

Chapter 5

The Cognitive Profile of NF1 Children: Therapeutic Implications

Natalie A. Pride and Kathryn N. North

5.1 Human Cognitive Studies in NF1 Children

5.1.1 Introduction

Cognitive impairment is one of the most common complications of NF1 in childhood; approximately 70 % of affected individuals have learning difficulties and/or neuropsychological deficits. Cognitive dysfunction is an important cause of lifetime morbidity as it impacts on an individual's scholastic achievement, employment opportunities, and overall quality of life. Over the past 15 years, a great deal of research has been devoted to characterising the cognitive phenotype of NF1. Although there is marked variability between individuals with NF1, a number of core neuropsychological features have been identified—which, in turn, provide a basis for studies of disease mechanism and targets for therapy. The purpose of this chapter is to summarise the features of the NF1 cognitive phenotype and current knowledge concerning pathogenesis and potential therapies.

5.1.2 General Intellect and Academic Functioning

Mental retardation was once thought to be frequent in NF1, with early studies reporting that approximately 30 % of individuals with NF1 have an intellectual disability (Samuelsson and Axelsson 1981). However, these studies focused

N.A. Pride

Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead Sydney, Sydney, Australia

K.N. North (✉)

University of Sydney, Sydney, Australia

e-mail: kathryn.north@health.nsw.gov.au

predominately on severely affected individuals and did not use quantitative psychometric assessment, resulting in ascertainment bias and gross overestimation of the frequency of mental retardation. Based on quantitative data from large cohorts of patients with a range of physical manifestations, it is now accepted that between 4 % and 8 % of individuals with NF1 fall into the intellectually impaired range ($IQ < 70$) compared to approximately 3 % in the general population (Hyman et al. 2005; North et al. 1997). Typically, full-scale IQ tends to fall within the average to low average range (high 80s to low 90s) (Hyman et al. 2005; Levine et al. 2006). Early studies reported a profile of better verbal skills and poorer perceptual organisational skills (Eliason 1986; Legius et al. 1995), although most studies have found a similar pattern of verbal and non-verbal skills (Ferner et al. 1996; Hyman et al. 2005; Moore et al. 2000; North et al. 1995). Some authors have proposed a particular neuropsychological model, non-verbal learning disorder (NVLD), to describe some aspects of the NF1 cognitive phenotype (Eliason 1986; Wang et al. 2000). The NVLD profile involves a pattern of poor mathematical ability; visuospatial, fine motor, and handwriting deficits; and social problems in the presence of sound verbal skills (Harnadek and Rourke 1994). Although deficits in mathematical ability and visuospatial skills are extremely common in NF1, there has been movement away from the conceptualisation of NF1 as an NVLD as recent studies have documented language, spelling, and reading impairments. Dyslexia, a specific reading disability, appears to be common in NF1 (Hofman et al. 1994; Mazzocco et al. 1995); one study found that approximately 50 % of their cohort met the diagnostic criteria for phonological dyslexia, i.e. impaired non-word reading and a specific difficulty in utilising spelling to sound rules to read (Watt et al. 2008). Specific impairments in phonological processing, including phoneme segmentation, rapid naming, phonological memory, word recognition, and decoding, have also been reported (Cutting and Levine 2010; Mazzocco et al. 1995). This pattern of deficits is comparable to the pattern of deficits seen in children with idiopathic reading disorders (Cutting and Levine 2010).

The reported frequency of learning disorder (LD) in NF1 varies across studies with estimates ranging between 30 % and 65 % (Brewer et al. 1997; Clements-Stephens et al. 2008; Ferner et al. 1996; Huson et al. 1988; Hyman et al. 2006; North et al. 1997). This variability in frequency is due to the use of different definitions of LD by different researchers. According to the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) (American Psychiatric Association 2000), an LD is diagnosed when the individual's achievement on individually administered, standardised tests in reading, mathematics, or written expression is substantially below that expected for age, schooling, and level of intelligence. A variety of statistical approaches can be used to establish that a discrepancy is significant. "Substantially below" is usually defined as a discrepancy of more than 2 standard deviations (SD) between achievement and IQ; however, a smaller discrepancy (between 1 and 2 SD) has also been used, resulting in inconsistency between studies. In one study involving a large cohort of 81 children with NF1 (and 49 unaffected controls), Hyman et al. (2006) examined the frequency of specific learning disabilities (SLD) as defined by a discrepancy of 2 SD between IQ

and achievement on co-normed standardised tests (WISC III and WIAT) and found that 20 % of their cohort presented with an SLD, 32 % had a general learning difficulty (impaired academic achievement commensurate with low IQ), and 48 % had age-appropriate academic abilities. A strong gender effect for SLD was also reported with the bulk of this group being male. This has important implications for assessment and remediation and suggests that females with NF1 are at no greater risk of SLD than those in the general population.

5.1.3 Visual Spatial Function

One of the hallmark features of the NF1 cognitive phenotype is visual spatial impairment, characterised by a problem accurately perceiving and interpreting visual information. The Judgement of Line Orientation Task (JLO) is a test that is consistently used to measure this ability in the NF1 literature, and approximately 80 % of studies have documented deficits on this test in children with NF1 (Dilts et al. 1996; Hofman et al. 1994; Hyman et al. 2005, 2007; Levine et al. 2006; Mazzocco et al. 1995; Schrimsher et al. 2003). Many of these studies report impairment on this measure in a large majority of their NF1 cohort. For example, Hyman et al. (2005) compared 81 children with NF1 to 49 unaffected siblings and found 56 % of NF1 children performed within the impaired range on the JLO (greater than 1 SD below the general population mean). Deficits on a range of other tests that are sensitive to visual spatial and visual perceptual function such as the Beery-Buktenica Visual-Motor Integration Test, the Rey Complex Figure Test, block design subtest of the Wechsler Intelligence Scales, and the Test of Visual Perceptual Skills have also been identified in NF1 (Dilts et al. 1996; Hyman et al. 2005).

5.1.4 Attention

Attention deficit hyperactivity disorder (ADHD) is a neurobiological disorder that is characterised by persistent and pervasive symptoms of inattention, hyperactivity, and impulsivity. Although the exact incidence of ADHD in NF1 is unknown, estimates have ranged from 33 % to 49.5 % of study cohorts (Hofman et al. 1994; Kayl et al. 2000; Koth et al. 2000; Mautner et al. 2002; Payne et al. 2011), a marked increase above the estimates of ADHD in the general population (5 %) (Polanczyk et al. 2007). The majority of studies have shown that children with NF1 are more likely to meet the criteria for predominately combined or inattentive subtype of ADHD, and the frequency of the ADHD diagnosis across genders in NF1 is generally equal. This is in contrast to ADHD in the general population where the incidence rate is 2.5–9.0 times higher in males than females (Durstun 2003).

Attention is not a unitary process but refers to a multifaceted range of cognitive processes that operate through a variety of neural networks. It is central to the process of information reduction, response selection, and planning for eventual actions. Deficits on a number of tasks designed to measure distinct facets of attention have been documented in NF1. Continuous Performance Tests (CPTs) such as the Test of Variables of Attention (TOVA) and the Kiddie's CPT are common measures used to assess sustained attention (using errors of omission) and are frequently found to be impaired in NF1. Higher rates of errors of omission have been documented in children with NF1 when compared to unaffected siblings (Mazzocco et al. 1995; Sangster et al. 2011) and normative data (Ferner et al. 1996). Conversely, normal levels of CPT errors of omission have been reported elsewhere (Dilts et al. 1996; Mautner et al. 2002). Although there is inconsistency in these findings, there is sufficient evidence from studies using alternative measures of sustained attention to support a true sustained attention deficit in this population (Hyman et al. 2005). Studies investigating other areas of attention such as selective attention have offered inconsistent findings. Ferner et al. (1996) administered the Stroop Task to 98 children with NF1 and 105 matched controls and found this task was consistently impaired in children with NF1. Nonetheless, this conclusion should be viewed with caution given that this task relies on other cognitive processes to be completed successfully including response inhibition and single-word reading. In a recent study, which used the Sky Search subtest from the TEA-Ch to assess selective attention, Payne et al. (2011) found that NF1 patients ($n = 199$) performed significantly worse than unaffected controls ($n = 55$). In contrast, Hyman et al. (2005) did not find any differences between children with NF1 ($n = 81$) and unaffected siblings ($n = 49$) on this same measure. Inconsistencies between studies regarding the presence of selective attention deficits are likely a result of variability in subject selection and choice of control group (i.e. unaffected siblings versus matched controls) further highlighting the need for well-characterised samples and appropriate controls. Nevertheless, attention deficits are one of the most common manifestations of the NF1 cognitive phenotype. Studies that identify the underlying neurobiology and biochemical mechanisms involved are likely to provide important insights into the best targeted therapies for ADHD in children with NF1 as well as the pathogenesis of ADHD in the general population.

5.1.5 Executive Function

Several behavioural characteristics, including an unstructured learning style, distractibility, impulsivity, failure to plan, and poor problem-solving skills, were identified in early studies of children with NF1; these characteristics are reminiscent of the kinds of impairments seen in patients with prefrontal cortical damage (Bawden et al. 1996; Eliason 1986; North et al. 1995). During recent years, there has been a significant increase in the body of literature supporting a primary role for

executive function deficits in the NF1 cognitive phenotype. Executive functions refer to a set of abilities that regulate and control other abilities and behaviour, e.g. the ability to problem-solve, shift attentional flexibility, monitor and change behaviour, and plan future behaviour when faced with novel tasks and situations. Executive dysfunction is thought to be a result of damage to the frontal regions of the brain, in particular, the prefrontal cortex, as well as subcortical regions. Deficits in a wide range of executive functions have been reported in NF1 including cognitive flexibility (Hyman et al. 2005; Joy et al. 1995; Payne et al. 2011; Zoller et al. 1997), set-shifting (Hofman et al. 1994; Mazzocco et al. 1995), abstract concept formation (Hyman et al. 2005; Payne et al. 2011), working memory (Huijbregts et al. 2010; Rowbotham et al. 2009), response inhibition (Ferner et al. 1996; Mautner et al. 2002), divided attention (Ferner et al. 1996; Payne et al. 2011), and planning (Bawden et al. 1996; Hofman et al. 1994; Hyman et al. 2005; Mazzocco et al. 1995; Payne et al. 2011; Roy et al. 2010). For the school-aged child with NF1, executive dysfunction may cause problems in several areas in the classroom. A rigid work style and cognitive inflexibility can contribute to difficulty adjusting to the school environment at an age-appropriate level, such that for some children a small departure in expected routine may result in adjustment difficulties and feelings of anxiety. Executive deficits can also make it difficult to start and finish work, keep track of assignments, and allocate their time. Executive dysfunction is associated with behavioural disturbance, social dysfunction, and reduced quality of life (Baron 2004; Lezak et al. 2004).

5.1.6 Memory and Learning

The terms “learning” and “memory” are often used interchangeably—even though they represent a range of diverse cognitive processes. Learning refers to how we acquire new information, whereas memory is the process by which that information is encoded, stored, and later retrieved. The hippocampus, located in the medial temporal lobe of the brain, has been linked to learning and memory function (Kandel et al. 2000). Distinct from these memory systems is working memory, which is heavily associated with the dorsolateral prefrontal cortex. Working memory is the ability to temporarily store and manipulate information in mind and is considered an executive function rather than part of the memory system. Although working memory impairment has been well documented in NF1 (see Sect. 5.1.4), controversy exists surrounding the presence of learning and memory deficits. While some studies report that the ability to learn and retrieve new information is intact in children with NF1 (Hyman et al. 2005; Joy et al. 1995; Moore et al. 1996), others do not (Ferner et al. 1996; Payne et al. 2012; Ullrich et al. 2010). The majority of these studies make it difficult to ascertain whether children with NF1 experience true memory impairment as the tests used to assess memory also require other cognitive functions such as language or visuospatial abilities. Recently, Payne et al. (2012) examined visuospatial learning in 71 children with NF1 and 29 unaffected controls



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