments in ADHD^{only} appears stable over childhood into young adulthood. Ameliorations of ADHD symptoms are not necessarily accompanied by cognitive improvements (Biederman et al., 2009). Similarly, the developmental course of cognitive impairments in NF1 seems stable (Cutting, Huang, et al., 2002; Pavol et al., 2006), mediated, however, by the presence or absence of T2 signal hyperintensities on MRI (Payne et al., 2013).

Attention

Attention functions are basic cognitive properties, which are necessary for almost every intellectual and practical activity. Since attention functions are involved in manifold processes like perception, memory, action planning and performance, problem-solving, spatial orientation and other, it is difficult to differentiate between attention functions and other cognitive functions at a conceptual and also at a functional level (Sturm, George, von Giesen, & Hildebrandt, 2012). According to (neuro-)psychological attention theories, at least five attentional components can be distinguished: [1] alertness, [2] sustained attention and vigilance, [3] spatial orientation of the attentional focus, [4] selective attention, and [5] shared/divided attention, attentional flexibility (Sturm, Herrmann, & Münte, 2009). Some authors propose that there are two basic dimensions of attention: intensity and selectivity of attention (Van Zomeren & Brouwer, 1994). While intensity describes the ability to activate and sustain attention, selectivity refers to the ability to select and prioritize certain stimuli (selective and shared/divided attention) (Van Zomeren & Brouwer, 1994). Spatial orientation of the attentional focus would be a separate dimension outside this taxonomy of attention.

In children with ADHD^{only} and NF1^{ADHD}, dysfunctions have been found in almost every component of attention. On functional test measures of attention variables (e.g. Test of Variables of Attention, (Greenberg, Kindschi, Dupuy, & Hughes, 2013)), children with ADHD^{only} tend to perform worse on impulse control (Commission Errors) than on sustained attention (Omission Errors). However, Mautner et al. (2002) found with the same test that children with ADHD^{only} displayed more deficits in sustained attention. Additionally, they performed subnormal on response time and response time variability (reflecting distractibility). Children with NF1^{ADHD} seemed especially impaired in impulse control in the study by Mautner et al. (2002), but they also performed subnormal on response time and response time variability. Lion-Francois et al. (2017) found in a sustained attention task that children with NF1^{ADHD} were impaired in the areas of intensive, selective, and executive attention, while children with ADHD^{only} were only impaired in response time.

Regarding the distribution of ADHD subtypes, some authors found that children with NF1^{ADHD}– like children with ADHD^{only}– most frequently present the combined subtype, whereas the hyperactive/impulsive subtype is very rare in NF1 (Pride et al., 2012).

Executive functions

The generic term executive functions refers to a family of top-down neurocognitive processes that enable humans to successfully master in novel environments as well as familiar settings by constant evaluation, adjustment of reactions, regulation of emotions, and control of outcomes (Baddeley, 2002). They are responsible for purposeful, goal-directed behavior (Anderson, 2002). Generally, executive functions develop from the age of about 2.5 years and do not reach their maturation until the early adulthood (Kubesch & Walk, 2009). The neuroanatomical correlates of executive functions are complex and widespread networks of frontal and superior parietal structures that develop in a difficult and lengthy process (Makris et al., 2007).

The definition of executive functions varies depending on the scientific perspective. One of the oldest descriptions of executive functions is Baddeley's model of working memory (Baddeley, 1988), which characterizes the "central executive" as a component of working memory. In this model, the "central executive" is responsible for the incorporation of the information from all other

components of the working memory (the phonological loop, the visuo-spatial sketchpad, the episodic buffer, and the long-term memory).

More recent models suggest that executive functions are a rather independent cognitive element, which includes working memory processes, but refers also to other multifaceted and clearly delimitable subcomponents (Miyake et al., 2000; Smith & Jonides, 1999). A well-accepted current model of executive functions was defined by Smith and Jonides (1999) and includes the subcomponents task management, attention and inhibition, planning, monitoring, and coding. In this model, attentional processes are incorporated under the umbrella term of executive functions. According to current research, attentional processes are closely linked to other components of executive functions and have to be taken into account when it comes to executive processes.

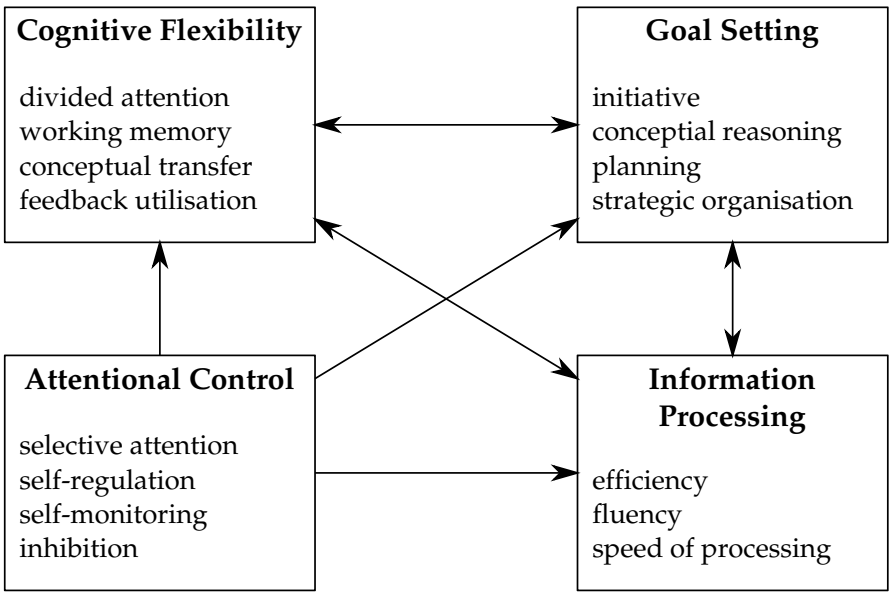

Figure 1.3. Proposed model of executive function (adapted from Anderson, 2002).

The present thesis takes the model of Anderson (2002) as a basis (see Figure 1.3). The authors proposed a model of executive functions with four distinct domains ([1] attentional control, [2] information processing, [3] cognitive flexibility, and [4] goal setting), which are considered discrete functions that are likely to be related to specific frontal systems. In this model, attentional control plays the leading role and influences all other executive domains, while the other three domains are inter-related and inter-dependent. Attentional control is responsible for selective and prolonged attentional processes, as well as for

the regulation and monitoring of actions, and thus for tactic and goal-directed behavior. Impairments in the domain of attentional control are likely to lead to impulsivity, lack of self-control, and problems with planning and organizing (Anderson, 2002).

Therefore, it is not surprising that executive dysfunctions seem to be a hallmark of ADHD. Executive dysfunctions have been well described for both, $ADHD^{only}$ and ADHD in NF1 (Potvin et al., 2015; Pride et al., 2012; Doyle, 2006; Biederman et al., 2004). Some authors even consider executive dysfunctions as the source of ADHD symptoms (Barkley, 1997), but more recent research results indicate that they are only a part but not the source of all ADHD symptoms (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

In $ADHD^{only}$, executive dysfunctions emerge independently from intelligence, age, sex, socio-economic status or ethnicity (Doyle, 2006) and even independently from the subtype of ADHD (Willcutt et al., 2005). Similarly to NF1, studies indicate that executive dysfunctions continue into adulthood in patients with $ADHD^{only}$ (Doyle, 2006).

In both patient groups, executive dysfunctions include deficits in inhibition, sustained attention, working memory and verbal fluency (Payne et al., 2012; Hervey, Epstein, & Curry, 2004). Especially working memory deficits are well described in both populations. In $ADHD^{only}$, poor performances in verbal and spatial domains of working memory are repeatedly reported for school-aged children (Martinussen & Tannock, 2006) and visuospatial working memory deficits were found even in preschool children with ADHD symptoms (Re, De Franchis, & Cornoldi, 2010). Furthermore, working memory deficits were rather linked to the inattention symptom dimension than to the hyperactive-impulsive symptom dimension (Martinussen & Tannock, 2006). In NF1, spatial working memory deficits were found independently of ADHD symptoms (Payne et al., 2012), but there are also studies showing that deficits in other working memory tasks (e.g. Digit Span and Letter-Number Sequencing of the WISC-IV) and problems with working memory skills in daily living (assessed with parent and teacher questionnaires) are more pronounced in $NF1^{ADHD}$ than in $NF1^{only}$ (Potvin et al., 2015; Pride et al., 2012). Also, verbal cognitive fluency seems to be affected in children with $NF1^{ADHD}$, but not in children with $NF1^{only}$ (Denkinger et al., 2018). Regarding impulse control, Mautner et al. (2002) found

that NF1 patients with ADHD reacted significantly more impulsively than patients with $NF1^{only}$, who did not differ from healthy controls.

Academic career

Both functional domains, attention and executive functions, are essential for other cognitive processes, and specifically for learning. Consequently, underachievement (i.e., academic performance below expectations according to intelligence) is common both in $ADHD^{only}$ and in NF1 (Ek, Westerlund, Holmberg, & Fernell, 2011). Given their long-term personal and economic consequences, more knowledge on the causes and potential remedy of attention and academic problems in patients with NF1 is of high clinical relevance.

Emotional profile

A study comparing the emotional profile of NF1 and $ADHD^{only}$ found close resemblance between patients with $NF1^{ADHD}$ and patients with $ADHD^{only}$, who both presented significantly lower life satisfaction, more excitability, aggressiveness, stress/tension, somatic distress and more emotional instability than patients with pure NF1 (Mautner, Granström, & Leark, 2015).

Quality of Life

According to the WHO QoL is defined as the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (WHOQOL Group, 1995).

Like in NF1 (as described above), available studies consistently report that children with $ADHD^{only}$ experience impaired QoL (Danckaerts et al., 2010; D. Coghill & Hodgkins, 2016; Marques et al., 2013; Thaulow & Jozefiak, 2012; Jafari, Ghanizadeh, Akhondzadeh, & Mohammadi, 2011; Pongwilairat, Louthrenoo, Charnsil, & Witoonchart, 2005). Lee et al. (2016) found that parents of children with $ADHD^{only}$ and children themselves rate their QoL lower than that of healthy controls regarding the domains physical functioning (moderate effect) and psychosocial functioning (strong effect). D. Coghill and Hodgkins (2016) found a significant correlation between symptom severity of $ADHD^{only}$ and QoL for parent/carer ratings and child ratings in questionnaires, with more

ADHD symptoms being associated with poorer QoL. However, the authors also believe that ADHD medication may help to improve health-related QoL in patients with ADHD^{only} (D. R. Coghill, Banaschewski, Soutullo, Cottingham, & Zuddas, 2017). Like in NF1, children with ADHD^{only} tend to rate their QoL higher than parents in proxy-reports (Galloway & Newman, 2017).

1.2.4. Treatment Effects of Methylphenidate

In terms of therapeutic interventions in ADHD, the combination of behavioral psychotherapy and medication is the gold standard (American Academy of Pediatrics, 2001). For medication, Methylphenidate (MPH) or atomoxetin are recommended, with MPH affecting the metabolism of dopamine and atomoxetin that of noradrenalin. The positive therapeutic effects of methylphenidate on the core symptoms of ADHD such as inattention, hyperactivity and impulsivity have repeatedly been confirmed (MTA Cooperative Group, 2004). Concerning the therapy of ADHD in NF1, pharmaceutical interventions with MPH have been shown to have similar positive effects on the core symptoms as in ADHD^{only} (Lion-Francois et al., 2014; Mautner et al., 2002), although it remains unclear how attention system dysfunction in human NF1 patients is actually linked to the dopaminergic system.

Additionally to positive effects of MPH on attention performance, it has a significantly positive effect on executive functioning (Barnett et al., 2001). Given the improvement of attention performance and executive functioning in children with ADHD being treated with MPH, one would expect a consecutive improvement of intellectual performance in the short term and academic achievement in the long term. Researchers suppose that ADHD leads – among others – to an inaccurate test-taking behavior, which might interfere with the performance on an intelligence test and therefore might underestimate a child's true ability when a test is administered to a child with ADHD, which is not taking stimulant medication.

However, in ADHD^{only}, the reported effects of treatment with MPH on intellectual performance are rather insignificant (Pietrzak, Mollica, Maruff, & Snyder, 2006). Several studies showed that medical treatment was accompanied by a significant, but small, increase of IQ scores (about 2–6 IQ points) in ADHD^{only}

(Tsai et al., 2013; Gimpel et al., 2005; Thurber & Walker, 1983; Kavale, 1982). Thus, the effect is of little clinical relevance.

In contrast, in patients with NF1, an analysis of retrospective data provides evidence for more significantly positive effects of MPH on general cognition (Lidzba, Granström, Leark, Krägeloh-Mann, & Mautner, 2014; Brown et al., 2010). Children with NF1 and ADHD that were medicated, improved in full-scale IQ by an average of 18 IQ points over several years. This large positive effect might be highly relevant for the academic career of the affected children, but due to the range of limitations inherent in retrospective data analyses, an interpretation of these results has to be done with caution.

1.3. Scope and Hypotheses

Data on the influence of ADHD on cognitive abilities and long-term cognitive development in NF1 is extremely scarce. Therefore, the first goal of the present thesis was to compare neuropsychological characteristics of $NF1^{ADHD}$ and $NF1^{only}$ with the purpose to gain information about the cognitive profile(s) of NF1, and to compare the attention profiles of $NF1^{ADHD}$ and $ADHD^{only}$ (Study 1). The second goal was to compare the intellectual development of children with $NF1^{ADHD}$ and $NF1^{only}$ over a prolonged time period, as well as to investigate treatment effects of methylphenidate on intellectual development in patients with $NF1^{ADHD}$ (Study 2).

1.3.1. Study 1: Analysis of Cognitive Characteristics of NF1 with and without ADHD

Up to now, in the relevant literature, patients with NF1 were considered to be generally impaired in manifold cognitive domains, including global intellectual functioning, short- and long-term memory, attention functions and executive functions. However, recent studies indicate that some combinations of cognitive dysfunctions in NF1 have more impact than others. Especially attention deficit and ADHD seem to raise the risk for a number of cognitive comorbidities.

So far, very few studies investigated cognitive aspects of NF1 considering the effect of presence or absence of ADHD. However, a retrospective study by

Lidzba et al. (2012) reveals negative effects of ADHD-symptoms on intelligence test performance, with differences in full-scale IQ up to one standard deviation between children with $NF1^{ADHD}$ and $NF1^{only}$. These findings are corroborated by a retrospective study by Potvin et al. (2015), who also found significant differences between patients with $NF1^{ADHD}$ and $NF1^{only}$ regarding intelligence, and additionally, regarding executive functions and memory skills. Furthermore, Mautner et al. (2002) found decreased attention functions in $NF1^{ADHD}$ compared to $NF1^{only}$.

The purpose of Study 1 was to expand the knowledge about the role of ADHD in NF1. Therefore, the cognitive profiles of $NF1^{ADHD}$ and $NF1^{only}$ were compared, which should help to extract NF1-typical cognitive characteristics and to differentiate between NF1-caused and ADHD-caused cognitive impairments. Additionally, a comparison of children with $NF1^{ADHD}$ and $ADHD^{only}$ was designed to define differences between these types of attention disorders, since an independent comorbidity of ADHD in NF1 seems unlikely. Furthermore, an analysis of quality of life was included, which should provide information about frequent secondary problems in NF1 and ADHD.

Five hypotheses were formulated for Study 1 and tested in a cross sectional comparison:

[H1] Intellectual ability:

ADHD is associated with reduced intellectual ability in NF1, as it is in children without NF1. NF1 per se is not generally associated with reduced intellectual ability.

[H2] Memory skills:

ADHD is associated with reduced memory skills in NF1, as it is in children without NF1.

[H3] Attention functions:

NF1 per se – as well as ADHD per se – is associated with reduced attention functions. $NF1^{ADHD}$ and $ADHD^{only}$ is associated with significantly more severe attention dysfunction than $NF1^{only}$, but $NF1^{only}$ is not spared in attention

functions. Additionally, $NF1^{ADHD}$ and $ADHD^{only}$ differ significantly in their attention profiles.

[H4] Executive functions:

ADHD is associated with reduced executive functioning in NF1, as it is in children without NF1. NF1 per se is not associated with reduced executive functioning.

[H5] Quality of life:

NF1 and ADHD as chronic diseases lead to impaired QoL.

1.3.2. Study 2: Longitudinal Analysis of Attentional and Intellectual Development in NF1

The aim of Study 2 was to investigate the long-term cognitive development of children with NF1. The intention was to clarify if an amelioration of attention functions is accompanied by an improvement of intellectual functioning in the long term.

This assumption may at first seem odd, because the course and profile of cognitive impairment in $ADHD^{only}$ appear stable over childhood into young adulthood and ameliorations of ADHD-symptom severity was not or in a rather small extent correlated with cognitive improvement (Hellwig-Brida, Daseking, Keller, Petermann, & Goldbeck, 2011; Biederman et al., 2009; D. R. Coghill, Rhodes, & Matthews, 2007; Gimpel et al., 2005). Similarly, the developmental course of cognitive impairments in NF1 seems stable (Pavol et al., 2006; Hyman et al., 2003; Cutting, Huang, et al., 2002), mediated, however, by the presence or absence of T2 signal hyperintensities on MRI (Payne et al., 2013). However, there is first tentative evidence for positive effects of ADHD treatment with methylphenidate on attention, and even more so on intellectual functioning in $NF1^{ADHD}$ (Lidzba et al., 2012). Potentially due to an inherently decreased learning capacity, patients with NF1 might, in terms of intellectual development, profit more from successful ADHD interventions than patients with $ADHD^{only}$.

Since the study by Lidzba et al. (2012) was conducted with retrospective data and the conclusions drawn from such data analyses have to be considered

with caution, Study 2 was designed to investigate prospectively the effects of an amelioration of attention functions on intellectual development in children with $NF1^{ADHD}$. Three hypotheses were formulated for a study with a longitudinal design:

[H1] Attention performance is a predictor for intellectual development

Attention dysfunction is significantly related to reduced intellectual functioning in the short and long term. Attentional functioning is a predictor for intellectual functioning.

[H2] Improvement of intellectual functioning

An amelioration of attention functions is accompanied by a significant improvement in intellectual functioning over a two-year-period. The expected effect is specific for children with NF1 and does not, or in a significantly smaller extent occur in children with $ADHD^{only}$.

[H3] Treatment effects

An intervention with methylphenidate is accompanied by a stronger improvement in intellectual functioning than other or no interventions (e.g. psychotherapy, occupational therapy) in patients with $NF1^{ADHD}$.

2. Methods

2.1. Study Design

2.1.1. Study Design and Framework

The present research project was conducted in a cooperation between the University Children's Hospital Tübingen (Dept. Pediatric Neurology) and the University Medical Center Hamburg-Eppendorf (Dept. Neurology, Neurofibromatosis Outpatient Unit). Since NF1 is a rare genetic disorder, the cooperation between the two largest German centers specialized in NF1 was necessary to recruit the number of patients needed for this project. 126 participants were consecutively recruited for this project from May 2013 until January 2016 and 111 participants were enrolled after checking for the inclusion and exclusion criteria. The total duration of the project mounts up to four and a half years, from May 1st, 2013 until December 31th, 2017.

Two studies were conducted in the context of this research project. In Study 1, patient characteristics were compared in a cross-sectional design. Study 2 includes data of the development of specific patient characteristics in a longitudinal design. To collect the longitudinal data, three assessments were performed with each participant within two years (see Figure 2.1). Between each assessment lay 12 months (+/- 2 month). The relatively long time period of 12 month between two assessments was chosen to avoid order effects (e.g. due to learning effects, practice effects, boredom).

2.1.2. Recruitment

Participants for the NF1 groups were consecutively recruited in the context of hospital service at the University Children's Hospital Tübingen (Dept. Pediatric Neurology) and the University Medical Center Hamburg-Eppendorf (Dept. Neurology, Neurofibromatosis Outpatient Unit). For the ADHD group,

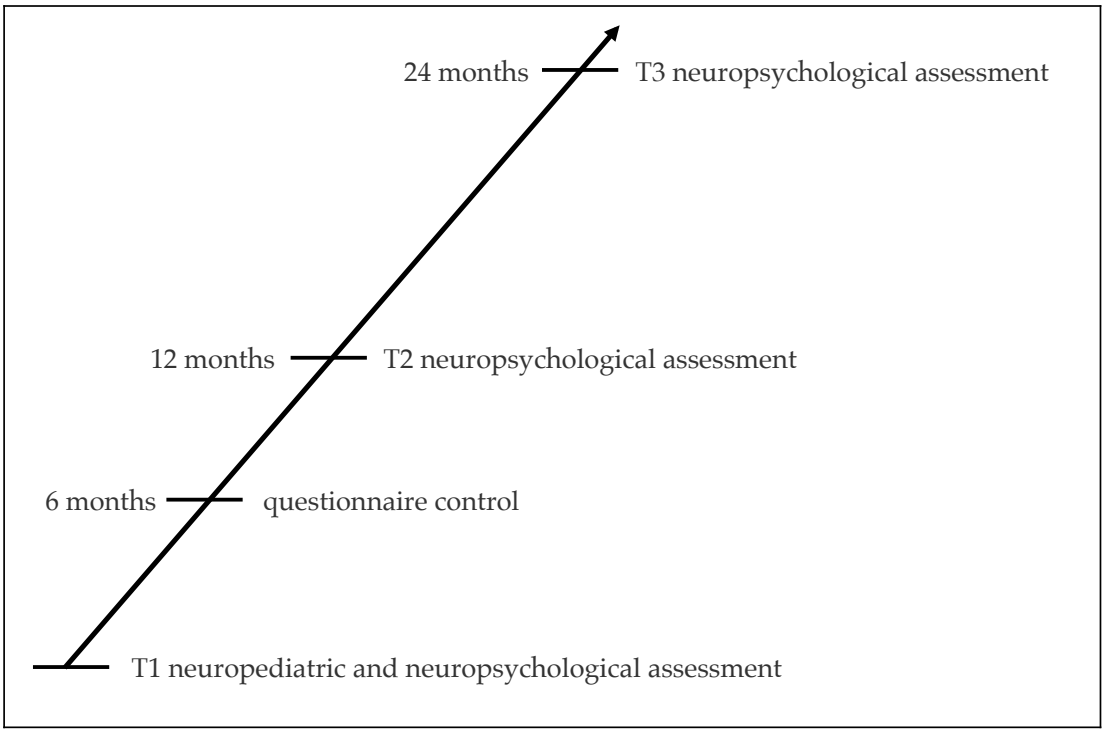

Figure 2.1. Study process.

participants were recruited exclusively at the University Hospital Tübingen (Dept. Pediatric Neurology, Dept. Child and Adolescent Psychiatry and Psychotherapy). Additional participants were recruited by advertisements in journals of NF1 and ADHD lay groups. Study participation was voluntary and was rewarded with a detailed test report (with therapeutic recommendations) for each assessment. Patients' assent and written informed consent of their caregivers were obtained prior to the investigations according to the 1964 Declaration of Helsinki and the approval of the local ethics committee (655/2012BO1).

2.1.3. Inclusion and Exclusion Criteria

Inclusion criteria comprised fulfillment of the diagnostic criteria of NF1 and/or ADHD, age between 6 and 12 years at the time of the enrollment, and an intelligence score between 70 and 115. Since existing literature shows that patients with NF1 as well as patients with ADHD tend to score below the average in intelligence tests, we recruited patients within the normal and low borderline range of intelligence, so that the sample would be representative for NF1 and

ADHD regarding intelligence. The age range of 6-12 years was chosen, because children of this age have a high potential for learning and cognitive development. Typical psychiatric comorbidities of NF1 and ADHD were allowed, including specific developmental disorders of speech and language, specific developmental disorders of scholastic skills, specific developmental disorder of motor function, conduct disorders and emotional disorders with onset specific to childhood.

Before the enrollment in this study, all participants passed through a neuropediatric examination to identify potential exclusion criteria, which included neurological diseases with intracranial manifestations like symptomatic optic nerve gliomas or brain tumor, traumatic brain injury, ischemia or hemorrhage. Additionally, participants were excluded for suspected or proven genetic syndromes other than NF1, explaining ADHD symptoms (e.g. Fragile-X), and for any form of epilepsy, very preterm birth (< 32 week of gestation; < 1500 gram) or severe psychiatric disorders (e.g. autistic disorders).

2.1.4. Study Population

Three groups of patients were included in the studies of the present thesis. The particular group of interest consisted of patients with NF1 plus ADHD ($NF1^{ADHD}$-group). Additionally, two control groups were recruited: one group with patients with $NF1^{only}$ ($NF1^{only}$-group) and another group with patients with $ADHD^{only}$ ($ADHD^{only}$-group). All together, 126 participants were recruited (see Figure 2.2). After checking for inclusion and exclusion criteria, 111 participants were enrolled in Study 1 and 66 participants were enrolled in Study 2. The differing number of participants in Study 1 and Study 2 is due to drop-outs during the course of the longterm study and the matched group design of Study 2. All participants suffering from NF1 fulfilled the diagnostic criteria for NF1 according to the National Institute of Health Consensus Development Conference statement (National Institutes of Health, 1988). All patients with ADHD fulfilled the diagnostic criteria according to the DSM-IV-TR (American Psychiatric Association, 2000)[1]. All participants were either native speaker of the German language or spoke German as their second language at

[1]In the present research project, the diagnostic criteria of the DSM-IV-TR were used to diagnose ADHD, since the DSM-5 was not published yet by the time the research project started (the DSM-5 was published on May 18th, 2013 and this research project started on

an adequate level. Further demographic data about the study populations is described in the following chapters about Study 1 and Study 2.

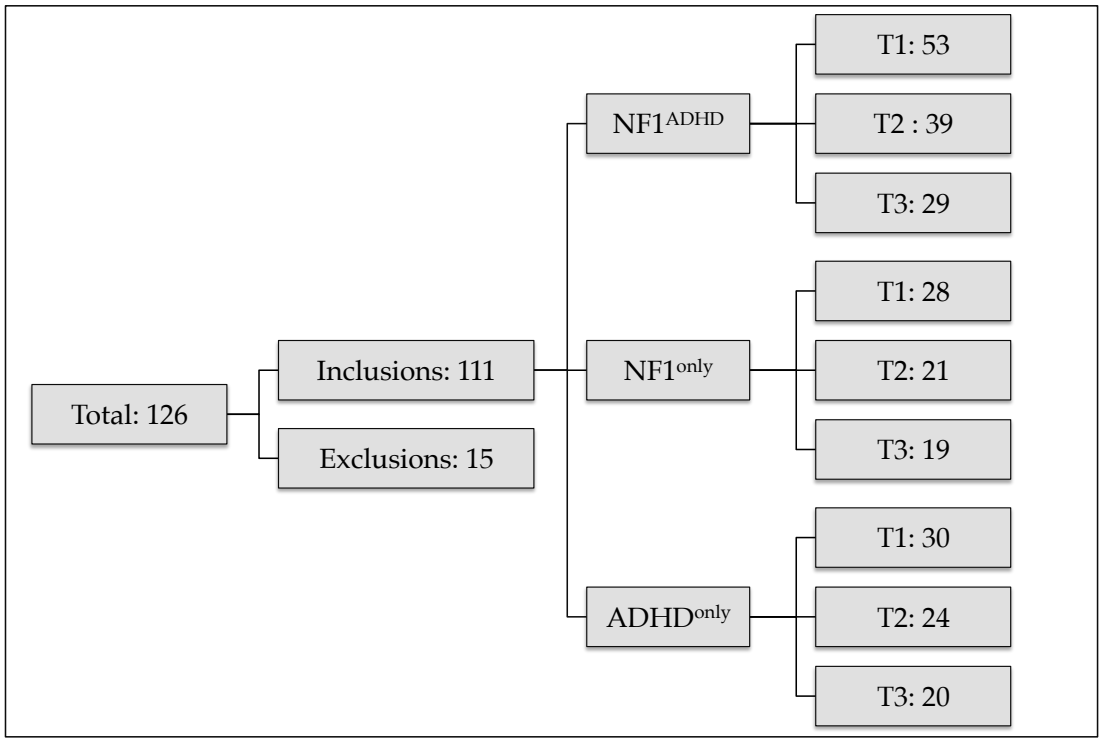

Figure 2.2. Number of patients that were recruited and enrolled.

2.2. Methods and Material

2.2.1. Neuropediatric Examination

In a neuropediatric examination, participants were checked for somatic exclusion criteria, for undetected NF1 in the ADHD^{only}-group, and were neurologically characterized. NF1 patients were assessed regarding their type of NF1 (familial type versus spontaneous mutation).

May 1st, 2013). Additionally, important diagnostic tools used in this project (e.g. Disyps-KJ, Conners-3) are based on the criteria of the DSM-IV-TR.

2.2.2. Interviews and Questionnaires for Patient Characterization

Information about (socio-)demographic data, comorbid disorders, medication, and therapeutic interventions prior to the assessment were collected in a standardized interview and by means of a questionnaire (*Soziodemographische Daten*). Some of the (socio-)demographic data were used to calculate the Socio-Economic Status (SES) of the participant, which was measured with the Winkler-Index (Winkler & Stolzenberg, 2009). The Winkler-Index takes into account the parents' educational achievement, their professional position and the family income.

Additionally, a clinical interview on the basis of the DSM-IV-TR-based *Diagnostik-System für psychische Störungen im Kindes- und Jugendalter* (Disyps-KJ) (Döpfner & Lehmkuhl, 1998) was conducted by a psychologist with the parents or caregivers of the participants, to confirm or reject the ADHD diagnosis, to investigate common comorbid disorders (e.g. Conduct disorders) and to collect data for patient characterizations.

Problem behavior was assessed with the German version of the *Child Behavior Checklist* (CBCL) (school-age version: CBCL6/18), which is a standardized parent questionnaire for children between 6 and 18 years. It consists of 118 items and provides scores for internalizing and externalizing problem areas, containing the subscales Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior (Arbeitsgruppe Deutsche Child Behavior Checklist, 1998).

2.2.3. Neuropsychological Assessments and Behavior Rating Scales

Intelligence

Intelligence was assessed with the German version of the *Wechsler Intelligence Scale for Children IV* (WISC-IV) (Petermann & Petermann, 2008), which is a standardized test to measure the general intellectual ability of children between 6.0 and 16.11 years. It generates a score for full-scale IQ and provides four primary index scores that describe the intellectual ability in separate cognitive domains

(Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index). Overall, full-scale IQ is derived from 10 primary subtests. The index Verbal Comprehension is measured with the three subtests Similarities (verbal concept formation, reasoning), Vocabulary (word knowledge, verbal concept formation), and Comprehension (verbal reasoning and conceptualization, evaluation and use of past experience, practical knowledge and judgement). For the Perceptual Reasoning Index, three subtests are conducted as well: Block Design (ability to analyze and synthesize abstract visual stimuli), Picture Concepts (abstract categorical reasoning ability), and Matrix Reasoning (perceptual organization, classification and spatial ability, simultaneous processing, knowledge of part-whole relationships). The index Working Memory is assessed with the two subtests Digit Span (short-term auditory memory, memory span, mental manipulation, cognitive flexibility, encoding, attention) and Letter-Number Sequencing (short-term auditory memory, memory span, mental manipulation, sequential processing, attention). The index Processing Speed is measured with the subtests Coding (psycho-motor speed, visual-motor coordination, visual scanning, short-term visual memory) and Symbol Search (visual-motor coordination, visual scanning, visual discrimination, short-term visual memory) (Wechsler, 2003).

Memory

Memory functions were assessed with the *Verbaler Lern- und Merkfähigkeitstest* (VLMT) (Helmstaedter, Lendt, & Lux, 2001). The VLMT is a German auditory verbal learning and memory test, which measures short-term and medium-term memory function as well as learning capacity. The VLMT measures Immediate Recall of a list of words (short-term memory), Delayed Recall of the same list of words after 30 minutes (medium-term memory) and Recognition of the learned words in a larger list of words. Additionally, it measures the loss of learned information resulting from an interference list (distraction).

Attention

Attention functions were measured with the visual condition of the eighth version of the *Test of Variables of Attention*® (T.O.V.A.) (Greenberg et al., 2013). The T.O.V.A. is a computer-based continuous performance test, which takes

about 21 minutes and measures Variability of Response Time (consistency), Response Time, Commission Errors (impulsivity), and Omission Errors (inattention). Additionally, it provides an Attention Performance Index (API), post-commission response times, and multiple or anticipatory responses, as well as an ADHD score, which is a comparison to an age/gender specific ADHD group. The T.O.V.A. uses simple visual geometric stimuli (to minimize the effects of cultural differences and learning problems) and presents them with a mid-range interstimulus interval of two seconds. Stimuli are presented for exactly 100 milliseconds. The test holds two conditions: a low frequency condition, where the target is presented very infrequently (3.5 times less than the distractor) and a stimulating condition, where the target is presented very frequently (3.5 times more often than the distractor). In the low frequency condition, people with attention problems and ADHD are expected to make an inappropriately high number of omission errors, while in the stimulating condition, they are expected to make inappropriately many commission errors. Additionally, ADHD-patients are expected to show slower overall response times and a higher variability of response times (Greenberg et al., 2013).

Functional aspects of attention were measured with the German edition of the long version of the Conners Rating Scales: *Conners Skalen zu Aufmerksamkeit und Verhalten - 3®* (Conners-3) (Lidzba, Christiansen, & Drechsler, 2013). The Conners-3 are standardized parent and teacher questionnaires for the characterization of children between 6 and 18 years of age with respect to severity of attention problems, executive functions and comorbidities. The Conners-3 parent version contain 107 items and six main scales: Inattention, Hyperactivity/-Impulsivity, Learning Problems, Executive Functioning, Defiance/Aggression and Peer Relations. They also provide a Global Index as a measure of general psychopathology and an ADHD Index, which serves as screening instrument and indicates if further assessment of ADHD is required.

Executive functions

Executive functions were assessed with the index Working Memory of the WISC-IV, the scale Commission Errors of the T.O.V.A., and the German version of the *Behavior Rating Inventory of Executive Function®* (BRIEF) (Drechsler & Steinhausen, 2013).

The BRIEF is a standardized parent and teacher questionnaire to assess functional aspects of executive dysfunction in situations of daily living in children between 6 and 16 years. The BRIEF includes 86 items that load on eight non-overlapping clinical subscales, which can be divided into two broader indices (Behavioral Regulation, Metacognition). It also generates a Global Executive Composite score that takes all subscales into account. The index Behavioral Regulation is derived from the three scales Inhibit, Shift and Emotional Control. The index Metacognition contains the five scales Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor, which can be further divided into Monitoring of Task Performance and Self Monitoring. The broad overview and the detailed differentiation of executive dysfunctions that the BRIEF provides, make it a very useful tool to identify subjects with ADHD (especially with the metacognition scales) and even to distinguish between different subtypes of ADHD (mainly with the behavioral regulation scales) (Drechsler & Steinhausen, 2013).

Quality of Life

Information about quality of life was collected with the standardized parent questionnaire *Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern* (Kiddo-Kindl) for children between 7 and 14 years (Ravens-Sieberer & Bullinger, 2000). It contains 24 items, which relate to six dimensions: Physical well-being, Mental well-being, Self-Esteem, Family, Friends, and School. For children with chronic diseases, there is an additional scale with six items regarding quality of life in respect to the disease (Disease Modul).

2.2.4. Procedure

ADHD was diagnosed by a neuropediatrician, a child and adolescent psychiatrist or a child and adolescent psychotherapist. At the baseline examination, ADHD diagnosis was confirmed or discarded on the basis of a standardized parent interview and the clinical impression. Every of the three assessments took about three to four hours and started with the learning trials of the VLMT, followed by the T.O.V.A. and the delayed recall of the VLMT. Subsequently, the WISC-IV was performed. At the same time as the child performed the tests, parents were interviewed and completed the questionnaires. The Disease

Modul of the Kiddo-Kindl was only applied to parents of children with NF1, not to parents of children with ADHD^{only}. After the assessment, parents were informed about the test results and counseled about therapy options. Teacher questionnaires (Conners-3 and BRIEF) were sent by mail. Every patient got a detailed test report about all results after each assessment.

Table 2.1 provides an overview about the assessment plan of the research project.

2.3. Statistical Analyses

Data was analyzed using the 23rd version of the IBM Statistical Package for Social Science (SPSS). As independent variable and between subject factor for the analyses of both studies served the group allocation of the patients (NF1^{ADHD}-group, NF1^{only}-group and ADHD^{only}-group). The level of significance was a priori set at $p < .05$ for all tests and adjusted by Bonferroni corrections in the case of multiple comparisons. Equality of variances for the groups was assessed for each dependent variable via Levene's test. Normality of distribution was analyzed by using the Shapiro-Wilk-test.

Table 2.1.

Assessment Plan

Neuropediatric, psychiatric, and neuropsychological assessment				
Assessment	**T1**[a]	**T1.1**[b]	**T2**[c]	**T3**[c]
Time in months	0	+6	+12	+24
Standardised confirmation of diagnosis and patient characterisation				
Neuropediatric examination to check for neurological exclusion criteria and to check for undetected NF1 in the ADHD group.	X			
Clinical Interview: confirm ADHD diagnosis and screen for common comorbidities.				
• Disyps-KJ; DSM-IV-based parent interview for assessing mental disorders in children and adolescents	X			
Behavior Rating Scales: standardized parent and teacher questionnaires for patient characterization with respect to attention, executive functions, and comorbidities.				
• Child Behavior Checklist (CBCL)	X	X	X	X
• Conners Skalen zu Aufmerksamkeit und Verhalten (Conners 3)	X	X	X	X
• Behavior Rating Inventory for Executive Functions (BRIEF)	X	X	X	X
Environmental factors				
Parent questionnaires to assess:				
• Socio-demographic background of the families	X	X	X	X
• Interventions	X	X	X	X
• Disease-related quality of life assessment in children (Kiddo-Kindl)	X	X	X	X
Neuropsychological assessment				
A 3-hour *neuropsychological assessment*, performed by a qualified psychologist using standardized tests:				
• Wechsler Intelligence Scale for Children (WISC-IV)	X		X	X
• Test for Variables of Attention (T.O.V.A.)	X		X	X
• Verbaler Lern- und Merkfähigkeitstest (VLMT)	X		X	X

[a]Baseline examination [b]Questionnaire follow-up [c]Follow-ups after 12 and 24 month

3. Study 1: Analysis of Cognitive Characteristics of NF1 with and without ADHD

3.1. Scope and Hypotheses

In the first study, we tested five hypotheses about children with NF1 with and without ADHD in a cross-sectional design. Children with ADHD^{only} served as control-group. Aim of Study 1 was to compare several cognitive functions of children with NF1 with and without ADHD and to reveal a cognitive profile, which is characteristic for NF1. Secondarily, we attempted to differentiate between characteristics of ADHD in NF1 and of ADHD^{only}. Additionally, quality of life of these patients was investigated (see H5).

[H1] Intellectual ability:

ADHD is associated with reduced intellectual ability in NF1, as it is in children without NF1. NF1 per se is not generally associated with reduced intellectual ability.

Predictions:

(a) Children with NF1^{ADHD} and children with ADHD^{only} perform significantly below the population norms on measures of intellectual ability, while children with NF1^{only} perform similar to the population norms.

(b) Children with NF1^{ADHD} score significantly lower on measures of intellectual ability than children with NF1^{only} or ADHD^{only}, because the combination of the diseases NF1 and ADHD leads to more crucial deficits in intellectual abilities.

[H2] Memory skills

ADHD is associated with reduced memory skills in NF1, as it is in children without NF1.

Predictions

(a) Children with $NF1^{ADHD}$ and children with $ADHD^{only}$ perform significantly worse than children with $NF1^{only}$ on all measures of verbal memory skills, because inattention and distractibility negatively influence memory skills.

[H3] Attention functions:

NF1 per se – as well as ADHD per se – is associated with reduced attention functions. $NF1^{ADHD}$ and $ADHD^{only}$ is associated with significantly more severe attention dysfunction than $NF1^{only}$, but $NF1^{only}$ is not spared in attention functions. Additionally, $NF1^{ADHD}$ and $ADHD^{only}$ differ significantly in their attention profiles.

Predictions:

(a) All children with NF1 and children with ADHD perform significantly below the population norms on one or more measures of attention functions.

(b) Children with $NF1^{ADHD}$ and children with $ADHD^{only}$ perform significantly worse than children with $NF1^{only}$ on all attention measures.

(c) Children with $NF1^{ADHD}$ show significantly more impulsive reactions and less impairment in sustained attention than children with $ADHD^{only}$, based on the results of Mautner and colleagues (Mautner et al., 2002).

[H4] Executive functions:

ADHD is associated with reduced executive functioning in NF1, as it is in children without NF1. NF1 per se is not associated with reduced executive functioning.

Predictions

(a) Children with $NF1^{ADHD}$ and children with $ADHD^{only}$ perform significantly below the population norms on measures of executive functions, since executive dysfunction is a hallmark of ADHD. Children with $NF1^{only}$ perform similar to the population norms on measures of executive functions.

(b) Children with $NF1^{ADHD}$ and children with $ADHD^{only}$ perform significantly worse than children with $NF1^{only}$ on all executive measures.

[H5] Quality of Life:

NF1 and ADHD as chronic diseases lead to impaired QoL.

Predictions

(a) All study participants show reduced QoL compared to population norms.

(b) Children with $NF1^{ADHD}$ show a significantly lower QoL than children with $NF1^{only}$ or $ADHD^{only}$.

3.2. Data Analyses and Results of Study 1

As described in the *Methods'* chapter, data was analyzed with the 23rd version of the IBM Statistical Package for Social Science (SPSS). Study 1 had a cross-sectional design, which means that data of the first assessment point of the research project was analyzed. Although the conditions of equality of variances and of normality of distribution were not met for all variables (see Appendix, Table A.1, Table A.2, Table A.3, and Table A.4), univariate analyses of covariance (ANCOVAs) and multivariate analyses of (co-)variance (MAN(C)OVAs) were conducted nevertheless, because ANCOVAs and MAN(C)OVAs are considered to be very robust against violations of these conditions (Bortz, 2010; Levy, 1980). Furthermore, there are no nonparametric alternatives for ANCOVAs or MAN(C)OVAs. For other group comparisons, nonparametric tests were conducted, if equality of variances or normality of distribution were not fulfilled.

For most of the assessments, there was no missing data. However, there was missing data for the VLMT in 1 participant. Also, there was missing data for calculating the SES in 8 participants, and for the analyses of the questionnaires Conners-3 (parent evaluation: 3; teacher evaluation: 21), BRIEF (parent evaluation: 25; teacher evaluation: 42), CBCL (4 participants) and Kiddo-Kindl (18 participants). Reasons for the missing data were that some participants were unable to perform certain assessments, or parents did not fill in the questionnaires neatly, or the questionnaires BRIEF and Kiddo-Kindl were at first not provided in the Neurofibromatosis Outpatient Unit in Hamburg. Additionally, parents did not always agree to contact teachers or teachers did not agree to complete the questionnaires. If data was missing in a certain analysis, all data of the corresponding participant was excluded in the analysis.

3.2.1. Choice of covariates

Since a random assignment of participants to groups was not possible in the present study design, age, sex distribution, SES, and full-scale IQ were considered as relevant demographic variables that could possibly have a meaningful or confounding influence on the results. These variables were tested for significant group differences with the intent to discuss them as covariates for further analyses.

Age was excluded as a potential covariate, because there were no significant group differences regarding age in our sample ($F(2, 111) = 1.454; p = .238; \eta^2 = .036$). Supplementally, all tests and questionnaires used in this study were standardized for age.

Furthermore, there were no significant group differences regarding SES ($F(2, 103) = 1.876; p = .159; \eta^2 = .194$). Therefore, SES was not treated as covariate in any of the analyses.

Sex distribution and full-scale IQ differed significantly between the groups (sex distribution: $\chi^2(1, N = 111) = 7.296, p = .024$; full-scale IQ: $F(2, 111) = 13.029; p < .001; \eta^2 = .194$).

Regarding sex distribution, it has to be considered that samples of patients with ADHD naturally have an uneven ratio between boys and girls, which is about 3 boys to 1 girl (Cuffe et al., 2005). Therefore, sex is an inherent differentiation of samples with ADHD and other samples and not a variable that differs because of chance or choise. As Miller and Chapman (2001) described in their article *Misunderstanding Analysis of Covariance*: "if a variable" – like sex distribution in our case – "is systematically related to the defining characteristic of the groups, removing variance associated with this variable could systematically alter the apparent nature of and the relationships between the groups." Therefore, sex should not be a covariate, if an ADHD patient group is compared to a healthy control group. In the present study, however, an ADHD group is compared to two other patient groups, of which the sex distribution and the extent of ADHD-associated characteristics are unknown so far. While the 3:1 ratio of boys to girls is met with 22 boys to 8 girls in the $ADHD^{only}$-group, there is only a trend to more boys (33) than girls (20) in the $NF1^{ADHD}$-group; whereas the sex distribution in the $NF1^{only}$-group is reversed with more girls (17) than boys (11). To minimize the bias that could possibly be associated with an uneven sex distribution between the groups (e.g. that boys exhibit more externalizing

problem behavior, agitation or impulsivity), sex was treated as a covariate for the analyses of test scales and parameters. For the analyses of the questionnaire data, sex was no covariate, because all questionnaires used in Study 1 were standardized for sex.

Full-scale IQ was chosen as a covariate for all analyses of test scales and parameters, as well as the questionnaire data. General intellectual ability is well known to be a moderator/mediator for the performance in other cognitive domains and group differences in any of these specific domains could simply be due to differences in general intellectual ability. Since the relation between intelligence and other cognitive abilities is of no theoretical interest in terms of our analyses for Study 1, we expect the use of full-scale IQ as a covariate to clarify the relation between our independent and dependent variables.

3.2.2. Group Characteristics of the Study Population

Data analyses

Demographic data for group characterization was analyzed with chi-square tests for sex, ADHD subtype, NF1 subtype, and therapeutic interventions, or a two-tailed Univariate Analysis of Variance (ANOVA) for SES. For age, the condition of equality of variances (Levene's test) was not fulfilled. As an alternative, the nonparametric Kruskal Wallis test was conducted. Severity of ADHD symptomatology was analyzed with a Multivariate Analysis of Variance (MANOVA) for the two subscales ADHD-index and Global-index of the Conners-3 parent evaluation. Group differences of severity of problem behavior were analyzed with an ANOVA for the total score of the CBCL and MANOVAs for the subscales.

Results

Altogether, 111 participants were enrolled in Study 1. Fifty-three participants were allocated to the group with $NF1^{ADHD}$. Twenty participants were female (37.7%) and 33 participants were male (62.3%). The mean age in this group was 8.873 years (SD: 1.692) and 25 participants (47.2%) had the familial type of NF1. Twenty participants (37.7%) in this group were suffering from the Inattentive Type and 33 participants (62.3%) from the Combined Type of ADHD. Eight participants (15.1%) were receiving stimulant medication for the treatment of

ADHD prior to the beginning of and during the study, and seven of these participants (13.2%) were receiving MPH.

For the NF1^{only}-group, 28 participants were enrolled, with 17 female participants (60.7%) and 11 male participants (39.3%) The mean age in this group was 8.360 years (SD: 1.352) and 19 participants (67.9%) were suffering from a sporadic mutation of the NF1-gene, while 9 participants (32.1%) had the familial type of NF1.

In the ADHD^{only}-group, 8 participants (26.7%) were female and 22 participants (73.3%) were male. The mean age of this group was 8.958 years (SD: 1.124). In this patient group, 14 participants (46.7%) fulfilled the criteria for the Inattentive Type and 16 participants (53.3) for the Combined Type of ADHD. Stimulant medication was taken by 2 participants (6.7%) of this group prior to and during the study. Both were treated with MPH.

There were no significant differences between the groups regarding age ($F(2, 111) = 1.454; p = .238; \eta^2 = .036$) or SES ($F(2, 103) = 1.876; p = .159; \eta^2_p = .194$). The SES was in the middle range for all three groups (Winkler-index: mean = 12.11, SD: 4.395). Sex, however, differed significantly between the groups ($\chi^2(1, N = 111) = 7.296, p = .024$). ADHD subtype and subtype of NF1 did not differ significantly between the two ADHD groups or rather the two NF1 groups (ADHD subtype: $\chi^2(1, N = 83) = 0.632, p = .490$, NF1 subtype $\chi^2(1, N = 81) = 1.699, p = .240$).

Data from parent questionnaires confirmed that our patient groups differed significantly with respect to observed symptoms of ADHD, distinguishing the NF1^{only}-group from both ADHD groups (ADHD-index: $F(2, 107) = 29.231; p < .001; \eta^2 = .360$). Regarding the two ADHD groups, there were significant main effects of the independent variable Group on the ADHD-index ($F(2, 81) = 4.484; p = .037; \eta^2 = .054$) and the Global-index ($F(2, 81) = 5.038; p = .028; \eta^2 = .060$) of the Conners-3, with the ADHD^{only}-group being rated as significantly more impaired. Mean values of all Conners-3 subscales (parent and teacher evaluation) are listed in Table A.6.

Table 3.1 summarizes data of explorative analyses for group characterizations (e.g. number of participants suffering from previous language disorders, different learning disabilities, depression or anxiety, as well as number of participants receiving any kind of therapy during the study).

Table 3.1.

Demographic data and group characteristics for Study 1

	Mean (SD), number or percent per group			p
	$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$	values
Number of participants	53	28	30	-
Sex (female/male)	20/33	17/11	8/22	.024* [b]
Age	8.873 (1.692)	8.360 (1.352)	8.958 (1.124)	.238 [a]
SES (Winkler-Index)	12.02 (4.906)	13.38 (4.215)	11.13 (3.461)	.159 [a]
familial/sporadic NF1	25/28	9/19	-	.240 [b]
ADHD/ADD	33/20	-	16/14	.490 [b]
Previous language disorders	24.4% (14)	14.3% (4)	23.3% (7)	.415 [b]
Learning Disabilities	16.9% (9)	3.6% (1)	3.3% (1)	.108 [b]
Dyslexia	15% (8)	3.6% (1)	20.0% (6)	.188 [b]
Dyscalculia	9.4% (5)	0% (0)	10.0% (3)	.519 [b]
Depression	0% (0)	0% (0)	3.3% (1)	.538 [b]
Anxiety disorders	1.9% (1)	3.6% (1)	3.3% (1)	.457 [b]
Oppositional defiant disorder	7.6% (4)	0% (0)	10.0% (3)	.325 [b]
Conduct disorder	3.8%(2)	0% (0)	6.7% (2)	.325 [b]
Occupational therapy	24.5% (13)	17.9% (5)	33.3% (10)	.708 [b]
Speech language therapy	17.0% (9)	17.9% (5)	10.0% (3)	.333 [b]
Psychotherapy	3.8% (2)	0% (0)	13.3% (4)	.143 [b]
Educational support	34.0% (18)	21.4% (6)	50.0% (15)	.250 [b]
Other therapies/support	22.6% (12)	17.9% (5)	23.3% (7)	.826 [b]
Methylphenidate	13.2% (7)	0% (0)	6.7% (2)	.094 [b]

[a] = ANOVA
[b] = Pearson Chi-Square

Data of the CBCL revealed significantly more problem behavior for both of the ADHD groups compared to the NF1^{only}-group ($F(2,107) = 9.785; p < .001; \eta^2 = .158$; NF1^{only}-group vs. NF1^{ADHD}-group: $p < .001$; NF1^{only}-group vs. ADHD^{only}-group: $p = .003$). For the scales Internalizing and Externalizing problem behavior, there was a significant group difference for the multivariate test (*Pillai's Trace*, $V = 0.162; F(4,107) = 4.596; p = .001; \eta^2 = .081$), but only externalizing problem behavior differed significantly between the groups ($F(2,107) = 9.693; p < .001; \eta^2 = .157$). Planned pairwise comparisons showed that the NF1^{only}-group was rated as significantly lower on externalizing problem behavior than both of the ADHD groups (NF1^{only}-group vs. NF1^{ADHD}-group: p = .001; NF1^{only}-group vs. ADHD^{only}-group: p < .001). The MANOVA for the subscales of the CBCL showed a significant main effect of Group (*Pillai's Trace*, $V = 0.525; F(16,107) = 4.357; p < .001; \eta^2 = .262$), with significantly less problem behavior in the NF1^{only}-group on the subscales Social Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior than in both of the ADHD groups (results of the CBCL analyses are listed in Table 3.2 and mean values of the CBCL are listed shown in Table A.10.).

Table 3.2.

Results of separate univariate analyses and planned pairwise comparisons of the CBCL

CBCL	N	df	F-value	sig.	partial η^2	post hoc comparisons
Total score	107	2	9.785	.000***	.158	A>B***, C>B**
Externalizing	107	2	9.693	.000***	.157	A>B**, C>B***
Internalizing	107	2	1.961	.146	.036	-
Anxious/Depressed	107	2	1.031	.360	.019	-
Withdrawn/Depressed	107	2	4.586	.012	.081	-
Somatic Complaints	107	2	.296	.744	.006	-
Social Problems	107	2	12.655	.000***	.196	A>B***, C>B*
Thought Problems	107	2	.644	.527	.012	-
Attention Problems	107	2	19.260	.000***	.270	A>B***, C>B***
Rule-Breaking Behavior	107	2	8.162	.001**	.136	A>B**, C>B**
Aggressive Behavior	107	2	9.886	.000***	.160	A>B***, C>B***

Significance levels: for the total score: *** < .001, ** < .01, * < .05, for the scales Internalizing and Externalizing problem behavior: *** < .0005, ** < .005, * < .025, for the subscales: *** < .000125, ** < .00125, * < .00625.
A = NF1^{ADHD}-group, B = NF1^{only}-group, C = ADHD^{only}-group
">" means "higher score/more problems" (e.g. A>B* = Group A has significantly higher mean scores and more problems in this area than group B.)

3.2.3. [H1] Intellectual Ability

Data analyses

For the analyses of intellectual ability, the full-scale IQ of the WISC-IV and all indices of the WISC-IV (Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed) served as dependent variables. The calculations were conducted with IQ-scores. For the comparison of the performance of the two ADHD groups with the normative sample, observed frequencies of subnormal performance were compared to the expected frequency from the normative sample (15.8%) by Pearson's nonparametric chi-square test. Full-scale IQ was compared between the three experimental groups via a Univariate Analysis of Covariance (ANCOVA) and the indices of the WISC-IV where compared with a Multivariate Analysis of Covariance (MANCOVA). Sex served as a covariate for these analyses. The level of significance for univariate analyses of the WISC-IV indices was set at $p < .0125$, because of the Bonferroni correction. For the index Perceptual Reasoning, Levene's test was significant, but the MANCOVA was conducted nevertheless for the reasons described above.

Results

The nonparametric chi-square tests for the comparison of the patient groups with the normative sample showed significantly more frequent subnormal performances in the $NF1^{ADHD}$-group for full-scale IQ, Perceptual Reasoning, Working Memory, and Processing Speed. For the $ADHD^{only}$-group and the $NF1^{only}$-group, there were no significant differences to the normative sample in the frequency of subnormal performances on any of the indices of the WISC-IV. Test statistic of the nonparametric chi-square tests is listed in Table 3.3.

The ANCOVA for the comparison of the performance of the three experimental groups revealed significant group differences on full-scale IQ ($F(2, 111) = 12.147; p < .001; \eta^2 = .185$). Planned post hoc comparisons showed significant differences between the groups, pointing out that the $NF1^{ADHD}$-group scored significantly lower in the intelligence test than the $NF1^{only}$-group ($p < .001$) and the $ADHD^{only}$-group ($p = .044$). Between the $NF1^{only}$-group and the $ADHD^{only}$-group, there were no significant differences. The covariate sex had no significant effect on the dependent variable.

Table 3.3.

Results of the nonparametric chi-square tests for the WISC-IV

WISC-IV scale	Group	N	subnormal performance	df	chi-square	Asymp. Sig.
Full-scale IQ	$NF1^{ADHD}$	53	30.2%	1	8.092	.004**
	$ADHD^{only}$	30	20.0%	1	0.377	.539
	$NF1^{only}$	28	3.6%	1	3.183	.074
Verbal Compehension	$NF1^{ADHD}$	53	13.2%	1	0.287	.592
	$ADHD^{only}$	30	6.7%	1	1.913	.167
	$NF1^{only}$	28	0%	1	-	-
Perceptual Reasoning	$NF1^{ADHD}$	53	26.4%	1	4.382	.036*
	$ADHD^{only}$	30	23.3%	1	1.240	.266
	$NF1^{only}$	28	0%	1	-	-
Working Memory	$NF1^{ADHD}$	53	47.2%	1	38.755	.000***
	$ADHD^{only}$	30	10.0%	1	0.781	.377
	$NF1^{only}$	28	10.7%	1	0.563	.453
Processing Speed	$NF1^{ADHD}$	53	37.7%	1	18.898	.000***
	$ADHD^{only}$	30	23.3%	1	1.240	.266
	$NF1^{only}$	28	7.1%	1	1.606	.205

*** < .001, ** < .01, * < .05
In the $NF1^{only}$-group, there were no subnormal performances for Verbal Comprehension or Perceptual Reasoning, therefore no test statistic could be calculated with SPSS.

On the multivariate test for the WISC-IV indices, the covariate sex was significantly related to the outcome variables ($F(4,111) = 3.351; p = .013; \eta_p^2 = .114$). Separate univariate ANCOVAs revealed a significant influence of sex on Processing Speed ($F(1,111) = 6.993; p = .009; \eta_p^2 = .061$), with girls clearly performing faster than boys in both ADHD groups. After correcting for the effect of the covariate, the significant effect of Group on the multivariate test remained (*Pillai's Trace*, $V = 0.212, F(8,111) = 3.109; p = .002; \eta^2 = .106$). Separate univariate ANCOVAs revealed significant main effects of Group on all WISC-IV indices: Verbal Comprehension ($F(2,111) = 5.739; p = .004; \eta_p^2 = .097$), Perceptual Reasoning($F(2,111) = 5.178; p = .007; \eta_p^2 = .088$), Working Memory ($F(2,111) = 7.817; p = .001; \eta_p^2 = .127$), and Processing Speed ($F(2,111) = 5.543; p = .005; \eta_p^2 = .094$). Mean scores of the WISC-IV are pictured in Figure 3.1 and listed in Table A.5.

Planned post hoc comparisons showed that the $NF1^{ADHD}$-group scored significantly lower than the $NF1^{only}$-group on all four indices of the WISC-IV (Verbal Comprehension $p = .003$; Perceptual Reasoning $p = .005$; Working Mem-

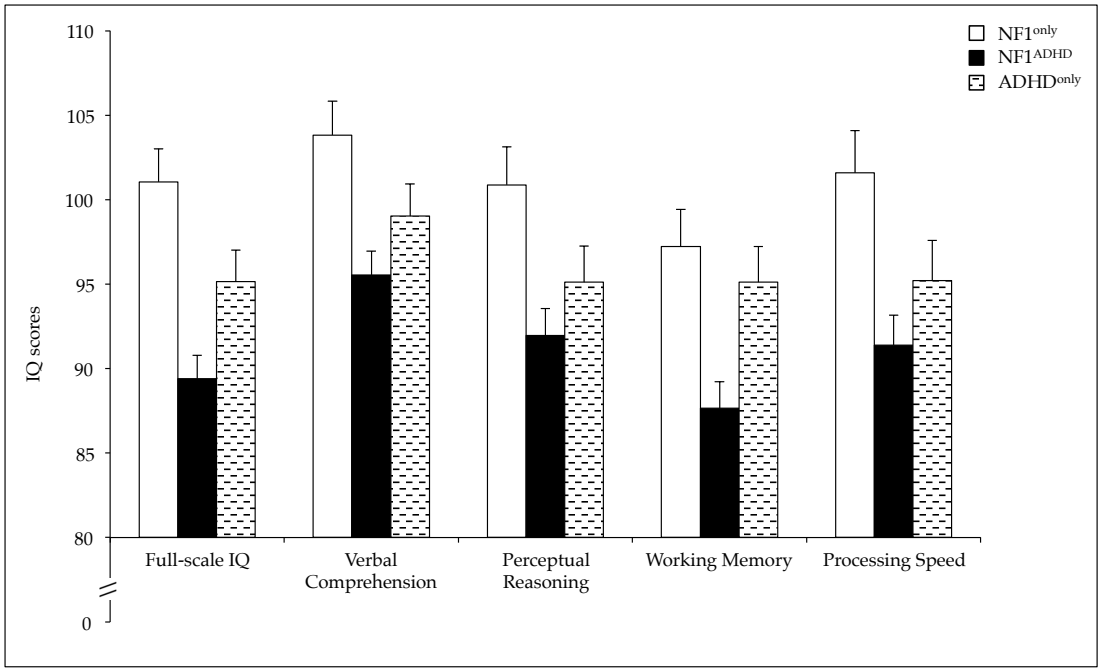

Figure 3.1. Mean values of the WISC-IV for all three patient groups. Significant group differences emerged between the $NF1^{only}$-group and the $NF1^{ADHD}$-group on full-scale IQ and on all four indices of the WISC-IV, as well as between the $ADHD^{only}$-group and the $NF1^{ADHD}$-group on full-scale IQ and the index Working Memory. Error bars show the standard error (SE) of the mean.

ory $p = .002$; Processing Speed $p = .004$). Compared to the ADHD^{only}-group, the NF1^{ADHD}-group scored significantly lower on the index Working Memory ($p = .016$), but not on the other indices. Between the NF1^{only}-group and the ADHD^{only}-group there were no significant differences. Figure 3.2 illustrates the intellectual profile of the three patient groups.

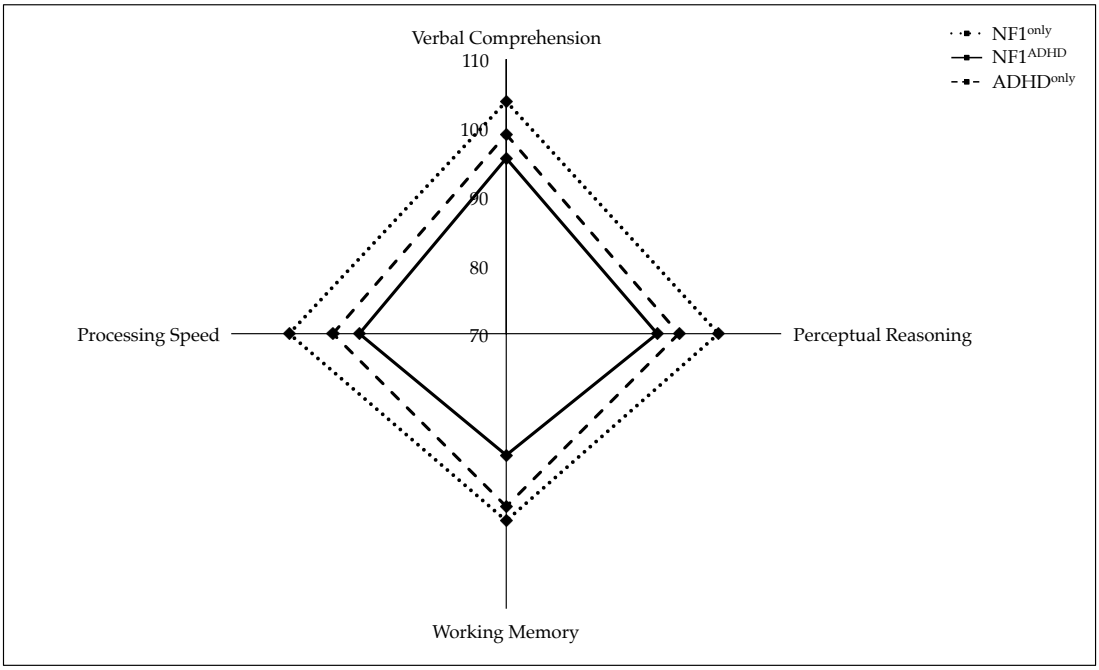

Figure 3.2. Intellectual profiles of the patient groups by mean values for the four indices of the WISC-IV. The figure demonstrates that patients of the NF1^{ADHD}-group are clearly restricted in their performance on all four indices compared to the other two groups.

3.2.4. [H2] Memory Skills

Data analyses

To explore the second hypothesis about memory skills, the main scales of the VLMT (Immediate Recall, Delayed Recall and Recognition) were compared with a MANCOVA. All scores of the VLMT were T-scores. Full-scale IQ and sex served as covariates for this analysis. The level of significance for separate univariate analyses was set at $p < .017$, because of the Bonferroni correction. Data was missing in one participant (NF1^{ADHD}-group) for the scale Recognition. This participant was excluded in the whole analysis.

Results

There were no effects of the covariates on the dependent variables and there was no significant main effect of Group in the multivariate test. Patient groups did not differ in their performance on any of the three scales of the VLMT (Immediate Recall, Delayed Recall and Recognition). The performance of all three experimental groups lay in the normal range for all scales. Mean values of the VLMT are illustrated in Figure 3.3 and listed in Table A.5.

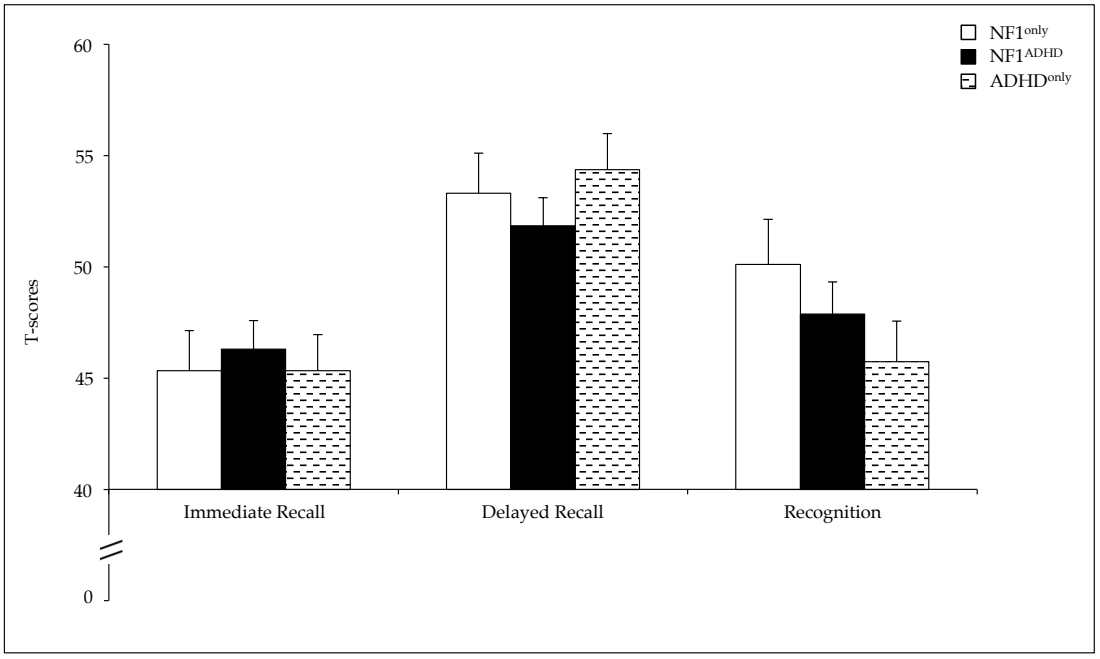

Figure 3.3. Mean values of the VLMT for all three patient groups. There were no significant differences between the groups. Error bars show the standard error (SE) of the mean.

3.2.5. [H3] Attention functions

Data analyses

To test the third hypothesis, the performances of all three experimental groups on the four parameters of the T.O.V.A. (Variability of Response Time, Response Time, Commission Errors and Omission Errors) were compared with the normative sample. Observed frequencies of subnormal performance were compared to the expected frequency from the normative sample (15.8%) by Pearson's nonparametric chi-square test.

For group comparisons, the main parameter of the T.O.V.A., the API, and all four sub-parameters (Variability of Response Time, Response Time, Commission Errors and Omission Errors) were tested for group differences with an ANCOVA or a MANCOVA, with full-scale IQ and sex as covariates.

Additionally, the extent of functional attention problems (Conners-3 subscales Inattention and Hyperactivity/Impulsivity, parent and teacher evaluation) was analyzed with MANCOVAs, with full-scale IQ as covariate. All scores of the T.O.V.A. are IQ-scores, while all scores of the Conners-3 are T-scores. The level of significance for separate univariate analyses of the four sub-parameters of the T.O.V.A. was set at $p < .0125$ and for univariate analyses of the Conners-3 subscales set at $p < .025$, because of Bonferroni corrections.

For the analyses of functional measures of attention functions, data of 3 parent evaluations (2 $NF1^{only}$-group, 1 $NF1^{ADHD}$-group) and 21 teacher evaluations (6 $NF1^{only}$-group, 12 $NF1^{ADHD}$-group, 3 $ADHD^{only}$-group) of the Conners-3 was missing. Analyses were therefore conducted with data of 108 participants for the parent evaluations and 90 participants for the teacher evaluations.

Results

The results of the nonparametric chi-square tests revealed significantly increased numbers of subnormal performances in the $NF1^{ADHD}$-group on all four sub-parameters of the T.O.V.A. and in the $ADHD^{only}$-group on Variability of Response Time, Response Time, and Omission Errors (see Table 3.4). For the $NF1^{only}$-group, the frequency of subnormal performances was only significantly increased on the parameter Omission Errors. Test statistic of the nonparametric chi-square tests is listed in Table 3.4.

The ANCOVA revealed a significant influence of the covariate full-scale IQ on the analysis ($F(4, 111) = 13.525; p < .001; \eta_p^2 = .113$), while the covariate sex had no influence. After accounting for the effect of the covariate full-scale IQ, a significant main effect of Group on the API remained ($F(2, 111) = 7.586; p = .049; \eta_p^2 = .055$). Planned pairwise comparisons showed a significant difference between the $NF1^{only}$-group and the $ADHD^{only}$-group ($p = .043$), but no differences between the $NF1^{ADHD}$-group and one of the other groups. Mean values of the API of the T.O.V.A. are illustrated in Figure 3.4 and listed in Table A.5.

Regarding the multivariate test on the four T.O.V.A. sub-parameters, the independent variable group had no significant effect on the outcome variables

Table 3.4.

Results of the nonparametric chi-square tests for the parameters of the T.O.V.A.

T.O.V.A. Parameter	Group	N	subnormal performance	df	chi-square	Asymp. Sig.
Variability of Response Time	$NF1^{ADHD}$	53	58.5%	1	71.897	.000***
	$ADHD^{only}$	30	40.0%	1	13.031	.000***
	$NF1^{only}$	28	17.9%	1	0.080	.777
Response Time	$NF1^{ADHD}$	53	39.6%	1	22.305	.000***
	$ADHD^{only}$	30	40.0%	1	13.031	.000***
	$NF1^{only}$	28	21.4%	1	0.640	.424
Commission Errors	$NF1^{ADHD}$	53	26.4%	1	4.382	.036*
	$ADHD^{only}$	30	26.7%	1	2.601	.107
	$NF1^{only}$	28	17.9%	1	0.080	.777
Omission Errors	$NF1^{ADHD}$	53	62.3%	1	85.202	.000***
	$ADHD^{only}$	30	33.3%	1	6.819	.009**
	$NF1^{only}$	28	32.1%	1	5.524	.019*

*** < .001, ** < .01, * < .05

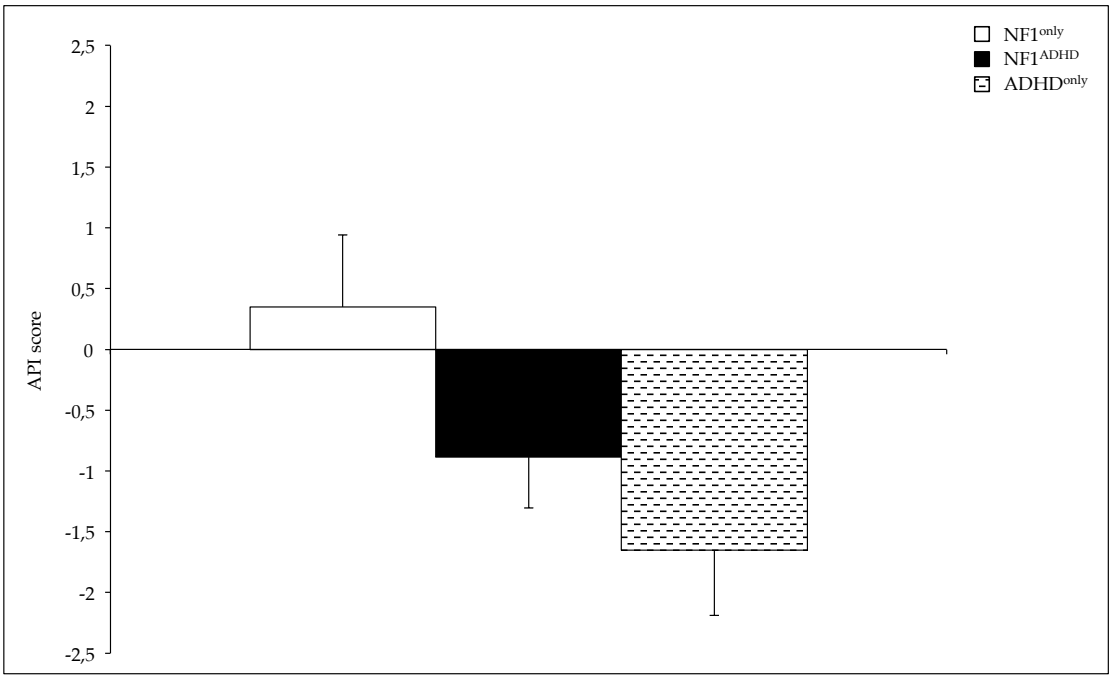

Figure 3.4. Mean values of the API for all three patient groups. Scores below zero indicate the likelihood of ADHD. The $NF1^{only}$-group differed significantly from the $ADHD^{only}$-group on the API score. Error bars show the standard error (SE) of the mean.

(for mean values see Figure 3.5 and Table A.5). Though, the covariates, full-scale IQ and sex, were significantly related to the outcome variables (full-scale IQ: $F(4, 111) = 5.294; p = .001; \eta_p^2 = .171$), sex: ($F(4, 111) = 8.741; p < .001; \eta_p^2 = .253$), with a positive correlation between higher intelligence scores and better scores on the sub-parameters Variability of Response Time, Response Time, and Omission Errors of the T.O.V.A. (for all groups). Also, girls performed clearly worse than boys regarding Omission Errors in all three experimental groups.

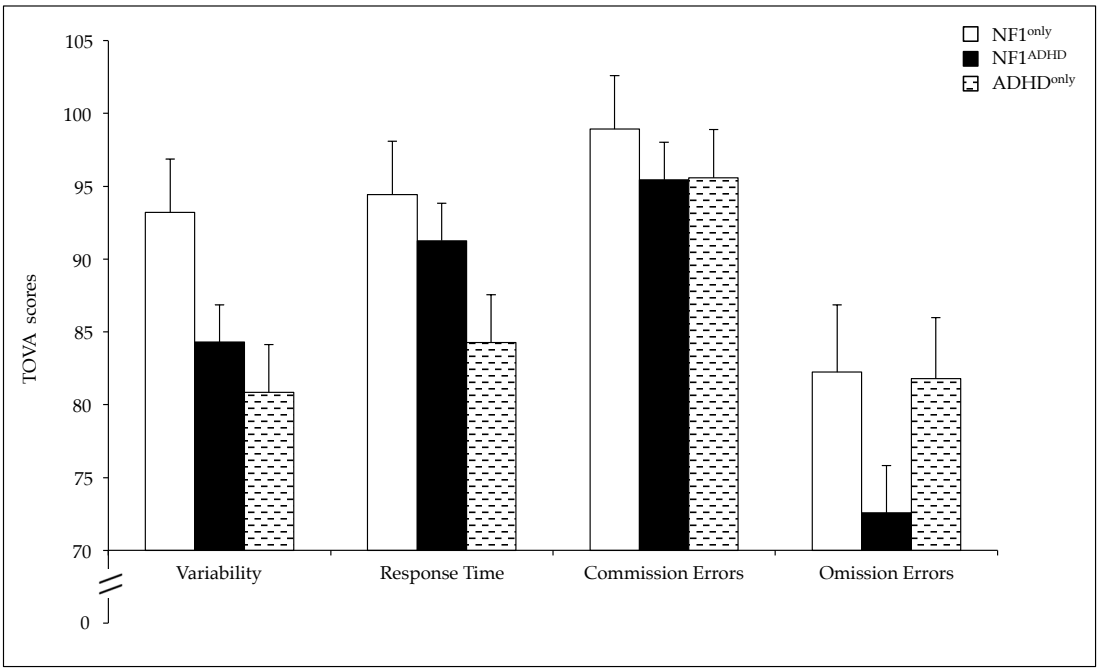

Figure 3.5. Mean values of the T.O.V.A. sub-parameters for all three patient groups. There were no significant differences between the patient groups. TOVA scores are conform with IQ scores, mean = 100, standard deviation = 15. Error bars show the standard error (SE) of the mean.

The MANCOVA for the Conners-3 subscales showed no significant effect of the covariate full-scale IQ on the multivariate tests of the parent or the teacher evaluation. For the independent variable, the multivariate tests showed significant relationships between group and the outcome variables (parent evaluation: *Pillai's Trace*, $V = 0.401, F(4, 111) = 13.052; p < .001; \eta^2 = .201$; teacher evaluation: *Pillai's Trace*, $V = 0.226, F(8, 111) = 5.471; p < .001; \eta^2 = .113$). On separate univariate analyses, significant main effects of Group were found on both Conners-3 subscales Inattention and Hyperactivity/Impulsivity in the parent evaluation, as well as the teacher evaluation (see Table 3.5). Planned

pairwise comparisons revealed significantly better evaluations for the NF1^{only}-group on Inattention and Hyperactivity/Impulsivity (parent and teacher evaluation) than for both of the ADHD groups (see Table 3.5). However, there were no significant differences between the two ADHD-groups. Mean values are illustrated in Figure 3.6) and listed in Table A.6.

Table 3.5.

Results of separate univariate analyses and planned pairwise comparisons of the Conners-3 parent and teacher evaluation

	N	df	F-value	sig.	partial η^2	post hoc comparisons
parent evaluation						
Inattention	108	2	32.442	.000***	.384	A>B***, C>B***
Hyperactivity/Impulsivity	108	2	13.464	.000***	.206	A>B***, C>B***
teacher evaluation						
Inattention	90	2	9.937	.000***	.188	A>B***, C>B**
Hyperactivity/Impulsivity	90	2	9.084	.000***	.174	A>B***, C>B**

*** < .0005, ** < .005, * < .025
A = NF1^{ADHD}-group, B = NF1^{only}-group, C = ADHD^{only}-group
">" means "higher score/more problems" (e.g. A>B* = Group A has significantly higher mean scores and more problems in this area than group B.)

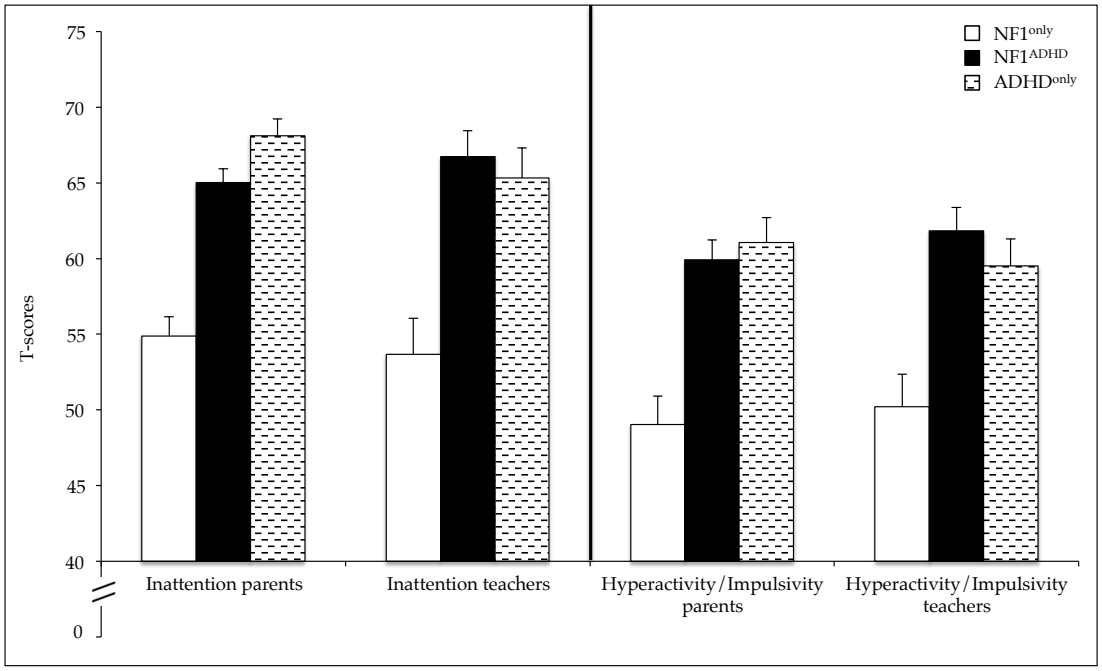

Figure 3.6. Mean values of the Conners-3 subscales Inattention and Hyperactivity/Impulsivity (parent and teacher evaluation) for the three patient groups. Significant differences emerged between the NF1^{only}-group and both ADHD groups. Error bars show the standard error (SE) of the mean.

3.2.6. [H4] Executive Functions

Data analyses

The forth hypothesis about executive functions was tested with nonparametric chi-square tests for the comparison of the performances of the experimental groups with the normative sample. Observed frequencies of subnormal performance were compared to the expected frequency from the normative sample (15.8%) by Pearson's nonparametric chi-square test. Dependent variables were the index Working Memory of the WISC-IV, the parameter Commission Errors of the T.O.V.A. and the main scale of the questionnaire BRIEF (Global Executive Composite score, parent and teacher evaluation).

Group comparisons of the experimental groups were conducted with univariate ANCOVAs for Working Memory and Commission Errors. Full-scale IQ and sex served as covariates in the analysis of Commission Errors. In the analysis of Working Memory, only sex, but not full-scale IQ was a covariate, due to high intercorrelation of the subscales with the main scale of the WISC-IV. The Global Executive Composite score of the BRIEF (parent and teacher evaluation) was compared via ANCOVAs, with full-scale IQ as covariate.

For the two broader indices and the subscales of the BRIEF, MANCOVAs were conducted for the parent and the teacher evaluation. Full-scale IQ served as a covariate in these analyses. The level of significance was Bonferroni adjusted for separate univariate analyses of the outcome variables and therefore set at $p < .025$ for the two broader indices (Behavioral Regulation Index and Metacognitive Index) and at $p < .005$ for the subscales. Although Levene's test of equality of variances was significant for several subscales, the MANCOVAs were conducted nevertheless, because of the reasons described above.

Data of 25 participants (18 $NF1^{ADHD}$-group, 7 $NF1^{only}$-group) was missing for the BRIEF parent evaluation and of 42 participants (26 $NF1^{ADHD}$-group, 14 $NF1^{only}$-group, 3 $ADHD^{only}$-group) for the BRIEF teacher evaluation. Participants with missing data were completely excluded from the analyses. In the analysis of the parent evaluation 86 participants, and in the analysis of the teacher evaluation 68 participants were included.

Results

The nonparametric chi-square tests for the comparison of the NF1^{ADHD}-group, the ADHD^{only}-group, and the NF1^{only}-group with the normative sample revealed significant main effects on Working Memory, Commission Errors and the Global Executive Composite (GEC) score of the BRIEF (parent and teacher evaluation) for the NF1^{ADHD}-group, which means that children with NF1^{ADHD} performed significantly more frequent in the subnormal range than healthy children. For the ADHD^{only}-group, there was a significant main effect on the GEC score of the BRIEF (parent and teacher evaluation), but no effects on Working Memory or Commission Errors (see Table 3.6). The NF1^{only}-group did not differ from the normative sample on any of the measures regarding the frequencies of subnormal performance.

Table 3.6.

Results of the nonparametric chi-square tests for executive measures

Dependent variable	Group	N	subnormal performance	df	chi-square	Asymp. Sig.
Working Memory	NF1^{ADHD}	53	47.2%	1	38.755	.000***
	ADHD^{only}	30	10.0%	1	0.781	.377
	NF1^{only}	28	10.7%	1	0.563	.453
Commission Errors	NF1^{ADHD}	53	26.4%	1	4.382	.036*
	ADHD^{only}	30	26.7%	1	2.601	.107
	NF1^{only}	28	17.9%	1	0.080	.777
GEC parent evaluation	NF1^{ADHD}	35	51.4%	1	33.039	.000***
	ADHD^{only}	30	66.7%	1	57.821	.000***
	NF1^{only}	21	0%	-	-	-
GEC teacher evaluation	NF1^{ADHD}	27	63.0%	1	44.723	.000***
	ADHD^{only}	27	51.9%	1	26.098	.000***
	NF1^{only}	14	0%	-	-	-

*** < .001, ** < .01, * < .05
Expected percentage of subnormal performances in the normative sample: 15.8% In the NF1^{only}-group, there were no subnormal performances for Verbal Comprehension or Perceptual Reasoning, therefore no test statistic could be calculated with SPSS.

The comparisons of the three experimental groups showed no significant group differences for Commission Errors, but significant main effects of Group on Working Memory ($F(2,111) = 7.817; p = .001; \eta_p^2 = .127$) and the GEC scores of the parent and teacher evaluations in the BRIEF (see Tables 3.7 and 3.8). The covariates had no effect on Working Memory and the GEC score of the parent evaluation. For the teacher evaluation, there was a significant influ-

ence of full-scale IQ on the dependent variable ($F(1, 68) = 4.134; p = .046; \eta_p^2 = .061$), but the main effect of Group remained after accounting for the effect of the covariate. Planned pairwise comparisons revealed that the NF1^{only}-group scored significantly better than the NF1^{ADHD}-group on the measures Working Memory ($p = .002$), GEC – parent evaluation ($p < .001$), and GEC – teacher evaluation ($p < .001$). Also, the NF1^{only}-group scored significantly better than the ADHD^{only}-group on the GEC scores of the parent and teacher evaluation (parent evaluation: $p < .001$; teacher evaluation: $p < .001$). Furthermore, there was a significant group difference between the NF1^{ADHD}-group and the ADHD^{only}-group on Working Memory ($p = .016$), with the ADHD^{only}-group performing better than the NF1^{ADHD}-group, but not on the GEC scores. For the mean values see Figure 3.7 and Figure 3.8.

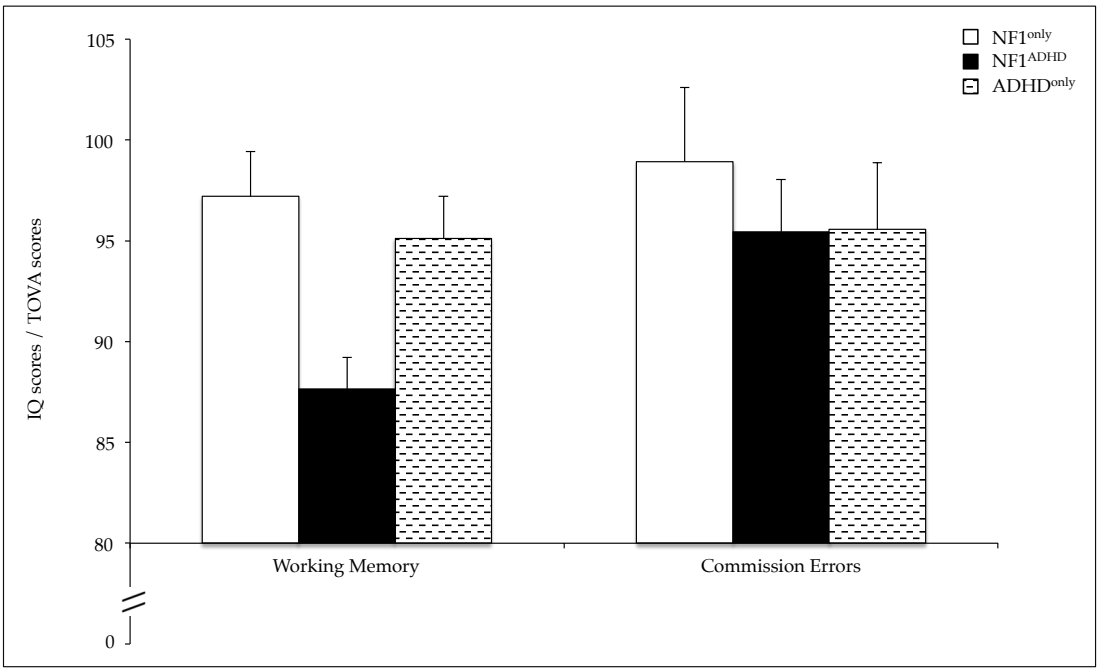

Figure 3.7. Mean values for Working Memory (WISC-IV) and Commission Errors (T.O.V.A.) for all three patient groups. Significant group differences emerged for Working Memory between the NF1^{only}-group and the NF1^{ADHD}-group as well as between the ADHD^{only}-group and the NF1^{ADHD}-group. TOVA scores are conform with IQ scores, mean = 100, standard deviation = 15. Error bars show the standard error (SE) of the mean.

The MANCOVAs of the the two broader indices of the BRIEF (Behavioral Regulation Index and Metacognition Index) showed significant main effects of the independent variable group in the parent evaluation (*Pillai's Trace*, $V =$

0.330, $F(4, 86) = 8.095; p < .001; \eta_p^2 = .165$) and the teacher evaluation (*Pillai's Trace*, $V = 0.286, F(4, 68) = 5.345; p = .001; \eta_p^2 = .143$). Significantly better ratings were found for the NF1^{only}-group than for the NF1^{ADHD}-group or the ADHD^{only}-group on both indices in the parent and teacher evaluation (see Table 3.7 and 3.8). The covariate full-scale IQ had no effect in the multivariate tests.

Table 3.7.

Results of the BRIEF parent evaluation

	N	df	F-value	sig.	partial η^2	post hoc comparisons
Global Executive Composite	86	2	17.000	.000***	.293	A>B***, C>B***
Behavioral Regulation Index	86	2	6.575	.002**	.138	A>B*, C>B**
Metacognition Index	86	2	19.564	.000***	.323	A>B***, C>B***
Inhibit	86	2	7.274	.001*	.151	A>B**, C>B**
Shift	86	2	4.218	.018	.093	-
Emotional Control	86	2	3.590	.032	.081	-
Initiate	86	2	8.177	.001*	.166	A>B*, C>B***
Working Memory	86	2	25.322	.000***	.382	A>B***, C>B***
Plan/Organize	86	2	15.927	.000***	.280	A>B***, C>B***
Organization of Materials	86	2	4.528	.014	.099	-
Monitor	86	2	16.143	.000***	.283	A>B***, C>B***
Monitoring of Task Performance	86	2	8.398	.000***	.170	A>B**, C>B**
Self Monitoring	86	2	11.390	.000***	.217	A>B***, C>B***

For the Global Executive Composite: *** < .001, ** < .01, * < .05
For the Behavioral Regulation Index and the Metacognition Index: *** < .0005, ** < .005, * < .025
For the subscales: *** < .0001, ** < .001, * < .005
A = NF1^{ADHD}-group, B = NF1^{only}-group, C = ADHD^{only}-group
">" means "higher score/more problems" (e.g. A>B* = Group A has significantly higher mean scores and more problems in this area than group B.)

The analysis of the subscales of the BRIEF parent evaluation revealed no effect of the covariate, but a significant effect of the independent variable Group (*Pillai's Trace*, $V = 0.550, F(20, 86) = 2.809; p < .001; \eta_p^2 = .275$). Separate ANCOVAs showed significant group differences for the subscale Inhibit of the Behavioral Regulation Index and the subscales Initiate, Working Memory, Plan /Organize, Monitor, Monitoring of Task Performance, and Self Monitoring of the Metacognition Index (see Table 3.7). The NF1^{only}-group was rated as significantly better than the NF1^{ADHD}-group or the ADHD^{only}-group on all sub-

scales mentioned above, while there were no significant differences between the $NF1^{ADHD}$-group and the $ADHD^{only}$-group (for means see Figure 3.8).

For the teacher evaluation, there was no significant effect of the covariate full-scale IQ on the multivariate test, but for the independent variable group (*Pillai's Trace*, $V = 0.537, F(20, 68) = 2.056; p = .010; \eta_p^2 = .269$). Significant group differences were found for the subscales Inhibit, Initiate, Working Memory, Plan /Organize, and Monitoring of Task Performance (see Table 3.8). Again, planned pairwise comparisons revealed that the $NF1^{only}$-group was rated as significantly better than the $NF1^{ADHD}$-group or the $ADHD^{only}$-group on all subscales mentioned above, while there were no significant differences between the $NF1^{ADHD}$-group and the $ADHD^{only}$-group (for means see Figure 3.8). All mean values of the BRIEF scales and subscales are listed in Table A.7 and Table A.8.

Table 3.8.

Results of the BRIEF teacher evaluation

	N	df	F-value	sig.	partial η^2	post hoc comparisons
Global Executive Composite	68	2	10.993	.000***	.256	A>B***, C>B***
Behavioral Regulation Index	68	2	5.216	.008*	.140	A>B*, C>B*
Metacognition Index	68	2	12.562	.000***	.282	A>B***, C>B***
Inhibit	68	2	8.394	.001*	.208	A>B**, C>B**
Shift	68	2	1.294	.281	.039	-
Emotional Control	68	2	1.147	.324	.035	-
Initiate	68	2	9.967	.000***	.238	A>B***, C>B**
Working Memory	68	2	6.175	.004*	.162	A>B**, C>B**
Plan/Organize	68	2	8.102	.001*	.202	A>B**, C>B**
Organization of Materials	68	2	3.470	.037	.098	-
Monitor	68	2	6.338	.003*	.165	A>B**, C>B**
Monitoring of Task Performance	68	2	6.941	.002*	.178	A>B**, C>B**
Self Monitoring	68	2	3.327	.042	.094	-

For the Global Executive Composite: *** < .001, ** < .01, * < .05
For the Behavioral Regulation Index and the Metacognition Index: *** < .0005, ** < .005, * < .025
For the subscales: *** < .0001, ** < .001, * < .005
A = $NF1^{ADHD}$-group, B = $NF1^{only}$-group, C = $ADHD^{only}$-group
">" means "higher score/more problems" (e.g. A>B* = Group A has significantly higher mean scores and more problems in this area than group B.)

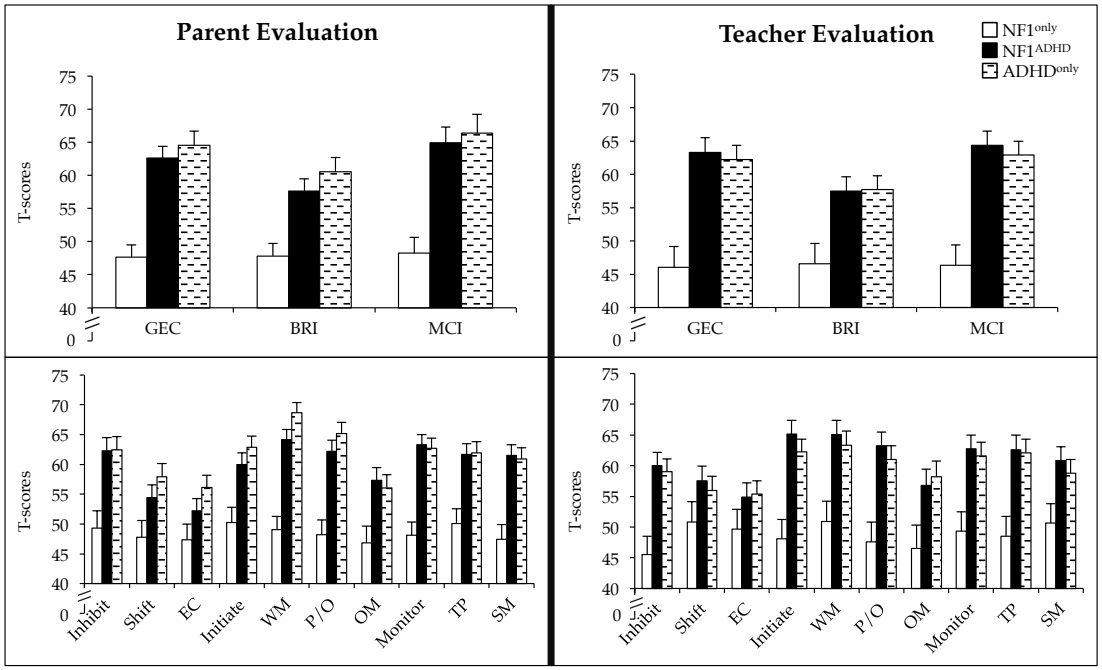

Figure 3.8. Mean values of the BRIEF scales and subscales for the three patient groups. Significant group differences emerged for every scale and almost every subscale between the NF1^{only}-group and the other two groups, see Tables 3.7 and 3.8. Error bars show the standard error (SE) of the mean.
Abbreviations: GEC = Global Executive Composite, BRI = Behavioral Regulation Index, MCI = Metacognition Index, EC = Emotional Control, WM = Working Memory, P/O = Plan/Organize, OM = Organization of Materials, TP = Monitoring of Task Performance, SM = Self Monitoring.

3.2.7. [H5] Quality of Life

Data analyses

QoL of each patient group was compared to population norms by Pearson's nonparametric chi-square test. Observed frequencies of subnormal scores were compared to the expected frequency from the population norms (15.8%). Dependent variables were the main scale and all subscales of the questionnaire Kiddo-Kindl.

QoL was also compared between the experimental groups with an ANCOVA for the total score and a MANCOVA for the subscales of the Kiddo-Kindl, with full-scale IQ as covariate. Data of 97 participants (45 $NF1^{ADHD}$-group, 22 $NF1^{only}$-group, 30 $ADHD^{only}$-group) could be analyzed. Levene's test of equality of variances was significant for the subscales Self-Esteem and Family, but the MANCOVA was conducted nevertheless, for the reasons described above.

Results

Most of the mean values of the Kiddo-Kindl lay in the normal range for all three experimental groups (see Figure 3.9 and Table A.9).

The nonparametric chi-square tests for the comparison of the experimental groups with the population norms revealed significant main effects for the $NF1^{ADHD}$-group on the total score of the Kiddo-Kindl and on the subscales Self-Esteem, Family, Friends, and Chronic disease. However, very important and surprising is that parents rated their children not only as subnormal on the subscales Family and Friends, but also as supernormal on the subscales Self-Esteem and Chronic disease. For the $NF1^{only}$-group, only the subscale Friends showed a significant main effect, with significantly more ratings in the subnormal range than expected by the population norms. For the $ADHD^{only}$-group, there were significant main effects on the total score of the Kiddo-Kindl and on the subscales Mental well-being, Family, and Friends. All significant effects for the $ADHD^{only}$-group arose from significantly more subnormal ratings (not supernormal ratings) (see Table 3.9).

For the group comparison, the ANCOVA revealed a significant main effect of Group on the total score of the Kiddo-Kindl ($F(2, 97) = 3.738; p = .027; \eta_p^2 = .074$), while the covariate had no effect on the dependent variable. Post hoc comparisons revealed that the $NF1^{only}$-group was rated as significantly better

Table 3.9.

Results of the nonparametric chi-square tests for Quality of Life

Dependent variable	Group	N	subnormal scores	df	chi-square	Asymp. Sig.
Total score	$NF1^{ADHD}$	45	28.9%	1	5.678	.017*
	$NF1^{only}$	22	9.1%	1	.763	.382
	$ADHD^{only}$	30	43.3%	1	16.884	.000***
Physical well-being	$NF1^{ADHD}$	45	24.4%	1	2.457	.117
	$NF1^{only}$	22	13.6%	1	.084	.772
	$ADHD^{only}$	30	13.3%	1	.148	.701
Mental well-being	$NF1^{ADHD}$	45	22.2%	1	1.345	.246
	$NF1^{only}$	22	13.6%	1	.084	.772
	$ADHD^{only}$	30	33.3%	1	6.819	.009**
Self-Esteem	$NF1^{ADHD}$	45	4.4%	1	4.416	.036*
	$NF1^{only}$	22	0.0%	-	-	-
	$ADHD^{only}$	30	6.7%	1	1.913	.167
Family	$NF1^{ADHD}$	45	35.5%	1	13.001	.000***
	$NF1^{only}$	22	4.5%	1	2.121	.145
	$ADHD^{only}$	30	33.3%	1	6.819	.009**
Friends	$NF1^{ADHD}$	45	51.1%	1	41.723	.000***
	$NF1^{only}$	22	36.4%	1	6.890	.009**
	$ADHD^{only}$	30	50.0%	1	26.088	.000***
School	$NF1^{ADHD}$	45	17.8%	1	.119	.730
	$NF1^{only}$	22	9.1%	1	.763	.382
	$ADHD^{only}$	30	26.7%	1	2.601	.107
Chronic disease	$NF1^{ADHD}$	45	2.2%	1	6.296	.012*
	$NF1^{only}$	22	4.5%	1	2.121	.145
	$ADHD^{only}$	30	0.0%	-	-	-

*** < .001, ** < .01, * < .05

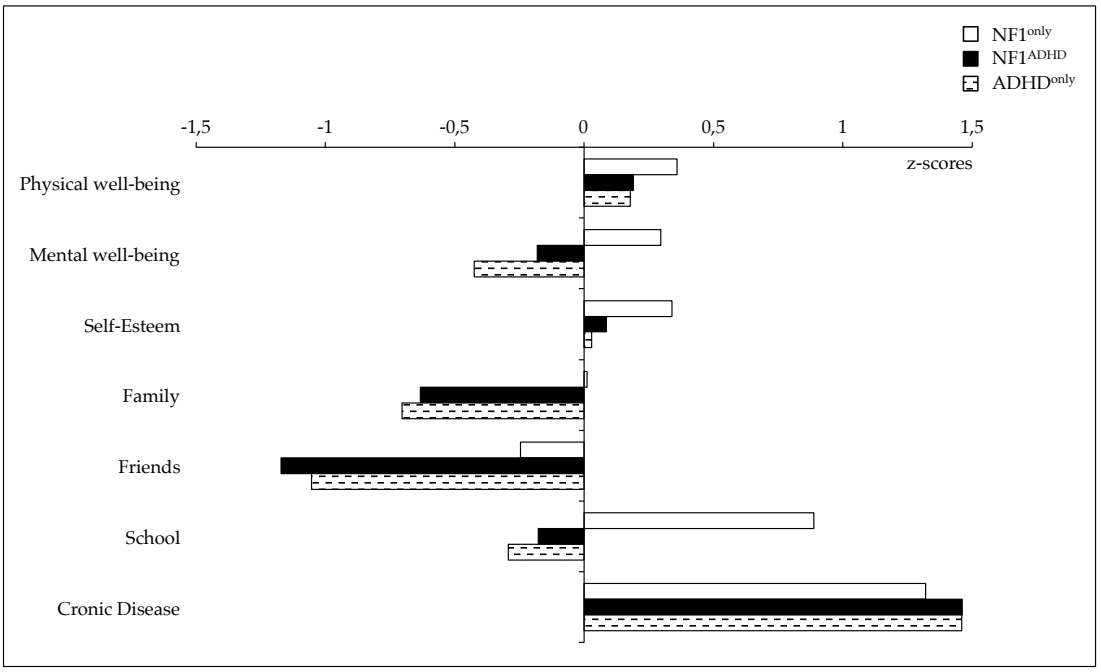

Figure 3.9. Mean values of the Kiddo-Kindl in z-scores for all three patient groups. The normal range of z-scores reaches from -1 to +1. Error bars show the standard error (SE) of the mean.

in quality of life than the ADHD^{only}-group ($p = .029$). Between the NF1^{ADHD}-group and the other two groups, there was no significant difference (NF1^{ADHD}-group vs. NF1^{only}-group: $p = .078$; NF1^{ADHD}-group vs. ADHD^{only}-group: $p = 1.000$). However, the MANCOVA for the subscales of the Kiddo-Kindl showed no significant group effect for the multivariate test. Also, there was no effect of the covariate full-scale IQ.

3.3. Discussion of Study 1

The aim of Study 1 was to identify the cognitive characteristics of NF1 with and without ADHD, and to distinguish between ADHD in NF1 and ADHD^{only}. The results yield a mixed picture, but mostly corroborate the hypotheses. The main finding is that the NF1 group of this study can be divided in two distinct subgroups at the level of neurocognitive characteristics: children with NF1^{only} and children with NF1^{ADHD}. An ADHD diagnosis seems to make a marked

difference in the cognitive profile of patients with NF1. The key results are briefly discussed below.

3.3.1. Intellectual Ability

Consistent with previous findings (Lidzba et al., 2012; Potvin et al., 2015) and as predicted by hypothesis 1, there was no reduction or impairment of intellectual functioning in children with $NF1^{only}$ as a group. They scored close to the intelligence mean score of 100 on all indices of the WISC-IV. In comparison, children with $NF1^{ADHD}$ showed reduced intellectual functioning on most indices of the intelligence test and had the lowest IQ scores of all three patient groups. Even though mean scores of all intelligence indices lay still within normal limits, the $NF1^{ADHD}$-group differed significantly from the $NF1^{only}$-group in all areas of intellectual ability, as Figure 3.2 shows.

Intellectual ability in $NF1^{only}$

The result of spared intellectual functioning in NF1 contradicts the consistent finding of earlier NF1 research (Hyman et al., 2005; North et al., 2002; Ferner et al., 1996). A lot of previous studies reported a generalized downward shift of IQ in NF1, but the authors of most of these studies treated the population as one homogeneous group and did not consider ADHD as a crucial factor for the intellectual outcome and therefore did not split their NF1 patient groups into subgroups. Two more recent studies, which analyzed retrospectively clinical patient data, show that NF1 patients without the additional cognitive burden of ADHD perform close to the average on intelligence tests (Lidzba et al., 2012; Potvin et al., 2015). The results of Study 1 confirm those results and indicate that ADHD is a specific risk factor for reduced intellectual abilities in NF1.

Effects of ADHD on intellectual ability in NF1

Regarding our predictions, hypothesis 1(a) was partly confirmed: children with $NF1^{ADHD}$ show reduced intellectual abilities compared to the normative sample, except for Verbal Comprehension. However, children with $ADHD^{only}$ did not show lowered intellectual abilities compared to the normative sample, which contradicts our expectations and earlier research results (Frazier et al., 2004).

Hypothesis 1 (b) could be partly confirmed, as well. Regarding full-scale IQ, the $NF1^{ADHD}$-group performed below the $NF1^{only}$-group and the $ADHD^{only}$-group, but the picture of the indices of the intelligence test is more diverse. While the $NF1^{ADHD}$-group performed significantly worse than the $NF1^{only}$-group on all indices, they only differed from the $ADHD^{only}$-group on Working Memory. Working Memory had the lowest scores of all indices of the WISC-IV in all three patient groups, but the performance was far more decreased in the $NF1^{ADHD}$-group than in the other two groups.

Intellectual profile of NF1

Similar to previous research (Potvin et al., 2015), our results show an uneven profile of intellectual abilities in children with NF1. Both NF1 groups showed a pattern of better verbal than visual-spatial skills and processing speed, and the most intense weakness in working memory. For children with $NF1^{ADHD}$, this intellectual profile equates exactly the profile which was found by Potvin and colleagues. For children with $NF1^{only}$, they found a slightly different profile with the most pronounced weakness in processing speed rather than in working memory. However, the results of the present study indicate that minor working memory problems might be associated with the NF1 condition, and are exacerbated by additional ADHD symptoms. In our sample, 10.7% of the $NF1^{only}$-group compared to 47.2% of the $NF1^{ADHD}$-group presented scores below the normal range on the index Working Memory. Considering that only 10.0% of the $ADHD^{only}$-group performed subnormally regarding working memory skills, it seems that the cognitive burden of the $NF1^{ADHD}$-group in working memory is more than a simple summation of the negative effects of NF1 and ADHD symptoms. Additionally, it is surprising that the $NF1^{only}$-group and the $ADHD^{only}$-group showed so few subnormal performances, because the expected number of the population norms would have been 15.8%.

3.3.2. Memory Skills

In contrast to previous findings in NF1 research (Descheemaeker et al., 2013; Billingsley et al., 2003; Ferner et al., 1996), there were no verbal learning or memory deficits in any of our patient groups, independently from gender, age, ADHD or NF1. However, not all former studies used a standardized test,

which limits their informative value. In the present study, all groups displayed scores within the normal range for Immediate and Delayed Recall, as well as for Recognition in the VLMT, as Figure 3.3 illustrates. Furthermore, children with $NF1^{ADHD}$ and children with $ADHD^{only}$ did not differ from children with $NF1^{only}$. Therefore, hypothesis 2 has to be rejected.

Spared verbal (and visual) memory skills in children with NF1 were found before in a study, where a standardized verbal learning test similar to the VLMT was used (Hyman et al., 2005). Comparing standard scores, they even found stronger memory skills than general intellectual skills in children with NF1.

3.3.3. Attention Functions

Hypothesis 3 (a) could be confirmed. The results of the attention measures show that the two ADHD groups presented reduced scores on nearly all parameters of the T.O.V.A. compared to the normative sample. Children with $NF1^{only}$ presented reduced scores on Omission Errors (reflecting inattention/-sustained attention). These results corroborate earlier findings of subclinical attention problems – especially regarding sustained attention – in children with NF1 without an ADHD diagnosis (Pride et al., 2012).

Hypothesis 3 (b) was partly confirmed: Children with ADHD– irrespective of NF1– were evaluated as significantly worse on hyperactivity/impulsivity and inattention than children with $NF1^{only}$ in the questionnaires. Children with $ADHD^{only}$ also performed below children with $NF1^{only}$ on the main parameter of the T.O.V.A., the API, but there were no differences on the sub-parameters of the T.O.V.A.. Also, the two NF1 groups differed neither on the API nor on the sub-parameters of the T.O.V.A.

Regarding hypothesis 3 (c), there were no significant quantitative differences in the attention functions of children with $NF1^{ADHD}$ and with $ADHD^{only}$, neither in the attention test nor in the parent or teacher evaluations. Therefore, hypothesis 3 (c) has to be rejected.

Attention profiles of $NF1^{ADHD}$ and $ADHD^{only}$

At first glance, the pattern of functional attention dysfunction in $NF1^{ADHD}$ seems to mimic that of $ADHD^{only}$ with mild hyperactivity/impulsivity (in the questionnaires) and moderate inattention (in the T.O.V.A. and the question-

naires). However, a closer look into the data reveals a more detailed picture: While the ADHD^{only}-group showed the lowest mean values on the T.O.V.A. sub-parameters Variability of Response Time and Response Time itself, the NF1^{ADHD}-group showed a more pronounced reduction of the mean score for Omission Errors (see Figure 3.5).

Furthermore, the frequencies of subnormal performances showed that children with NF1^{ADHD} were more affected regarding attention dysfunction than children with ADHD^{only}. Nearly twice as many children with NF1^{ADHD} (62.3%) than children with ADHD^{only} (33.3%) showed subnormal performances on Omission Errors. Also, Response Time Variability was more often reduced in NF1^{ADHD} (58.5%) than in ADHD^{only} (40.0%). Finally, even though the ADHD^{only}-group performed much worse on Response Time regarding mean scores (ADHD^{only}-group: $M = 84.28$, NF1^{ADHD}-group: $M = 91.27$), the frequencies of subnormal performances showed nearly no difference between the two ADHD groups (ADHD^{only}-group: 40.0%, NF1^{ADHD}-group: 39.6%), which indicates that children with ADHD^{only} are not more often affected in response time than children with NF1^{ADHD}, but if so, they are more severely affected and perform much slower.

Overall, the above mentioned differences in the attention domain lead to the assumption that the attention profile of NF1^{ADHD} differs from that of ADHD^{only}. Children with with NF1^{ADHD} seem to be especially affected regarding inattention, while children with ADHD^{only} seem to have more serious problems with response times. These results are partly in line with the findings of a recent study, where children with ADHD^{only} showed inferior response times to children with NF1^{ADHD} in a sustained attention task (Lion-Francois et al., 2017). Additionally, the authors found that children with NF1^{ADHD} showed lower overall performances in the areas of intensive, selective, and executive attention. The authors took these performance differences as evidence for the assumption that the two conditions ADHD^{only} and NF1^{ADHD} are fundamentally different from each other and concluded that the condition NF1^{ADHD} is not only the sum of NF1 and ADHD, and that ADHD symptomatology does not contribute to all attentional deficits in NF1 (Lion-Francois et al., 2017).

Our results are also confirmed by other studies showing that symptoms of inattention are more prevalent in NF1 than other attention problems (Pride et al., 2012) and they support the idea that certain deficits are rather associ-

ated with NF1 than merely the result of a comorbid ADHD symptomatology (Galasso et al., 2014; Huijbregts, 2012).

Subclinical attention problems in NF1

The concept of attention problems in NF1, which are independent from an ADHD diagnosis, is corroborated by further results of Study 1: The frequencies of subnormal performances on all four parameters of the T.O.V.A. were higher than the expected values for the normal (healthy) population (max. 15.8%, if one takes percentile rank as a basis) for all of our patient groups. This is not surprising for children suffering from ADHD, but it is unexpected for the $NF1^{only}$-group. Even if there is still a marked difference between NF1 patients with and without an additional ADHD diagnosis, the number of below average performances in the $NF1^{only}$-group is high, especially in the areas of distractibility (Variability of Response Times) and inattention (Omission Errors). Subclinical attention problems seem to be prevalent among children with $NF1^{only}$ and might be an inherent cognitive feature of the NF1 condition. Some authors assume that the downstream effects of the unique etiology underlying ADHD in NF1 result in a relatively homogeneous and "inattentive" phenotype (Pride et al., 2012). Affected inattention/sustained attention in children with $NF1^{only}$ was found before (Pride et al., 2012), but affected performances in other areas of attention function are an unexpected and novel finding that requires further investigation.

3.3.4. Executive Functions

Conform to hypothesis 4, both ADHD groups showed reduced executive functions, while children with $NF1^{only}$ were not impaired in any area of executive functions. These results confirm the assumption that executive dysfunctions are rather associated with ADHD than with NF1 per se.

Hypothesis 4 (a) was mostly confirmed: children with $NF1^{ADHD}$ showed significantly reduced executive functions compared to the normative sample on the test measures (Working Memory; Commission Errors) and showed significant impairment in the parent and teacher questionnaires (GEC of the BRIEF). Children with $ADHD^{only}$, however, had significant impairment only in the parent and teacher questionnaires.

Hypothesis 4 (b) was also confirmed in most parts: children with $NF1^{ADHD}$ scored significantly below children with $NF1^{only}$ on most executive test measures and most questionnaire scales. Also, the $ADHD^{only}$-group was rated as significantly worse than the $NF1^{only}$-group on most scales of the parent and teacher questionnaires.

Questionnaire data

Regarding the results of the BRIEF, the parent and teacher evaluations show pronounced differences between the $NF1^{only}$-group and the two ADHD groups on the GEC and the two broader indices Behavioral Regulation Index and Metacognition Index, as Figure 3.8 illustrates. These results suggest that executive dysfunctions in situations of daily living are not associated with the NF1 condition itself, but are a hallmark of ADHD. The results of the present study support the findings of Pride et al. (2012), who also found that children with $NF1^{only}$ were rated as significantly better by parents and teachers in the BRIEF than children with $NF1^{ADHD}$. The results of the comparison of the GEC scores (BRIEF) of the $NF1^{ADHD}$-group and the $ADHD^{only}$-group with the normative sample shows significantly more subnormal performances for both groups. These results are in line with our expectations and indicate a high prevalence of executive dysfunctions, since the GEC score is composed of eight different subscales and presents a comprehensive overview of executive dysfunction in situations of daily living. Concerning the subscales of the BRIEF, children with $NF1^{ADHD}$ and $ADHD^{only}$ were rated as impaired and as significantly worse than the $NF1^{only}$-group in most areas. The results indicate that children with $NF1^{ADHD}$ and $ADHD^{only}$ are similarly impaired in executive functions regarding situations at home and situations at school. Additionally, the parent and teacher evaluations the two ADHD groups are conform with each other except for the subscale Self-Monitoring, where parents rated the $NF1^{ADHD}$-group and the $ADHD^{only}$-group as impaired, but teachers did not. This high concordance of parent and teacher evaluations corroborates the validity of the present data and cannot be taken for granted. In previous studies, parent ratings have suggested significantly more impairment than teacher ratings (Payne et al., 2011; Dilts et al., 1996).

Test measures

The comparison between our ADHD groups revealed only minor differences for working memory (WISC-IV). Children with $NF1^{ADHD}$ performed significantly worse than children with $ADHD^{only}$, and the $ADHD^{only}$-group did not differ from the normative sample. These results resemble those of Potvin and colleagues (Potvin et al., 2015). They compared index scores of the WISC-IV and found that children with $NF1^{ADHD}$ scored significantly worse on working memory than children with $ADHD^{only}$ or $NF1^{only}$, even though all patient groups scored significantly below the average of the population norms in the study of Potvin et al. (2015). Payne et al. (2012) also found children with $NF1^{ADHD}$ to have impairment in working memory and to differ significantly from healthy children. Pride et al. (2012), however, found no significant group differences for performance based tests of executive function, including working memory (WISC-III:Freedom From Distractibility).

In contrast to the data of Potvin et al. (2015), the $NF1^{only}$-group in the present study did not show significant impairment of working memory skills, neither in the neuropsychological test nor in the questionnaires (see Figure 3.7 and Figure 3.8). These results confirm our hypothesis that executive dysfunction is a hallmark of ADHD and not of NF1 per se.

The results for the $NF1^{ADHD}$-group on impulse control partly confirm and partly contradict earlier studies. In the present study, children with $NF1^{ADHD}$ showed more frequently impairment in impulse control, than healthy children, as found by Mautner et al. (2002) and Payne et al. (2012), too. However, Payne et al. (2012) also found that children with $NF1^{only}$ performed worse than healthy children, which cannot be affirmed by the present results.

For the $ADHD^{only}$-group, the lack of significant differences between our patients and the normative sample in the results of the neuropsychological tests (working memory and impulse control) is particularly surprising, since executive dysfunctions in the working memory area are well documented for patients with $ADHD^{only}$ (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Martinussen & Tannock, 2006; Potvin et al., 2015). For impulse control, the study situation is not entirely clear, with both, impaired (Willcutt et al., 2005; Losier, McGrath, & Klein, 1996) and unimpaired findings (McGee, Clark, & Symons, 2000). However, the results of the present study do not necessarily mean that there are no working memory impairments or impulse control

deficits in the present ADHD^{only}-group. The results of the neuropsychological tests are contrary to the results of the external assessments. In the questionnaires, the ADHD^{only}-group was explicitly rated as impaired in working memory and impulse control (BRIEF subscales: Inhibit and Working Memory).

Discrepancies between different measuring types

Discrepancies between test measures and external assessments are not new in research on attention functions and executive functions. It is well known that the setting of a neuropsychological test holds different demands for a subject than a situation of daily living, were more distraction is around. Neuropsychological tests are normally conducted in an artificial laboratory situation, where it is quiet and distractions are reduced to a minimum. The assessment of skills in such a controlled situation is, however, only a snapshot and correlates only to a limited extend with the abilities in daily living. Studies with different measuring types for ADHD symptoms and executive dysfunctions found substantial discrepancies between neuropsychological tests and functional measures, indicating that functional ratings of ADHD symptoms have higher ecological validity and are superior to neuropsychological tests in predicting deficits in daily living (Barkley & Murphy, 2010; Barkley & Fischer, 2011; Pride et al., 2012). Barkley and Fischer (2011) found that children with ADHD present far more problems with executive dysfunctions in daily living than the results of neuropsychological tests revealed. Another study also found only a low level of correlation between commission errors in the T.O.V.A. and parents' evaluations of impulse control in the questionnaire BRIEF (Bodnar, Prahme, Cutting, Denckla, & Mahone, 2007). Therefore, the parent and teacher evaluations of the present study might probably be more meaningful than the test measures in terms of working memory impairments and impulsivity.

Another possible explanation for discrepancies is that different instruments are tapping different functions, each with certain underlying neuroanatomical structures (Stuss and Alexander (2000), as cited in Payne et al. (2011)). Recent research classified executive functions into "cold" functions – associated with the dorsolateral prefrontal cortex – and "hot" functions – primarily associated with the ventromedial or orbitofrontal prefrontal cortex. While the cold executive functions are described as more "cognitive" in nature (including working memory, attention, and organization skills), the hot executive functions are as-

sociated with impulse control, response inhibition, and social cognition (Chan, Shum, Toulopoulou, and Chen (2008); Grafman and Litvan (1999), as cited in Payne et al. (2011)). Payne et al. (2011) assume that external assessments such as questionnaires rather record hot executive functions, because they assess observable behavior, while test measures rather record cold executive functions, because they are more demanding in terms of cognitive skills. In any case, the authors conclude that both types of measures have the capacity to detect meaningful impairments and therefore should be included in neuropsychological evaluations (Payne et al., 2011).

3.3.5. Quality of Life

Hypothesis 5 about children with NF1 and/or ADHD (as chronic diseases) suffering from reduced QoL was partly confirmed.

Hypothesis 5 (a) was confirmed in most parts. Both ADHD groups showed reduced QoL on the total score of the Kiddo-Kindl and two respectively three out of seven subscales. Children with $NF1^{ADHD}$ showed reduced QoL regarding familial aspects (frequency of being uneasy/comfortable at home, conflicts with one's parents) and building/maintaining friendships, while children with $ADHD^{only}$ showed reduced QoL regarding mental well-being (frequency of having fun, being lethargic, feeling lonely, and feeling anxious/unconfident), familial aspects, and building/maintaining friendships. Children with $NF1^{only}$, however, only showed reduced QoL in the area "Friends" (building/maintaining friendships).

Hypothesis 5 (b) has to be rejected. Not children with $NF1^{ADHD}$, but children with $ADHD^{only}$ had the lowest QoL scores and the highest number of impaired areas. Additionally, they were rated with significantly poorer global QoL than children with $NF1^{only}$. These results indicate that it is not NF1 per se or the cumulation of the two chronic diseases NF1 and ADHD that severely reduces QoL, but, ADHD itself is the crucial factor.

QoL in NF1

The results of the present study partly contradict findings of previous research, which consistently reported lower global QoL in children and adolescents with NF1 compared to healthy children or population norms (Vranceanu et al., 2015;

Cipolletta et al., 2018; Garwood et al., 2012; Krab et al., 2009; Wolkenstein et al., 2009; Oostenbrink et al., 2007; Graf et al., 2006). In contrast, our results show that the differentiation between children with NF1^{only} and NF1^{ADHD} is again very important. Children with NF1^{only} had no globally decreased QoL in the present study and seemed to be affected in only one area of the questionnaire (subscale Friends). Literature on QoL in NF1 reports that protective factors might be higher parental education, the familial type of NF1, and good family relationships (Graf et al., 2006; Oostenbrink et al., 2007). Negative predictors for QoL, on the other side, include problems with emotional functioning, cognitive functioning, and learning disabilities, socioemotional problems, perceived disease severity by parents, and teacher reported behavioral problems, as well as male sex and physical complaints like orthopedic problems, presence of plexiform neurofibromas, more disease complications, and greater pain interference (Vranceanu et al., 2015; Wolters et al., 2015; Wolkenstein et al., 2009; Oostenbrink et al., 2007; Graf et al., 2006).

In the present NF1^{only}-group, there were less children with the familial type of NF1 (about 1/3) than in the NF1^{ADHD}-group (about 1/2), which could have a negative effect on their QoL. However, the SES (which is composed of the scores for parents' educational achievement, parents' professional position, and family income) was higher, but not significantly so, in the present NF1^{only}-group than in the NF1^{ADHD}-group or the ADHD^{only}-group. Additionally, the NF1^{only}-group was spared in almost every domain of cognitive functioning and presented very view learning disabilities, thus they profit from a combination of many protective factors proposed by other authors (Vranceanu et al., 2015; Wolters et al., 2015; Wolkenstein et al., 2009; Oostenbrink et al., 2007; Graf et al., 2006).

Compared to the NF1^{only}-group, the NF1^{ADHD}-group of the present study was rated with poorer global QoL and with lower QoL regarding family and friends (see Figure 3.9), and they presented several of the risk factors named above.

QoL in ADHD^{only}

Regarding ADHD without NF1, the results of the present study corroborate previous findings of decreased global QoL in children with this disease (Danckaerts et al., 2010; D. Coghill & Hodgkins, 2016; Marques et al., 2013; Thaulow

& Jozefiak, 2012; Jafari et al., 2011; Pongwilairat et al., 2005). The ADHD^{only}-group was especially rated as impaired regarding the global score and mental well-beeing, family and friends. For the domain of physical functioning, the present study found no impairment for children with ADHD^{only} compared to the population norm, but other studies also found merely a moderate effect of ADHD on this domain of QoL in parent proxy-reports (Lee et al., 2016). For the domains emotional, social and School functioning, Lee et al. (2016) reported strong effects of ADHD symptoms on QoL, which is confirmed by the present results except for the domain School functioning (see Figure 3.9).

Effects of ADHD on QoL in NF1

A comparison between the NF1^{ADHD}-group and the ADHD^{only}-group shows that the children of these patient groups were rated similarly regarding their QoL, even if the severity of impairments in QoL was more pronounced in ADHD^{only}. The results support and extend the findings of Mautner et al. (2015), who investigated the effect of ADHD on life satisfaction and personality in adults with NF1. The authors found that ADHD in NF1 had a statistically significant negative impact on overall life satisfaction and especially affected general health, self-satisfaction, sexuality, and family/friends. Additionally, the results of Mautner et al. (2015) show that adults with ADHD^{only} had the lowest scores regarding overall life satisfaction compared to patients with NF1^{ADHD} and NF1^{only}, which is conform with the present results.

One surprising finding of Study 1 is that parents of children with NF1^{ADHD} rated QoL on the subscales Self-Esteem and Chronic Disease of the Kiddo-Kindl as supernormal. The subscale Self-Esteem consists of four items about the sense of well-being and satisfaction about oneself, while the Disease Modul includes items about worries in daily living concerning the disease. The results indicate that NF1 as a chronic disease has only little impact on situations of daily living for the affected children and adolescents in the age-group studied – at least in the perception of their parents.

3.3.6. Conclusion of Study 1

The results of Study 1 indicate that there are – at least – two distinct profiles of NF1 with one group being far more affected than the other.

The cognitive profile of children with $NF1^{ADHD}$ is characterized by reduced intellectual abilities (in the lower normal range), minor to moderate attention problems with general attention problems (subnormal scores on the API of the T.O.V.A.), distractibility (reduced scores on Variability of Response Time) and moderate inattention (reduced scores on Omission Errors). Executive dysfunctions were affected regarding working memory, impulsivity (Commission Errors, T.O.V.A.), and functional aspects of executive functions in situations of daily living (inhibition, initiative, working memory, planning/organizing, monitoring of task performance and self monitoring). Additionally, quality of life seems to be moderately reduced with respect to familial aspects and building/maintaining friendships. Verbal memory skills are spared in $NF1^{ADHD}$.

The cognitive profile of children with $NF1^{only}$ reveals almost entirely unimpaired cognitive functions. Children with $NF1^{only}$ were found to have normal intellectual abilities, unimpaired verbal memory skills, and unimpaired executive functions. Regarding attention functions, they showed no problems with hyperactivity or impulsivity, but mild problems with inattention, which was expected. Quality of life was mostly unimpaired except for building/maintaining friendships.

Regarding attention characteristics of ADHD in NF1 and of $ADHD^{only}$, the results of Study 1 show that there are differences in certain attention dysfunctions of children with $NF1^{ADHD}$ and children with $ADHD^{only}$. The $NF1^{ADHD}$-group was far more affected regarding inattention (T.O.V.A. Omission Errors), while the $ADHD^{only}$-group showed markedly slower response times (T.O.V.A. Response Time). These results indicate that attention deficit in NF1 is rather associated with the NF1-condition than merely due to a comorbid ADHD diagnosis.

4. Study 2: Analysis of Attentional and Intellectual Development in NF1

4.1. Scope and Hypotheses

Study 2 examines attention performance as a possible predictor for intellectual development in NF1 in a longitudinal design. The aim was to gain knowledge about the complex interaction between attentional and intellectual abilities and the specificity of attention deficit in NF1. Three patient groups ($NF1^{ADHD}$-group, $NF1^{only}$-group, and $ADHD^{only}$-group) were investigated to answer the question of the course and development of intellectual functions in NF1, dependent and independent from attention dysfunctions and an amelioration of them.

Since an improvement of intellectual abilities as a possible consequence of an amelioration of attention functions will be the result of a cumulative effect, it can only become obvious after a relatively long observation time. In the present study, the time interval between the examinations was 12 months. Shorter intervals would have carried the risk of improved test performances because of retest effects. The longest interval between the first and the third examination added up to 24 months.

Three hypotheses were formulated and tested:

[H1] Attention performance is a predictor for intellectual development

Attention dysfunction is significantly related to reduced intellectual functioning in the short and long term. Attentional functioning is a predictor for intellectual functioning.

Predictions:

(a) Children with $NF1^{ADHD}$ and with $ADHD^{only}$ perform significantly worse on measures of intellectual functioning than children with $NF1^{only}$ at all three assessment points.

(b) Attention performance at the first assessment point predicts intellectual performances at all three assessment points.

[H2] Improvement of intellectual functioning

An amelioration of attention functions is accompanied by a significant improvement in intellectual functioning over a two-year-period. The expected effect is specific for children with NF1 and does not, or in a significantly smaller extent occur in children with $ADHD^{only}$.

Predictions:

(a) Children with $NF1^{ADHD}$ with improvement in attention functions perform significantly better in measures of intellectual functioning at the third assessment point.

(b) Children with $ADHD^{only}$ show no significant improvement in intellectual functioning at the third assessment point, even if they improved in attention functions.

(c) Children with $NF1^{only}$ show no modification of their intellectual functioning.

[H3] Treatment effects of MPH in NF1

An intervention with methylphenidate is accompanied by a stronger improvement in intellectual functioning than other or no interventions (e.g. psychotherapy, occupational therapy) in patients with $NF1^{ADHD}$.

Predictions:

(a) Patients with $NF1^{ADHD}$, who were treated with MPH, show a significantly stronger improvement in intellectual functioning after a two-year-period compared to patients with $NF1^{ADHD}$, who were treated with other interventions or who received no treatment.

4.2. Data Analyses and Results of Study 2

Data was analyzed as described in the *Methods'* chapter.

Study 2 had a longitudinal design, which means that data across three assessment points was analyzed. For Study 2 a matched group design was chosen to control for individual differences between the subjects. Subjects of three groups ($NF1^{ADHD}$-group, $NF1^{only}$-group, and $ADHD^{only}$-group) were matched for age and SES. As far as possible, they were also matched for ADHD-subtype regarding the two patient groups suffering from ADHD. During the matching procedure, sex was excluded as a matching-factor, because the patient groups differed widely in the distribution of sex and it would have been impossible to generate a sufficiently large number of participants in each single group.

Equality of variances was met for all dependent interval and ratio variables of Study 2. Normality of distribution was met for all ratio variables of demographic data and all variables of intellectual performance. Regarding attention performance, normality of distribution was not met for the Attention Performance Index (API) of the T.O.V.A. at the first and the third assessment point (T1 and T3) and for the difference between the API of T3 minus T1 for a part of the patient groups (see Appendix, Table A.11). For the analyses of Study 2, the violations of normality of distribution did not have any consequences. The variables in question served as dependent variables in bias corrected partial correlation analyses, and there are no nonparametric alternatives for these analyses.

There were only very few missing data. For the calculation of the SES, data was missing in one participant of the $NF1^{only}$-group. Data of the API of the T.O.V.A. of T3 was also missing in one participant of the $NF1^{only}$-group. Therefore, it was not possible to calculate the difference between the API of T3 minus T1 for this one person.

4.2.1. Choice of Covariates

For Study 2, age and sex distribution were chosen as covariates. Age was chosen despite the fact that groups were matched for age and there were no significant differences between the groups in age (ANOVA: $F(2, 66) = 1.039; p = .360; \eta^2 = .032$), because of the possibility of even little age differences being relevant for the benefit of therapeutic interventions in the long term. So far,

it remains unknown, at what age children profit more from early interventions regarding attention dysfunctions. Young children might be too young for a successful attention training, while older children might have less developmental potential (neurologically) for ameliorations through a training than younger children do. Regarding treatment of ADHD symptoms with medication, there is first evidence that children between 6-8 years profit more from MPH treatment than children between 9-12 years concerning general intellectual functioning (Tsai et al., 2013). However, ADHD symptom severity was not differently moderated by MPH treatment in different age groups in the study by Tsai et al. (2013).

Sex distribution was treated as a covariate, because there were wide differences between the groups ($\chi^2(1, N = 66) = 7.700, p = .026$) – as mentioned above – which might have kept the risk of biases.

4.2.2. Characteristics of the Study Population

Data analyses

Like in Study 1, demographic data was analyzed with chi-square tests for sex, ADHD subtype, and NF1 subtype, or two-tailed ANOVAs for age and SES. Severity of attention dysfunction was compared between the groups by two-tailed ANOVAs with the dependent variables API of the T.O.V.A. and ADHD-index of the Conners-3 parent evaluation at the first examination (T1).

Normality of distribution and equality of variances were met for the ratio variables age, SES, and ADHD-index. The API of the T.O.V.A. did not meet the criterion of normality of distribution, as mentioned before. The nominal and ordinal variables were not tested for normality of distribution, because these data naturally do not follow a normal distribution.

Regarding therapeutic interventions, the use of occupational therapy, psychotherapy, and MPH was analyzed for group differences with chi-square tests. All three patient groups were compared concerning occupational therapy and psychotherapy. The frequency of the use of MPH was only compared between the two ADHD groups, since participants of the NF1^{only}-group were not diagnosed with ADHD and therefore were not treated with stimulant medication.

Results

After the matching procedure, 22 subjects in each patient group were left. All in all, 66 participants were included in Study 2.

In the $NF1^{ADHD}$-group, 11 participants (50.0%) were female and 11 participants (50.0%) were male. The mean age of this group was 8.754 years (SD: 1.352). Nine participants (40.9%) suffered from the familial type of NF1. Nine participants (40.9%) had the Inattentive Type and 13 participants (59.1%) the Combined Type of ADHD. Four participants (18.2%) were taking MPH for the treatment of ADHD prior to the beginning of the study and during the study. Additionally, 6 participants started taking MPH during the study, so that 10 participants (45.5%) were receiving MPH at the time of the last examination. The SES lay in the middle range (Winkler-index: mean = 12.773, SD: 3.939).

In the $ADHD^{only}$-group, 5 participants (22.7%) were female and 17 participants (77.3%) were male. The mean age of this group was 8.966 years (SD: 1.254). 12 participants (54.5%) fulfilled the criteria for the Inattentive Type of ADHD and 10 participants (45.5) for the Combined Type of ADHD. One participant (4.5%) received MPH prior to the beginning of the study and 3 additional participants received MPH during the course of the study. The SES lay in the middle range (Winkler-index: mean = 11.136, SD: 3.256).

In the $NF1^{only}$-group, 14 female participants (63.6%) and 8 male participants (36.4%) were enrolled. The mean age was 8.383 years (SD: 1.461). Sixteen participants (72.7%) were suffering from a sporadic mutation of the NF1-gene, while 6 participants (27.3%) had the familial type of NF1. The SES lay in the middle range (Winkler-index: mean = 12.857, SD: 3.953).

The distribution of sex differed significantly between the groups ($\chi^2(2, N = 66) = 7.700, p = .026$), with an even sex ratio in the $NF1^{ADHD}$-group, slightly more girls than boys in the $NF1^{only}$-group, and profoundly more boys than girls in the $ADHD^{only}$-group.

No significant differences between the groups were found for age ($F(2, 66) = 1.039; p = .360; \eta^2 = .032$), SES ($F(2, 65) = 1.477; p = .236; \eta_p^2 = .045$), ADHD subtype ($\chi^2(1, N = 44) = 0.820, p = .547$), or NF1 subtype ($\chi^2(1, N = 44) = .910, p = .526$). As expected, there were significant group differences regarding the severity of attention dysfunction. Groups differed significantly on the API of the T.O.V.A. ($F(2, 66) = 5.171; p = .008; \eta^2 = .141$) and the ADHD-index of the Conners-3 parent evaluation ($F(2, 66) = 19.809; p < .001; \eta^2 = .390$) at

the first assessment point with the $NF1^{only}$-group being significantly less impaired on both variables than the $NF1^{ADHD}$-group and the $ADHD^{only}$-group (see Table 4.1).

Also, there were no significant differences between the three groups regarding therapeutic interventions like the use of occupational therapy ($\chi^2(2, N = 60) = .996, p = .703$) or psychotherapy ($\chi^2(2, N = 61) = 1.802, p = .768$) during the process of the study. However, the frequency of MPH therapy differed between the two ADHD groups at the end of the study ($\chi^2(2, N = 44) = 5.350, p = .045$), but not in the beginning ($\chi^2(2, N = 44) = 2.031, p = .345$). Participants of the $NF1^{ADHD}$-group were treated with MPH significantly more frequently than participants of the $ADHD^{only}$-group.

Table 4.1 summarizes data of explorative analyses for group characterizations.

Table 4.1.

Demographic data and group characteristics for Study 2

	Mean (SD), number or percent per group			p
	$NF1^{ADHD}$	$ADHD^{only}$	$NF1^{only}$	values
Number of participants	22	22	22	-
Sex (female/male)	11/11	5/17	14/8	.026* [b]
Age at T1	8.754 (1.352)	8.966 (1.254)	8.383 (1.461)	.360 [a]
SES (Winkler-Index)	12.773 (3.939)	11.136 (3.256)	12.857 (3.953)	.236 [a]
familial/sporadic NF1	9/13	6/16	-	.526 [b]
ADHD/ADD	9/13	12/10	-	.547 [b]
API at T1	-1.476 (3.785)	-1.445 (2.856)	1.181 (2.684)	.008** [a]
C3 [c] ADHD-index at T1	63.238 (7.127)	65.455 (6.375)	54.273 (5.054)	.000*** [a]
Occupational therapy	31.8% (7)	40.9% (9)	22.7% (5)	.703 [b]
Psychotherapy	4.5% (1)	9.1% (2)	0% (0)	.768 [b]
Methylphenidate at T1	18.2% (4)	4.5% (1)	-	.345 [b]
Methylphenidate at T3	45.5% (10)	13.6% (3)	-	.045 [b]

[a] = ANOVA
[b] = Pearson Chi-Square
[c] = Conners-3

4.2.3. [H1] Attention is a Predictor for Intellectual Development

Data analyses

To test the first part (a) of hypothesis 1, a repeated measures analysis of covariance, as well as three separate ANCOVAs for each assessment point (3 times) were conducted with full-scale IQ of the WISC-IV as dependent variable. Age and sex served as covariates. The level of significance was set at $p < .05$ for each separate analysis.

For hypothesis 1 (b), the two NF1 groups were combined with each other, because the results of Study 1 showed that children with NF1 without ADHD partly present at least subclinical attention problems. The purpose of the present analyses was to investigate the longterm effect of all forms of attention problems on intellectual development in NF1, as well as the absence of attention problems in NF1. Additionally, the statistical power of the analyses improves with a bigger patient group. In a first step, the correlation between the API of the T.O.V.A. at the first assessment point and intellectual performance at each of the three assessment points (full-scale IQ at T1, T2, and T3) was separately tested for the combined NF1-group and the $ADHD^{only}$-group with second-order partial correlation analyses (Pearson's correlation coefficient). Effects were controlled for age and sex. In a second step, multiple linear regressions (method: forced entry) were calculated for the combined NF1-group and for the $ADHD^{only}$-group to predict the intellectual performance (full-scale IQ) at the first, second and third assessment point based on SES and the attention performance (API of the T.O.V.A.) at the first assessment point.

Results

The results of the repeated measures ANCOVA showed that the covariates had no significant effects and there was no statistically significant effect of Time on full-scale IQ (see Table 4.2).

The separate ANCOVAs of full-scale IQ for the first and second assessment point showed significant differences between the groups (see Table 4.2). In both analyses, the covariates had no significant effect. Planned pairwise comparisons revealed a significantly better performance of the $NF1^{only}$-group compared to the $NF1^{ADHD}$-group at the first and second assessment point (T1:

$p = .002$; T2: $p = .008$), while there were no significant differences between the ADHD^{only}-group and any of the NF1 groups.

The ANCOVA for the third assessment point showed only a marginally significant effect of the independent variable Group on full-scale IQ and no effect of the covariates (see Table 4.2). Again, the NF1^{only}-group presented much higher scores in full-scale IQ than the NF1^{ADHD}-group. Mean values of the WISC-IV full-scale IQ are pictured in Figure 4.1 and mean values of all WISC-IV indices for all three assessment points are listed in Table A.12.

Table 4.2.

Results of the repeated measures analysis and the separate univariate analyses of group differences on full-scale IQ

WISC-IV (full-scale IQ)	N	df	F-value	sig.	partial η^2	post hoc comparisons
Repeated measures analysis	66	2	1.644	.202	.052	-
ANCOVA for T1	66	4	3.363	.015*	.181	A<B**
ANCOVA for T2	66	4	3.027	.024*	.166	A<B**
ANCOVA for T3	66	4	2.480	.053	.140	-

*** < .001, ** < .01, * < .05
A = NF1^{ADHD}-group, B = NF1^{only}-group, C = ADHD^{only}-group
"<" means "lower score/more problems" (e.g. A<B* = group A has significantly lower mean scores and more problems than group B)

Bias corrected partial correlation analyses for calculating the relationship between attentional functioning and intellectual functioning showed that the attention performance was significantly correlated with the intellectual performance in the combined NF1-group as well as the ADHD^{only}-group. The combined NF1-group showed significant positive correlations for attention performance at the first assessment point and for intellectual performance at each of the three assessment points (see Table 4.3 and Figure 4.2).

For the ADHD^{only}-group, the correlation between attention functions and intellectual performance at the first assessment point was marginally not significant, while the correlations at the second and third assessment point were significant (for results see Table 4.3 and Figure 4.2). Mean values of all T.O.V.A. parameters for all three assessment points are listed in Table A.13.

The multiple linear regressions for the combined NF1-group revealed significant regression equations for all three assessment points (T1: $F(2,40) = 4.737, p = .014$ with $R2 = .192$; T2:$F(2,40) = 7.197, p = .002$ with $R2 = .265$; and T3: $F(2,40) = 5.121, p = .010$ with $R2 = .204$). The API of the T.O.V.A.

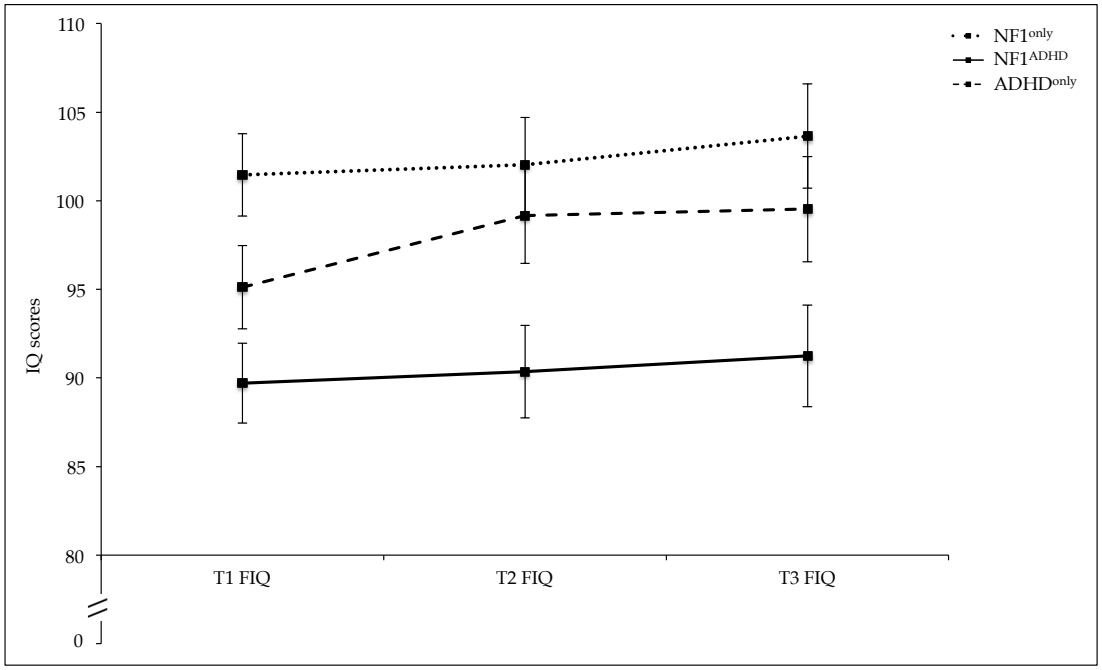

Figure 4.1. Mean values of the WISC-IV for T1, T2 and T3 for all three patient groups. Significant group differences emerged between the NF1^{only}-group and the NF1^{ADHD}-group at T1 and T2. Error bars show the standard error (SE) of the mean.

at the first assessment point was a significant predictor for full-scale IQ at the first, the second and the third assessment point for the combined NF1-group, while SES was no significant predictor at any assessment point, see Table 4.4.

For the ADHD^{only}-group, none of the regression models could significantly predict the outcome variable, which means: there was no model fit at any assessment point (T1: $F(2,19) = 1.373, p = .277$ with $R2 = .126$; T2:$F(2,19) = 2.547, p = .105$ with $R2 = .211$; and T3: $F(2,19) = 2.603, p = .100$ with $R2 = .215$). Table 4.4 shows – in the analyses for the ADHD^{only}-group– that some of the regression coefficients have a significant impact on the outcome variable, but these significance tests are not accurate and can not be interpreted, because the overall models did not fit.

Table 4.3.

Results of the correlation analyses for the relationship between attention functions and intellectual functioning

Correlation between attention functions and	Combined NF1-group			ADHD^{only}-group		
	r	*BCaCI*	*p*	*r*	*BCaCI*	*p*
full-scale IQ at T1	.405	[.081, .636]	.008**	.420	[-.001, .763]	.065
full-scale IQ at T2	.464	[.158, .689]	.002**	.565	[.198, .796]	.009**
full-scale IQ at T3	.392	[.007, .646]	.010*	.539	[.097, .778]	.014*

*** < .001, ** < .01, * < .05

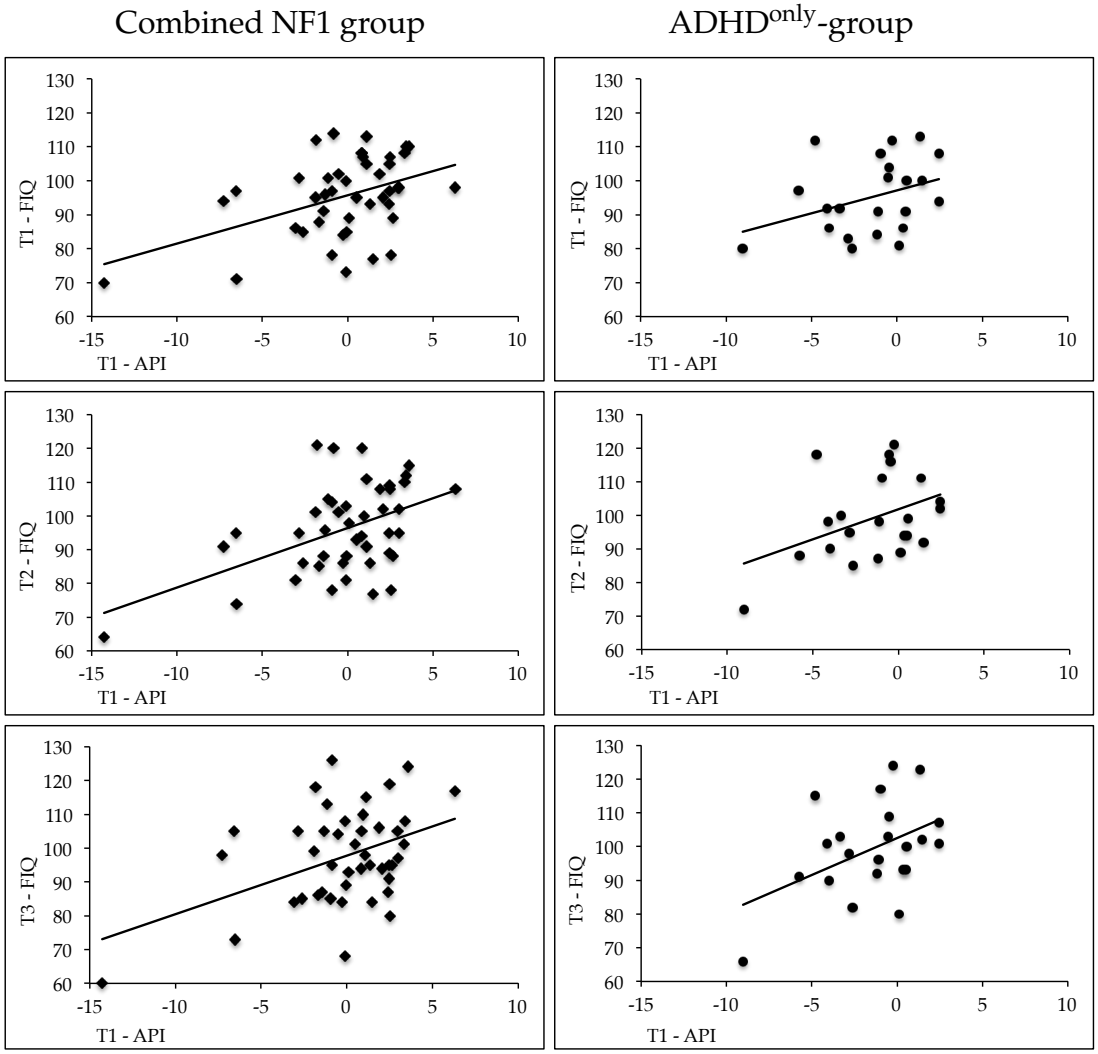

Figure 4.2. Correlations between the API score of T1 and the full-scale IQ (FIQ) scores of T1, T2, and T3 for the combined NF1 group (left side) and the ADHD^{only}-group (right side). Significant correlations between attention performance and intellectual performance emerged in almost every of the analyses, except for the first assessment point in the ADHD^{only}-group.

Table 4.4.

Results of multiple regression analyses about predictors for full-scale IQ at the first, second and third assessment point

Combined NF1-group					ADHD^{only}-group				
1. assessment point					1. assessment point				
	b	SE(b)	*β*	*p*		*b*	SE(b)	*β*	*p*
Step 1					Step 1				
Constant	93.809	6.231	-	.000***	Constant	94.861	8.737	-	.000***
SES	.117	.466	.039	.804	SES	.033	.754	.010	.966
Step 2					Step 2				
Constant	91.998	5.707	-	.000***	Constant	95.134	8.381	-	.000***
SES	.278	.427	.093	.520	SES	.187	.729	.055	.800
API	1.441	.470	.439	.004**	API	1.377	.832	.358	.114
R^2 = .002 for Step 1; $\triangle R^2$ = .190 for Step 2					R^2 = .002 for Step 1; $\triangle R^2$ = .126 for Step 2				
2. assessment point					2. assessment point				
	b	SE(b)	*β*	*p*		*b*	SE(b)	*β*	*p*
Step 1					Step 1				
Constant	90.414	7.058	-	.000***	Constant	92.355	9.094	-	.000***
SES	.460	.527	.135	.389	SES	.613	.851	.159	.479
Step 2					Step 2				
Constant	88.057	6.218	-	.000***	Constant	92.734	9.094	-	.000***
SES	.669	.466	.196	.159	SES	.827	.792	.215	.309
API	1.874	.512	.500	.001**	API	1.911	.902	.435	.048*
R^2 = .018 for Step 1; $\triangle R^2$ = .246 for Step 2					R^2 = .025 for Step 1; $\triangle R^2$ = .186 for Step 2				
3. assessment point					3. assessment point				
	b	SE(b)	*β*	*p*		*b*	SE(b)	*β*	*p*
Step 1					Step 1				
Constant	93.195	7.638	-	.000***	Constant	97.517	10.980	-	.000***
SES	.337	.574	.091	.561	SES	.166	.948	.039	.863
Step 2					Step 2				
Constant	90.922	7.007	-	.000***	Constant	97.964	9.990	-	.000***
SES	.539	.525	.146	.310	SES	.418	.869	.099	.636
API	1.808	.577	.446	.003**	API	2.253	.991	.466	.035*
R^2 = .008 for Step 1; $\triangle R^2$ = .196 for Step 2					R^2 = .002 for Step 1; $\triangle R^2$ = .214 for Step 2				

*** < .001, ** < .01, * < .05

4.2.4. [H2] Improvement of Intellectual Functioning

Data analyses

The second hypothesis about an amelioration of intellectual functioning in dependence of improved attention functions in children with $NF1^{ADHD}$ was tested with a repeated measures ANCOVA. In a first step, the $NF1^{ADHD}$-group was divided into two groups: group 1 consisted of participants, who improved in the API of the T.O.V.A. over the two-year-period. Group 2 consisted of participants, who declined in the API over the two-year-period. In a second step, those new groups were compared regarding their performance in intellectual functioning at the first and the third assessment point with a repeated measures ANCOVA. Sex and age served as covariates in these analyses.

Additionally, a second-order partial correlation analyses (Pearson's correlation coefficient) was conducted to calculate the relationship between changes in attention functions (API of T3 minus API of T1) and changes in intellectual functions (full-scale IQ of T3 minus full-scale IQ of T1) over the two-year-period. Effects were controlled for sex and age.

To explore the hypothesis that the expected effect is specific for children with $NF1^{ADHD}$ (H2b), the same analyses as described above were conducted for the $ADHD^{only}$-group.

Hypothesis 2(c) was tested with a repeated measures ANCOVA with sex and age as covariates. Full-scale IQs of T1 and T3 of the $NF1^{only}$-group were compared.

Results

Concerning the $NF1^{ADHD}$-group, eleven patients were allocated to each new group, but it was only a coincidence that the original group split up in two parts of equal size. The repeated measures ANCOVA showed no significant effect of Time on full-scale IQ ($F(1,22) = 1.149; p = .298; \eta_p^2 = .060$) and the covariates sex and age had no effect. Figure 4.3 shows the mean values for full-scale IQs for the two new subgroups API+ and API-. Figure 4.4 illustrates the bias corrected partial correlation analysis, which yielded no significant correlation between changes in attention functions and changes in intellectual functioning, either ($r = .191, BCaCI[-.425, .665], p = .421$).

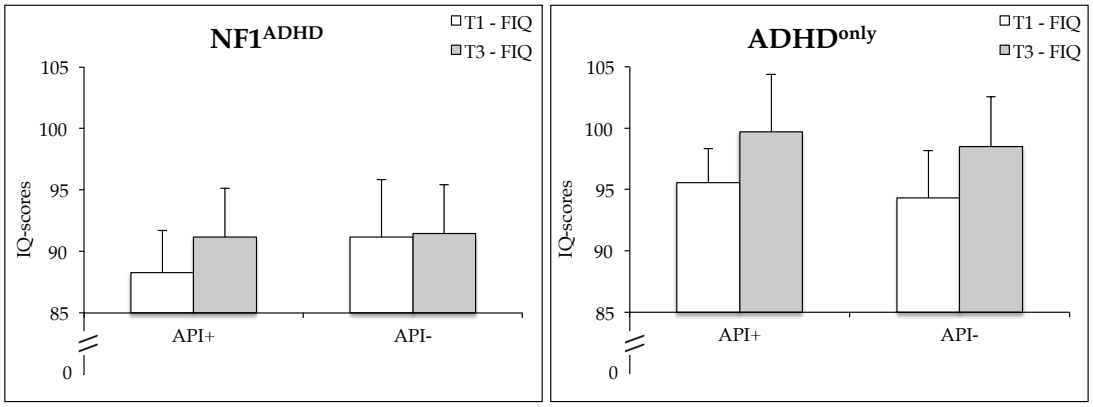

Figure 4.3. Mean values for full-scale IQs of T1 and T3 in the subgroups API+ (improvement of attention performance) and API- (decline of attention performance) for the NF1^{ADHD}-group and the ADHD^{only}-group. Error bars show the standard error (SE) of the mean.

For the ADHD^{only}-group, the two new groups consisted of 16 participants, who improved in attention functions (group 1), and 6 participants, who declined in attention functions (group 2). The results of the different analyses showed the same picture for the ADHD^{only}-group as for the NF1^{ADHD}-group. There was no significant effect of Time on full-scale IQ in the repeated measures ANCOVA ($F(1,22) = .013; p = .911; \eta_p^2 = .001$) and no effect of the covariates sex and age. Figure 4.3 shows the mean values for full-scale IQs for the two new subgroups API+ and API-. Figure 4.4 illustrates the bias corrected partial correlation analysis, which did not show a significant correlation between changes in attention functions and changes in intellectual functioning ($r = .053, BCaCI[-.331, .458], p = .825$).

The repeated measures ANCOVA to compare full-scale IQs of the NF1^{only}-group showed no significant modification in intellectual functioning over the two-year-period ($F(1,22) = .003; p = .955; \eta_p^2 < .001$) and no effects of the covariates sex and age.

4.2.5. [H3] Treatment Effects of MPH in NF1

Data analysis

In a first step, participants of the NF1^{ADHD}-group were allocated to two new groups: one group that received MPH during the term of the study (MPH+

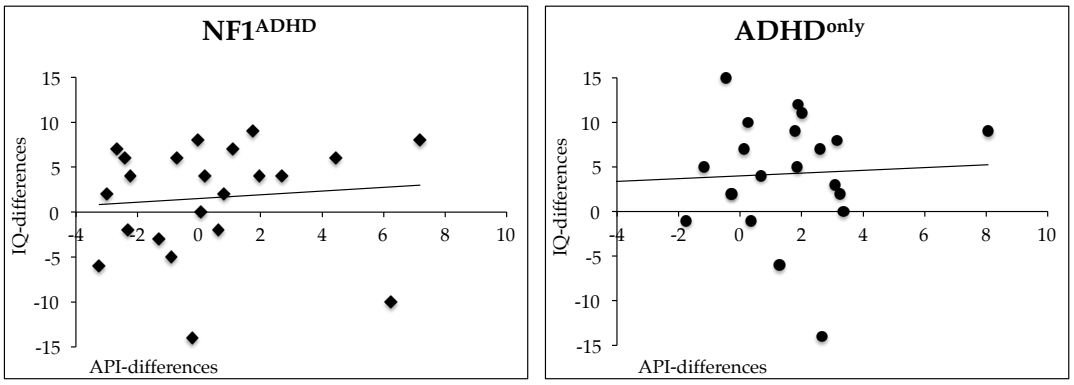

Figure 4.4. Correlation between changes in the API (T3 minus T1) and changes in full-scale IQ (T3 minus T1) for the $NF1^{ADHD}$-group and the $ADHD^{only}$-group. Both correlation analyses were not significant.

group) and another group that did not receive MPH (MPH- group). Afterwards, a univariate ANCOVA with sex and age as covariates was conducted with the purpose to investigate, if treatment with MPH is superior to other treatments/interventions regarding improvement of attention functions. The dependent variable was the differences of the Attention Performance Index (API) of the T.O.V.A. of T3 minus T1. To test the third hypothesis about a major advancement of stimulant medication (MPH) on intellectual functioning compared to other or no interventions, a univariate ANCOVA was conducted with sex and age as covariates. The dependent variable for this analysis was the difference of the intellectual performances (full-scale IQ) of T3 minus T1.

Results

The $NF1^{ADHD}$-group originally consisted of 22 participants, 10 of whom received MPH during the term of the study.

The comparison of participants receiving MPH and participants not receiving MPH did not result in significant differences in the improvement of attention functions (API of the T.O.V.A.) ($F(1,22) = .535; p = .474; \eta_p^2 = .029$) nor in significant differences in the improvement of intellectual functioning (full-scale IQ) ($F(1,22) = .434; p = .518; \eta_p^2 = .024$). The covariates had no effect on the dependent variables in both analyses. Figure (4.5), however, shows small but not significant differences between the groups.

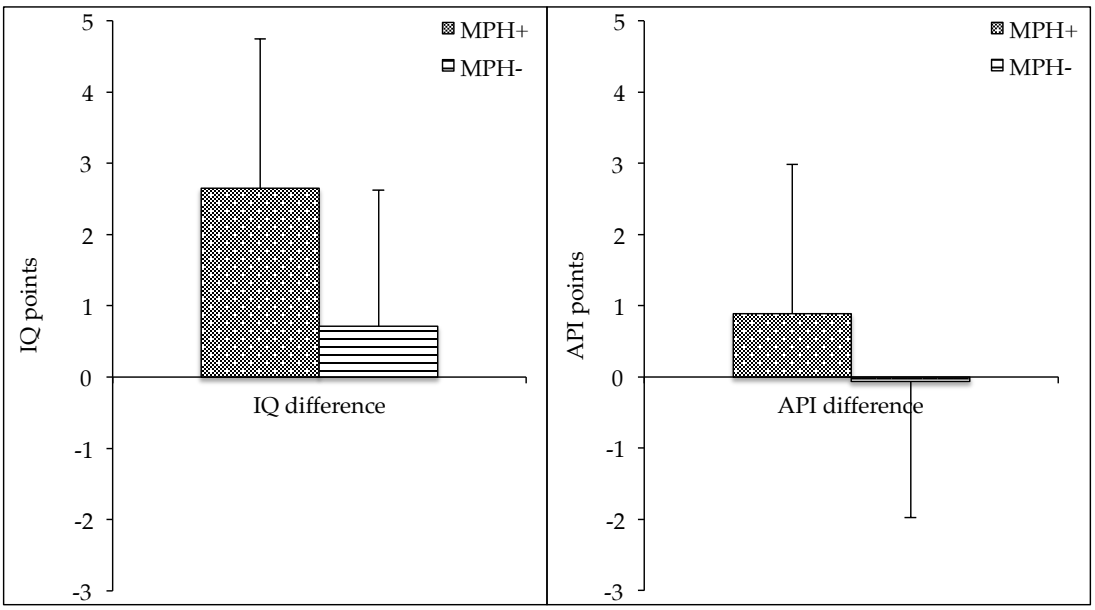

Figure 4.5. Mean values for changes in the full-scale IQ and the API between T1 and T3 for the groups MPH+ and MPH-. Error bars show the standard error (SE) of the mean.

Looking at the courses of the attentional and intellectual performances of single patients receiving MPH, no trend towards or against an improvement over the two-year-period is evident. Reasons could be the very low number of patients and the great heterogeneity of the duration and dose of the MPH therapy (see Table 4.5). However, the duration of the MPH therapy seems to correlate with IQ changes to some extent (see Figure 4.6).

Table 4.5.

Data on full-scale IQs, API scores, and MPH duration and doses in single NF1^{ADHD} patients receiving MPH

NF1^{ADHD} patients	Full-scale IQ T1	Full-scale IQ T3	API score T1	API score T3	MPH[a] duration	MPH[a] dose
1	112	118	-1.83	2.61	2	25
2	108	105	0.86	-0.44	21	10
3	100	108	-0.09	-0.12	60	7,5
4	97	105	-6.56	0.62	41	15
5	95	101	0.51	-0.21	1	10
6	89	95	2.64	0.24	6	30
7	78	80	2.52	3.33	26	7,5
8	73	68	-0.09	-0.99	24	10
9	71	73	-6.52	-9.52	72	10
10	70	60	-14.27	-8.04	12	40

[a]: MPH duration in months and MPH dose in milligram at T3

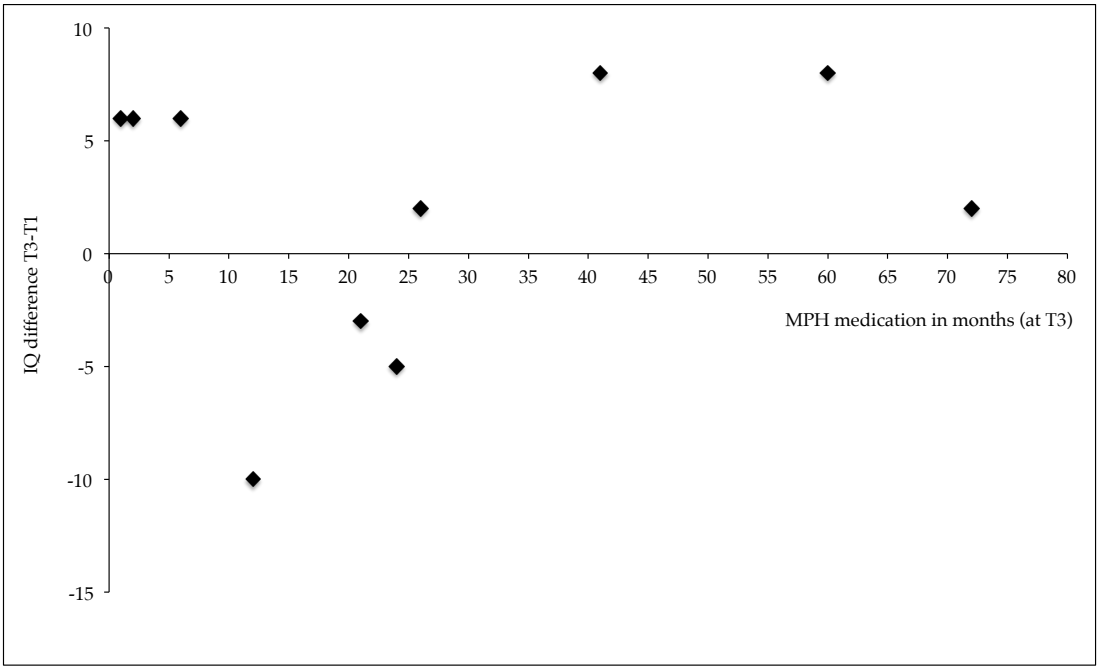

Figure 4.6. Correlation between the duration of MPH treatment and changes in full-scale IQ between T1 and T3 for patients with NF1^{ADHD} that were treated with MPH. The correlation was not significant.

4.3. Discussion of Study 2

4.3.1. Attention Performance as Predictor for Intellectual Development

The longitudinal results of Study 2 corroborate the assumption that attention dysfunction is related to reduced intellectual functioning in NF1. Attention dysfunction was not only correlated with reduced intellectual functioning in the short and long term (see Figure 4.2), but was also a significant predictor for the short-term outcome and for the long-term development of intellectual functioning in children with NF1. This means that there is a causal link between the extend of attention deficit and the level of intellectual functioning in NF1.

Significant correlations between attention dysfunction and intellectual functioning were also found for children with ADHD^{only} (see Figure 4.2), but attention dysfunction could not predict intellectual functioning in this group. The relationship between attention deficit and intellectual functioning in ADHD^{only} seems to be rather categorial than dimensional. Thus, the first hypothesis [H1] was confirmed for both NF1 patient groups, but only partly confirmed for the ADHD^{only}-group.

Regarding patients with NF1, research results on this topic are rather inconsistent. Our results are in line with the findings of newer studies (Potvin et al., 2015; Lidzba et al., 2012; Pride et al., 2012). Lidzba et al. (2012) confirm the association between attention dysfunction and intellectual difficulties in patients with NF1. They found that NF1 patients with ADHD and ADD symptoms performed significantly worse on intelligence measures than those without ADHD or ADD. Pride et al. (2012) also found that inattention and executive dysfunction are predictive for academic achievement and significantly undermine intellectual performance in NF1, even if the authors concluded from their data that inattention and executive dysfunction are general characteristics of NF1, which cannot be confirmed by the present data (see Study 1). An older study, however, found no association between sustained attention problems and lowering of IQ in children with NF1 (Hyman et al., 2005). In this study, only SES was a significant predictor of general intellectual functioning (Hyman et al., 2005). In the present study, SES was not a predictor for intellectual functioning, neither in NF1 nor in ADHD^{only}, but this may be due to the fact that the

SES lay in the middle range for every group and there were no large deviations inbetween the groups.

For children with ADHD^{only}, previous research consistently provides evidence for an association between ADHD and academic achievement, as well as intellectual functioning (Biederman et al., 2009; Frazier et al., 2004), even if symptom severity of ADHD was not found to be correlated with the extent of intellectual dysfunction (Tsai et al., 2013; Naglieri, Goldstein, Delauder, & Schwebach, 2005). The present results for the ADHD^{only}-group also show no significant correlation between attention performance (which may represent ADHD symptom severity) and intellectual performance at baseline, but the symptom severity at baseline correlated significantly with the intellectual performance after one and after two years. This is a finding of great clinical relevance, since it indicates long-term cognitive disadvantages, which are somehow related to the behavioral characteristics of ADHD.

4.3.2. Improvement of Intellectual Functioning

Regarding the second hypothesis [H2] of Study 2, the results are contrary to the expectations and could not support the assumption that improvement of attention function is associated with an improvement of intellectual functioning. All of the patient groups showed only moderate, not significant modifications of intellectual functioning (see Figure 4.1), even if full-scale IQ increased slightly over the two-year term of the study (NF1^{ADHD}: + 1.5 IQ points, NF1^{only}: +2.2 IQ points, ADHD^{only}: +4.4 IQ points). However, improved attention functions had no (significant) effect on intellectual functioning and development – neither in NF1 nor in ADHD^{only}– as Figure 4.3 and Figure 4.4 illustrate.

In the NF1 research area, there are previous studies showing a significant improvement of intellectual functioning over time (Lidzba et al., 2014; Payne et al., 2014), but these studies investigated a far longer time period than the present study and were partially conducted with retrospective data. Additionally, the positive progressions on intellectual functioning were not entirely and not necessarily associated with changes in attention functions. A study of Lidzba et al. (2014) investigated the long-term effect of MPH treatment in children with NF1^{ADHD} and found a significant positive effect of the medication (and other therapeutic interventions) on attention performance and on intelligence test

scores. The authors found that the relationship between improved attention and improved intelligence was not (entirely) responsible for the amelioration of intellectual functioning, because the improvement of intelligence test scores stayed significant after controlling for changes in attention measures. Therefore, the authors assumed that pharmacotherapy, specifically treatment with MPH, has a specific positive effect on cognitive development in NF1, which is not limited to attention improvement (Lidzba et al., 2014).

Another study on long-term development of intellectual functioning in NF1 found significant improvement in general cognitive performance over an 18-year-period. However, the positive effect was limited to patients with discrete T2 hyperintensities in childhood that decreased or resolved over time (Payne et al., 2014). In this study, a relationship between T2 hyperintensities and attention function was not investigated, and something like a second order relationship between an amelioration of attention function and intellectual functioning seems rather unlikely.

Regarding the present ADHD^{only}-group, it was expected that there is no effect of improved attention function on intellectual functioning [H2b]. Previous literature showed that the course of neurocognitive function is relatively independent from the course of ADHD (Biederman et al., 2009). The results of Study 2 are in line with this previous research and show no relationship between an amelioration of ADHD symptoms and an improvement of intellectual functioning in children with ADHD^{only}. Like in NF1, some previous studies on ADHD^{only} rather found a positive effect of MPH itself on intelligence test performance than a second order relationship between improved attention function by MPH that resulted in improved intellectual functions (Tsai et al., 2013; Gimpel et al., 2005). Consistent with other previous research, Tsai et al. (2013) found that children with ADHD^{only} perform significantly worse on intelligence tests than healthy controls (at an average of 9 IQ points on full-scale IQ). Furthermore, they demonstrated that long-term MPH treatment has a positive effect on intelligence test performance (plus 2.3–3.6 full-scale IQ points after one year of treatment). However, the improvement of IQ scores was not correlated with a decrement of ADHD symptoms or baseline ADHD severity. The authors assumed that MPH may possibly produce a different benefit such as more accuracy on the test.

4.3.3. Treatment Effects of MPH in NF1

In the present study, treatment with MPH did not have a significant positive effect on attentional or intellectual functioning (see Figure 4.5) and MPH treatment did not differ from other treatment options regarding the benefits. Therefore, hypothesis 3 [H3] has to be rejected. However, the present data is not comparable to the studies of Lidzba et al. (2014) or Tsai et al. (2013), because the number of children receiving MPH in the present study was limited and there was no possibility for a controlled, randomized allocation of the patients to a MPH-group and a no-MPH-group. Additionally, the duration and dosage of the medical treatment differed strongly in those patients receiving MPH, which weakens the comparability and generates a very heterogeneous group. Due to the small sample size and the heterogeneity of the sample, the statistical power of the present data is limited in its ability to detect changes in intellectual functioning between pre- and post-treatment. Furthermore, some patients were even treated with MPH before the start of the study, which is why there is no pre-treatment data in these cases. Because of these profound limitations, the results are rather not representative for the entire $NF1^{ADHD}$ population and a well-founded statement can not be made. Further research on the effect of MPH on cognitive development and especially intellectual functioning in NF1 is urgently needed.

4.3.4. Conclusion

The results of Study 2 lead to the conclusions that firstly, attention functions are correlated with intellectual functioning in NF1 and attention performance can predict intellectual performance in NF1. Secondly, there are marked differences in the intellectual abilities of patients with NF1 with and without ADHD, which stay stable over – at least – a two-year-period. Thirdly, intellectual ability in NF1 does not seem to be modified by changes in attention functions, but intellectual ability seems to increase slightly over time. Fourthly, the results of the present study do not allow a statement about the effect of MPH on cognitive development in NF1, because of too many limitations. Maybe, the investigation interval of two years is too short to observe intellectual development and its determinants in NF1. Further longitudinal studies with a prospective design

and randomized controlled trials are required to investigate treatment effects of MPH and other therapeutic interventions on cognitive development in NF1.

5. General Discussion

5.1. Results of the Present Thesis

The present thesis investigated cognitive characteristics of children with NF1 with and without ADHD, as well as the influence of attention deficit on intellectual development in NF1.

Study 1 presented cross-sectional data, which indicates that there exists more than one cognitive profile in NF1. The condition $NF1^{ADHD}$ can be clearly distinguished from the condition $NF1^{only}$ at the level of neurocognitive characteristics. In $NF1^{only}$, the cognitive profile was characterized by average intellectual abilities, average verbal memory skills, mostly average attention functions, and average executive functions. Quality of life was also mostly in the normal range. The only issues of children with $NF1^{only}$ were mild problems with inattention and mild deficiencies in social skills (building/maintaining friendships). In contrast, the cognitive profile of $NF1^{ADHD}$ included a downward shift of intellectual abilities (in the lower normal range), which has formerly been assigned to the whole NF1 patient group in most previous NF1 studies (North et al., 2002; Ferner et al., 1996). Furthermore, the profile of $NF1^{ADHD}$ included minor general attention problems and moderate inattention, as well as moderate executive dysfunctions (regarding working memory, impulsivity/inhibition, initiative, planning/organizing, monitoring of task performance and self monitoring). Quality of life was reduced regarding familial aspects and social skills (building/maintaining friendships).

The heterogeneity of the incidence of certain cognitive deficiencies and of ADHD in the NF1 population seems surprising at first glance, since NF1 is a monogenetic disorder. Nevertheless, it is well known that NF1 is no homogeneous medical condition and the diversity of cognitive traits might be explained by different phenotype expressions. Other factors than the mutation of the NF1-gene alone seem to add to the specific clinical phenotype (Kehrer-

Sawatzki & Mautner, 2009). Evidence suggests that factors like sex, age, specific cell type, genomic modifiers, and micro-environmental influences determine the cognitive and behavioral phenotype triggered by the NF1 condition. Different levels of Ras and dopamine activity in specific combinations are proposed to contribute to diverse cognitive profiles in NF1: High levels of Ras activity plus slightly reduced levels of dopamine may lead to severe spatial learning and memory deficits, while high levels of Ras activity plus heavily reduced levels of dopamine may result in severe attention problems and mild learning deficits (Diggs-Andrews & Gutmann, 2013). However, to elucidate the role of Ras, dopamine or other neurotransmitters on learning, memory, and attention deficits in NF1, further research is needed.

Study 2 presented longitudinal data on the cognitive development of children with NF1. The results of Study 2 showed that the differences in intellectual abilities between children with $NF1^{only}$ and children with $NF1^{ADHD}$ stayed stable over time, although both NF1 patient groups seemed to slightly improve in their intellectual abilities over the two-year-interval of the study, which might be explained by maturation processes. Further research will have to take care of this concern and exclude mere maturation processes in intellectual development in NF1. Regarding attention functions, the results of Study 2 indicated that the relationship between attention and intellectual ability in NF1 is dimensional as well as causal. The level of attentional functioning was not only correlated to the level of intellectual functioning, but also predictive for future intellectual performances. However, intellectual abilities could not be modified by changes in attention functions in the present study, which might be due to the limited duration of the present research project. Furthermore, the investigation of an expected positive effect of MPH treatment on attention and intellectual development in NF1 was not successful, because of too many methodological limitations. Therefore, Study 2 can not contribute to answer the open questions about the effect of MPH on cognitive functions in NF1.

Concerning a differentiation of $NF1^{ADHD}$ from $ADHD^{only}$, the results of the present thesis indicate that certain deficits in the attention domain are specific for $NF1^{ADHD}$ and are rather associated with the NF1 condition than merely the result of comorbid ADHD in NF1. Study 1 showed that children with $NF1^{ADHD}$ were especially affected regarding inattention, while children with $ADHD^{only}$

had more serious problems with response times. Additionally, Study 2 showed that attention deficits were dimensionally and causally linked to intellectual deficiencies in NF1, while the relationship between attention deficit and intellectual functioning in $ADHD^{only}$ was rather categorial and not causal.

5.2. Limitations

There are some limitations to consider when interpreting the results of this thesis, which ask for a critical discussion. At first, limitations associated with sample characteristics are reflected and in the following, limitations associated with methodology and study design are discussed.

First of all, participants recruited for the $NF1^{ADHD}$-group and the $ADHD^{only}$-group of this project partly had an indication for clinical neuropsychological diagnostics because of developmental, behavioral, or academic problems. Therefore, we can not totally rule out that the intellectual and attention performance of these participants might be worse than that of others with $NF1^{ADHD}$ or $ADHD^{only}$. Additionally, participants for the two NF1 groups were recruited from all over Germany and were highly motivated to participate despite long traveling times and the fact that we could not reward them in any way. In contrast, participants for the ADHD control group were all recruited from the local area around Tübingen and dropped out from the study more often than the NF1 patients. The greater availability of specific diagnostics for patients with $ADHD^{only}$ and the lower rate of complications might be one reason for the lower motivation in the $ADHD^{only}$-group to participate and to stay until the end of the present study project. All in all, the $ADHD^{only}$-group was rather small considering the prevalence of $ADHD^{only}$ and, additionally, the number of participants taking medication for the treatment of ADHD was unusually small, which might limit the representativeness of the sample for the entire ADHD population.

Second, both studies presented in this thesis are missing a comparison group of healthy children. Such a group would have provided additional information about the differentness of the neurocognitive profile of children with $NF1^{only}$, $NF1^{ADHD}$, or $ADHD^{only}$ from those of healthy children and could have given rise to meaningful treatment implications. Ideally, further studies should inves-

tigate siblings in a comparison group to control for genetic or environmental factors.

Third, the three patient groups investigated in Study 1 were of very different group sizes, which might limit the statistical power of the analyses and affect type II error rates. Furthermore, the sample size in Study 2 was relatively small, which leads to several limitations: (a) Results of studies with small sample sizes are restricted in their generalizability, because the statistical power to detect group differences is reduced. (b) Outliers and hidden covariates might have a strong influence or interfere with real effects. We met these concerns by matching the groups for age and SES, and controlling most of the analyses for the covariates age and sex. Additionally, we assessed possible covariates and found no differences between groups for NF1 subtype or ADHD subtype, and for the frequency of therapeutic interventions.

Fourth, an influence of sex on the results could not be ruled out. In Study 1 as well as in Study 2, sex distribution was uneven in all three patient groups. The majority of participants of the $ADHD^{only}$-group was male, while it was reversed in the $NF1^{only}$-group. In the $NF1^{ADHD}$-group, the sex distribution was 3:2 boys to girls in Study 1. Even though we controlled for sex in most of the analyses, qualitative differences between boys and girls regarding ADHD symptomatology and cognitive dysfunction could still have influenced the results. Research in the NF1 area shows that male gender seems to be a specific risk factor for cognitive dysfunction in NF1. In an animal design that investigated the role of sex as a modifier of neuronal dysfunction in NF1, only male mice were found to be impaired in learning and memory, which was associated with reduced hippocampal dopamine levels and increased hippocampal Ras activation (Diggs-Andrews et al., 2014). Regarding learning and memory deficits in humans, male NF1 patients were found to be seven times more likely to exhibit specific learning deficits than females (Hyman et al., 2005). In the present work, the results of Study 1 show significant effects of sex. On the one hand, boys performed worse on Processing Speed (WISC-IV) than girls in both ADHD groups. Since the majority of the $NF1^{ADHD}$-group were boys and the majority of the $NF1^{only}$-group were girls, it is conceivable that the significant difference in intellectual functioning between the two NF1 groups is partly due to the effect of sex. On the other hand, however, girls performed worse on Omission Errors (T.O.V.A.) than boys in all three patient groups. Regarding

ADHD in general, these results would match the fact that the inattentive subtype is more common in girls than the combined or hyperactive subtype – at least in the general population (Spencer, Biederman, & Mick, 2007). However, in the present $ADHD^{only}$-group, the inattentive subtype was equally common as the combined subtype in girls and in the $NF1^{ADHD}$-group, girls even presented the combined subtype slightly more often than the inattentive subtype. One explanation for the incongruence of the ADHD subtypes with the performances in the test measures could be that the ADHD subtypes of our patients might rather match functional ratings of ADHD symptoms than neuropsychological test performances. Nonetheless, future studies must obviously control for sex and ADHD subtype effects.

Fifth, a further limitation is the absence of differentiation between the inattentive and the combined subtype of ADHD in the analyses, which was due to the relatively small sample size of the ADHD control group. Even though the distribution of subtypes did not differ significantly between the $NF1^{ADHD}$-group and the $ADHD^{only}$-group, we can not guarantee that there was no effect of slight differences in the frequency of the subtypes on the results. Additionally, we can not contribute to the open questions on the distribution and consequences of ADHD subtypes in NF1.

Sixth, we assessed attention functions only with one continuous performance test and one attention questionnaire. Although the T.O.V.A. is very useful in predicting ADHD in individuals, it might not measure single attention functions in a sufficiently differentiated way to distinguish between $NF1^{ADHD}$ and $ADHD^{only}$. For further studies on this topic, the use of more elaborate test batteries is recommended to address different domains of attention and also executive functions and to gain a more detailed picture of the profiles of $NF1^{ADHD}$ compared to $ADHD^{only}$.

Seventh, external assessments of ADHD symptoms, attention functions, executive functions, and QoL were conducted via parent and teacher questionnaires, which does not meet the so-called gold standard for the assessment of behavioral symptoms. A clinical observation of a child's behavior in different situations of daily living would be preferable to questionnaires, because a rating by parents and teachers might be influenced by social expectations or negative/positive experiences with the child. A clinical observation would be desirable for future studies investigating behavioral symptoms in NF1, but it is

probably only rarely possible in the context of most research projects for logistical reasons.

Eighth, no randomized controlled trial was conducted for Study 2 of the present thesis. In designing the study, we had determined that a randomization of medication across groups for a long-term study would be ethically inappropriate . Therefore, it was not possible to control the decision for or against a treatment with MPH. Parents or caregivers decided to start with medication after medical advice, but the decision was not based on a clinical evaluation. Since many influencing factors affect the treatment decision of parents or caregivers, this is a very ambiguous variable, which is difficult to control.

Ninth, in the clinical practice other treatments were often conducted (e.g. occupational therapy, cognitive behavior therapy) in combination with MPH treatment or even exclusively, but an interference of the medication effect with a possible effect of other treatments or the effect of other treatments themselves on intellectual functioning were not investigated in the present study. Future studies will have to meet this concern.

Tenth, Study 2 was designed to investigate long-term effects regarding the cognitive development of children with NF1, because we assumed that such a basic deficit like attention dysfunction has a cumulative, negative effect on intellectual functioning. Additionally, we hypothesized that an improvement of cognitive functions as a result of an intervention with medication would also rather be a long-term development. Therefore, the design of Study 2 contained follow-up assessments over a time period of two years. However, it seems that the study duration was still too short to observe major changes in the cognitive development of children with NF1, irrespective of whether or not it concerns a negative influence of attention dysfunction, the possible positive effect of a MPH treatment, or plain maturation processes in intellectual functioning.

5.3. Conclusion and Implications

The present thesis contains a cross-sectional neurocognitive investigation as well as longitudinal analyses of the intellectual development of children with NF1. While cross-sectional studies have already been conducted several times in NF1 research, the present work is the first to prospectively investigate long-term effects of attention deficit on intellectual development in children with

NF1. Also, it is the first attempt to examine treatment effects of MPH on intellectual development in NF1 in a prospective design. Despite some drawbacks associated with methodological issues and study design, the present work gives first evidence for diverse cognitive characteristics and different developmental courses in-between the NF1 population. The present findings support the assumption that there are – at least – two distinct cognitive profiles of NF1 with one group being far more affected than the other. Attention deficit is a specific risk factor for intellectual dysfunction in NF1 and the condition $NF1^{ADHD}$ entails an additional cognitive burden. Moreover, ADHD is not a mere comorbidity in NF1, but certain attention deficits seem to be associated with the NF1 condition.

Also, the longitudinal results lead to some important conclusions, despite the unsuccessful outcome of the attempts to find an effect of changes in attention functions on intellectual functioning and to elucidate the effect of MPH on intellectual development in NF1. Attention deficit in NF1 is causally linked to intellectual functioning in the short and long term and leads to decreased intellectual functioning, which stays stable over time. We assume from the results of previous research that MPH might help to improve intellectual functioning in patients with $NF1^{ADHD}$, but it was impossible to appropriately investigate this issue in the present research project.

However, the results of the present thesis emphasize how important it is to record ADHD and attention deficit as a factor in future neurocognitive investigations and may give rise to further investigations on neurobiological causes of cognitive dysfunction in NF1. Building subgroups of patients on the basis of neurocognitive characteristics could also be a good practice for other neurological diseases to gain valuable information.

Furthermore, the findings of the present thesis entail implications for potential treatment options for children with $NF1^{ADHD}$ and might encourage research on the development of cognitive training, which is specifically adapted to the neuropsychological profile and the requirements of children with $NF1^{ADHD}$.

A. Appendix

A.1. Supplemental Data for Study 1

A.1.1. Equality of Variances and Normality of Distribution

Table A.1.

Equality of variances via Levene's test and normality of distribution via Shapiro-Wilk-test for all dependent variables of the neuropsychological assessments of Study 1

	Dependent variable	equality of variances (sig.)	normality of distribution (sig.)		
			$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
WISC-IV	full-scale IQ	.089	.221	.562	.137
	Verbal Comprehension	.917	.107	.040*	.983
	Perceptual Reasoning	.022*	.071	.142	.997
	Working Memory	.123	.052	.176	.019
	Processing Speed	.436	.095	.521	.946
VLMT	Immediate Recall	.837	.017*	.071	.006**
	Delayed Recall	.320	.038*	.057	.033*
	Recognition	.524	.034*	.242	.064
T.O.V.A.	API	.983	.000***	.168	.015*
	Variability of RT	.573	.040*	.018 *	.010*
	Response Time	.416	.465	.003**	.015*
	Commission Errors	.946	.026*	.000***	.595
	Omission Errors	.466	.000***	.000***	.000***

*** < .001, ** < .01, * < .05

Table A.2.

Equality of variances via Levene's test and normality of distribution via Shapiro-Wilk-test for the dependent variables of the Conners-3 parent and teacher evaluation

Dependent variable	equality of variances (sig.)	normality of distribution (sig.)		
		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
	parent evaluation			
Inattention	.996	.014*	.259	.000***
Hyperactivity/Impulsivity	.269	.092	.802	.026*
	teacher evaluation			
Inattention	.744	.001**	.448	.000***
Hyperactivity/Impulsivity	.180	.014*	.532	.171

*** < .001, ** < .01, * < .05

Table A.3.

Equality of variances via Levene's test and normality of distribution via Shapiro-Wilk-test for the dependent variables of the BRIEF parent and teacher evaluation

Dependent variable	equality of variances (sig.)	normality of distribution (sig.)		
		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
	parent evaluation			
Global Executive Composite	.021*	.316	.682	.263
Behavioral Regulation Index	.010*	.007**	.111	.048*
Metacognition Index	.007**	.219	.139	.092
Inhibit	.003**	.016*	.001**	.075
Shift	.095	.013*	.023*	.650
Emotional Control	.044	.006**	.205	.349
Initiate	.692	.027*	.241	.153
Working Memory	.046*	.150	.101	.056
Plan/Organize	.008*	.669	.039*	.027*
Organization of Materials	.065	.090	.210	.001**
Monitor	.064	.116	.660	.379
Monitoring of Task Perform.	.113	.118	.127	.259
Self Monitoring	.318	.109	.010*	.092
	teacher evaluation			
Global Executive Composite	.131	.641	.028*	.665
Behavioral Regulation Index	.004**	.570	.013*	.019*
Metacognition Index	.188	.669	.012*	.583
Inhibit	.005**	.670	.115	.035*
Shift	.993	.575	.001**	.015*
Emotional Control	.365	.007**	.002**	.003**
Initiate	.643	.695	.020*	.209
Working Memory	.976	.064	.008**	.521
Plan/Organize	.587	.197	.012*	.409
Organization of Materials	.160	.000***	.000***	.012*
Monitor	.866	.282	.113	.422
Monitoring of Task Perform.	.543	.127	.013*	.066
Self Monitoring	.844	.221	.026*	.063

*** < .001, ** < .01, * < .05

Table A.4.

Equality of variances via Levene's test and normality of distribution via Shapiro-Wilk-test for the dependent variables of the Kiddo-Kindl

Dependent variable	equality of variances (sig.)	normality of distribution (sig.)		
		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
Total Score	.280	.178	.631	.135
Physical well-being	.196	.001**	.004**	.168
Mental well-being	.270	.000***	.005**	.061
Self-Esteem	.022*	.423	.056	.788
Family	.016*	.002**	.209	.113
Friends	.484	.010*	.177	.075
School	.588	.030*	.048*	.037*
Chronic Disease	.297	.002**	.009**	.005**

*** < .001, ** < .01, * < .05

A.1.2. Mean Values and Standard Errors

Table A.5.

Mean values and standard errors of the mean (SE) for all dependent variables of the neuropsychological assessments of Study 1

	Dependent variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
WISC-IV	Full-scale IQ	Mean	89.409	101.055	95.159
		SE	1.390	1.954	1.867
	Verbal Comprehension	Mean	95.545	103.831	99.028
		SE	1.422	1.998	1.910
	Perceptual Reasoning	Mean	91.964	100.879	95.110
		SE	1.601	2.250	2.150
	Working Memory	Mean	87.650	97.215	95.117
		SE	1.569	2.205	2.107
	Processing Speed	Mean	91.399	101.590	95.212
		SE	1.771	2.489	2.379
VLMT	Immediate Recall	Mean	46.292	45.326	45.324
		SE	1.285	1.810	1.639
	Delayed Recall	Mean	51.831	53.313	54.368
		SE	1.265	1.781	1.613
	Recognition	Mean	47.881	50.110	45.736
		SE	1.428	2.011	1.821
T.O.V.A.	API	Mean	-0.888	0.349	-1.652
		SE	0.417	0.593	0.536
	Variability	Mean	84.294	93.225	80.837
		SE	2.560	3.644	3.289
	Response Time	Mean	91.270	94.442	84.277
		SE	2.559	3.643	3.289
	Commission Errors	Mean	95.450	98.935	95.566
		SE	2.583	3.677	3.319
	Omission Errors	Mean	72.569	82.234	81.809
		SE	3.252	4.629	4.179

Mean values for the WISC-IV and the T.O.V.A. in standard scores: mean = 100, SD = 15;

Mean values for the VLMT in T-scores: mean = 50, SD = 10

Table A.6.

Mean values and standard errors of the mean (SE) for all variables of the Conners-3 parent and teacher evaluation

Dependent variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
	parent evaluation			
Inattention	Mean	65.036	54.868	68.119
	SE	0.882	1.280	1.109
Hyperactivity/Impulsivity	Mean	59.910	49.031	61.061
	SE	1.306	1.895	1.642
Learning Problems	Mean	65.300	50.961	62.600
	SE	1.749	1.665	1.197
Executive Functioning	Mean	64.580	49.115	65.600
	SE	1.389	1.326	1.446
Defiance/Aggression	Mean	56.462	48.769	57.300
	SE	1.414	1.057	1.678
Peer Relations	Mean	60.865	52.500	59.700
	SE	1.468	1.741	2.051
ADHD Index	Mean	62.431	53.615	65.533
	SE	0.907	0.959	1.126
Global Index	Mean	60.255	50.154	64.500
	SE	1.139	1.433	1.528
	teacher evaluation			
Inattention	Mean	66.739	53.677	65.325
	SE	1.710	2.378	1.977
Hyperactivity/Impulsivity	Mean	61.844	50.212	59.508
	SE	1.540	2.142	1.781
Learning Problems	Mean	65.050	54.864	61.778
	SE	1.448	1.596	1.616
Executive Functioning	Mean	63.275	50.646	63.889
	SE	1.600	1.436	1.732
Defiance/Aggression	Mean	50.231	50.000	49.519
	SE	1.329	0.431	0.422
Peer Relations	Mean	63.488	60.818	65.481
	SE	1.465	1.518	1.444
ADHD Index	Mean	65.073	55.091	64.704
	SE	1.508	1.660	1.827
Global Index	Mean	62.805	54.182	63.852
	SE	1.559	1.634	1.723

Mean values in T-scores: mean = 50, SD = 10

Table A.7.

Mean values and standard errors of the mean (SE) for the dependent variables of the BRIEF parent evaluation

Dependent variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
Global Executive Composite	Mean	62.582	47.655	64.562
	SE	1.808	2.381	1.828
Behavioral Regulation Index	Mean	57.657	47.836	60.515
	SE	2.134	2.811	2.158
Metacognition Index	Mean	64.909	48.262	66.390
	SE	1.826	2.405	1.846
Inhibit	Mean	62.241	49.304	62.406
	SE	2.217	2.920	2.242
Shift	Mean	54.441	47.801	57.958
	SE	2.127	2.802	2.150
Emotional Control	Mean	52.231	47.351	56.118
	SE	2.016	2.655	2.038
Initiate	Mean	60.013	50.290	62.849
	SE	1.896	2.497	1.916
Working Memory	Mean	64.146	49.016	68.652
	SE	1.684	2.217	1.702
Plan/Organize	Mean	62.208	48.220	65.171
	SE	1.848	2.434	1.868
Organization of Materials	Mean	57.336	46.837	56.089
	SE	2.123	2.796	2.146
Monitor	Mean	63.332	48.147	62.677
	SE	1.691	2.227	1.709
Monitoring of Task Performance	Mean	61.654	50.067	61.924
	SE	1.860	2.450	1.880
Self Monitoring	Mean	61.476	47.421	60.917
	SE	1.867	2.459	1.887

Mean values in T-scores: mean = 50, SD = 10

Table A.8.

Mean values and standard errors of the mean (SE) for the dependent variables of the BRIEF teacher evaluation

Dependent variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
Global Executive Composite	Mean	63.246	46.048	62.210
	SE	2.228	3.132	2.149
Behavioral Regulation Index	Mean	57.447	46.582	57.732
	SE	2.146	3.017	2.070
Metacognition Index	Mean	64.315	46.367	62.865
	SE	2.152	3.026	2.076
Inhibit	Mean	60.046	45.498	58.991
	SE	2.143	3.013	2.067
Shift	Mean	57.571	50.792	55.981
	SE	2.389	3.359	2.304
Emotional Control	Mean	54.872	49.650	55.346
	SE	2.292	3.223	2.211
Initiate	Mean	65.145	48.131	62.231
	SE	2.203	3.097	2.125
Working Memory	Mean	65.032	50.910	63.348
	SE	2.372	3.335	2.288
Plan/Organize	Mean	63.239	47.620	61.032
	SE	2.269	3.190	2.189
Organization of Materials	Mean	56.806	46.539	58.211
	SE	2.671	3.756	2.577
Monitor	Mean	62.743	49.297	61.621
	SE	2.267	3.187	2.187
Monitoring of Task Performance	Mean	62.620	48.497	62.085
	SE	2.330	3.276	2.248
Self Monitoring	Mean	60.846	50.630	58.790
	SE	2.267	3.187	2.187

Mean values in T-scores: mean = 50, SD = 10

Table A.9.

Mean values and standard errors of the mean (SE) for the dependent variables of the Kiddo-Kindl

Dependent variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
Physical well-being	Mean	0.190	0.359	0.179
	SE	0.207	0.305	0.245
Mental well-being	Mean	-0.181	0.297	-0.424
	SE	0.205	0.303	0.243
Self-Esteem	Mean	0.087	0.340	0.029
	SE	0.102	0.151	0.121
Family	Mean	-0.632	0.012	-0.703
	SE	0.198	0.292	0.234
Friends	Mean	-1.171	-0.245	-1.054
	SE	0.228	0.335	0.269
School	Mean	-0.177	0.887	-0.293
	SE	0.184	0.270	0.217
Cronic Disease	Mean	1.461	1.319	1.459
	SE	0.165	0.243	0.195

Mean values in z-scores: mean = 0, SD = 1

Table A.10.

Mean values and standard errors of the mean (SE) for all variables of the CBCL

Dependent variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
Total Score	Mean	63.882	54.5	62.767
	SE	1.269	1.777	1.654
Externalizing	Mean	59.824	50.962	61.467
	SE	1.355	1.898	1.767
Internalizing	Mean	58.412	54.923	60.467
	SE	1.475	2.066	1.923
Anxious/Depressed	Mean	58.647	54.5	60.8
	SE	1.103	1.544	1.438
Withdrawn/Depressed	Mean	58.020	56.308	59.3
	SE	1.090	1.527	1.422
Somatic Complaints	Mean	60.275	59.231	58.767
	SE	1.255	1.757	1.636
Social Problems	Mean	69.510	56.808	64.033
	SE	1.475	2.066	1.923
Thought Problems	Mean	57.510	55.731	55.433
	SE	1.243	1.741	1.621
Attention Problems	Mean	68.667	56.038	67.333
	SE	1.222	1.711	1.593
Rule-Breaking Behavior	Mean	58.980	52.269	58.367
	SE	1.001	1.402	1.305
Aggressive Behavior	Mean	61.882	53.577	62.833
	SE	1.217	1.704	1.586

Mean values in T-scores: mean = 50, SD = 10

A.2. Supplemental Data for Study 2

A.2.1. Equality of Variances and Normality of Distribution

Table A.11.

Equality of variances via Levene's test and normality of distribution via Shapiro-Wilk-test for the dependent variables of Study 2

Dependent variable	equality of variances (sig.)	normality of distribution (sig.)		
		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
	Demographic data			
Age	.393	.096	.266	.413
SES	.575	.820	.642	.991
	WISC-IV			
full-scale IQ T1	.101	.669	.824	.142
full-scale IQ T2	.609	.358	.072	.494
full-scale IQ T3	.772	.764	.848	.745
IQ difference T3-T1	.608	.033*	.251	.515
	T.O.V.A.			
API T1	.621	.001**	.022*	.175
API T3	.095	.027*	.286	.157
API difference T3-T1	.920	.066	.039*	.000***

*** < .001, ** < .01, * < .05

A.2.2. Mean Values and Standard Errors

Table A.12.

Mean values and standard errors of the mean (SE) for the dependent variables of the WISC-IV at T1, T2, and T3

	Dependent Variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
T1 WISC-IV	FIQ	Mean	89.703	101.457	95.113
		SE	2.258	2.318	2.343
	Verbal Comprehension	Mean	95.190	105.095	99.079
		SE	2.134	2.191	2.215
	Perceptual Reasoning	Mean	92.385	101.530	94.675
		SE	2.556	2.624	2.653
	Working Memory	Mean	88.792	96.732	94.703
		SE	2.388	2.452	2.478
	Processing Speed	Mean	90.671	100.635	95.830
		SE	3.010	3.091	3.124
T2 WISC-IV	FIQ	Mean	90.346	102.029	99.170
		SE	2.607	2.677	2.706
	Verbal Comprehension	Mean	98.536	107.105	104.187
		SE	2.633	2.837	2.733
	Perceptual Reasoning	Mean	92.432	99.877	103.407
		SE	2.758	2.972	2.863
	Working Memory	Mean	86.985	96.179	96.626
		SE	2.525	2.721	2.621
	Processing Speed	Mean	89.263	102.358	91.503
		SE	2.866	3.088	2.975
T3 WISC-IV	FIQ	Mean	91.234	103.648	99.528
		SE	2.866	2.943	2.975
	Verbal Comprehension	Mean	99.230	107.318	104.906
		SE	2.608	2.678	2.707
	Perceptual Reasoning	Mean	93.725	100.450	101.325
		SE	3.043	3.125	3.158
	Working Memory	Mean	85.985	98.353	96.117
		SE	2.755	2.829	2.860
	Processing Speed	Mean	91.306	104.397	93.297
		SE	2.852	2.928	2.960

Mean values in standard scores: mean = 100, SD = 15

Table A.13.

Mean values and standard errors of the mean (SE) for the dependent variables of the T.O.V.A. at T1, T2, and T3

	Dependent Variable		$NF1^{ADHD}$	$NF1^{only}$	$ADHD^{only}$
T1 T.O.V.A.	API	Mean	-0.878	0.470	-1.331
		SE	0.669	0.688	0.660
	Variability	Mean	83.933	94.191	81.649
		SE	3.991	4.109	3.941
	Response Time	Mean	89.420	93.539	86.495
		SE	3.973	4.090	3.923
	Commission Errors	Mean	101.378	100.043	94.443
		SE	3.830	3.944	3.782
	Omission Errors	Mean	73.687	84.955	81.903
		SE	4.960	5.106	4.897
T2 T.O.V.A.	API	Mean	-0.441	0.369	-0.856
		SE	0.665	0.721	0.657
	Variability	Mean	85.938	92.906	85.238
		SE	4.545	4.931	4.490
	Response Time	Mean	92.117	93.971	87.410
		SE	3.752	4.071	3.707
	Commission Errors	Mean	95.039	106.905	101.274
		SE	4.197	4.554	4.147
	Omission Errors	Mean	77.380	85.437	86.769
		SE	4.416	4.791	4.363
T3 T.O.V.A.	API	Mean	-0.576	1.042	-0.499
		SE	0.658	0.690	0.650
	Variability	Mean	83.631	95.276	85.651
		SE	4.145	4.343	4.095
	Response Time	Mean	90.674	98.691	92.803
		SE	3.226	3.380	3.187
	Commission Errors	Mean	104.659	104.720	101.881
		SE	3.252	3.408	3.213
	Omission Errors	Mean	77.496	89.625	84.090
		SE	4.915	5.150	4.856

Mean values in standard scores: mean = 100, SD = 15

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