EMPOWERING POTENTIAL

WORKING MEMORY CHARACTERISTICS AND TRAINING POSSIBILITIES IN CHILDREN WITH INTELLECTUAL DISABILITIES AND/OR NEURODEVELOPMENTAL DISORDERS

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Empowering potential

Working memory characteristics and training possibilities in children with intellectual disabilities and/or neurodevelopmental disorders

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General introduction

Introduction

The aim of this thesis is to investigate the role of working memory (WM) abilities in the daily life and learning of children with intellectual disabilities (ID) and/or comorbid neurodevelopmental disorders. Despite the importance of WM in daily functioning, this neurocognitive function has been under-researched in children with ID and developmental disorders, such as attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and learning disorders (LD), regarding their daily functioning and learning. This thesis examines the WM strengths and weaknesses of these children, as well as possible shared underlying neurocognitive mechanisms. Additionally, this thesis explores the potential for WM improvement through neurocognitive training and the role of coaching.

The present chapter provides a theoretical background to contextualize our studies on WM in this population. The topics covered in this chapter include the definition of ID, the co-occurrence with neurodevelopmental disorders, the definition of WM, existing research on WM in children with ID and/or neurodevelopmental disorders, and the effects of WM training and the role of coaching. Lastly, we present the specific research questions that we aim to answer through this thesis and the contents of the thesis.

Intellectual disabilities

The classification of ID has undergone significant changes in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), and it is now categorized as a neurodevelopmental disorder. The name of the condition has also changed, with "mental retardation" replaced by the more neutral term "intellectual disability". According to the DSM-5, ID begins during the developmental period and involves limitations in both intellectual functioning and adaptive behavior across the conceptual, social, and practical domains. The conceptual domain includes competencies related to memory, language, reading, writing, arithmetic reasoning, practical knowledge, problem solving, and decision making. The social domain includes empathy, interpersonal communication skills, the ability to form friendships, and social judgment. While the practical domain includes self-care, money management, leisure activities, self-management of behavior, and planning tasks at school. The severity level (mild, moderate, severe, or profound) of ID is determined by the child's adaptive functioning and is no longer solely based on IQ score. Therefore, the DSM-5 places greater emphasis

on adaptive functioning, as it determines the level of support needed in daily functioning and/or the care required. It also reduces reliance on IQ scores, while emphasizing the importance of clinical judgement. The DSM-5 additionally highlights the limitations of diagnostic tools and warns clinicians to be aware of these limitations.

To understand this new definition of ID in the DSM-5, it is important to know the history of its development. In the DSM-IV, a stringent IQ threshold of 70 was used, which, in clinical practice, led to the miraculous phenomenon that someone could alternate between having and not having an ID based on different scores on repeated IQ tests. For this reason, over the years, the field has increasingly used confidence intervals to display IQ test results (e.g., total IQ between 62-76), instead of a single score. In the DSM-5, the goal was to avoid including a stringent IQ threshold in the diagnostic criteria, while also making it clear that an IQ of 90 cannot indicate an ID. The DSM-5 criteria now require a deficiency in intellectual functioning that is established with an individualized standardized intelligence test, but deliberately does not specify a hard stringent cutoff score. This prevents clinicians from placing an excessive emphasis on individual IQ scores and making drastic decisions based on them. However, the accompanying text of the DSM-5 explicitly states the deficiency as exhibiting an IQ of 70 or lower. In this way, an attempt was made to provide guidance to clinicians (by mentioning an IQ of 70 or lower in the accompanying text), while also allowing for flexibility (by not including an IQ cut-off score in the criteria).

In clinical practice, children with IDs often present with a wide range of behavioral, practical, and academic difficulties and represent a significant burden on the mental healthcare system. A meta-analysis estimating the prevalence of ID in young people from 35 studies in the general population showed a prevalence of 1.5% to 2.1% based on the DSM-IV or ICD10 classification (Maulik et al., 2011). However, two recent studies using the same classification reported a lower prevalence of 1.2% (Maenner et al., 2016; Westerinen et al., 2017). None of the studies used the DSM-5 or ICD-11 criteria, which includes limitations in adaptive functioning.

Mild to borderline intellectual disability (MBID)

In the DSM-IV, the classification for borderline intellectual functioning (BIF) is based only on IQ (70-85), regardless of the patient's daily functioning. In the DSM-5, this criterion is no longer applicable, and a clinician's assessment is much more important in making a classification. The DSM-5 indicates that BIF may be relevant for classification, as it signifies a lack of adaptive functioning that may require specific support in daily functioning and/or care. The distinction

between BIF and mild ID (MID) is now based on the clinician's assessment. In practice, the BIF classification is used when there is a reason for concern or an expectation of a negative impact on the course of treatment/prognosis without meeting the criteria for MID. The prevalence of BIF is estimated to be as high as 10% (Roeleveld et al., 1997; Simonoff et al., 2006; Westerinen et al., 2017).

In this thesis, the focus is on children with MID and BIF defined according to the descriptions presented: they have respectively an IQ score < 70 or between 70 and 85 and have additional problems with adaptive behavior skills. In the Netherlands, children with BIF, who also experience (serious) additional problems, can access care intended for children with MID. This policy is implemented because this type of care often provides the most appropriate support. Therefore, although "MBID" isn't an official term in the DSM-5, we use it in this thesis to refer to the entire group of children with MID and BIF.

Understanding ID: a nuanced approach

In addition to the criteria decribed above, clinical practice has shown that children with MBID have heterogeneous deficits in cognitive functioning. MBID is a broad term that encompasses a range of intellectual abilities, and the cause of disability can vary greatly among individuals. Some children with MBID may have a genetic condition that affects their cognitive development, whereas others may have experienced brain trauma or infection during development (Carulla et al., 2013; World Health Organization, 2019). Additionally, environmental and psychosocial determinants (i.e., low socioeconomic status, low maternal education, malnutrition, and inadequate access to healthcare) are considered significant risk factors for MBID (Emerson, 2007; Nelson & Gabard-Durnam, 2020; Parnes et al., 2009; Trawicka et al., 2019). Given the complexity and variability of the factors that contribute to MBID, it is not surprising that even within the same category of MBID, children can have different strengths and weaknesses, and are at greater risk of developing neuro-developmental disorders which makes this group challenging to understand in clinical practice.

In the literature, two different theories concerning IDs have been put forward. The debate between developmental and difference theories of ID continues to be relevant. The developmental theory suggests that children with IDs develop at a slower rate than those without an ID but follow a similar trajectory. The difference theory argues that children with IDs have specific neurocognitive deficits that result in atypical development (Bennet-Gates & Zigler, 1998). For children with MBID, it is unclear which theory may be more applicable. When assessing the intellectual abilities of children with MBID, it is important to consider both their chronological and mental ages, as suggested

by Bayliss et al. (2005). Comparing their performance to typically developing children of the same chronological age may not be informative, as children with MBID are expected to perform at a lower level in most areas. Instead, comparing their performance to typically developing children of the same mental age can reveal specific areas of strength or difficulty.

In summary, the cause and nature of IDs in children remain complex and multifactorial, and recent research highlights the need for a more nuanced approach to assessing and understanding the neurocognitive abilities of children with IDs. Therefore, there is a critical need to develop effective interventions specifically tailored to these children.

MBID and comorbid neurodevelopmental disorders

Numerous studies have found that the prevalence rates of psychopathology in children with IDs range from 30% to 63% (Einfeld, Ellis & Emerson, 2011; Totsika et al., 2011; de Ruiter, 2013). Furthermore, studies comparing the prevalence of psychopathology in children with or without an ID found an increased risk (relative risk 2.8-4.5) for those with ID (Einfeld & Tonge, 1996). A population-based study also found a two- to three-fold increased risk in children with IDs compared to those without an ID, and this risk remained when compared to mental-age-matched children without an ID (Totsika et al., 2011). Few studies have reported psychopathology prevalence estimates specifically for children with MID, with rates ranging between 16% and 57% (Dekker et al., 2002; Einfeld & Tonge, 1996; Strømme & Diseth, 2000). Regarding psychopathology in children with BIF, only two studies have reported estimated prevalence rates, ranging from 15% to 20%, and odds ratios between 1.6 and 4.3 compared to peers without BIF (King et al., 2019; Emerson, Einfeld & Stancliffe, 2010).

Looking at psychopathology in more detail, 40–83% of children with ASD also meet the criteria for ADHD, while 28–87% of children with ASD exhibit ADHD symptoms (Mansour et al., 2017). Furthermore, numerous studies have reported a high comorbidity rate between learning disabilities (LD) and ADHD, with the prevalence rate ranging from 15% to 50% of children with ADHD meeting the criteria for LD and vice versa (Gayán et al., 2005; Langberg et al., 2010; Willcutt et al., 2012). Additionally, between 30% and 80% of children with ASD meet the criteria for ID (Baio, 2014; Itzchak, et al., 2008; Leyfer et al., 2006), and co-occurring ADHD and ID can be found in up to 14% of cases (Dekker & Koot, 2003; Strømme & Diseth, 2000). To our knowledge, there are currently no prevalence studies on psychopathology among young people with IDs that include adaptive functioning in their definition of ID.

Surprisingly, the severity of ID does not seem to be associated with the risk of mental health disorders among patients with IDs (Dekker et al., 2002; Einfeld & Tonge, 1996; Molteno et al., 2001; Strømme & Diseth, 2000). However, one study reported significantly higher rates of mental disorders in patients with more severe IDs than in those with less severe IDs (Molteno et al., 2001).

Neurocognitive functioning

The extent to which neurocognitive functions are affected in children with MBID is not fully understood, and research findings are mixed. While a meta-analysis demonstrated that children with IDs scored lower than their average intelligence peers in inhibition tasks, this difference was not observed in adults (Bexkens et al., 2013; Danielsson et al., 2010). Similarly, some studies found that children with MBID performed worse than their peers with average intelligence on cognitive flexibility tasks, but only when mental age was not considered (Danielsson et al., 2012; Henry & MacLean, 2002). However, in terms of response inhibition and cognitive flexibility, other studies have claimed that children with MBID show similar abilities to typically developing children, but with lower accuracy due to reduced self-monitoring (Ponsioen, 2001).

Furthermore, the processing speed of children with MBID is delayed, particularly in more complex tasks (Ponsioen & Van der Molen, 2002). Differences were observed in inhibition performance and processing speed; however, they were not consistent across the tasks used to measure these aspects of executive functioning (Schuiringa et al., 2017). The performance of children with MBID is often dependent on task structure, with worse performance on more unstructured tasks. Children with MBID often fail to perform such tasks in daily life because of their inability to adequately analyze and integrate relevant stimuli (Ponsioen, 2001). Overall, children with MID perform well on simple and structured tasks but struggle on more complex tasks, which are common in daily life (Collot d'Escury, 2007). This might be explained by a lower WM capacity, as unstructured tasks place greater demands on WM ability.

In addition, children with MBID and comorbid neurodevelopmental disorders exhibit WM problems and slower processing speeds, especially in situations where quick or complex responses are required (Santegoeds et al., 2022). This slower response time may be a significant factor in their performance on tasks that aim to measure higher-order neurocognitive processes that are often overlooked. This suggests that certain attentional processes, such as arousal regulation and sustained attention, may be relatively spared in children with MBID and comorbid neurodevelopmental disorders when controlling for processing speed (Santegoeds et al., 2022). According to this study, neuro-cognitive vulnerabilities are not solely responsible for internalizing and externalizing problems in children with MBID and comorbid neurodevelop-

mental disorders. Instead, the authors suggested that the relationship between the child's support needs, necessary adaptations (e.g., due to reduced processing capacity), and the environment's inability to offer the necessary adaptations may be more relevant in explaining these issues. However, even after controlling for IQ, children with both MBID and externalizing behavioral problems exhibited significantly worse WM performance (Schuiringa et al., 2017).

Therefore, although children with MBID and comorbid neurodevelopmental disorders may have similar IQ scores, they exhibit a heterogeneous range of neurocognitive impairment and clinical symptoms (Patel et al., 2020). This diversity in neurocognitive impairment and symptom manifestation makes it challenging to identify shared underlying factors within this clinically heterogeneous group. Nevertheless, identifying shared factors could aid in understanding the behavior of these children. It is currently unclear whether subgroups exist within this heterogeneous group of children with MBID and comorbid neurodevelopmental disorders at a neurocognitive level that can be related to behavioral correlates.

Working memory

One of the most prominent models concerning WM is Baddeley's multi-component WM model (Baars & Franklin, 2003; Cowan, 2005; Ashkenazi et al., 2013; D'Esposito & Postle, 2015; Kim et al., 2015). This model was first introduced by Baddeley and Hitch in 1974, and it revolutionized the rigid and dichotomous view of memory as either short- or long-term (see Figure 1; Baddeley & Hitch, 1974). The term "working memory" was first introduced by Miller, Galanter and Pribram in 1960.

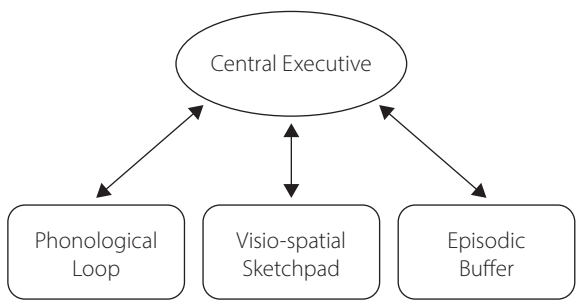

Figure 1: Schematic of Baddeley's Model (Baddeley, 2000a)

According to the multicomponent WM model, WM is a multicomponent system that manipulates information storage for greater and more complex neurocognitive utility (Baddeley & Hitch, 1974; Baddeley, 1996, 2000b). The model posits that WM consists of three subcomponents: the phonological loop (or verbal WM), the visuospatial sketchpad (or visual–spatial WM), and the central executive, which involves the attentional control system (Baddeley & Hitch, 1974; Baddeley, 2000b). In 2000, Baddeley introduced the episodic buffer, which is a temporary storage system that modulates and integrates different types of sensory information (see Figure 1), as another component of the WM model (Baddeley, 2000a).

The central executive functions as the "control center" which oversees the manipulation, recall, and processing of information (verbal or non-verbal) for meaningful functions such as decision-making, problem-solving, or manuscript writing. According to Baddeley and Hitch (1974), the information received during WM engagement can also be transferred to long-term storage. WM is not merely an extension and a useful version of short-term memory; it appears to be more closely related to activated long-term memory, as suggested by Cowan (2005, 2008), who emphasized the role of attention in WM. His conjectures were later supported by Baddeley (2010).

In addition, research has shown that there is a moderate correlation between WM and IQ, suggesting that the two constructs are separable but closely related. WM seems to be a significant predictor of academic achievement, even when controlling for IQ. In other words, WM abilities uniquely contribute to academic success, over and above the contribution of IQ (Alloway & Alloway, 2010). In addition, WM and IQ are related to various aspects of academic achievement. For example, WM has been found to be a better predictor of math and reading achievement than IQ (Alloway, 2009; Shinaver, Entwistle & Söderqvist, 2014). WM is also a stronger predictor of academic achievement in children with learning difficulties, such as dyslexia, than IQ (Swanson & Kim, 2007; Alloway & Alloway, 2010).

WM in children with MBID and/or neurodevelopmental disorders

WM deficits are a fundamental problem for many children with MBID and are associated with poor adaptive behavior and an increased risk of academic and social impairments (Cornish et al., 2012; Gilotty et al., 2002). Several studies have shown that children with MBID experience deficits in all three sub-components of WM compared with their peers without MBID (Henry, 2001; Van der Molen et al., 2007; Maehler & Schuchardt, 2009). However, research on children with IDs compared with mental-age-matched children has given inconsistent results. Some studies have found that these children do not

perform worse than their mental-age-matched peers on measures of the central executive component of WM, suggesting a developmental delay (Henry & MacLean, 2002; Van der Molen et al., 2007). Another study indicated a developmental delay in the visual-spatial sketchpad (Numminen et al., 2000), while some have even found evidence of structural differences that favored children with IDs (Henry & MacLean, 2002; Rosenquist et al., 2003). However, research has consistently shown that children with IDs perform worse than their mental-age-matched peers in the phonological loop, indicating a specific structural deficit in this area (Jarrold, Baddeley & Hewes, 2000; Henry, 2001; Henry & MacLean, 2002; Rosenquist et al., 2003; Hasselhorn & Mähler, 2007; Van der Molen et al., 2007). As the results of studies investigating the WM abilities of children with MBID have been inconsistent, and few have differentiated between subgroups with different degrees of ID, the specific WM strengths and weaknesses of these children have not yet been clearly established.

WM deficits are commonly observed in children with ADHD, owing to differences in the structure and function of certain brain regions. The prefrontal cortex, which is responsible for executive functions such as attention, impulse control, and WM, is particularly affected in children with ADHD (Cortese et al., 2012). Children with ADHD are known to have reduced activation in the dorsolateral prefrontal cortex, a region that plays a critical role in WM manipulation, compared with typically developing children. Additionally, there is evidence of decreased connectivity between the prefrontal cortex and other brain regions involved in WM, such as the parietal cortex (Cortese et al., 2012; Faraone et al., 2015). These structural and functional differences may explain the WM deficits observed in children with ADHD. Furthermore, ADHD symptoms such as impulsivity and inattention can further exacerbate WM deficits. Children with ADHD may have difficulty filtering out distractions and maintaining attention on the task at hand, which can interfere with the encoding and retrieval of information from the WM (Martinussen et al., 2005). Therefore, WM deficits in children with ADHD are likely due to differences in brain structure and function as well as symptoms that interfere with attention and information processing.

Children with ASD often exhibit deficits in WM, which can be attributed to differences in the structure and function of specific brain regions. For example, a study using magnetoencephalography identified atypical WM-related activity in the frontal, temporal, and parietal regions of children with ASD (Urbain, Pang & Taylor, 2015). Furthermore, a systematic review of functional neuroimaging studies found that individuals with ASD show functional brain asymmetries during memory processing in three anatomical planes (Desaunay et al., 2023). This review revealed that ASD participants had greater activity in the left

hemisphere than in the right, particularly in the posterior brain regions, including the hippocampus, and that individuals with ASD tend to rely more on the ventral (occipito-temporal) streams for memory processing rather than the dorsal (occipito-parietal) streams.

ASD and ADHD are separate neurodevelopmental disorders that exhibit common behavioral, neuropsychological, and neurobiological characteristics (Rommelse, et al., 2010; Rommelse, et al., 2011). Grey matter reductions in the left medial temporal lobe were observed as structural abnormalities in both clinical groups compared with controls (Brieber et al., 2007). This study suggests that shared structural deviations in the medial temporal lobe may be due to a generalized delay in brain development, which could lead to memory deficits. In contrast, the structural abnormalities found in the inferior parietal lobe may explain the attentional deficits observed in both ASD and ADHD. Furthermore, abnormalities in the prefrontal cortex have been observed in children with ADHD and LDs (Arnsten & Rubia, 2012; Barbey, Koenings & Grafman, 2013; Lazar & Frank, 1998). It has been suggested that ADHD, and LDs may share genetic risk factors and co-occur as neurocognitive disorders (Sexton et al., 2012). Although ADHD, ASD, and LDs have distinct diagnostic criteria, they share common neuropsychological features, suggesting the need for a more integrated approach to their assessment and treatment.

In summary, WM deficits are commonly observed in children with various neurodevelopmental disorders, including MBID, ADHD, ASD, and LDs. These deficits are associated with poor adaptive behavior, and academic and social impairments. They can be attributed to differences in the structure and functioning of specific brain regions involved in WM. Although there are some shared structural and functional abnormalities across these disorders, each has its distinct features and diagnostic criteria. The specific strengths and weaknesses of WM in these children has not yet been clearly established. However, research suggests that differences in brain structure and function may contribute to these deficits. In addition, there are shared neuropsychological and neuro-biological characteristics between these disorders. This suggests a need for a more holistic approach to assessing and treating these children.

Working memory training

McNab et al. (2009) suggest that WM capacity may be improved through training and that even small improvements in WM capacity can result in significant progress in the classroom and daily life functioning (Minear & Shah, 2006). For children with MBID, who commonly exhibit WM deficits and frequently face adaptive and academic achievement problems, computerized

working memory training (WMT) may be a promising intervention that can be performed at home and/or at school. WMT appeals to their relatively strong visual abilities (Van der Molen et al., 2014), can be customized to each child's specific WM strengths and weaknesses because of its adaptive nature, and is motivating due to its gamified elements (Dovis et al., 2012; Sadeghi et al., 2020). Limited research has been conducted on WMT in children with MBID. However, the scarce research available has demonstrated that WMT can enhance academic performance, especially in reading and math, among these children (Danielsson et al., 2015; Söderqvist et al., 2012; Van der Molen et al., 2010).

In addition, studies in children with learning problems have reported improvements in reading performance and academic achievement after WMT (Loosli, et al., 2012; Dahlin, 2011; Holmes, Gathercole & Dunning, 2009). Others have found no transfer effects on non-trained neurocognitive tasks or academic achievement in children with severe LDs and comorbid ADHD (Gray et al., 2012). There have been some promising results in studies involving children with ADHD. These studies demonstrate improvements in non-trained visuo-spatial WM tasks, neurocognitive function, and parental ratings of inattention and hyperactivity–impulsivity for up to three months following training. For instance, a multicenter, randomized, controlled, double-blind study conducted by Klingberg, Forssberg and Westerberg (2002) showed such improvements, while other studies have reported positive long-term transfer effects on visual WM capacity and ADHD deficits (Hovik, Saunes, Aarlien & Egeland, 2013; Bigorra et al., 2016).

However, meta-analyses have been more critical and suggested that better evidence is required before neurocognitive training can be designated as an effective intervention for ADHD, due to limited generalization and a lack of long-term effects (Cortese et al., 2015; Hodgson, Hutchinson & Denson, 2014; Rapport et al., 2013; Sonuga-Barke et al., 2013; Westwood et al., 2023). Additionally, two other reviews have raised concerns regarding the long-term effects of WM training in diverse patient groups and with different types of WM training methods (Melby-Lervåg & Hulme, 2013; Shipstead, Redick & Engle, 2012). On the other hand, critics question the arguments and conclusions drawn from these reviews and argue that WM capacity, attention, and academic abilities do improve after Cogmed WM training (Shinaver, Entwistle & Söderqvist, 2014). Furthermore, the effectiveness of computerized WMT in diverse patient groups cannot easily be applied to children with MBID and neurodevelopmental disorders, given their distinct neurocognitive profile, as noted by Danielsson et al. (2012).

The inconsistent findings regarding the effectiveness of WMT could be due to the impact of coaching. Randomized controlled designs in most studies require blinded coaching. This prohibits coaches from tracking progress or adjusting training programs based on participant performance. However, personalized coaching using real-time data can tailor training programs to address specific needs, potentially enhancing the effectiveness of neuro-cognitive training. Foster (2019) supports the efficacy of coaching-based neurocognitive training programs, demonstrating larger effect sizes than similar studies without coaching. For example, while Melby-Lervåg and Hulme (2013) reported effect sizes of less than 1.0 for WM outcomes, Foster's study achieved effect sizes of 1.76, 1.28, and 1.45, suggesting that coaching significantly influences participant performance. Although research has not yet explored whether active coaching benefits far-transfer tasks, it may assist participants in learning effective strategies and understanding tasks better, leading to improved WM performance and greater transfer to other neuro-cognitive functions or daily life activities.

Overall, more research is needed to fully understand the potential benefits and limitations of neurocognitive training for children with MBID and/or neurodevelopmental disorders.

Research questions

The present thesis focuses on investigating WM abilities in children with MBID and/or comorbid neurodevelopmental disorders (ADHD, ASD, and/or LDs). This thesis has two main objectives: a) to uncover the neurocognitive characteristics of children with MBID and/or comorbid neurodevelopmental disorders, and b) to study the effectiveness of WMT in these children and the role of coaching during the treatment period.

When children with MBID perform worse than their chronologically age-matched peers, but at the same level as their mentally age-matched peers, it could indicate that their WM abilities develop typically, but at a delayed rate. However, when children with MBID perform worse than their chronological and mental age-matched peers, it would suggest poor WM abilities as well as delayed development. Also, identifying neurocognitive subtypes within a heterogeneous group of children with MBID and neurodevelopmental disorders may help us better understand the shared mechanisms underlying MBID and comorbid ADHD and/or ASD in relation to behavioral outcomes.

Additionally, a computerized WMT program will be provided to children with neurodevelopmental disorders, including those with comorbid MBID. This program will investigate the effectiveness of WMT and its impact on related neurocognitive abilities, academic achievement, and behavioral outcomes. This thesis will also explore the role of coaching during the WM treatment process.

The following research questions will be addressed:

1. Are there differences in WM abilities between children with MBID and typically developing children of the same chronological age, or younger, typically developing children of the same mental age?
2. Do neurocognitive subgroups exist within the heterogeneous group of children with MBID and comorbid neurodevelopmental disorders, and if so, do these subgroups differ in behavioral correlates?
3. Can WM be effectively trained in children with neurodevelopmental disorders with or without MBID, and if so, does this affect other neurocognitive abilities and/or behaviors?
4. What is the role of coaching during WM treatment in children with MBID and neurodevelopmental disorders?

Chapter 2 focuses on WM characteristics in children with MBID (IQ range: 50-85). In this chapter, the results of a systematic review of 11 papers are presented, which investigates whether WM in children (aged 4 to 18) with MBID differs from that of typically developing children of the same chronological age, or from younger, typically developing children of the same mental age. When applicable, we differentiated between subgroups with different degrees of IDs.

Chapter 3 presents the results of a latent profile analysis in a clinical-based sample (n = 118) of children (aged 10y 0m – 13y 11m) with MBID (60< IQ <85) and ADHD and/or ASD, exploring subgroups that are homogeneous at a cognitive level. This study is performed to further our understanding of the shared mechanisms underlying MBID and comorbid ADHD and/or ASD in relation to behavioral correlates.

Chapter 4 describes a naturalistic, open-label, non-randomized, controlled intervention study, researching WMT effects in different groups of children (n = 99), aged between 7 and 17 years with neurodevelopmental problems, i.e., ADHD, LDs, or learning problems. Training efficacy was determined by WM capacity improvement, changes in ADHD symptom behavior, and daily experienced executive functioning.

Chapter 5 shows the results of a triple-blind, placebo-controlled, randomized clinical trial investigating whether adaptive computerized WMT leads to significantly more improvement on a non-trained visuospatial WM task compared to a non-adaptive control WMT (placebo) in children (aged 10y 0m – 13y 11m) with BIF (70< IQ <85) and neurodevelopmental disorders (ADHD and/or ASD). As secondary outcome measures, we used the scores on several non-trained neuropsychological and neurocognitive near and far-transfer tasks as well as behavioral measures.

Chapter 6 reports the design and results of a double-blind, randomized controlled trial on the effectiveness of a prolonged but less intensive version of WMT, with personalized coaching and feedback on neurocognitive functioning, academic performance, and behavioral symptoms in children (aged 10y 0m – 13y 11m) with neurodevelopmental disorders (ADHD and/or ASD) and MBID, compared to a prolonged but less intensive version of WMT without personalized coaching and feedback.

Chapter 7 provides a summary of the study results and an overview of the main conclusions of this thesis. Implications for clinical practice and future research are discussed.

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2

Working memory in children with mild to borderline intellectual disabilities: A Systematic review of strengths and weaknesses

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Abstract

Background: Limitations in Working Memory (WM) appear to play a crucial role in the development of learning problems and behavioral problems in children with Mild to Borderline Intellectual Disabilities (MBID). Increasing our understanding about WM strengths and weaknesses in this vulnerable population, offer more insight into what type of support is best for these children.
Method: This review employed a systematic literature review (N=11) to investigate whether WM in children (aged 4 to 18) with MBID (IQ range 50-85) differs compared to (1) typically developing children of the same Chronological Age (CA) and (2) younger, typically developing children with the same Mental Age (MA).
Conclusion: The visuospatial WM system is a relatively strong aspect, in particular for those higher functioning MBID children (IQ range between 70-85). In contrast to this, verbal WM performance appears to be rather weak in this group. This verbal WM deficiency contributes to problems with reading, writing and numeracy. It is, therefore, important to stimulate WM both at home and at school from an early age. Additionally, training programs could be initiated that focus not only on enhancing WM but also on acquiring memory strategies to increase generalizability to daily activities.

Introduction

Estimates of the prevalence of Mild to Borderline Intellectual Disabilities (MBID; IQ score 50-85) in the general population vary greatly, according to the definitions and methods used. In Western countries, the population prevalence of Mild Intellectual Disabilities (MID) is estimated to be 0.7% (Westerinen, Kaski, Virta, Almqvist, & Iivanainen 2007). On the basis of the normal distribution of intelligence in the general population, 2.14% would have a IQ in the 50–70 range (MID) and 13.59% in the 71–84 range Borderline Intellectual Functioning (BIF). Children with MBID encounter a diversity of learning problems, such as spelling, reading and/or numeracy (e.g. Verhoeven, & Vermeer, 2006). These problems appear often to be persistent and demand additional alternative support at school (Simonoff et al., 2006). Limitations in working memory (WM) appear to play a crucial role in the development of these learning problems, as well as in the development of behavioural problems both in typically developing children (e.g. Bull, Espy, & Wiebe, 2008) and in children with MBID (Schuiringa et al., 2017). The conclusion from an integrative review into WM of people with a learning disability was that WM performance is determined by the interaction between two types of moderators: personal characteristics (IQ, chronological and mental age) on the one hand, and task characteristics (verbal, visuospatial, executive functioning) on the other. The cognitive task burden influences this process (Lifshitz, Kilberg, & Vakil, 2016). This study included a broad population both in terms of age range (children and adults), and the degree of intellectual disability (mild to borderline). Furthermore, people with intellectual disabilities and a specific syndrome (e.g. Down's syndrome) were also included in this study. This hinders any conclusions about WM functioning in a more specific target group, i.e. children with MBID without diagnosed syndromes, as certain syndromes have specific WM profiles (Gathercole, & Alloway, 2006). Given that standardized interventions developed for cognitively able children are often too complex for these children, due to their limited cognitive and adaptive skills, it is important to start searching for alternatives. The more because children with MBID represents a significant group within mental health care. Prevalence studies have estimated that approximately 39% of children with a full-scale IQ score between 30 and 80 have an additional *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* (DSM-IV) diagnosis (Dekker & Koot, 2003), compared to approximately 22% in the general population (Verhulst, van der Ende, Ferdinand, & Kasius, 1997) and are comparable with estimates found in other studies (e.g. Emerson, 2003). Increasing our understanding will also offer more insight into what type of support is best for these children. Therefore, it is important to gain - through literature review -

more insight into the strengths and weaknesses of WM in this vulnerable group of children.

WM has been extensively investigated in recent years and is viewed as a central construct within cognitive psychology. Baddeley's (1986) WM model is the most utilised model within clinical practice and science for typically developing children aged 4 and above (Alloway, Gathercole, Willis, & Adams, 2004), as well as for children with learning problems (Gathercole, & Alloway, 2008) and for children with MBID (Henry, 2012). The WM model comprises four components: The visuospatial sketchpad, phonological loop, central executive and episodic buffer. The visuospatial sketchpad and phonological loop are responsible for the temporary storage of visual and verbal information, respectively. The so-called automatic rehearsal process can activate incoming information for the phonological loop. This is affected by the rate of speech and word length (Russel, Jarrold, & Henry, 1996). Both the visuospatial sketchpad and phonological loop are coordinated by the central executive. This is an active attention system, which both saves and processes stored information, and uses information from long-term memory to carry out complex cognitive activities. Tasks that concurrently invoke the visuospatial sketchpad, phonological loop and central executive, are presumed to be WM tasks. The fourth component, the episodic buffer, stores information in a multidimensional code; this is also directed by the central executive and serves as a temporary link between the visuospatial sketchpad and phonological loop and long term memory (Baddeley, 2000a).

This review employed a systematic literature review to investigate WM in children with MBID. The review evaluated whether WM in children with MBID differs compared to (1) typically developing children of the same chronological age (CA) and (2) younger, typically developing children with the same mental age (MA). It was assumed that children with MBID would do less well on WM tasks compared to children of the same CA, but as well as children with the same MA. This expectation is in line with the developmental theory that assumes that children with MBID achieve a lower cognitive ceiling compared to CA control children; however, it contrasts with the "difference" or "defect" theory, which assumes that children with MBID also do less well than children in the MA control group (Bennet-Gates, & Zigler, 1998). This review will enhance our knowledge of the strengths and weaknesses of WM for this target group. This knowledge will lead to new insights regarding scholastic abilities, (individual) treatment options and support at school, ensuring an improvement in the care of children with MBID.

Method

Literature review

Normally, a meta-analysis of WM studies in the MBID population would be the best method to investigate the above hypotheses. Lifshitz, Stein, Weiss and Vakil (2011) published a meta-analysis of 40 studies focused on explicit memory in adults with MBID. This highlighted that people with MBID in general perform worse on explicit memory tasks compared to both CA and MA control groups. However, it should be noted that the aetiology of MBID in these studies was very diverse. Cohen (1988, 1992) observed that important information could be lost as a result of the 'summative effect' - information that could be of importance to the further treatment of specific patient groups falling significantly below the range of average performance. Therefore, given the heterogeneity of the MBID target group, a different method was selected, i.e. a systematic review, to enable a more detailed focus on how the differences in outcomes arise and what this may potentially mean for clinical practice.

Relevant studies were searched in the following databases: Psycinfo, Medline and Pubmed with publication dates from January 1970 to June 2018. A combination of the following terms was used: 'mild intellectual disabilities', 'mild mental retardation', 'lower intellectual functioning', 'borderline intellectual functioning', in combination with the following terms: 'working memory', 'phonological loop', 'visuospatial sketchpad', 'visuo/visuospatial/verbal working memory'. Studies describing the relationship between WM in children (aged 4 to 18) with MBID (IQ range 50-85) were included.

Procedure

The original search returned 905 articles. The title and abstracts of these articles were screened by two researchers in line with the inclusion criteria, resulting in 62 potential articles. These articles were read in full and screened by these same two researchers according to the inclusion criteria. The references in these articles were also checked for potential additional relevant articles. Studies were excluded if (1) the IQ ranges of the participating children were lower than 50 or higher than 85, (2) children were diagnosed with a genetic syndrome: it is assumed for certain syndromes that they have specific WM profiles (Gathercole, & Alloway, 2006), (3) there was no comparison between children with MBID and typically developing children in the same age range (CA control group), and/or younger, typically developing children with the same mental age (MA control group). Finally, (4) only internationally peer-reviewed journals were selected. Figure 1 provides an overview of the selection procedure. The search resulted in 11 relevant articles. Table 1 describes the most important features of

these studies. The following conclusion may be drawn from this table: 36% of the studies included a CA control group, 18% a MA control group and 45% included both. Furthermore, the distribution in the studies between children aged 4-12 years (55%) and adolescents aged 12-18 (45%) was approximately equal. Only three studies (27%) focused exclusively on verbal WM, the other studies (82%) focused on both verbal and visuospatial WM.

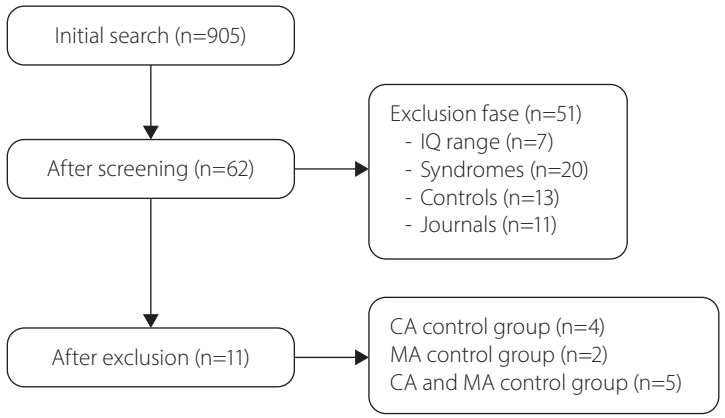

Figure 1: Flow chart study selection

Note: CA: chronological age. MA: mental age. IQ: Intelligence Quotient.

Results

Chronological age control group

In 8/9 studies, it appeared that children with MBID had a lower WM span compared to the CA control group (mean r = 0.6 (large effect size), range 0.39 – 0.83). Significant differences between the groups were found on virtually all the tasks, both in terms of verbal WM and visuospatial WM. One study revealed different outcomes, i.e. children with MBID had comparable scores on visuo-spatial WM tasks compared to typically developing children in the same age range (Henry, 2001). In this study, the average 12-year old children were divided into two groups based on IQ scores: an IQ range between 70-85 (higher functioning) and an IQ range between 50-70 (lower functioning). The higher functioning children with MBID scored comparably on visuospatial WM tasks compared to the CA control group; this was not the case for lower functioning children with MBID and only appeared to be the case for the visuospatial domain. On verbal WM tasks both the children with higher and lower IQ ranges scored worse compared to the CA control group. This difference in functioning on verbal WM tasks was also found by Schuchardt, Gebhardt and Maehler (2010), both for low functioning and high functioning children with MBID. Unfortunately, visuospatial WM was not investigated in this study. In contrast to the previous studies, Alloway (2010) demonstrated that higher functioning children with MBID performed worse on visuospatial WM tasks compared to the CA control group. It should be noted here that the children with MBID in this study were compared to a control group with a mean IQ of 118 (above average), meaning this control group was potentially less representative and could have led to an erroneous lower score.

In addition to comparisons with CA groups, some researchers have also compared a group of lower functioning children to a group of higher functioning children with MBID. Saeed and Tahir (2016) concluded that higher functioning children with MBID performed better on certain visuospatial WM tasks, and on one of the three verbal WM tasks, compared to lower functioning children with MBID. In a study by Henry (2001), higher and lower functioning children with MBID scored comparably on all three of the represented verbal WM tasks. The difference in the cut-off score employed in the studies by Saeed and Tahir (low functioning IQ score 40-65, high functioning IQ 66-79) and Henry (low functioning IQ score 50-70, high functioning IQ score 70-85) may, perhaps, explain the difference in these findings. The differences in the applied ranges did, after all, lead to a lower mean IQ score in Saeed and Tahir's study, compared to that by Henry. Saeed and Tahir (2016) did not investigate whether the higher functioning children with MBID also performed on the verbal or visuospatial

WM tasks compared to a CA control group, as they only compared the total group with MBID to the CA control group.

In summary, our review shows clear differences in WM span between children with MBID compared to a CA control group. Children with MBID have, in general, a lower WM span, in terms of verbal as well as visuospatial WM, compared to typically developing children in the same age range. Lower functioning children with MBID (IQ range 50-70) have poorer scores on verbal and visuospatial WM tasks compared to higher functioning children with MBID (IQ range 70-85). In comparison with chronological age-group peers, verbal WM may be viewed as a weakness for both higher and lower functioning children with MBID, whereas in contrast to this, visuospatial WM appears to follow a normal development, and may be viewed as a strength for higher functioning children with MBID, as it might be related to intellectual functioning.

Mental age control group

In seven studies, a comparison was made between children with MBID and a matched control group comprising younger children of average ability with the same MA, see Table 1 for an overview. The outcomes in terms of verbal WM were not unanimous. Some studies demonstrated that children with MBID performed less well on verbal WM tasks (Russel et al., 1996; Van der Molen et al., 2009; Van der Molen et al., 2010), whereas other studies showed that children with MBID had comparable or even better scores compared to a MA control group (Danielsson et al., 2012; Henry, & MacLean, 2002; Henry, & Winfield, 2010; Schuchardt et al., 2010; Van der Molen et al., 2010). Van der Molen et al. (2009) only found these differences after correcting for behavioral problems. When the results from the different studies are set side by side, it is noticeable that children with MBID with a MA of 7 or younger (irrespective of CA) perform worse on verbal WM tasks compared to younger children of average ability with the same MA (Russel et al., 1996). In contrast, children with MBID with a MA of 7 or older perform comparably or even better than seven-year-old children of average ability (Danielsson, Henry, Messer, & Rönnberg, 2012; Henry, & MacLean, 2002; Henry, & Winfield, 2010; Schuchardt et al., 2010). An exception to this is the studies by Van der Molen and colleagues (2009, 2010). It should be noted here that differences in demographic details may have influenced these differences. For instance, in the studies by Schuchardt et al. (2010) and Van der Molen et al. (2009) children with a comparable age and IQ range (15 years, IQ 60-70) were compared with a different MA control group (7.1 and 10.5 years, respectively). It is reasonable to assume that the adolescents in the Van der Molen study performed worse on verbal WM tasks than the MA control group because this MA control group was considerably older than those in the other

studies. The weak correlations between different IQ tests used in the relevant studies and the different ways in which MA was calculated could explain the cause of the differences found between the studies.

The majority of studies demonstrated that children with MBID perform as well as the MA control group when focusing on the visuospatial WM in children with MBID, compared to a MA control group (Henry, & Winfield, 2010; Schuchardt et al., 2010; Van der Molen et al., 2009, 2010). Henry, & MacLean (2002) demonstrated that children with MBID even performed better than the MA control children. Children with MBID performed worse on a visuospatial WM (Odd-one-out) compared to a MA control group in two studies (Danielsson et al., 2012; Russel et al. 1996). In the Danielsson et al. study it remains unclear what the average IQ of the children with MID was and how the associated MA was calculated for these children, which hinders the comparison between this and other studies.

In summary, it may be stated that there are differences in verbal WM performance between children with MBID and younger, typically developing children with the same MA. When the mental age of children with MBID is lower than 7 years (irrespective of the chronological age), they score worse on verbal WM tasks compared to a MA control group. On the other hand, when MA is above 7 years (irrespective of chronological age) the verbal WM performance is in line with typically developing seven year aged children. In contrast to verbal WM, the visuospatial WM of children with MBID appears to be in line with their MA and is, therefore, a relative strength of these children.

Table 1: WM in children with MBID compared to CA and/or MA matched controls

Study authors	N	Mean age (SD months)	Mean IQ (SD)	Material	Result
Alloway (2010)	39 BIF	9.8 (12) range 7.11-11.7	77 (4.5) range 70-85	Verbal WM*: (Listening recall, Counting recall, Backward digit recall)	BIF<CA
	39 TD CA	9.8 (12) range 8.1-11.11	118 (8.2) range 99-133 *WASI*	Visuo-spatial WM*: (Mr X, Spatial recall, Odd-one-out)	BIF<CA
Danielsson et al. (2012)	22 MID	13.2 (14)	IQ range 50-70	Verbal WM: Listening recall	MID<CA MID=MA
	22 TD CA	12.3 (12)	IQ not reported	Visuo-spatial WM: Odd-one-out	MID<CA MID<MA
	22 TD MA	7.3 (9) no information how MA is determined	IQ not reported *Short version BAS-II*		
Henry (2001)	10 BIF	11.11 (5)	76 (3.3) range 70-85	Verbal WM: Reverse digit span	MID=BIF<CA
	21 MID	11.11 (5)	61 (3.9) range 55-70	WM*: (Listening span, Odd-one-out span)	MID<BIF=CA
	25 TD CA	11.11 (4)	105 (9.3) range 84-123 *Short version BAS-II*		
Henry, & MacLean (2002)	53 MID	11.9 (5.5) range 11.17-13.50	57 (11.7) range 40-79	Verbal WM: Reverse digit span	MID<CA MID=MA
	45 TD CA	12.1 (4.5) range 11.33-12.92	104 (9.3) range 84-123	Listening span	MID<CA MID>MA
	41 TD MA	7.9 (5.5) range 7.0-8.92 No information how MA is determined	101 (12.3) range 82-136 *Short version BAS-II*	Visuo-spatial WM: Spatial Span	MID<CA MID>MA
				Odd-one-out span	MID<CA MID=MA
Henry, & Winfield (2010)	35 MID	12.6 (6.6)	57 (10.9) range 39-75	Verbal WM: Listening span	MID=MA
	32 TD MA	7.5 (8.5) MA based on IQ test age equivalents	101 (12.6) range 83-126 *Short version BAS-II*	Visuo-spatial WM: Spatial span Odd-one-out span	MID=MA MID=MA
Meahler, & Schuchardt (2009)	27 MBID	8.9 (12.5)	75 (7.5) range 55-85	Verbal WM: Backward digit span Backward word span	MID<CA MID<CA
	27 TD CA	9.0 (12.4)	101 (11.4) range 84-123 *K-ABC*		
Russel et al. (1996)	22 MID	11.1 (24.6)	62 (VIQ)	Verbal WM: Counting (numbers) task	MID<MA
	22 TD MA	6.3 (6.0) MA based on verbal BPV-S scores	101 (VIQ) *BPV-S*	Visuo-spatial WM: Sum tasks Odd-one-out span	MID<MA MID<MA

Table 1: Continued

Study authors	N	Mean age (SD months)	Mean IQ (SD)	Material	Result
Saeed, & Tahir (2016)	32 MBID	9.8 (36) range 4.7-16.0	67 (10.4) range 40-79	Verbal WM: Listening recall Counting recall Backward digit recall	 MBID<CA MBID<CA MBID<CA
	23 TD CA	10.5 (6) range 4.0-15.8	101 (10.8) range 84-122 *WISC-IV / WPSSI-III*	Visuo-spatial WM: Odd-one-out Mister X Spatial span	 MBID<CA MBID<CA MBID<CA
Schuchardt et al. (2010)	19 BIF	10.9 (4.9)	81 (6.1) range 70-84	Verbal WM: Backward digit span	 MID<BIF<CA MID=BIF=MA
	19 BIF	15.8 (5.8)	83 (6.3) range 70-84	Visuo-spatial WM: Counting (dots) span	 MID<BIF<CA MID=BIF=MA
	22 MID	15.1 (13.9)	62 (6.0) range 50-69		
	25 TD CA	15.5 (5.5)	110 (9.9) range 90-115		
	22 TD MA	7.1 (4.0) MA based on raw scores on CMMS	105 (8.6) range 90-115 *CMMS. CFT. HAVIK-IV. K-ABC. SON 5 ½ -17*		
Van der Molen et al. (2009)	49 MBID	15.1 (11.8) range 13-17	VIQ 69 (9.0), PIQ 72 (9.8)	Verbal WM: Backward digit recall	 MBID<CA MBID<MA
	39 TD CA	15.2 (5.7) range 13-16	VIQ 99 (7.5), PIQ 99 (18.8)	Listening recall	MBID<CA MBID<MA
	29 TD MA	10.5 (10.7) range 8-12 MA = (TIQ x age)/100)	VIQ 101 (9.0), PIQ 98 (11.4) *WISC-III*	Visuo-spatial WM: Odd-one-out	 MBID<CA MBID=MA
Van der Molen et al. (2010)	39 MBID 39 CA 26 MA	15.1 (12.0) 15.2 (5.7) 10.1 (12.2) (TIQ x age)/100)	65 (5.3) 100 (7.6) 97 (7.8) *WISC-III*	Verbal WM: Backward digit recall Listening recall Visuo-spatial WM: Odd-one-out	 MBID<CA MBID=MA MBID<CA MBID<MA MBID<CA MBID=MA

Note: BAS-II: British Ability Scales II. BIF: borderline intellectual functioning (IQ 70-85). BPV-S: British Picture Vocabulary Scale. CA: chronological age. CFT: Culture Fair Intelligence Test. CMMS: Columbia Mental Maturity Scale. HAVIK-IV: Hamburg-Wechsler-Intelligenztest Für Kinder-IV. K-ABC: Kaufman Assessment Battery for Children. MA: mental age. MBID: children with mild to borderline intellectual disabilities (IQ 50-85). MID: mild intellectual disability (IQ 50-70). PIQ: Performance Intelligence Quotient. SON: Snijders-Oomen Non-verbal intelligence test. TD typically developing children. WASI: Wechsler Abbreviated Scale of Intelligence. WISC-III/ IV: Wechsler Intelligence Scale for Children – 3rd / 4rd Edition. VIQ: Verbal Intelligence Quotient. WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence – 3rd Edition. WM: working memory.
* Compound scores

Discussion

This systematic review aimed to detail the strengths and weaknesses in WM of children with MBID (IQ between 50-85). This is important to enable special support and develop (individual) treatment methods for this group of children with limited cognitive and adaptive skills. Children with MBID were compared with typically developing children at the same chronological age and/or with younger, typically developing children at the same mental age.

The results demonstrated that the visuospatial WM of lower functioning children with MBID (IQ score 50-70) was comparable to that of younger, typically developing children at the same mental age. This is in line with the developmental theory that states that children with intellectual disabilities develop in a comparable way to the average ability children, albeit that this development is slower. Contrary to expectations, we observed that higher functioning children with MBID (IQ score 70-85) had a visuospatial WM functioning comparable to that of typically developing *age-group peers*; there did not appear to be any deficiency in general.

In respect of verbal WM, it was difficult to make a distinction between high and low functioning children with MBID due to few publications in this area. It may, however, be concluded that children with MBID and a mental age above 7 years function comparably or even better than younger typically developing children with the same mental age, irrespective of chronological age. However, for mental age younger than 7 years, children with MBID perform less well than younger, typically developing children at the same mental age: There appears to be a structural defect in verbal WM. However, as far as we know there is no neurological proof for this defect. It should be noted here that the mental ages of the children with MBID included in this systematic review were on average not younger than 6 years, and therefore this statement is based on a very narrow age range. Nevertheless, this finding agrees with studies in adults with MBID and a mental age below 7 years (Carreti, Belacchi, & Cornoldi, 2010; Lanfrachi, Cornoldi, & Vianello, 2002). These studies also demonstrated that individuals with a learning disability and an average mental age between 5.6 and 6.6 years perform worse on verbal WM tasks compared to younger, typically developing children at the same mental age.

Aside from the relatively robust conclusions that may be drawn from this study, there are also some more nuanced remarks. It may be concluded, when focusing on research aimed at visual equivalence effects (visually different items are remembered better than visually equivalent items; Hitch, Woodin, & Baker, 1989) in children with MBID, that these are found in children with MBID as well as in younger, typically developing children at the same mental age.

This could suggest that children with MBID can use visual code strategies to solve visuospatial WM recall tasks in line with their mental age (Rosenquist et al., 2003; Russel et al., 1996). In the study by Rosenquist et al. (2003) children with MBID even performed better on visual equivalence tasks than expected on the basis of their mental age. The ability to utilise properly developed visual coding strategies (storing meaningful visual imagery), could be the basis for the fact that the visuospatial WM appears to be a (relative) strength for children with MBID. This relatively simple skill is already present around age 5 in typically developing children (Palmer, 2000). It is possible that children with MBID tend to employ their strong (visual WM) side at an earlier stage to solve problems, meaning that in the course of their development their (verbal WM) shortcomings continue to increase.

This study only reviewed working memory, and not short-term memory. However, defects in short-term memory could perhaps explain the defects demonstrated in this study. For instance, children with MBID and a mental age of 7 years or younger (irrespective of chronological age) are unable to automatically repeat incoming information (Hasselhorn, & Maehler, 2007; Henry, & Conners, 2008; Rosenquist et al., 2003; Russel et al., 1996). This is something that typically developing children can do at that age (Gathercole, & Hitch, 1993), which is an important advantage to prevent information disappearing (too rapidly) from STM. This lack of automatic rehearsal could be interpreted as being indicative of slowed or erratic development of verbal WM in lower functioning MBID children (with a mental age below 7 years). This is in line with conclusions drawn by Jarrold, Baddeley and Hewes (2000) in their research about short term memory in individuals with Down Syndrome. They also argue that it is not clear whether the onset of rehearsal in atypically developing individuals is determined by age or by intellectual level.

Perhaps children with MBID and a mental age younger than 7 years perform worse on verbal WM tasks than younger, typically developing children at the same mental age because they basically possess inadequate verbal skills to compensate for their more limited verbal STM (Russel et al., 1996). It could be that the older children with MBID have an advantage in terms of longer-term exposure to language practice compared to typically developing younger children at the same mental age. This would, perhaps, mean they had more compensation options available to solve WM tasks. There appears to be a pivotal point when children with MBID reach a mental age around 10 years, and they are no longer able to match typically developing children at the same mental age in terms of verbal WM performance (van der Molen et al., 2010). This could be the cognitive ceiling for children with MBID; they are no longer able to compensate for their lower verbal STM capacity and/or lack of (increasingly

more complex) automatic rehearsal strategies. This type of cognitive ceiling could also occur in the visuospatial domain.

Maehler and Schuchardt (2009) investigated the visuospatial STM in children with MBID (mean age 9 years, mean IQ score 75). This group scored worse on four out of five visuospatial STM tasks; however, on one task (a simple Corsi Block tasks) they performed as well as a CA control group. On the other hand, in a study by Schuchardt et al. (2010) older children (mean age 15 years, mean IQ 83) with MBID scored worse on the same visuospatial STM task. This could suggest that the development of visuospatial STM in higher functioning children with MBID (IQ 70-85) potentially progresses in the same way as typically developing at the same age for a certain period (up to the start of adolescence). Whether this is also the case for visuospatial WM tasks and/or for lower functioning children with MBID was not further investigated in these two studies; however, it is conceivable that a cognitive ceiling also occurs for the visuospatial domain in children with MBID. It is anticipated that this ceiling is higher for the visuospatial domain (late adolescence) than the verbal domain (start of adolescence) and that these ceilings are reached earlier than for typically developing children. This is in line with the developmental theory which supposes that development in children with MBID is comparable to, but slower and completed earlier than that of typically developing children (Bennet-Gates, & Zigler, 1998). Furthermore, it agrees with findings from Van der Molen, Henry and Van Luit (2014) who concluded that verbal STM does not develop any further beyond the age of 10.

The current study shows that WM is weak in lower functioning children with MBID. This is unfortunate as WM is associated with poorer school performances. In general, children with MBID have difficulties with scholastic abilities (e.g. Verhoeven, & Vermeer, 2006). They require support more often at school (Simonoff et al., 2006). Several studies have demonstrated that reading and writing tax verbal WM skills in particular (e.g. Bull et al., 2008; Zheng, Swanson, & Marcoulides, 2011). Numeracy skills in typically developing children are particularly associated with visuospatial WM (Holmes, & Adams, 2006). Hereby, it should be noted that verbal WM appears to be crucial for the basics of numeracy (e.g. learning to count). This is in agreement with studies into school performance of children with MBID, which have demonstrated that verbal WM plays an important role in learning (Henry, & Winfield, 2010; Jansen, Van der Molen, & De Lange, 2013) and is associated, amongst other things with numeracy skills (Henry, & Winfield, 2010). The fact that children with MBID have, in particular, shown structural shortcomings in their verbal WM capacity, may explain their problems in learning to read and write and the automatization of numerical skills.

It has been shown that STM in children with MBID could be improved through teaching verbal repetition strategies (Brown, Campione, Bray, & Wilcox, 1973; Engle, & Nagle, 1979; Kramer, & Engle, 1981). However, this did not lead to better results compared to training without any specific strategy related instructions (Kramer, & Engle, 1981). Children with MBID can improve their ability to repeat items in the correct order through training on verbal STM tasks such as these. However, when children with MBID had to undertake different, more ecological memory tasks (e.g. a recall task), they did not use the newly acquired repetition strategies by themselves. There are, therefore, question marks about the generalizability of these training programs.

There are also various computer programs, such as Cogmed (Klingberg et al., 2005) or Braingame Brian (Prins et al., 2010), which purport to train visuospatial as well as verbal short term memory (STM) and WM. These programs are not only aimed at the weaker (verbal) aspect of children with MBID, but may also provide a boost to their relatively stronger (visual) aspects. This could lead to an increase in information processing capacity and/or compensation strategies in solving cognitive scholastic tasks, amongst others. Intensive and adaptive computer training programs have been shown to be effective for children with an attention disorder (ADHD) (see review by Chacko et al., 2013) and for children with learning problems (Roording-Ragetlie, Klip, Buitelaar, & Slaats-Willemse, 2016). Progress on (untrained) STM and WM tasks and other neurocognitive functions, such as inhibitory control, complex reasoning and numerical skills was maintained up to 3 to 6 months after training (Klingberg et al., 2005). However, the generalizability of these training programs has been disputed. Three meta-analytic reviews of the effectiveness of WM training concluded that these types of programs mainly display transient, training-specific effects, which are barely generalizable to daily activities (Hodgson, Hutchinson, & Denson, 2012; Melby-Lervag, & Hulme, 2013; Shipstead, Redick, & Engle, 2012). The inconsistent findings in terms of the effectiveness of WM training could be explained by variability between participants, such as age, status (Klingberg, 2010), motivation, training progression (Jaeggi, Buschkuehl, Jonides, & Shah, 2011), better performance on verbal WM tasks at the start of training (Söderqvist et al., 2012a), baseline cognitive capacity (Mackey, Hill, Stone, & Bunge, 2011) and/or variability in the gene coding of the dopamine transporter (*DAT1*), (Söderqvist et al., 2012b).

In children with MBID, training both the visuospatial, as well as verbal STM and WM capacity through learning different memory strategies, could be very promising as shown in a meta-analytic review (Danielsson, Zottarel, Palmqvist, & Lanfranchi, 2015). The studies included children with MBID and Down syndrome and showed large improvements in verbal and visuospatial STM

compared to WM (Moalli, 2006). A study into a visuospatial WM training program, the Odd Yellow method in adolescents with only MBID (13-16 years, IQ 55-85) showed significant progress in verbal short-term memory. These results were maintained up to 10 weeks after the training, and also showed significant improvements at follow-up in terms of visual WM, numerical skills and daily memory (Van der Molen et al., 2010). Another study demonstrated that children with MBID (6-12 years) showed progress in WM and language comprehension once they had completed Cogmed WM training (Söderqvist et al., 2012a). Only visuospatial WM was trained in this version, and no effects were determined regarding abstract reasoning ability. The most important aspects of training success appeared to be gender (girls were more successful), age (adolescents benefit more), IQ (the higher, the better), lack of co-morbidity, and higher baseline verbal WM prior to the start of training. No significant training effects were found a year after training. Probably, the training should either be presented with longer and/or more sessions or should be regularly repeated to maintain the positive effects. Butler, Miller, Lee and Pierce (2001) reviewed the literature about the numeracy training for children with MBID and concluded that frequent and "drill-and-practice" were potentially the effective ingredients within this type of training program. Jansen et al. (2013) demonstrated that children with MBID made progress on automation of calculation tasks when they practiced regularly on a numeracy program that provided direct feedback.

In summary, it may be stated that limitations in WM in children with MBID play a role in their learning difficulties. Structural shortcomings in verbal WM in children with MBID may lead to increasing problems with learning numerical skills, reading and writing. This may be caused by a limited WM capacity and not using effective strategies. Training interventions purely aimed at learning verbal repetition strategies have shown an insufficient effect in these children, as the newly learned strategies to enhance processing capacity barely generalize into untrained, daily memory tasks. Training programs that both train WM and teach strategies appear to link in better with these children, given their learning appears to be sensitive to direct and frequently provided feedback and receive support in the generalization of the learned material in daily practice. The influence of individual differences (gender, age, IQ, baseline WM capacity) of children with MBID should be explored further within effectiveness studies of training interventions, in addition to the effect of training duration and intensity.

It is recommended, based on the findings in this review, that future research is aimed at what type of children with MBID and/or what type of pre-conditions lead to individual training success, for instance using multiple

N=1 studies (Gagnier et al., 2014). In addition to the various child factors, future research could also focus on the effect of coaching within training and/or the effect of training when this is presented for longer and more intensively to children with MBID and to what extent the involvement of the environment (parents, teachers) leads to an increase in generalisation from the learned to daily practice. This is in line with research mentioning that training and challenging WM is necessary for improving them, but benefits will be greater if emotional, social and physical needs are also addressed (Diamond, & Ling, 2016). Furthermore, the age at which WM training should be offered to children with MBID should be investigated in more detail. It is possible that children with MBID benefit the most from training around a MA of 10 years, given they then benefit from the highest baseline (Söderqvist et al., 2012a). This would be in line with a review of WM training in children with learning disabilities, which showed that children aged 10 and older profited more from training (Peijnenborgh, 2016).

One limitation of this study is the fact that, due to the pre-stipulated inclusion criteria, only part of the included studies was aimed at the various aspects of WM in this target group and, therefore, conclusions may only be drawn on the basis of these details. The conclusions above should, therefore, be considered in this light. Another limitation is that in some cases, different inclusion methods were used between the included studies. In the majority of cases, children were included or excluded on the basis of a total IQ, but in one case this was done on the basis of verbal IQ (Russel et al., 1996). Given that it is known that children with MBID mostly score lower on their verbal capacities, compared to their performance capacities, a proportion of the included children with MBID would have been recruited on a lower IQ than expected on the basis of clinical practice. Inclusion on the basis of total IQ would perhaps do more justice to the heterogeneity of this target group. On the other hand, one may ask whether the specific shortcomings in terms of verbal WM in children with MBID continue to persist when correcting for verbal IQ, although the Russel et al. (1996) study demonstrated that verbal WM shortcomings remained, despite inclusion based solely on verbal IQ.

These limitations aside, this review provides a contribution to clinical practice. It is of importance for mental health carers and teachers to recognize and acknowledge WM problems, to develop interventions for this specific group in special to prevent any further asymmetrical development. In addition to this, the awareness of the potential of WM training in certain children with MBID is an important aspect to be included in the care of children with MBID. Moreover, finally, it is important, where ever possible, to make use of the relatively strong visuospatial aspect to optimize the learning of children with MBID.

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3

Cognitive functioning in children with mild to borderline intellectual disabilities and neurodevelopmental disorders: A latent profile approach

Based on:

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Abstract

Background: Mild to borderline intellectual disability (MBID), Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) often co-occur and show considerable diversity in cognitive impairment and symptom representation, both within and across disorders. Limited literature exists on their shared underlying cognitive mechanisms. This study aims at identifying subgroups that are homogeneous at a cognitive level to enhance our understanding of shared mechanisms underlying MBID and comorbid ADHD and/or ASD in relation to behavioural correlates.

Method: A latent profile analysis (LPA) was performed on total IQ score, sustained attention, inhibition, verbal and visual working memory, and academic achievement in a clinic sample (n = 118) of children (aged 10;0-13;11) with MBID (60<IQ<85) and ADHD (53%), ASD (25%) or both (20%). Profiles were compared on several behavioural symptom scales (ADHD symptoms, social behaviour and daily executive functioning).

Results: LPA revealed a solution with three cognitive profiles that were characterized by differences in speed-accuracy trade-off and cognitive performance. Profile 1 (70% of the participants) can be described as a *"high accuracy-high speed" subgroup*, profile 2 (21%) as a "*high accuracy-low speed"* subgroup, and profile 3 (9%) as an "*instable accuracy/speed"* subgroup. These unique cognitive profiles exhibited varying levels of performance on both cognitive and academic achievement tasks but did not differ in the level of ADHD behaviour symptoms, social behaviour or in daily experienced executive functioning problems.

Discussion: This study is a first step in cognitive subtyping of a heterogeneous group of children with neurodevelopmental disorders. These children seem to differ in their ability to use coping strategies when facing cognitive challenges. Behavioural problems may occur due to a discrepancy between the necessary adaptations because of their cognitive problems, and the insufficient compensation provided by their environment. Based on these findings, a personalized cognitive transdiagnostic treatment would be recommended.

Attention-Deficit/Hyperactivity Disorder (ADHD), autism spectrum disorder (ASD) and Intellectual Disability (ID) (American Psychiatric Association [APA], 2013) are neurodevelopmental disorders known to have high prevalence rates in childhood. In general, the average prevalence of ID in young people is estimated at 1.5% to 2.1% (Maulik et al., 2011), ASD prevalence worldwide has been estimated from 0.08% to 9.3% (Chiarotti & Venerosi, 2020) and ADHD between 2.6 and 4.5% (Polanczyk et al., 2015). These neurodevelopmental disorders often co-occur. Approximately 40% to 83% of children with ASD also meet the criteria for ADHD, whereas other studies indicate that 28% to 87% of children with ASD also show symptoms of ADHD (Mansour et al., 2017). Furthermore, between 30% and 80% of the children with ASD also meet the criteria for ID (Baio, 2014; Itzchak, Lahat, Burgin, & Zachor, 2008; Leyfer et al., 2006) and prevalence rates of co-occurring ADHD and ID are as high as 14% (Dekker & Koot, 2003; Strømme & Diseth, 2000). Even though these disorders often co-occur and constitute a large proportion of global disability, limited literature exists on the shared underlying mechanisms.

The group of children with intellectual disability can be characterized as heterogeneous. The cognitive impairments and clinical symptoms of these children may vary widely, despite quite similar overall total IQ scores (Patel et al., 2020; Santegoeds et al. 2021). The DSM-5 acknowledges this fact and emphasizes the importance of using neuropsychological assessments to evaluate individual cognitive profiles, rather than relying on a single overall total IQ score (American Psychiatric Association, 2013).

Also in neurodevelopmental disorders, large differences in cognitive-intellectual profiles are found. In autism, IQ variability is stated as a primary factor contributing to the heterogeneity in this disorder (Munson et al. (2008)), and in children with ADHD, differences in IQ profiles are found to be linked to differences in symptomatology and outcome (Agnew-Blais et al. (2020)). Children with mild to borderline intellectual disabilities (MBID; i.e. an IQ between 50 and 85) and comorbid ADHD and/or ASD, frequently experience a wide range of social and behavioural challenges, making them a vulnerable and challenging group in mental health care. Due to the diversity in cognitive impairment and symptom representation, identifying the shared underlying factors may be valuable in understanding behaviour.

Hence, a useful approach may be to empirically subtype such a heterogeneous group of children into subgroups that may be characterized by more homogeneous sets of underlying mechanisms. One of the strategies to identify distinct classes in such groups is to segment based on cognitive performance rather than clinical symptoms. Cognitive performance can be measured more objectively than clinical symptoms and is potentially more closely linked to the

neurobiological underpinnings of the disorders (Gottesman & Gould, 2003). Research has demonstrated that cognitive subtyping can effectively reveal the underlying mechanisms of ASD and ADHD. Van der Meer et al. (2016) used latent class analyses on cognitive performance and behavioural symptom scales to identify a four-class solution with different speed-accuracy trade-offs associated with varying levels of ASD and ADHD symptoms. The latent profile analysis in a group of children aged 8 to 13 years conducted by Dajani et al. (2016) resulted in a three-class solution with differences in executive function between typical children and those with ASD, ADHD, or both. The same type of analysis on children and adolescents aged 6 to 15 years with both ID, ADHD, and/or ASD showed a four-class solution based on WISC-IV indices (Marquez-Caraveo et al.; 2021). The four classes were "lower cognitive profile", "lower working memory (WM)", "higher WM", and "higher cognitive profile". Each class had unique characteristics, such as low WM index scores or high scores on all WISC-IV indices, and were mostly associated with children with ID, ASD, ADHD, or a combination of these disorders. So far, a latent class analysis on a heterogeneous group of children with MBID, ADHD, and/or ASD using a wide neuropsychological assessment to identify distinct profiles in relation to behavioural correlates, has not been performed.

The aim of this study is to identify subgroups that are homogeneous at the cognitive level within a heterogeneous group of children with MBID and comorbid neurodevelopmental disorders (ADHD and/or ASD). Children will undergo a neuropsychological assessment, and the cognitive subgroups will be compared on behavioural symptoms of ASD, ADHD, and executive functioning.

Based on previous results (van der Meer et al., 2016), we hypothesize that a latent profile analysis will identify a cognitive subtype with inaccurate and slow performance across a range of tasks that is associated with the highest levels of behavioural symptoms of ASD, ADHD, and daily experienced executive function problems. Furthermore, we expect that children performing more accurately at a relatively faster pace will show the lowest levels of behavioural symptoms of ASD, ADHD and daily experienced executive function problems.

Methods

Participants and procedure

The data used in the current study are collected from two clinical WM training RCTs in children with MBID and neurodevelopmental disorders (ASD, ADHD, or both), conducted at Karakter child and adolescent psychiatry in the Netherlands between May 2012 and July 2021. These studies are approved by

the Medical Research and Ethics Committee (MREC) region Arnhem-Nijmegen in The Netherlands, registered under NL32435.091.10. and NL52647.091.15 and are also registered in the Dutch Trial Register, numbers NL2798 and NTR5223.

Care providers were instructed to inform eligible children and their legal representatives about the study. Legal representatives of the children who were interested, were contacted subsequently by a member of the research team. Signed informed consent was obtained before participation, where parents signed informed consent for children younger than 12 years of age. All children received monetary compensation after participation.

A total of 587 children were screened for eligibility and 120 were enrolled in the current study. Although eligible, candidates often refused to participate (67% of screened and eligible candidates). The main reasons for refusal were the unavailability of time to participate due to other treatments and/or a busy family schedule. The inclusion criteria were children: (1) aged between 10 years 0 months and 14 years 0 months at the time of inclusion, (2) with a recent IQ score (<1½ years old) between 60 and 85 on the Wechsler Intelligence Scale 3rd edition (Wechsler, 2000) and (3) classified with ADHD, ASD or both according to the DSM-IV/DSM-5 (American Psychiatric Association, 2000; 2013) by a certified mental health psychologist and/or psychiatrist. Two participants dropped out of the study before the neuropsychological assessment took place and were therefore excluded from the analysis, resulting in a total of 118 participants (Fig. 1).

All participants completed a neuropsychological assessment, conducted by trained researchers who followed a written test protocol with a total duration of approximately 90 minutes. Furthermore, children's parents or legal representatives were asked to fill out behavioural questionnaires, online or on paper, and send them back by e-mail.

Measures

The cognitive assessment of the participating children consisted of eight tests measuring five cognitive domains: sustained attention, inhibition, verbal- and visual WM and academic achievement, resulting in fifteen variables in total (Table 1). These cognitive tests together with total IQ scores, resulted in a total of sixteen variables that were used in analyses.

Furthermore, we collected information about behavioural measures consisting of three questionnaires measuring behavioral symptoms of ADHD, social behaviour and daily executive functioning as rated by parents or caretakers (Table 1). The total scores of the three questionnaires (three variables) were used for secondary analyses.

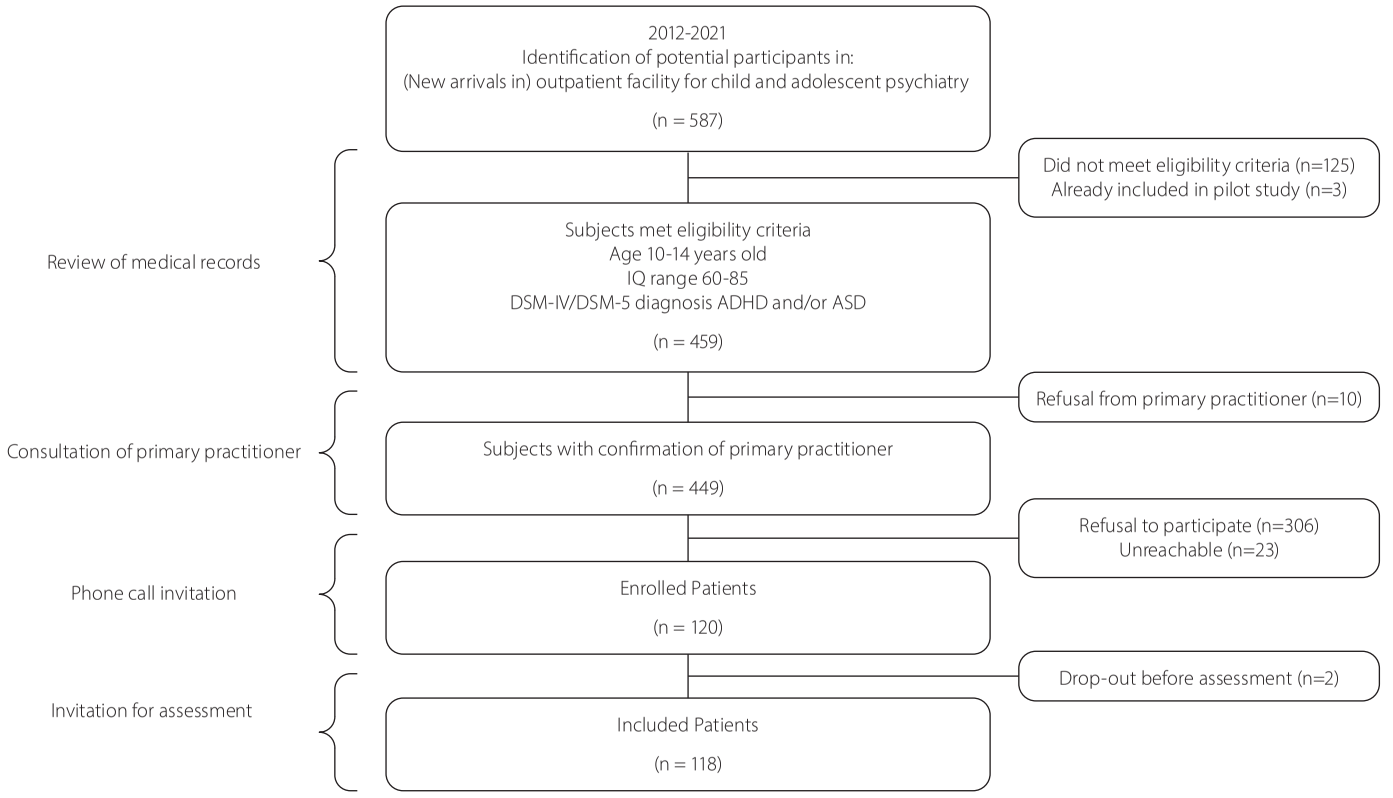

Figure 1: Study flow chart.

Table 1. Description of Cognitive Measurements and Behavioural Questionnaires.

Cognitive Measurements		
Variable Name	**Abbreviation**	**Description**
Sustained Attention_Dots	SAD	Sustained Attention_Dots (Amsterdamse Neuropsychologische Taken [ANT; de Sonneville, 2009]) Participants should discriminate between patterns consisting of 3, 4 (target signal) or 5 dots. The probability of a yes vs no response is 1:2. Therefore, with increasing time-on-task a response bias (for the no-response key) is induced.
Speed: reaction time	SAD RT	Overall reaction time (ms)
Speed: reaction time hits	SAD RT Hits	Reaction time on the target signal (ms)
Speed: reaction time stability	SAD stability	Stability of the overall reaction time
Error: Impulsivity	SAD impulsivity	Misses of the target signal
Error: Inattention 1 - low n	SAD inattention 1	False alarm: response when three dots are presented
Error: Inattention 2 - high n	SAD inattention 2	False alarm: response when five dots are presented
Go-NoGo	GnG	Go-NoGo (inhibitory control, ANT; de Sonneville, 2009). It contains a presentation of Go and NoGo signals in the centre of the screen to indicate whether the child should press a button.
Speed: reaction time	GnG RT	Overall reaction time (ms)
Speed: Inattention	GnG inattention	Misses off the target signal
Speed: Impulsivity	GnG impulsivity	False alarm: response when NoGo signal is presented
Backward digit recall	BDR	Backward Digit Recall (verbal WM; Pickering & Gathercole, 2001). A sequence of up to 7 digits is presented verbally to the participants and they are asked to recall this sequence in reverse order. The outcome measure is the amount of correctly recalled sequences, ranging from 0 to 36.

Table 1. Continued.

Cognitive Measurements		
Variable Name	**Abbreviation**	**Description**
Listening Recall	LR	Listening Recall task (verbal WM; Pickering & Gathercole, 2001). Participants are asked to judge the veracity of a series of short sentences, and to recall the last word of that sentence (or sequence of last words of sentences in case of multiple items). Outcome measure is the amount of correctly recalled sequences of last words, ranging from 0 to 36.
Spatial Span	SS	Spatial Span (visuo-spatial WM; Automated Working Memory Assessment [AWMA]; Alloway, 2007). A card is shown with two shapes of which the right one has a red dot on top. The child must decide whether the shape at the right is the same or opposite to the left shape. Simultaneously, the position of the red dot(s) must be remembered after each trial. Trials start with one card, up to sequences with 6 cards. Scores can vary from 0 to 42.
Block Recall	BR	Backward block Recall task (visuo-spatial WM; Pickering & Gathercole, 2001). A researcher taps a sequence of up to nine identical spatially separated blocks, after which the participant is asked to mimic the tapping of that sequence in reverse order. The outcome measure is the amount of correctly recalled sequences, ranging from 0 to 54.
Arithmetic Speed test	TTR	A Dutch arithmetic task named "Arithmetic Speed test" (de Vos, 1992) assesses arithmetic automation as a measure of academic achievement. Participants are asked five times (add, subtract, multiply, divide, mixed) to correctly answer as many as possible and up to 200 written out automation of mathematics questions of increasing difficulty within one minute. The amount of total correctly answered questions serves as the outcome measure, ranging from 0 to 200.
Reading Speed test	BRUS	A Dutch reading task named "Reading Speed test" (Brus & Voeten, 1999) measures reading automation as a measure of academic achievement. Children are asked to read as many as possible words of increasing difficulty out loud within one minute. The amount of words correctly read out serves as the outcome measure, ranging from 0 to 116.
Total Intelligence Quotient	TIQ	Total Intelligence Quotient is measured with a shortened version of the Wechsler intelligence test (Kort et al., 2005).
Behavioural Symptoms		
Variable Name	**Abbreviation**	**Description**
AVL	AVL	The total score on the ADHD-Vragenlijst (AVL; Scholte & van der Ploeg, 2005). This is an additional measure to determine behavioural symptoms of ADHD. It contains 18 behaviours that are rated by the child's parents in terms of frequency of occurrence in the last six months on a 5-point Likert scale (0 = Never, 1 = Sometimes, 2 = Average, 3 = Often, 4 = Very often), resulting in a possible total score range from 0 to 72. Higher scores indicate more reported behavioural symptoms of ADHD.
VISK	VISK	The total score of the Dutch version of Children's Social Behaviour Questionnaire (Vragenlijst voor Inventarisatie van Sociaal gedrag van Kinderen [VISK]; Hartman et al., 2007a). This is a questionnaire to determine behavioural symptoms of ASD. Parents report on their child's behaviour of the last 2 months, and it contains 49 statements. The behaviours are rated on a 3-point Likert scale (0 = Never, 1 = Sometimes, 2 = Often), resulting in a total score between 0 and 98.
BRIEF	BRIEF	The total score on the Behaviour Rating Inventory of Executive Functioning (BRIEF; Smidts & Huizinga, 2009), as filled out by parents. This questionnaire provides insight into the child's executive function problems (experienced daily at home). It contains 75 behaviours that are rated in terms of frequency of occurrence in the last six months on a 3- point Likert scale (1 = never, 2 = sometimes, 3 = often), resulting in a possible total score between 75 and 225.

Statistical analyses

All sixteen cognitive variables (Table 1) were subjected to a latent profile analysis (LPA) using the TidyLPA package (Rosenberg et al., 2019) in Rstudio version 1.2 (Rstudio, 2018). LPA is a statistical method to identify subgroups of participants who have similarities in their responses to a set of variables (profiles). Successive LPA models were fitted to the cognitive data, starting with a one profile model, and increasing up to five profiles. To identify the model with the optimal number of profiles, multiple fit indices can be evaluated. Methodological research has not yet identified a fit index that is universally recommended, and the fit indices do not always point to the same number of profiles as the best model (Johnson, 2021). Therefore, it is recommended to use a set of indices in combination with an examination of the profile solutions themselves for interpretability to identify the best model (Johnson, 2021). In the current study the fit of each model was examined through the Bayesian Information Criteria (BIC; Schwarz, 1978), the Sample-Size Adjusted BIC (SABIC; Sclove, 1987) and the Bootstrapped Likelihood Ratio test (BLRT; McLachlan & Peel, 2000). For the BIC and SABIC, lower values indicate a better fit. However, in practice, these values may not always reach a minimum but continue to decrease when profiles are added (Johnson, 2021). In that case, the point of the largest decrease can give more insight. The BLRT compares the model with *k* profiles to the model with *k* – 1 profiles, for which a *p*-value below .05 indicates a statistically significant improvement in model fit compared to the model with one fewer profile (Johnson, 2021). Furthermore, entropy (a classification accuracy measure) was also considered to determine the optimal LPA model. Entropy values range between 0 and 1, and a value closer to one is indicative of better separation of the profiles (Heeren et al., 2017).

Due to the absence of age-appropriate standards for children aged 13 years and older, 12-year-old norms were used for the de GNG measure (n = 30). In total 9.4% of the data of the norm-referenced cognitive measurements was missing (SAD; n =21, GnG; n = 15, SS; n = 2, TTR; n = 1, Brus; n = 1; TIQ; n = 4), but the pattern satisfied the missing at random assumption indicated by the Little's Test (χ^2 = 74.0 , df = 77, p = .58), (Little, 1988). Because LPA does not allow for missing values, the missing cognitive measures were imputed by predictive mean matching with the Multivariate imputation by chained equation (MICE) package in Rstudio (MICE; van Buuren & Groothius-Oudshoorn, 2011). Imputation was performed five separate times and averaged, resulting in one dataset. After imputation, the variables from the SAD and GNG tasks were mirrored so a higher score is indicative of better performance for all cognitive measures.

Participants were categorized by their most likely latent profile for further analysis. Comparisons of demographics (age, gender, IQ, medication use and ADHD/ASD diagnosis), behavioral symptoms (AVL and VISK), and daily executive functioning (BRIEF) across cognitive latent profiles were conducted through ANOVA for continuous data and the chi-squared test for categorical data in IBM SPSS Statistics 25 (IBM SPSS, 2017). Furthermore, all cognitive measurements were standardized for interpretation purposes.

We employed a leave-one-out subsampling procedure as our replication technique, wherein we randomly selected a hundred subjects and repeated the process five times.

Results

Study population characteristics

The average age of children included in this study was 11.5 years old (± 1.2 SD), mostly boys (73%), and with a mean total IQ score of 74.9 (± 6.4 SD). Most of children (53%) were diagnosed with ADHD, 25% with ASD, and 20% with both ADHD and ASD. Also, 53% of the study population used medication, of which 78% stimulants (Table 2). Medication was taken according to the prescription, also during the testing phase.

Almost all cognitive and behavioural measures in this study population showed clinical scores when compared to typically developing children (standardised z-scores ≥ -1.5, T-scores ≥ 65). No standardised scores were available for the WM and academic achievement tasks. See Table 3 for an overview.

Profile description

LPAs were based on fit indices and visual inspection of the figures (Nylund, Asparouhov, & Muthén, 2007). Fit indices of the LPA for one to five profiles are presented in Table 4. Taking together all the indices, the three- and four-profile solutions were considered best. Looking at the group size and fit indices in combination with the most informative profile properties the three-profile solution was chosen as the best fitting solution.

Table 2. Demographic Characteristics of the Total Group (*n* = 118)

	Mean	(SD)
Age	11.5	(1.2)
Total IQ	74.9	(6.4)
	n	**%**
Sex		
Male	86	73%
Female	32	27%
Medication		
No	55	47%
Yes	60	53%
If yes,		
Stimulants	47	78%
Antipsychotics	9	15%
Other	4	7%
Missing	3	3%
Diagnosis		
ADHD	62	53%
ASD + ADHD	24	20%
ASD	29	25%
Missing	3	3%

Note. ADHD = Attention-deficit/hyperactivity disorder (ADHD); ASD = Autism spectrum disorder; SD = Standard Deviation.

The cognitive profiles are presented in Figure 2. Roughly, these profiles were typified by qualitative differences in accuracy-speed trade-offs and cognitive performance. Profile 1 (70% of the participants), which can be described as a *"high accuracy-high speed"* (HH) subgroup, showed a cognitive profile that is characterized by a relatively high speed-high accuracy trade-off and relatively high scores on cognitive and academic achievement tasks. Profile 2 (21%) can be described as a *"high accuracy-low speed"* (HL) subgroup and is characterized by a low speed and relatively high accuracy trade-off and middling scores on cognitive and academic achievement tasks. Profile 3 (9%) can be described as an *"instable accuracy/speed"* (I) subgroup and shows an instable speed-accuracy trade-off and low scores on cognitive and academic achievement tasks. The scores of the subgroups on the cognitive measures are provided in Table 5.

Table 3. Cognitive measurements and behavioural measurements of the total group (*n* = 118).

	Standardised Z-scores		Raw scores	
	Mean	**(SD)**	**Mean**	**(SD)**
SAD				
Speed				
SAD RT	-2.0	(1.8)	1368.3	(411.6)
SAD RT Hits	-2.1	(1.7)	n.a.	
SAD stability	-2.1	(1.4)	n.a.	
Errors				
SAD impulsivity	-1.4	(2.2)	33.5	(28.5)
SAD inattention 1	-0.9	(2.1)	9.1	(11.0)
SAD inattention 2	-0.9	(2.2)	12.5	(12.6)
GnG				
Speed				
GnG RT	0.4	(1.0)	456.7	(85.9)
Errors				
GnG inattention	0.0	(1.1)	0.4	(0.9)
GnG impulsivity	-2.3	(2.8)	2.9	(2.8)
Verbal working memory				
BDR	n.a.		11.2	(3.9)
LR	n.a.		12.0	(3.7)
Spatial working memory				
SS	n.a.		14.2	(6.0)
BR	n.a.		23.1	(4.9)
Academic				
TTR	n.a.		63.4	(34.0)
BRUS	n.a.		52.9	(21.2)
TIQ	n.a		74.9	(6.4)
	T-scores		**Mean**	**(SD)**
AVL Total score (n = 111)	80		38.1	(15.2)
BRIEF (n = 106)				
Behaviour regulation	65		57.2	(10.1)
Metacognition	66		99.6	(14.5)
Total score	66		156.3	(22.8)
VISK Total score (n = 102)	80		41.6	(14.3)

Note. SAD = Sustained Attention_Dots; SAD RT = Speed reaction time; SAD RT Hits = SAD Speed reaction time hits; SAD stability = SAD Speed reaction time stability; SAD impulsivity = SAD Error Impulsivity; SAD inattention 1 = SAD Error Inattention 1 - low n; SAD inattention 2 = SAD Error Inattention 2 - high n; GnG = Go-NoGo; GnG RT = Go-NoGo Speed reaction time; GnG inattention = Go-NoGo Speed Inattention; GnG impulsivity = Go-NoGo Speed Impulsivity; BDR = Backward digit recall; LR = Listening Recall; SS = Spatial Span; BR = Block Recall; TTR = Arithmetic Speed test; BRUS = Reading Speed test; TIQ = Total Intelligence Quotient; AVL = ADHD questionnaire; BRIEF = Behaviour Rating Inventory of Executive Functioning; VISK = Children's Social Behaviour Questionnaire; SD = Standard Deviation.

Table 4. Fit Statistics for Latent Profile Analysis (*n* = 118).

Number of profiles	BIC	SABIC	BLRT_p	Entropy
One	10080.25	9979.09		1.00
Two	9893.18	9738.28	0.01	0.83
Three	**9758.12**	**9549.47**	**0.01**	**0.95**
Four	9720.26	9457.88	0.01	0.91
Five	9740.33	9424.20	0.01	0.92

Note. The fit statistics together with the most informative profile properties suggested the three-profile solution best fitted the data; BIC = Bayesian Information Criteria; SABIC = Sample-Size Adjusted BIC; BLRT_p = Bootstrapped Likelihood Ratio test *p*-value.

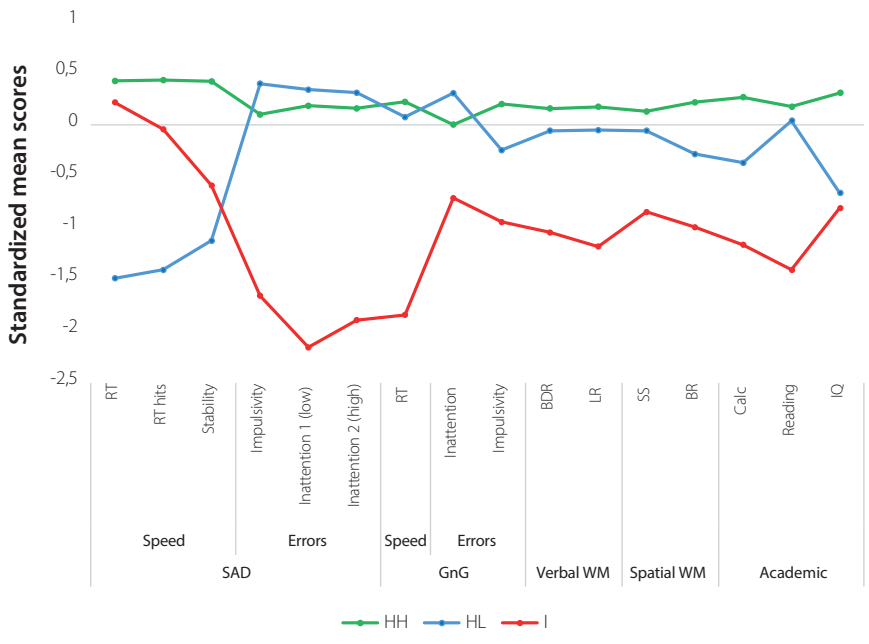

Figure 2: The Latent Cognitive Profiles from LPA.

BDR; Backward Digit Recall, BR; Block Recall, Brus; Speed reading test, Calc; Calculation, GnG; Go-Nogo test, HH; *high accuracy-high speed* subgroup, HL; *high accuracy-low speed* subgroup, LR; Listening Recall, RT; Reaction Time, SAD; Sustained Attention Dots, SS; Spatial Span, I; *instable accuracy/speed* subgroup, IQ; Intelligence Quotient, TTR; Arithmetic Speed test, WM; Working Memory.

Table 5. Cognitive measures in the distinct cognitive profiles.

	HH (n = 82)		HL (n = 25)		I (n = 11)	
	Score	z-score within group	Score	z-score within group	Score	z-score within group
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SAD						
Speed						
SAD RT	-1.3 (1.0)	0.4 (0.6)[a]	-4.6 (1.3)	-1.5 (0.8)[b]	-1.6 (1.3)	0.2 (0.8)[a]
SAD RT Hits	-1.4 (0.9)	0.4 (0.5)[a]	-4.5 (1.8)	-1.4 (1.0)[c]	-2.2 (1.0)	0.0 (0.6)[b]
SAD stability	-1.5 (1.1)	0.4 (0.7)[a]	-3.7 (1.2)	-1.1 (0.9)[b]	-2.9 (1.0)	-0.6 (0.7)[b]
Errors						
SAD impulsivity	-1.1 (1.8)	0.1 (0.8)[a]	-0.5 (1.5)	0.4 (0.7)[a]	-5.0 (2.8)	-1.7 (1.3)[b]
SAD inattention 1	-0.5 (1.2)	0.2 (0.6)[a]	-0.1 (1.1)	0.3 (0.5)[a]	-5.4 (3.5)	-2.2 (1.7)[b]
SAD inattention 2	-0.5 (1.6)	0.2 (0.7)[a]	-0.2 (1.3)	0.3 (0.6)[a]	-5.1 (3.3)	-1.9 (1.5)[b]
GnG						
Speed						
GnG RT	0.7 (0.8)	0.2 (0.7)[a]	0.5 (0.9)	0.1 (0.9)[a]	-1.5 (1.3)	-1.8 (1.2)[b]
Errors						
GnG inattention	0.0 (0.9)	0.0 (0.9)[a]	0.3 (1.1)	0.3 (1.0)[a]	-0.8 (1.6)	-1.7 (1.5)[b]
GnG impulsivity	-1.7 (1.8)	0.2 (0.7)[a]	-3.0 (3.5)	-0.2 (1.3)[b]	-4.9 (4.8)	-0.9 (1.7)[c]
Verbal working memory						
BDR	11.8 (3.7)	0.2 (1.0)[a]	11.0 (4.0)	-0.1 (1.0)[a]	7.1 (2.8)	-1.0 (0.7)[b]
LR	12.6 (3.6)	0.2 (1.0)[a]	11.8 (3.1)	-0.1 (0.8)[a]	7.6 (3.0)	-1.2 (0.8)[b]
Spatial working memory						
SS	15.0 (6.1)	0.1 (1.0)[a]	13.8 (5.8)	-0.1 (1.0)[a]	9.1 (2.6)	-0.8 (0.4)[b]
BR	24.2 (4.4)	0.2 (0.9)[a]	21.7 (4.9)	-0.3 (1.0)[b]	18.3 (4.5)	-1.0 (0.9)[c]
Academic						
TTR	72.5 (32.9)	0.3 (1.0)[a]	50.9 (26.5)	-0.4 (0.8)[b]	23.9 (15.6)	-1.2 (0.5)[c]
BRUS	56.7 (18.8)	0.2 (0.9)[a]	53.8 (18.0)	0.0 (0.9)[a]	23.1 (23.2)	-1.4 (1.1)[b]
TIQ	76.8 (5.6)	0.3 (0.9)[a]	70.2 (6.0)	-0.7 (0.9)[b]	69.7 (5.6)	-0.8 (0.9)[b]

[a,b,c]Within a row, means without a common superscript differ ($p < 0.05$).
Note. . SAD = Sustained Attention_Dots; SAD RT = Speed reaction time; SAD RT Hits = SAD Speed reaction time hits; SAD stability = SAD Speed reaction time stability; SAD impulsivity = SAD Error Impulsivity; SAD inattention 1 = SAD Error Inattention 1 - low n; SAD inattention 2 = SAD Error Inattention 2 - high n; GnG = Go-NoGo; GnG RT = Go-NoGo Speed reaction time; GnG inattention = Go-NoGo Speed Inattention; GnG impulsivity = Go-NoGo Speed Impulsivity; BDR = Backward digit recall; LR = Listening Recall; SS = Spatial Span; BR = Block Recall; TTR = Arithmetic Speed test; BRUS = Reading Speed test; TIQ = Total Intelligence Quotient; SD = Standard Deviation.

Profile comparison

Table 5 displays a comparison of cognitive measures and academic achievement among three cognitive profiles. In general, profile 1 (HH) shows significantly higher scores on cognitive measures and academic achievement tasks than profile 2 (HL) and/or 3 (I) (RT Hits ($F(2,115 = 71.5$, $p < .001$); Stability ($F(2,115 = 42.6$, $p < .001$), GnG Impulsivity ($F(2,115 = 8.2$, $p < .001$); Spatial WM; BR ($F(2,115 = 9.6$, $p < 0.01$), TTR ($F(2,115 = 7.8$, $p < .001$), TIQ ($F(2,115 = 16.3$, $p < .001$)). Profile 2 is characterized by significantly slower scores on a sustained attention task compared to profile 1 but is mostly equally accurate (Speed Hits ($F(2,115 = 71.5$, $p < .001$)). On the other hand, profile 3 shows significantly lower scores on all cognitive measures and academic achievement tasks compared to profile 1 and/or 2 (SAD Impulsivity ($F(2,115 = 24.5$, $p < .001$), SAD Inattention 1 ($F(2,115 = 54.4$, $p < .001$), SAD Inattention 2 ($F(2,115 = 34.6$, $p < .001$), GnG Speed ($F(2,115 = 31.7$, $p < .001$), GnG Inattention ($F(2,115 = 4.2$, $p = .018$), GnG Impulsivity ($F(2,115 = 8.2$, $p < .001$), Verbal WM; BDR ($F(2,115 = 12.9$, $p < .01$), LR ($F(2,115 = 23.4$, $p < .01$), Brus ($F(2,115 = 15.1$, $p < .001$)). Additionally, profile 3 displays significant inaccuracies on most attention tasks with unstable speed, exhibiting significantly higher scores on sustained attention speed and significantly lower scores on Go-Nogo speed.

Demographic characteristics were compared between the three cognitive profiles (Table 5). There was a significant difference in age between profile 3 (I) ($M_{age} = 10.6$, $SD_{age} = 1.0$) compared to profiles 1 (HH) and 2 (HL) ($M_{age} = 11.6$, $SD_{age} = 1.2$ and $M_{age} = 11.8$ $SD_{age} = 1.0$) respectively ($F(2,115 = 4.1$, $p = .018$). Furthermore, profile 1 showed a significantly higher IQ score ($M_{IQ} = 76.8$, $SD_{IQ} = 5.6$) compared to profile 2 ($M_{IQ} = 70.2$, $SD_{IQ} = 6.0$) and profile 3 ($M_{IQ} = 69.7$, $SD_{IQ} = 5.6$) (Table 4). No significant differences were found between profiles for medication use (χ^2 (8, N = 118) = 4.9, p = .77), diagnosis (χ^2 (4, N = 115) = 4.5, p = .34. or gender (χ^2 (2, N = 115) = 0.3, p = .85).

Behavioral characteristics of the profiles

Next, we examined whether the cognitive profiles differed in behavioral symptoms of ADHD, social behavior, and daily experienced executive functioning problems. No group differences were found in behavioral symptoms and daily experienced executive functioning problems (see Table 6).

Table 6. Demographic Characteristics and behavioural measures in the distinct cognitive profiles.

	high accuracy-high speed group		high accuracy-low speed group		instable accuracy/speed group		p-value[a]
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Age	11,6[a]	(1,2)	11,8[a]	(1,0)	10.6[b]	(1,0)	.02
Total IQ	76.8	(5.6)	70.2	(6.0)	69.7	(5.6)	<.001
	n	%	n	%	n	%	p-value[b]
Gender							.85
Male	61	74%	17	68%	8	73%	
Female	19	23%	7	28%	3	27%	
Missing	2	2%	1	4%	-		
Medication							.77
No	39	48%	10	40%	6	55%	
Yes	41	50%	14	56%	5	45%	
If yes,							
Stimulants	33	80%	9	64%	5	100%	
Antipsychotics	5	12%	4	29%	-		
Other	3	7%	1	7%	-		
Missing	2	2%	1	4%	-		
Diagnosis							.34
ADHD	42	51%	11	44%	9	82%	
ASD + ADHD	20	24%	8	32%	1	9%	
ASD	18	22%	5	20%	1	9%	
Missing	2	2%	1	4%	-		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	p-value[a]
AVL Total score (n = 111)	36.6	(15.6)	41.0	(14.1)	42.9	(13.9)	.27
BRIEF (n = 106)							
Behaviour regulation	57.2	(10.2)	56.4	(9.9)	59.0	(10.4)	.79
Metacognition	99.5	(14.8)	99.6	(15.3)	99.7	(10.9)	.99
Total score	155.9	(23.6)	156.0	(22.4)	158.7	(19.9)	.93
VISK Total score (n = 102)	41.3	(12.6)	40.7	(16.2)	44.7	(21.3)	.75

Note. [a,b,c]Within a row, means without a common superscript differ ($p < 0.05$).
ADHD = Attention-deficit/hyperactivity disorder (ADHD); ASD = Autism spectrum disorder; AVL = ADHD questionnaire; BRIEF = Behaviour Rating Inventory of Executive Functioning; VISK = Children's Social Behaviour Questionnaire; SD = Standard Deviation.
[a] Anova
[b] Chi square test

Discussion

The aim of this study is to identify subgroups that are homogeneous at the cognitive level within a heterogeneous group of children with MBID and comorbid neurodevelopmental disorders (ADHD and/or ASD). This cross-disorder perspective tries to map cognitive profiles toward behavioural profiles, instead of defining groups based on behavioural symptom data and comparing group differences in cognitive functioning. Our main finding is that latent profile analysis in a clinical sample revealed a three-profile solution. Profile 1 (70% of the participants) can be categorized as a "high accuracy-high speed" (HH) subgroup. This subgroup exhibit a cognitive profile marked by a relatively high trade-off between speed and accuracy, as well as relatively high scores on both cognitive and academic achievement tasks. Profile 2 (21%) is classified as a "high accuracy-low speed" (HL) subgroup. This subgroup demonstrates a low speed and relatively high accuracy trade-off, as well as middling scores on cognitive and academic achievement tasks. Profile 3 (9%) is labelled as an "instable accuracy/speed" (I) subgroup. This subgroup shows an unstable trade-off between speed and accuracy, along with low scores on both cognitive and academic achievement tasks. These findings are in line with our hypothesis and previous literature on children with ADHD/ASD without intellectual disability showing that distinct cognitive profiles are mainly differentiating at the speed/accuracy trade-offs (Rommelse et al., 2016).

In clinical practice, this pattern of three distinct profiles is also evident. Profile 1 may reflect a 'protective' profile, consisting of sufficient basic cognitive skills and therefore performing relatively high on cognitive and academic achievement tasks. Profile 2 is a group of children that may have a coping strategy of working at a slower pace to maintain accuracy in their tasks. However, when cognitive complexity rises or when time is a crucial factor for performance, these children may struggle to adapt and experience lower scores as a result. The smallest group (9% of the study population) has a 'risk' profile. Children in this group face difficulties with any cognitive task. This subgroup is characterized by high/instable speed with many inattentive and impulsive errors in the sustained attention task and low speed and relatively many inattentive and impulsive errors in the Go-Nogo task. It seems that the information processing of this subgroup is out of control: in case of simple decision making tasks, it takes them a long time to make a decision. Too often the decision made turns out to be wrong. If a task is complex or has a long duration the speed of information processing is quick and instable and too many (impulsive) errors are made. In contrast, profile 2 is capable of taking extra time when required, and therefore performs slower but overall better compared to profile 3.

Looking at the cognitive profiles more closely, profile 1 is associated with higher IQ and profile 1 and 2 are associated with older age. It can be argued that the differences in subgroup performance are solely correlated with variations in age or IQ scores. However, it should be noted that profiles 2 and 3 exhibit comparable IQ scores but demonstrate different subgroup performances, which supports the idea that disparities in performance among subgroups may have other contributing factors beyond just differences in age and intelligence scores. Additionally, it is important to note that standardized scores are employed for analysis whenever possible. As such, age is considered when utilizing these measures, including all variables of the SAD, GNG, and IQ scores. Additionally, profiles remain consistent when the analysis is repeated using only raw scores for all variables. This also supports the notion that discrepancies in performance between subgroups on variables lacking standardized scores may not necessarily be attributed to IQ or age differences.

Furthermore, our study does not show differences in ADHD/ASD behaviour symptoms and daily experienced executive function problems between the three cognitive profiles (see Table 5). Our hypothesis was that a cognitive subtype characterized by slow and inaccurate performance across a range of tasks would be associated with the highest levels of ADHD/ASD behaviour symptoms and daily executive function problems, while children performing more accurately and at a relatively faster pace would show the lowest levels of these symptoms. This was not supported by the findings. There are two potential reasons for these contrasting results. First, it is possible that the cognitive outcomes cannot be translated directly into daily behaviour: the impulsive errors on the tests may reflect broader information processing difficulties rather than true impulsivity, as noted by Metin et al. (2013). Second, regardless of the degree of cognitive impairment these children may anyway experience behavioural and executive function problems due to a discrepancy between the required support because of their cognitive problems and the insufficient compensation provided by their environment, as stated by Meppelder et al. (2015).

Even though profile 3 may be viewed as an combined (inattentive and impulsive) presentation associated with ADHD, these findings may be indicative of differences in processing speed and the efficiency of information processing. It has been suggested that reaction time and accuracy performance in ADHD reflect inefficient rather than impulsive information processing (Metin et al., 2013). Also, children with MBID are thought to have difficulties with information processing in general (Nieuwenhuijzen et al., 2011). Even though this idea of distinct cognitive subtypes that differ on speed-accuracy trade-offs that can be indicative of the efficiency of information processing, this idea requires further

empirical testing with multiple measurements of processing speed. Looking more closely at processing speed as the underlying mechanism in ADHD, ASD and MBID may influence the current interventions that are used (Antshel, Zhang-James, Wagner, Ledesma, & Faraone, 2016). Instead of relying on categorical models to address symptoms, a dimensional impairment perspective may lead to more effective treatments, as not all children with neurodevelopmental disorders require the same cognitive interventions. Therefore, treatments should be tailored to the child's dimensional impairment. Additionally, it will be interesting for future research to concentrate on therapeutic benefits for children within distinct subgroups.

Although this study provides valuable insights, there are some limitations that need to be acknowledged. Firstly, the analysis is conducted on only one sample, which restricts the generalizability of the findings. In addition to our leaving a subsample out procedure as a replication of our study, a replication using independent samples is required to validate the results. Secondly, medication use is not considered in this study. It is possible that medication, such as psychostimulantia, influenced performance on cognitive tests and improved impulsivity errors (Campez et al., 2021). Therefore, the cognitive profiles found in this study may not accurately represent the biological underpinnings of the disorders in the absence of medication use. Nonetheless, given the high prevalence of medication usage in MBID youth with co-morbid ADHD and/or ASD, the current results have significant clinical relevance (Al-khudairi, Perera, Solomou, & Courtenay, 2019; Antshel et al., 2016). Lastly, due to time limitations for testing, only a selection of cognitive functions that are sensitive to disorder-specific difficulties are assessed (Danielsson et al., 2012). Future studies should consider incorporating a larger selection of cognitive measures.

In conclusion, the group of children with MBID and comorbid neuro-developmental disorders (ADHD and/or ASD) can be segmented into three cognitive subtypes with different speed-accuracy trade-offs. These subtypes may be associated with different cognitive abilities and academic achievement, but not with different severity of behavioural symptoms related to ADHD or ASD, nor with difficulties in executive functioning in everyday situations. These findings suggest that these children vary in their ability to use coping strategies when facing cognitive challenges. Behavioural problems may occur due to a discrepancy between the required adaptations because of their cognitive problems, and the insufficient compensational support provided by their environment. Therefore, a personalized transdiagnostic cognitive treatment approach may be helpful to address their unique needs.

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4

Working Memory Training in Children with Neurodevelopmental Disorders

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Abstract

In a naturalistic open label non-randomized controlled intervention study, Cogmed© working memory (WM) training effects were compared between different groups of children (n = 99; 65 boys, 34 girls), aged between 7 and 17 years with neurodevelopmental problems, i.e. ADHD (n = 45), learning disorders (LD, n = 34) or learning problems (n = 20). Training efficacy after 25 sessions was measured by WM capacity improvement, ADHD DSM-IV rating scale and the BRIEF. It was hypothesized that training effects may lie on a continuum with those of the LD group at the lower end and those of the learning problems group at the upper end. Results partly confirmed the hypothesis in that all groups improved significantly with ADHD-children or children with learning problems showing the best results.

Introduction

Today's changing society (bigger, stronger, faster) including rapid developments in information technology places a high burden on the immature brains of children. Typically developing children usually perform well in a more stressful daily life, however children vulnerable to developing Attention-Deficit Hyperactivity Disorder (ADHD) or learning disabilities may struggle to perform well in these conditions. The concept of working memory (WM) needs to be explored thoroughly in order to understand the difficulties children may encounter in environments with increased demands.

WM allows individuals to store, manipulate and retrieve task-relevant information in the presence of irrelevant distraction (Baddeley, 1992; Unsworth & Engle, 2007). These cognitive capacities are of great importance in acquiring knowledge and new skills in daily life or at school. Substantial problems arise when WM deficits occur, requiring appropriate remedial support (Gathercole & Alloway, 2006; Klingberg, 2010; Kenworthy, Yerys, Anthony, & Wallace, 2008). Poor WM capacities are viewed as serious risk factors for learning disabilities and academic failure (Gathercole & Pickering, 2000; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011), as well as maladjusted (classroom) behaviour and may play an important role in the development of neurodevelopmental disorders, such as ADHD and learning disabilities (Aronen, Vuontela, Steenari, Salmi, & Carlson, 2005; Denckla, 1996).

According to Barkley's model, children with ADHD often suffer from deficits in executive functions, such as attentional control, inhibition and WM (Barkley, 1997). In this model WM deficits are seen in terms of down- stream primary inhibitory impairments. WM deficits may also serve as potential core components of ADHD responsible for inhibition deficits (Rapport, Chung, Shore, & Isaacs, 2001). Several meta-analytic reviews have stated that WM problems may be a key deficit or at least one of the core deficits in ADHD (Kasper, Matt Alderson, & Hudec, 2012; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Martinussen & Tannock, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

In respect of academic achievements, WM is seen as a strong predictor of reading abilities (Swanson & Beebe-Frankenberger, 2004) and mathematical skills over time (Gathercole, Tiffany, Briscoe, Thorn, & The ALSPAC Team, 2005; Mazzocco & Kover, 2007; Toll, Van der Ven, Kroesbergen, & Van Luit, 2011), even when controlling for IQ (Alloway & Alloway, 2010; Cain, Oakhill, & Bryant, 2004). Findings from meta- analyses indicate that children with reading disabilities as well as children with mathematical disabilities experience problems particularly with the verbal domain of WM (Swanson, Zheng, & Jerman, 2009; Friso-van

den Bos, van der Ven, Kroesbergen, & van Luit, 2013). Children with severe disabilities in mathematics have also been found to have deficits in spatial WM (Passolunghi & Mammarella, 2012).

It is apparent that WM problems seem to be relevant in both children with ADHD as in children with learning disabilities. Poor classroom behaviour and weak academic performance based on WM problems apply to both groups (Novik et al., 2006). From a neurobiological point of view, the shared WM deficits in children with ADHD and learning disabilities are not surprising. It is known that the dorsolateral prefrontal circuit function is associated with manipulating information in WM (Barbey, Koenings, & Grafman, 2013) and that children with neurodevelopmental disorders, such as ADHD or learning disabilities, show abnormalities in the prefrontal cortex (Arnsten & Rubia, 2012; Lazar & Frank, 1998). Therefore, problems involving frontal systems or executive functions are not exclusive to ADHD: these are also prevalent in children with learning disabilities. Furthermore, it has been suggested that ADHD and learning disabilities could be viewed as co-occurring disorders sharing neurocognitive deficits based on shared genetic risk factors (Sexton, Gelhorn, Bell, & Classi, 2012).

ADHD and learning disabilities therefore seem to have more in common than might be expected at first glance from a neuropsychological point of view. However, these neurodevelopmental problems are quite diverse in terms of diagnostic criteria. ADHD is defined by a pervasive pattern of symptoms of hyperactivity, impulsivity and/or inattention that is associated with impaired functioning (American Psychiatric Association, 2000). The term learning disabilities on the other hand refers to a heterogeneous group of disorders and problems that can be divided roughly into two groups: specific learning disorders (LD), and general learning problems. LD, like dyslexia or dyscalculia, refer to specific problems in a single domain of learning capacities or academic achievements. For instance, dyslexia is characterized by a specific and significant impairment in the development of reading skills (problems with accurate or fluent word recognition, poor decoding, poor spelling), while dyscalculia is characterized by a specific impairment in the acquisition of mathematical skills (problems with processing of numerical information, learning arithmetic facts, performing accurate and fluent calculations). Low IQ, visual or auditory acuity, mental or neurological disorders, psychosocial adversity, a lack of language proficiency or education, or inadequate educational instruction may not interfere with this specific impairment (American Psychiatric Association, 2013). LD occur in about 3% to 6% of all school aged children (Schulte- Korne, 2010; Shalev, 2000) with prevalence rates similar to ADHD (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

The group of children with general learning problems is a quite difficult group to differentiate, but has significant clinical relevance. The term general learning problems refers to non-specific and possibly co-occurring disabilities in the following areas: 1) receptive language; 2) expressive language; 3) basic reading skills; 4) reading comprehension; 5) written expression; 6) mathematical calculation and reasoning; and 7) attention (Lyon, 1996). The group of learning problems is a heterogenic group characterized by a broad range of symptoms covering diverse academic achievement problems. Although symptoms may (at some stage) not meet DSM criteria for ADHD or LD, they may be associated with sub-threshold psychiatric problems. Children with learning problems may be "overlooked" struggling students, meeting minimal academic standards, often caused by processing strength and weaknesses that adversely affect school achievement. An expert panel consensus about specific LD observed the difficulty in distinguishing between children with LD and low achievers. This panel underlined the need to provide early preventive interventions based on specific (neuro-)cognitive strengths and weaknesses (Hale et al., 2010).

Without proper preventive treatment, neurocognitive problems and learning problems may develop into serious psychiatric problems and school drop-out. Learning problems are also associated with secondary psychosocial characteristics such as the lack of self-esteem (McNamara, Vervaeke, & Willoughby, 2008). Children with ADHD, LD or learning difficulties need effective treatment in order to avoid gaps in their development and prevent mental health problems. First-line treatment for moderate to severe ADHD constitutes psycho-stimulants combined with parental training and/or behavioral therapy. On the other hand psychological treatments should be offered as first-line treatment for preschool and older children with mild and moderate ADHD (Trimbos-Instituut, 2005; Atkinson & Hollis, 2010). Pharmacological treatments decrease ADHD symptoms in most children with ADHD (Ostberg & Rydall, 2012). Nevertheless, alongside the concerns about potential side-effects, a considerable percentage still remains with behavioral or cognitive problems at a two year follow-up, (MTA Cooperative Group, 2004; Swanson & Volkow, 2009; Van der Loo-Neus, Rommelse, & Buitelaar, 2011). Other interventions, such as neuro-feedback, diets and cognitive training need further research to confirm potential positive effects (Sonuga-Barke et al., 2013). Research has also shown that WM impairments in children with ADHD can be positively influenced by a combination of incentives and stimulant medication (Strand et al., 2012). For LD, intensive evidence-based remedial interventions, such as the Lindamood program for children with dyslexia or the Number Race game for children with dyscalculia, may improve learning-related performance, however these interventions alone may not be

sufficient (Alexander & Slinger-Constant, 2004; Butterworth, 2010). Furthermore, in learning problems such as decoding difficulties or reading comprehension problems, early intervention methods do not directly result in improvements in reading skills (see for a review Snowling & Hulme, 2012).

While evidence has been mounting that WM impairments might be one of the core deficits in ADHD, LD and learning problems, research has also started to establish that WM capacity may be plastic and trainable (McNab et al., 2009). In terms of ADHD, a multicenter randomised controlled double-blind study has demonstrated improvements in a non-trained visuo-spatial WM task and on other neurocognitive functions as well as on parent ratings of inattention and hyperactivity-impulsivity up to 3 months after training (Klingberg, Forssberg, & Westerberg, 2002; Klingberg et al., 2005). Other randomised controlled trials have shown that systematic WM training in children with ADHD resulted in positive long-term near transfer effects on visual WM capacity (Hovik, Saunes, Aarlien, & Egeland, 2013) and in positive long-term far-transfer effects on ADHD deficits (Bigorra, Garolera, Guijarro, & Hervas, 2015). Furthermore, a review on the efficacy of Cogmed WM training, has shown this system to be a potentially efficacious treatment for older children with ADHD (Chacko et al., 2013).

Two meta-analyses on non-pharmacological interventions for ADHD have been more critical and suggest that better evidence for the efficacy of cognitive training (attention training and WM training) is required before these interventions may be designated as effective interventions for ADHD (Cortese et al., 2015; Hodgson, Hutchinson, & Denson, 2012; Sonuga-Barke et al., 2013). A meta-analysis on several cognitive training programs in children with ADHD showed moderate improvements in STM performance in studies using training STM alone (such as Cogmed WM training)—however distal transfer effects were negligible (Rapport, Orban, Kofler, & Friedman, 2013). Additionally, two other reviews highlighted areas of concern in terms of the WM training effects in diverse patient groups, as well as with the different types of WM training methods. Inconsistent findings within and between studies has created doubt about the long-term effects and the generalization of the trained task effects (Melby-Lervag & Hulme, 2012; Shipstead, Redick, & Engle, 2012). Conclusions from these reviews have been criticized by others who have argued that WM capacity, attention and academic abilities do improve after Cogmed WM training (Shinaver, Entwistle, & Söderqvist, 2014).

Furthermore, it has been shown that in typically developing children WM training enhances reading performance, e.g. speed and comprehension (Loosli, et al., 2012). With respect to learning problems, WM training-induced improvements were found on non-trained visuo-spatial and verbal storage and

manipulation tasks. Furthermore, a distal transfer effect was found in that (not trained) academic achievements improved after the intervention: significant gains with respect to mathematical ability were reported up to 6 months after training (Holmes, Gathercole, & Dunning, 2009). A randomized controlled trial on the efficacy of WM training on reading skills in children with special needs reported improved performance on reading comprehension, related to an increased WM capacity (Dahlin, 2011). A randomised controlled trial in adolescents with severe LD and comorbid ADHD showed effects of Cogmed WM training on two of the three trained WM tasks (Gray et al., 2012). However, no transfer effects were found on non-trained cognitive tasks, parent- or teacher-rated ADHD symptoms, or measures of academic achievement. Supplemental analysis showed significant effects of time (regardless of training program) on cognitive attention, reading and mathematics as well as on parent-reported ADHD symptoms. In conclusion, studies on the efficacy of WM training in children with ADHD, LD or learning problems are inconclusive. Further exploration of direct and distal transfer training effects is therefore needed.

Studies to-date on the efficacy of Cogmed have examined training effects in patients from one diagnostic category and compared those with normal controls or placebo conditions (e.g., ADHD: Chacko et al., 2013; learning problems: Holmes et al., 2009). The present study adds to the literature by comparing training effects between different diagnostic groups, i.e. ADHD, LD and learning problems. Studying these different subgroups with neurodevelopmental problems is of great interest, since they represent a large proportion of the clinical population. In addition, comparing different diagnostic groups that differ in the extent of WM deficits may shed light on the range of treatment effects that can be achieved.

The aim of this study is to examine differences in efficacy of WM training in three groups of children with neurodevelopmental problems, i.e. ADHD, LD and learning problems. Apart from aetiology, differences in WM and learning problems between these three groups can be found in terms of the severity of neurocognitive impairments (Willcutt et al., 2010). Children with learning disabilities generally perform worse on WM tests compared to children with ADHD (Lazar & Frank, 1998). It is known from the literature that children with general learning problems have mixed but relatively higher WM scores compared to children with LD (Jeffries & Everatt, 2004). Therefore, the largest training effects are expected in the learning problems group characterized by milder, less pervasive cognitive or WM problems, compared to the other groups, due to the higher degree of sensitivity of these children to training.

Methods

Subjects

Subjects were recruited in fifteen independent private practices (Psychological Primary Health Care) in the Netherlands, selected by BeterBrein, the Dutch Cogmed© licence holder at the time of the study. Subjects were asked by their therapist to participate in this study facilitated by the mental healthcare cooperation UVIT/VGZ. The children were attending private practices for the treatment of attention or memory problems or other learning difficulties that were interfering with their academic achievements. The Cogmed training was free of charge for the subjects.

The inclusion criteria for this study were children aged between 4 to 17 years of age, with a DSM-IV-TR classification of ADHD or LD (dyslexia, dyscalculia or learning disorder not otherwise specified), diagnosed (according to DSM-IV-TR criteria) by a registered clinical psychologist in an independent private practice. For those cases of dyslexia and dyscalculia, the diagnoses were based on the Dutch guidelines for these learning disorders (Masterplan dyslexia; http://masterplandyslexie.nl/nl/pages/ masterplan). Children in the same age range with learning problems (but without a DSM-IV diagnosis) were also included. These children were experiencing academic achievement problems (lower grades than expected) and mixed neuropsychological impairments (memory- or attention problems in the classroom), as well as learning-related behavioural problems (Alloway & Alloway, 2010). Learning problems were diagnosed according to an official Dutch system that monitors academic achievement at school supplemented by the clinical opinion of the clinical psychologist and reports by parents and teachers about the child's development. For these children treatment of their learning problems had been recommended by a registered clinical psychologist in an independent private practice.

Subjects were excluded where there was 1) a medical illness requiring immediate treatment as this meant that participating in an intensive training would be too demanding; 2) a motor or perceptual disability preventing the subject from using the computer program; 3) no access to a personal computer with an internet connection at home or in school; 4) a lack of motivation (e.g. willingness on the part of the parents to participate, but not on the part of the child); or 5) a co-morbid (psychiatric) diagnosis.

A total of 122 children were recruited. Seventeen children were excluded due to a co-morbid diagnosis: Rett's syndrome (n = 3), Expressive Language Disorder (n = 2), Autism Spectrum Disorder (n = 1), Developmental Coordination Disorder (n = 1), and Internalizing problems such as anxiety, depressive and psychosomatic symptoms (n = 9). One child was excluded as the treatment was

not in line with the diagnosis. This particular child was diagnosed with LD and was taking ADHD related medication. Six children were excluded due to missing data (outcome measure questionnaires not completed by the parents before and after training). Data from 99 children were analysed. Seventy-nine subjects were diagnosed with a DSM-IV-TR classification of ADHD or LD. Forty-five of these children were diagnosed with ADHD (inattentive subtype (n = 25), combined subtype (n = 13), not otherwise specified (NOS n = 7). Thirty-four children were diagnosed with LD (dyslexia (n = 25), dyscalculia (n = 3), not otherwise specified (NOS n = 6)). Twenty subjects did not meet the criteria for a DSM-IV-TR classification. These children were experiencing learning problems, such as mild symptoms of inattention and/or academic achievement or learning related behaviour problems (see Figure 1).

Seven children were taking psycho-stimulants (Concerta (n = 1), Ritalin (n = 5), Medikinet (n = 1)). Psycho- stimulant use was not an exclusion criterion, since exclusion of the medicated children might preclude generalisation of the results. The dosage of the medication remained stable during the five-week training period. Criterion for inclusion was room for improvement, defined as "still having significant DSM-IV-TR related ADHD problems interfering with daily life". This was the case in these seven children (all diagnosed with ADHD).

Outcome Measures

Behavioural outcome was measured by the total score of inattention and ADHD hyperactive/impulsive symptoms to the Dutch version of the ADHD rating scale (ADHD Vragen Lijst, AVL; Scholte & Van der Ploeg, 2005). In this rating scale eighteen ADHD related items, based on the DSM-IV-TR, are measured on a five point scale. Behavioural outcome was also measured by the total score and WM subscale of executive function problems (experienced daily) from the Dutch version of the Behaviour Rating Inventory of Executive Function checklist (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000; Smidts & Huizinga, 2009). The Dutch version of the BRIEF has a high reliability (total score BRIEF: Cronbach's $\alpha = 0.93$; test-retest reliability 0.86) and a high convergent validity when compared with the Child Behavior Checklist (CBCL: total score BRIEF and total score CBCL $r = 0.75$), (Verhulst, Van der Ende, & Koot, 1996). The ADHD rating scale and the BRIEF were completed by parents before, and 4 - 6 weeks after training.

WM capacity improvement was measured by the Cogmed computer program on two Cogmed© components (visual data link and input module recall) on training days two and three less the mean score on the two highest scores on these components.

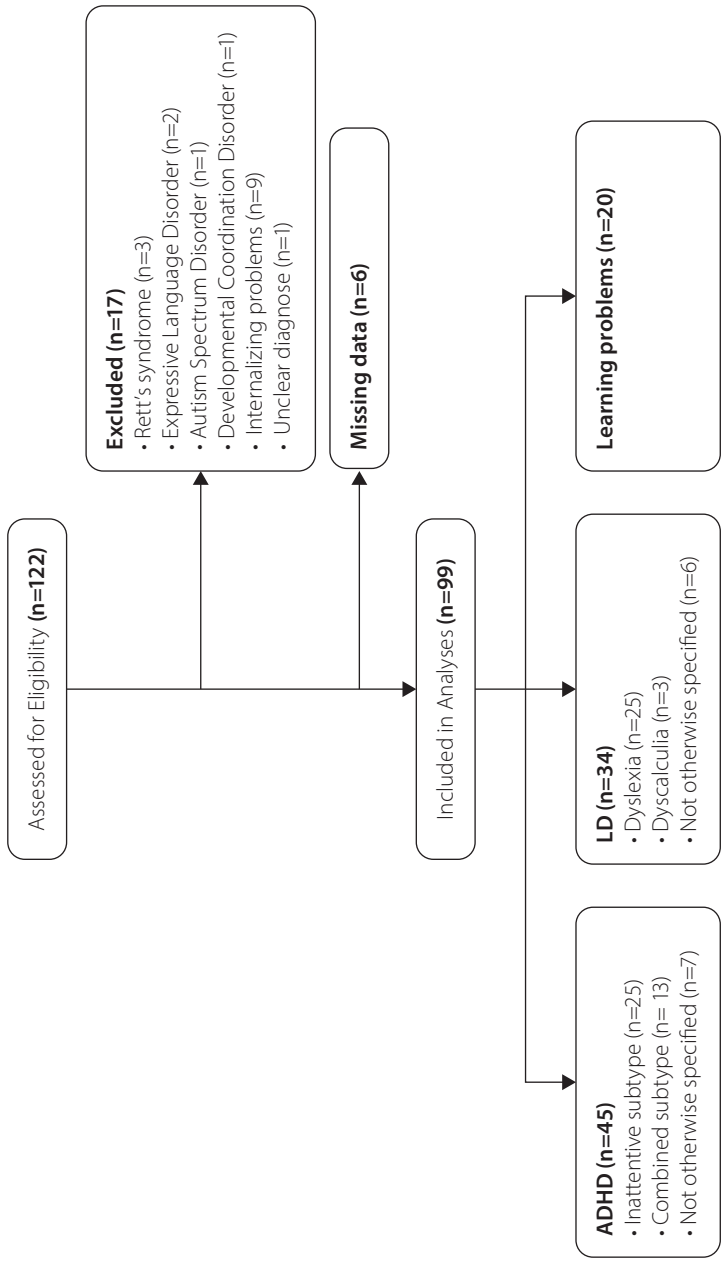

Figure 1: Flow diagram of included children.

Intervention

Cogmed WM training consists of 13 verbal and visual short-term memory and WM tasks, implemented using a computer program (Cogmed©, Stockholm, Sweden). A child will complete eight different task on each training session. An example of a verbal WM task is Decoder. In this particular task, some letters will be said aloud, while three letters are shown at the same time with the corresponding letter highlighted. The child needs to remember the letters that he/she hears and select the letters by clicking on them without becoming distracted by the other non-corresponding letters shown on the display. An example of a verbal WM task is Rotating data link. In this particular task a number of lamps will be highlighted in a successive order. The child needs to remember the order. Before the child gives an answer, the entire panel will be turned through 90 degrees. When the program says "go", the child clicks on the circles in the order in which the lamps were highlighted, however they need to remember that the panel has turned 90 degrees. The JM version for toddlers only includes visual short-term and WM tasks. The RM version for children aged between 7 to 17 years, includes verbal and visual short-term and WM tasks (JM; n = 4, RM; n = 95). The children in the JM condition were all 7 years of age, diagnosed with ADHD and free of medication.

The program was provided on a compact disc and used by the child on a personal computer at home, supervised by a parent. This supervision included additional task instructions, encouraging the child to continue with the tasks when training becomes more difficult, taking a break when fatigued, or avoiding external distractors. The children undertook the same amount of sessions (25 in total) and exercises (8 different exercises each training session and 15 rehearsals per exercise). Total training time depended on the time needed to finish the complete training including the breaks taken between the exercises, and the difficulty level they reached, as this led to more items to remember and therefore a (little) longer time required to respond. Responses were made by clicking on displays using the computer mouse. The difficulty level was automatically adjusted, on a trial-by- trial basis, to match the WM span of the child on each task. Children were assigned a unique ID code to ensure anonymity. Task performance was uploaded in a log file. Adherence to training was monitored through weekly telephone calls by a personal coach, who provided feedback about individual performances. The personal coach followed a strict protocol as part of the training program. Motivational features were included as part of the program to enhance adherence to training. During the training sessions the child received positive verbal feedback from the computer. Furthermore high scores were displayed after each task; there was also an "energy" counter shown which could be used on a fun racing game after each

training day was completed. The racing game was only included as a reward and did not load on WM. Children had a free choice whether to play the game. After each week of training the child received a small reward (e.g. doing something fun with dad, choosing dinner).

Procedures

Parents of children meeting the criteria were informed verbally about the study. Children and their parents who were willing to participate in the study were sent more detailed written information, which specified the inclusion criteria in terms of diagnostic classification, age and the need for a computer with internet access. All inclusion and exclusion criteria were checked by a psychologist at the screening visit with the child and one of the parents. The parents of the included children were asked to complete the baseline questionnaires (AVL, BRIEF). Detailed information about the computer program was provided and the parents were asked to sign an agreement detailing treatment goals and to the requirement to complete at least 25 days of training. Appointments for weekly supportive coach calls were arranged. These coach calls were used to discuss technical difficulties and information about training progress. The post-intervention visit took place 5 to 6 weeks after the baseline visit, at which the same questionnaires were completed by the parent. A social validation questionnaire was sent a couple of days after the post-intervention visit to measure client satisfaction with regard to the training program, procedures and the psychologist's coaching.

Statistical Analysis

Descriptive statistics are reported for each variable of interest for the three groups (ADHD, LD and learning problems). Categorical variables are presented as counts and percentages; continuous variables include the mean and standard deviation. First univariate analyses were carried out. An one-way ANOVA was conducted to determine if age was different for the three groups (ADHD, LD and learning problems). A chi-square test was used to examine whether there was an association between gender, use of medication, the Cogmed version and the group (ADHD, LD and learning problems). An independent-samples t-test was run to determine if there were differences in the AVL, BRIEF and Cogmed WM capacity between gender, between use of medication and between Cogmed version.

Secondly, we looked at the percentages of children in the (sub)clinical range at pre-treatment in the three different groups for the AVL (normal range (0-11), (sub)clinical range (≥12) (Scholte & van der Ploeg, 2005) and the BRIEF (normal range (0 - 49), (sub)clinical range (≥50)) (Smidts & Huizinga, 2009). For WM start index, mean ± standard deviation are presented.

A 2 × 3 repeated measures ANOVA was run to determine the effect of AVL, BRIEF and Cogmed WM capacity between pre-treatment and post-treatment for the three groups (ADHD, LD and learning problems). Post hoc Bonferroni t-tests were used to detect differences between the individual three groups where the main for group was statistically significant. Since univariate analyses showed no effect of age, gender or use of medication for any of the outcome variables and for the three groups (ADHD, LD and learning problems) these covariates were not included in the further analyses. Effect sizes are reported using the Partial eta-squared. Effect sizes of 0.8 are considered large and effect sizes between 0.5 and 0.8 are moderate. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 21.0).

Results

The majority of subjects were boys in all groups. Mean age in all groups was 10.3 years (range: 7 to 17). Most of the children were free of medication. In 25% of the total sample, information about medication use was unknown. However, in most cases this involved children in the LD or learning problems groups. In these groups, it is not plausible that the children used ADHD related medication due to the medication policy in primary health care, e.g. in the Netherlands, children with LD or learning problems are not diagnosed or treated by doctors but by psychologists and these professionals are not allowed to prescribe medication. In seven children with ADHD (7% of the total sample) information about medication use was missing. See Table 1 for descriptive details of the subjects and medication use.

As shown in Table 2, at baseline the larger proportion of children with LD fell into the normal AVL-I range (standardized residual: 2.4), whereas children with ADHD and learning problems mostly fell into the clinical range. The baseline measure in terms of hyperactivity/impulsivity symptoms were alike for the three groups with the majority of the children falling into the normal range. Furthermore, Brief total score and WM start index did not differ at baseline between groups. The WM start index was at a normal range, compared to other clinical groups of children treated with Cogmed WM training (mean 73, aged 7 - 17; Cogmed manual).

Table 1. Subject characteristics (n = 99).

		ADHD n = 45		Learning disorder n = 34		Learning problems n = 20		p-value[a]
		n	%	n	%	n	%	
Gender	Boy	32	71%	18	53%	15	75%	0.149
	Girl	13	29%	16	47%	5	25%	
Medication	No	31	69%	18	53%	18	90%	0.292
	Yes	7	16%	0	0%	0	0%	
	Unknown*	7	16%	16	47%	2	10%	
Version cogmed	J/M	4	9%	0	0%	0	0%	0.082
	R/M	41	91%	34	100%	20	100%	
		ADHD n = 45		Learning disorder n = 34		Learning problems n = 20		p-value[b]
		Mean	±SD	Mean	±SD	Mean	±SD	
Age		10.3	±2.5	10.3	±2.4	10.3	±2.5	0.998

Note: ADHD = Attention Deficit Hyperactivity Disorder, SD = Standard Deviation. *Unlikely that medication was subscribed in the LD and learning problems group, because of medication policy in primary health care in The Netherlands.
[a] Chi-square test
[b] Anova

There was a significant main effect with small to moderate effect sizes for three outcome measures (AVL-I $F(1, 93) = 122.4$, $p < 0.0001$, partial $\eta^2 = 0.57$; AVL-H/I $F(1, 93) = 45.9$, $p < 0.0001$, partial $\eta^2 = 0.33$; BRIEF Total $F(1, 95) = 35.3$, $p < 0.0001$, partial $\eta^2 = 0.27$; and a high effect size for WM index $F(1, 96) = 901.9$, $p < 0.0001$, partial $\eta^2 = 0.90$), suggesting that all groups (ADHD, LD and learning problems) profit from training in terms of their inattention symptoms, hyperactivity/impulsivity symptoms, overall executive function problems and WM capacity (Figure 2 & Table 3).

There was a statistically significant interaction between group and time for hyperactivity/impulsivity symptoms (AVL-H/I, $F(2, 93) = 3.30$, $p = 0.041$, partial $\eta^2 = 0.07$). Furthermore, the results showed a statistically significant interaction effect with small effect sizes for the BRIEF (Total $F(2, 95) = 5.32$, $p = 0.006$, partial $\eta^2 = 0.10$). Post hoc Bonferroni analysis revealed that at post treatment BRIEF was statistically different between LD and ADHD ($p = 0.0006$) and the AVL-H/I

Table 2. Baseline measurements (n = 99).

		ADHD n = 45		Learning disorder n = 34		Learning problems n = 20		p-value[c]
		n	%	n	%	n	%	
AVL-I[a]	Normal range	7	16%	17	50%	4	20%	0.002[e]
	(Sub)clinical range	37	82%	16	47%	15	75%	
	Missing	1	2%	1	3%	1	5%	
AVL-H/I[a]	Normal range	29	64%	27	79%	14	70%	0.298
	(Sub)clinical range	15	33%	6	18%	5	25%	
	Missing	1	2%	1	3%	1	5%	
BRIEF total[b]	Normal range	11	24%	17	50%	5	25%	0.145
	(Sub)clinical range	33	73%	17	50%	15	75%	
	Missing	1	2%	1	3%	1	5%	
		ADHD n = 45		Learning disorder n = 34		Learning problems n = 20		p-value[d]
		Mean	±SD	Mean	±SD	Mean	±SD	
WM start index		78.4	±12.9	75.8	±10.5	74.9	±15.0	0.501

[a] Normal range (0 - 11), (sub)clinical range (≥12) for AVL were based on the manual (Scholte & van der Ploeg, 2005)
[b] Normal range (0 - 49), (sub)clinical range (≥50) for BRIEF were based on the manual (Smidts & Huizinga, 2009)
[c] Chi-square test. Missing category was not included in the Chi-square test
[d] ANOVA
[e] A significantly larger group of children with LD fall in the normal AVL-I range (std. residual: 2.4);
Note: ADHD = Attention Deficit Hyperactivity Disorder, SD = Standard Deviation, AVL-I = inattention scale AVL, AVL-H/I = Hyperactivity/Impulsivity scale AVL, BRIEF Total = Total score BRIEF, WM = Working Memory.

was borderline statistically significantly between LD and ADHD ($p = 0.057$). This suggests that children with LD profit less from training regarding hyperactivity/impulsivity symptoms and overall executive function problems, compared to children with ADHD. No interaction effects were found on inattention symptoms and Cogmed improvement index.

We also re-ran the analyses excluding children using psychopharmaceuticals (n = 7), the young children treated with the J/M-version of Cogmed WM training (n = 4) and children with dyscalculia (n = 3). The significant main effects and interactions effects on all outcome measures stayed the same.

Table 3. Main effects and Interaction effects on the AVL, BRIEF and Cogmed WM capacity between pre-treatment and post-treatment for the three groups (ADHD, LD and learning problems).

	ADHD n = 45		Learning disorder n = 34		Learning problems n = 20		Main effect[a]	Interaction effect[a]
	Before	After	Before	After	Before	After	p/η^2	p/η^2
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD		
AVL-I	17.1 ±6.0	11.2 ±5.4	12.5 ±6.4	8.2 ±4.4	15.7 ±5.8	9.7 ±5.3	p <0.0001 η^2 = 0.568	p = 0.282 η^2 = 0.027
AVL-H/I	9.5 ±6.5	6.6 ±4.6	6.0 ±6.3	4.4 ±4.2	8.3 ±6.9	3.8 ±4.0	p <0.0001 η^2 = 0.331	p = 0.041[c] η^2 = 0.066
BRIEF Total	56.4 ±10.3	51.0 ±9.2	50.7 ±11.7	49.5 ±10.0	54.4 ±9.3	47.6 ±10.1	p <0.0001 η^2 = 0.271	p = 0.006[b] η^2 = 0.101
WM index	78.4 ±12.9	104.4 ±16.4	75.8 ±10.8	100.9 ±13.1	74.9 ±15.1	103.3 ±15.2	p <0.0001 η^2 = 0.904	p = 0.359 η^2 = 0.21

[a]Repeated Measure
[b]group difference Bonferroni Post Hoc test between LD and ADHD (p = 0.006)
[c]group difference Bonferroni Post Hoc test between LD and ADHD (p = 0.057)
Note: ADHD = Attention Deficit Hyperactivity Disorder, SD = Standard Deviation, AVL-I = inattention scale AVL, AVL-H/I = Hyperactivity/Impulsivity scale AVL, BRIEF Total = Total score BRIEF, WM index = Working Memory index Cogmed.

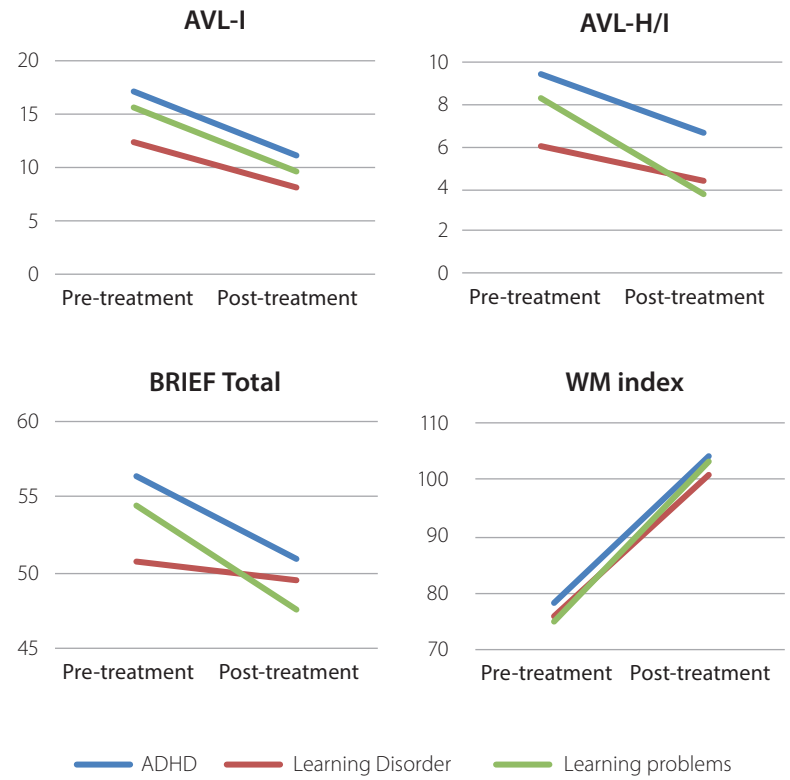

Figure 2: AVL, BRIEF and Cogmed WM capacity between pre-treatment and post-treatment for the three groups (ADHD, Learning disorder and learning problems).

Discussion

This study examined the efficacy of Cogmed WM training in three groups of children with neurodevelopmental problems, i.e. ADHD, LD and learning problems. It was hypothesized that training effects may lie on a continuum with those of the LD group at the lower end and those of the learning problems group at the upper end, due to differences in the distribution of WM problems between groups and therefore differences in sensitivity to training.

The results partly confirmed our continuum hypothesis. A significant main effect with small to moderate effect sizes was found on inattention symptoms, hyperactivity/impulsivity symptoms, overall executive function problems and with a high effect size for WM capacity, suggesting that all groups (ADHD,

LD and learning problems) benefit from training. Furthermore, significant interaction effects with small effect sizes revealed that children with LD profit less from training in respect of hyperactivity/impulsivity symptoms and overall executive function problems, compared to children with ADHD. All groups profit equally from training regarding behavioural attention and WM capacity.

An explanation for the differences in improvement between the LD group versus the ADHD group on overall executive functioning problems, could be that the LD group may need more time to establish behavioural and EF-related improvements in daily life. This delayed effect has also been found on academic skills in a study on Cogmed training effects using a comparable group (Holmes et al., 2009). Immediately after training, small non-significant effects were found on measures of academic skills, however six months after training mathematics performance appeared to be significantly improved (Holmes et al., 2009). It sounds reasonable that it takes some time to experience the benefits of cognitive training in daily life in activities requiring higher order cognitive functioning, such as WM and EF.

Perhaps another explanation could be that for the LD group the training is not primarily WM training but attention training. This is in line with the finding that 37% of the self-reports of Cogmed trained LD children showed enhanced attentional focus (Holmes et al., 2009). WM and controlled attention are closely related and improvement in WM capacity might mediate improvements in attention. WM and controlled attention rely on the same mechanisms of sustained neural activity and top-down excitation, and the same multi-model frontoparietal network (Klingberg, 2010). In this way, connected neural systems might explain WM training-related generalization effects to controlled attention (Klingberg, 2010).

A final explanation for the differences in efficacy of WM training in LD may be that other cognitive factors play a more crucial role in LD, such as comprehension, listening and writing (Semrud-Clikeman, 2005), and phonological deficits in cases of dyslexia and a deficient number module in cases of dyscalculia (Landerl, Fussenegger, Moll, & Willburger, 2009).

It could also be posited that the lack of differences in the LD group may be purely due to the measures chosen. The improvement in the inattention measure was only about 4 points and could have been purely due to chance. However, in this particular group the inattention symptoms were scored at a subclinical level before training (AVL inattention cut-off score stands at 12 points), reaching an average level after training. Therefore we believe that this still is a clinically relevant finding, since children with dyslexia often have attention problems and vice versa. Tannock and Brown (2000) reported that 12% - 24% of the children diagnosed with dyslexia also had ADHD, and 15% - 30% of the children diagnosed with ADHD (without considering sub-types) were estimated to have comorbid dyslexia.

As mentioned earlier, children with LD seem to profit less from training compared to children with ADHD on hyperactivity/impulsivity problems. This is a rather remarkable finding since treatment effects on hyperactivity/impulsivity problems in children with LD may not be expected in light of classification criteria and behavioural problems experienced daily (American Psychiatric Association, 2013; Lyon, 1996). When looked at more closely, children in our study with learning problems showed a considerably higher baseline measurement regarding hyperactivity/impulsivity problems (meaning more problems) compared to children with LD. Perhaps the fact that there was less room for improvement in the LD group may explain the difference found in terms of benefit between these groups. The learning problems group is a rather diffuse and heterogeneous group with non-specific and possibly co-occurring disabilities compared to the rather isolated problems in the LD group. It is therefore plausible that some children in the learning problems group experienced more hyperactivity/impulsivity problems than considered prior to the study. This could also explain why the LD group did not show an effect when the interaction was considered. Other research has shown that children with reading disabilities have lower WM span levels, yet as they age they show similar WM growth, compared to children without reading disabilities. In addition, inhibition difficulties, more so than WM difficulties, constrain growth in reading performance (Jerman, Reynolds, & Swanson, 2012). Furthermore, these findings in the learning problems group could be caused by statistical phenomena, such as a reduced power and increased risk of Type II errors.

Our results suggest that Cogmed© WM training could be an effective training program for children with neurodevelopmental problems with the best results for children with ADHD or learning problems. These findings add to the accumulating evidence that WM training may indeed reduce attention and memory problems, learning difficulties and academic achievement problems, and suggest plasticity of the brain in children with neurodevelopmental problems across a wide age range.

However, the results should be viewed in light of some limitations. A major limitation of this study is the absence of a randomized design and a control condition. Therefore, the positive results in this study were not controlled for unspecific factors, such as invested time and attention, therapist interaction, or brain maturation. However, clinical intervention studies are valuable because of their realistic character and better fit to daily life. The children participating in this study received active weekly Cogmed coaching, which might be (one of the) the most important component(s) in the training program. In previous

randomized controlled trials on the efficacy of Cogmed, coaching was solely based on encouraging and motivating parents and children, and – in contrast to Cogmed in clinical practice—could not be based on individual training results as the coach was blinded to group assignment (due to the triple-blind design).

Another limitation could be that the only WM measurement used in this study was the WM capacity improvement index measured by the Cogmed© computer program itself, which is not a pure clinical measure and is susceptible to practice effect. On the other hand, differences in practice level might be of interest, given we know that improvement index levels between individuals can be quite various. Therefore it might be of value that this study has demonstrated that some groups of clinical patients benefit more from training than others and therefore show more improvement on trained tasks than others. Furthermore, the fact that the parent reports were not anonymised, and (potentially more neutral) teacher ratings were not included may have created an expectancy bias resulting in more positively rated training effects (Caspi & Bootzin, 2002; Sonuga-Barke et al., 2013). However, our results showed no observer bias effect for children with LD on BRIEF measures, as the (mild) behavioral problems still remained after training. Additionally, the results may be interpreted as parent-reported improved quality of life.

Meta-analyses have been sceptical about the efficacy of training programs such as Cogmed, however these reviews mostly represent children diagnosed with psychiatric disorders, e.g. moderate to severe ADHD, often in combination with other comorbid psychiatric disorders. An important point not stressed in these reviews is the potential influence of the severity of the neuro-developmental problems. Our study focused on mild behavioural and learning disabilities. The majority (71%) of the ADHD group was diagnosed with the inattentive subtype or "not otherwise specified" and none of the ADHD children had comorbid disorders. Although all subjects were diagnosed by a range of practitioners we consider this group as a mixed group of children without a full psychiatric disorder, even though this could possibly have led to a potential contribution to variability within the diagnosis of children within the sample, especially the heterogenic learning problems group. However, in our opinion this is an important and large group of children at risk of developing a psychiatric disorder/severe LD or leaving school early. Neurocognitive problems and learning disabilities may be precursors of psychiatric disorders. So, while evidence for WM training induced generalization effects in complex psychiatric populations is not convincing, our study shows that Cogmed WM training might be (more) useful for children with relatively mild or subthreshold psychiatric disorders or learning disabilities at risk for a severe psychiatric disorder. This might prevent the development of a full psychiatric disorder or severe academic achievement

problems. Our findings show that this "at risk-group" of children profit from a relatively short, but intensive Cogmed training program. Therefore, low cost interventions such as Cogmed WM training could possibly prevent the development of severe neuropsychiatric disorders.

Another point to take into account is that medication use in this sample seems low. An explanation could be found in the way the Dutch mental health care system works. In the Netherlands, children with mild psychiatric disorders are diagnosed and treated in (private) psychological practices by psychologists (not doctors), and not in child psychiatric centers or hospitals. In line with the ADHD guidelines (Trimbos-Instituut, 2005; Atkinson & Hollis, 2010) psychological treatments are offered as first-line treatment for children with mild ADHD. Comorbidity in this relatively mild ADHD group is less likely compared to children with full-blown ADHD that are treated in child psychiatric hospitals.

Further longitudinal research on WM training is needed in large groups of children with different levels of severity of neurodevelopmental disorders to examine the effect of severity, age, distal transfer and long-term effects (Klingberg, 2010; Chacko et al., 2013). The training program could be extended by training-related exercises at home in order to enhance transfer and generalisation effects. Incorporation of WM tasks in daily life could improve executive functioning and academic achievements.

Future research should use a randomized placebo-controlled design in a naturalistic setting, and blind ratings of subjective behavioural change in daily life. Studies could also include multiple ecologically valid measures of neuro-cognitive functioning to measure near and distal transfer effects when comparing groups of children with neurodevelopmental disorders. In doing so, it would be interesting to use the baseline WM capacity level, measured with an independent neuropsychological assessment, to include only those children with actual WM deficits in the training problem (as we are aware that WM deficits in the patient groups described are based on group results, which does not mean that some individuals do not experience WM problems at all). Furthermore, more research focussing on the underlying (secondary) mechanism of WM training, e.g. the role of systematic coaching during training is needed. The above is in line with three recent meta-analytic reviews reporting that WM training programs produce short-term, specific training effects that do not generalize (Melby-Lervag & Hulme, 2012; Shipstead et al., 2012; Sonuga-Barke et al., 2013). Isolated WM training might not be adequate to improve executive functioning in daily life (Diamond & Lee, 2011). Social-emotional and physical development, by means of sports, nutrition and mindfulness are important elements to create a healthy and stimulating breeding ground to learn to deal with all sorts of daily life events.

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5

Working Memory Training in Children with Borderline Intellectual Functioning and Neuropsychiatric Disorders: A Triple-Blind Randomized Controlled Trial

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Abstract

Background: Poor working memory, lower IQ and maladaptive behaviour form a triple disability known to have negative effects on the academic and social development of children with borderline intellectual functioning (BIF; IQ: 70<IQ<85) and neuropsychiatric disorders (attention-deficit hyperactivity disorder (ADHD) and/or autism spectrum disorder (ASD)). Treatment possibilities for these children are scarce and hardly evidence based.
Objective: This study primarily investigated whether adaptive computerised working memory training (WMT) may lead to significantly more improvement on a non-trained visuospatial WM task compared to a non-adaptive control WMT (placebo) in children with BIF and neuropsychiatric disorders. As secondary outcome measures, we used the scores on several non-trained neuropsychological near and far-transfer tasks as well as behavioural measures.
Design, Setting, Participants: We conducted a triple-blind placebo-controlled randomised clinical trial in 72 children (aged 10;0 – 13;11 years, 53 boys, 19 girls) with BIF and comorbid neuropsychiatric disorders (ADHD = 37, ASD = 21, both = 14) that were referred to child and adolescent psychiatry care, between May 2012 and March 2019.
Interventions: Children completed the Dutch version of Cogmed WMT, either the adaptive training version or the non-adaptive placebo version, 25 sessions (30-45 minutes a day), for 5 weeks.
Main Outcome Measure: The primary outcome measure was the score on a non-trained visuo-spatial working memory task. The primary outcome was measured before and directly after 5 weeks of WMT, and again 6 months after training.
Results: A total of 375 children were screened for eligibility and 72 were randomised. No significantly higher levels of improvement over time were found on our primary outcome measure in the experimental WMT group compared to the placebo control WMT, nor in the secondary (near and far-transfer tasks) or tertiary (behavioural measures) outcome measures. However, this study did show changes over time for these measurements for both the experimental and placebo condition.
Conclusions: This study was unable to document superior training effects over time of an adaptive WMT in children with BIF and neuropsychiatric disorders, compared to a placebo (non-adaptive) WMT. The objectively documented changes over time in the non-adaptive WMT arm suggest that these children with persistent impairments in WM may benefit from a structured learning environment that is associated with improvement of neurocognitive functioning and coping strategies. Further research is needed to examine which elements of cognitive training may be useful for which specific patients and to study long term effects of training.

Introduction

Children with borderline intellectual functioning (BIF: 70<IQ<85) show deficits in neurocognitive functioning and adaptive behaviour. The prevalence of BIF is estimated to be up to 10% (Roeleveld et al., 1997; Simonoff et al., 2006; Westerinen et al., 2017). About one third of the children with BIF may have a comorbid neuropsychiatric disorder, the most common being attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD; Strømme & Diseth, 2000). These comorbid disorders may aggravate the problems in adaptive functioning and hinder development. Regular treatments, such as cognitive-behavioural therapies, are often too complex for children with BIF and ADHD and/or ASD due to lower intellectual abilities and less well-developed adaptive skills. Furthermore, this group is known to have a lower treatment response to ADHD medication (40-54% responders) compared to patients with an average IQ (70% responders) and also suffer from more serious adverse effects (e.g., Simonoff et.al., 2013). Also, these children are more likely to grow up in lower socio-economic environments and face adversity, which are factors associated with poorer mental health in the general population (Emerson & Brigham, 2015). Thus, there is a need to extend the evidence-base for effective interventions for these patients. Interventions using computer technology like computerised cognitive training might fill this gap.

Children with BIF are found to have a primary cognitive deficit in working memory (WM; Roording-Ragetlie et al., 2018). Similarly, ADHD and ASD are also characterised by persistent impairments in WM (Kasper et al., 2012; Kenworthy et al., 2008; Martinussen et al., 2005). Such WM impairments in children with BIF and neuropsychiatric disorders are related to poor adaptive behaviour (Gilotty et al., 2002), heightened vulnerability to academic and social impairments (Cornish et al., 2012) and reduced quality of life (Chiang & Wineman, 2014). Therefore, it is important to investigate whether WM can be strengthened in these children. Even a small amount of progress in this cognitive capacity may lead to significant progress in classroom and daily life functioning (Minear & Shah, 2006). Furthermore, a computerised working memory training (WMT) might be ideal for children with BIF, because it can take place at home and/or school, appeals to their relatively stronger visual abilities (Van der Molen et al., 2014) and is motivational due to the gaming elements (Dovis et al., 2012; Sadeghi et al., 2020).

Note that several meta-analyses are critical about the efficacy of WMT. Inconsistent findings within and between studies raise doubts about the long-term effects and generalization of the trained task effects (Melby-Lervag et al., 2016; Rapport et al., 2013; Shipstead et al., 2012). Further, despite improving

WM performance, cognitive training had limited effects on ADHD symptoms according to assessments based on blinded measures (Cortese et al., 2015). However, results on the efficacy of computerised WMT in large and diverse patient groups cannot simply be extrapolated to children with BIF and neuropsychiatric disorders due to their unique neurocognitive profile (Danielsson et al., 2012). A study in children with ASD and co-morbid ADHD, partially similar to the group in the present study, showed improvement in attention and focus, impulsivity, emotional reactivity, and academic achievement after computerised WMT. It has been suggested that computer-based interventions seem to engage the unique learning style of this population (Weckstein et al., 2017). Furthermore, studies in children with BIF show improvements in short-term memory (STM) and WM as well as in academic achievements after WMT (Danielsson et al., 2015; Söderqvist et al., 2012a; Van der Molen et al., 2010). Moreover, it is known that improvement in training progress varied largely between individual children with intellectual disabilities, due to variability in demographic characteristics (Söderqvist et al., 2012a).

Klingberg and colleagues (2005) studied the difference between an active (adaptive) Cogmed WMT and a placebo (non-adaptive) version of the training and found a significant improvement on a non-trained visuo-spatial WM task in children with ADHD who completed the active WMT. However, that study did not include children with co-morbid BIF. Therefore, the main objective in the present study is to examine whether performance on a non-trained visuospatial WM task shows greater improvement from baseline to endpoint for the adaptive versus the non-adaptive version of a computerised WMT in children with BIF and neuropsychiatric disorders (ADHD and/or ASD). In the adaptive version the difficulty level is automatically adjusted, on a trial-by-trial basis, to match the WM span of the child on each task. Non-adaptive means that the difficulty level of the tasks never exceeded the starting level of three items.

Methods

Study Design

Children with BIF and neuropsychiatric disorders (ADHD and/or ASD) were recruited from an outpatient facility for paediatric psychiatry in the Netherlands to participate in this triple-blind controlled clinical trial (between May 2012 and March 2019). The study was characterised as triple-blind, since the participants (children, parents, teachers), the training coaches and the investigators were all blind to both the treatment condition and the coaching or training progress.

Care providers were asked to inform eligible children and their legal representatives about the study, and for written consent on sharing contact details with the research team. A member of the research team then contacted the legal representatives providing them with more information about the study and answering questions. By agreement to participate representatives were asked for written informed consent, and children provided oral consent (or written consent ≥ 12 years).

After inclusion and exclusion criteria were checked (see section Study Population), children were individually randomised into two groups to evaluate the efficacy of an adaptive WMT (Cogmed version R/M) compared to a non-adaptive placebo WMT (Placebo version R/M). This study is approved by The Medical Research and Ethics Committee (MREC) region Arnhem-Nijmegen in The Netherlands, registered under NL32435.091.10. This trial is registered in the Dutch Trial Register, number NL2798 (https://www.trialregister.nl/trial/2798).

The study consisted of four phases (see Figure 1 for the study flow chart). In the first phase (baseline; T0), the children underwent a neuropsychological assessment, and parents and teachers filled out questionnaires about the child's behavioural symptoms. Second, children performed the training either at home or at school. Third, approximately one week after completion of the training (post-treatment; T1), the neuropsychological assessment was repeated. Parents and teachers again filled out the same set of questionnaires as at T0. Finally, part of the neuropsychological assessment and the same questionnaires were administered once more approximately six months after completion of the training (follow-up; T2).

Study Population

Participants were selected by means of four inclusion criteria. Subjects were (1) aged between 10 years 0 months and 13 years 11 months (M = 11.7, SD = 1.2), (2) had a recent IQ score (<1½ years old) between 70 and 85 (BIF; M = 76.5, SD = 4.8), (3) were classified with a neuropsychiatric disorder by a certified mental health psychologist and/or psychiatrist, i.e., ADHD (53%), ASD (29%) or both (18%) according to the DSM-IV (American Psychiatric Association, 2000) and (4) had access to a computer with internet connection and speakers at home and/or at school. Children on medication were only included if there was "room for improvement" with respect to the experienced ADHD symptoms. This was based on a (sub)clinical score on ADHD symptoms according to the DSM-IV, and stable medication dosages during study participation (ADHD medication n = 29, antipsychotic n = 7, and other n = 4). Based on these criteria, a mental health psychologist determined one's eligibility for participation using

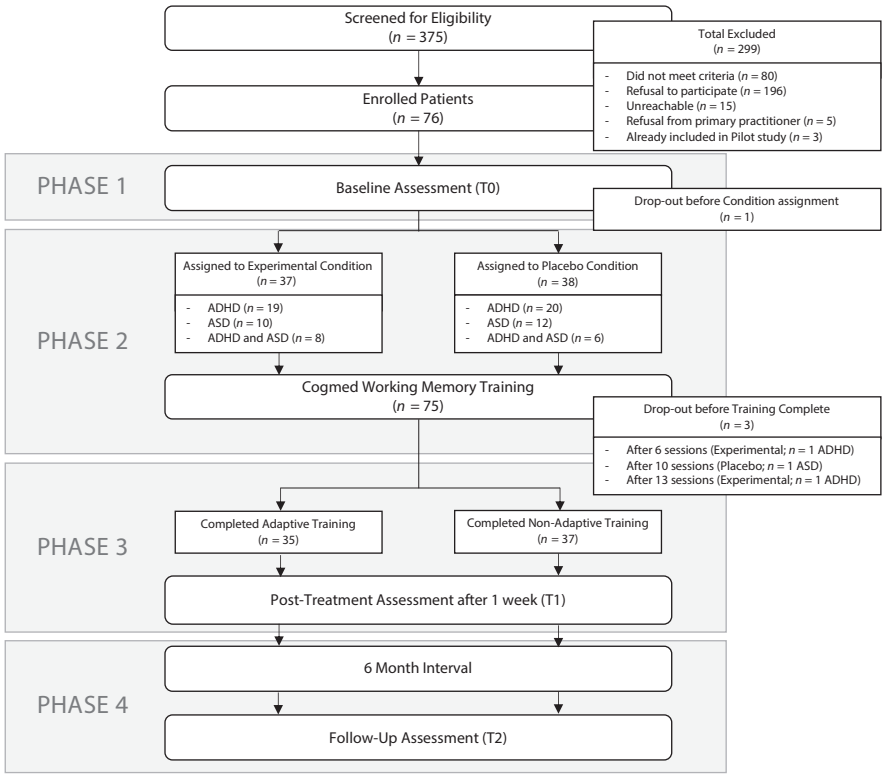

Figure 1: Study flow chart.

information extracted from the electronic medical record, additional ADHD and/or ASD DSM-IV rating scales (see paragraph Study Outcomes), and a shortened intelligence test if the results of a prior test were >1½ years old (Kort et al., 2005).

Study Interventions

Condition 1: Cogmed Working Memory Training. Children completed the Dutch version of the adaptive Cogmed Working Memory Training (WMT; version R/M; Klingberg et al., 2002). The computerised WMT consisted of 13 verbal and visual STM and WM tasks (Cogmed Cognitive Medical Systems AB Stockholm, Sweden).

Participating children completed 8 different tasks during each training session. An example of a verbal WM task is Decoder. In this particular task, letters are read out and lights flash at the same time. When solicited, the child

must recall the letter associated with a given light. The program was provided online and used by the child on a personal computer at home and/or school, supervised by a parent and/or teacher. Responses were made by clicking on displays using the computer mouse. The difficulty level was automatically adjusted, on a trial-by-trial basis, to match the WM span of the child on each task. Children were assigned a unique ID code and task performance was uploaded in a log file.

During the training sessions, the child received positive verbal feedback from the computer. In addition to this, all-time high scores were displayed after each task and there was an "energy" counter that could be used on a fun racing game completed after each training day. The racing game was voluntarily and only included as a reward and did not load on WM. After each week of training the child received a small reward (e.g., choosing what to eat for dinner). Children trained for a period of 5 weeks, 5 days a week (25 days and 200 exercises in total), with an estimated time spent per day between 35 and 45 min. Normally, in clinical practice, a licensed Cogmed coach provides personalised coaching and feedback on the child's performance by telephone, according to a strict protocol (on a weekly basis) with the parent or aide and also with the participating child. Because of the triple-blind design of our study, the coaching was not personalised but consisted of generic encouragement of the child according to a standardised protocol.

Condition 2: Placebo Cogmed Working Memory Training. The placebo condition was identical to the treatment condition, except for the adaptivity. In the placebo condition, the difficulty level of the tasks never exceeded the starting level of three items. This way, the placebo condition relied less on WM capacity. The placebo WMT works under this assumption that children as young as 4 years old are able to remember at least three chunks of information (Gathercole et al., 2004). By keeping the difficulty level of the trials in the non-adaptive (placebo) WMT on a low level of one to three items instead of adapting it to match the WM span of the child, this version of the training should not improve one's WM span (Klingberg et al., 2005).

Study Outcomes

The primary outcome measure is the score on the Spatial Span task. This task was administered as implemented in the Automated Working Memory Assessment (AWMA; Alloway, 2007). The child views a picture of two arbitrary shapes, where the shape on the right has a red dot on it. The child identifies whether the shape on the right is the same as or opposite to the shape on the left. The shape with the red dot may also be rotated. At the end of each trial, the child has to recall the location of each red dot on the shape in sequence, by

pointing to a picture with three compass points. There are six items per trial, starting with one stimulus card up to a maximum of six stimulus cards, depending on the performance of the child. If the child answers at least four out of six items correctly (i.e. he/she correctly identifies the sequence of the locations of the red dots), the subsequent trial with an additional stimulus card added to the sequence is performed. Scores are given for every correct answer and can vary from 0 to 36 (6 items 6 trials).

For secondary outcome measures, we used the scores on several near-transfer tasks (non-trained verbal and visuo-spatial STM and verbal WM) and far-transfer tasks (arithmetic, reading, daily memory, fluid IQ, inhibition control and sustained attention). As tertiary outcomes, we examined six behavioural measures. All secondary and tertiary outcome measures are presented in Table 1.

Randomisation

Individual randomisation was done by an independent person not involved in this research project, and provided through sealed envelopes. Four strata were constructed based on sex and diagnosis, to balance the treatment groups with respect to these important characteristics (the stratification factors). A block randomization schedule with varying block sizes was performed separately within each stratum to reduce the possibility of selection bias. Participants were informed about the allocated intervention after the post-treatment assessment.

Sample Size

Data from the Klingberg et al. (2005) study was used to determine the sample size. They found a mean improvement on their span-board task of 0.82 (*SD* 1.01) in the high-intensity group and 0.15 (*SD* 0.81) in the low-intensity group after WMT. An a priori sample size calculation suggested that with an alpha error level of 0.5% and an expected drop-out rate of 10%, a total sample size of 100 would give a power of 81.2% to detect between-group treatment effects with an effect size of 0.6 (Klingberg et al., 2005).

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 24.0.0 (IBM Corp., 2016). First, we checked if participants in the experimental group and placebo group were sufficiently comparable in terms of descriptive statistics.

Our primary analysis was conducted using an intent-to-treat approach, and therefore included all randomised patients that were willing to complete, both, a pre-WMT and post-WMT neuropsychological assessment. A two-way repeated measures ANOVA was used to determine whether any change on the

Table 1 Secondary and Tertiary Outcome Measures.

	Secondary Outcome Measures		Tertiary Outcome Measures
	Near-Transfer Measures	Far-Transfer Measures	Behavioural Measures
1	Block Recall task (visuo-spatial STM; Pickering & Gathercole, 2001). A researcher taps a sequence of up to nine identical spatially separated blocks, after which the participant is asked to mimic the tapping of that sequence. The amount of correctly mimicked sequences serves as the outcome measure, ranging from 0 to 54.	Sustained Attention Dots reaction time and errors (Amsterdamse Neuropsychologische Taken [ANT; de Sonneville, 2009]) Participants should discriminate between patterns consisting of 3, 4 (target signal) or 5 dots. The probability of a yes vs no response is 1:2. As a consequence, with time-on-task a response bias (for the no-response key) is induced.	Total DSM-IV symptom-scores for ADHD, determined by means of the ADHD DSM-IV rating scale, as rated by the investigator (DuPaul et al., 1998) using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). Eighteen symptoms are rated, resulting in a possible range for this measure of 0 to 54.
2	Visual Patterns Test (visual-spatial STM; Della Sala et al., 1997). The participant is shown matrix patterns of black and white squares in grids of different sizes and of increasing difficulty and are asked to memorize these patterns. The amount of correctly remembered patterns serves as the outcome measure, ranging from 0 to 42.	Go-NoGo reaction time and errors (inhibitory control, ANT; de Sonneville, 2009). It contains a presentation of Go and NoGo signals in the centre of the screen to indicate whether or not the child should press a button.	Total DSM-IV symptom-scores for ASD, determined by means of the ASD DSM-IV rating scale specifically made for this study, as rated by the investigator (see Appendix A), using a 4-point Likert scale (0 = never occurs, 1 = occurs sometimes, 2 = occurs often, 3 = occurs very often). Twelve symptoms are rated, resulting in a possible range for this measure of 0 to 36.

Table 1 Continued.

	Secondary Outcome Measures		Tertiary Outcome Measures
	Near-Transfer Measures	**Far-Transfer Measures**	**Behavioural Measures**
3	Digit Recall task (verbal STM; Pickering & Gathercole, 2001). A sequence of up to 8 digits is presented verbally to the participants and they are asked to recall this sequence in forwards order. The outcome measure is the amount of correctly recalled sequences, ranging from 0 to 42.	Raven Standard Progressive Matrices task (fluid IQ; Raven et al., 1996) is made up of five sets of diagrammatic puzzles exhibiting serial change in two dimensions simultaneously. Each puzzle has a part missing, which the participant has to identify among the options provided. The amount of correctly identified missing puzzle parts serves as the outcome measure, ranging from 0 to 60.	The total score on the ADHD-Vragenlijst (AVL; Scholte & van der Ploeg, 2005), as filled out by parents and teachers. This is an additional measure to determine behavioural symptoms of ADHD. It contains 18 behaviours that are rated by the child's parents in terms of frequency of occurrence in the last six months on a 5-point Likert scale (0 = Never, 1 = Sometimes, 2 = Average, 3 = Often, 4 = Very often), resulting in a possible total score range from 0 to 72.
4	Non-Word List Recall task (verbal STM; Pickering & Gathercole, 2001). The participant is asked to repeat a series of non-words of differing syllable length and complexity of sound combinations. The amount of correctly repeated non-words serves as the outcome measure, ranging from 0 to 36.	Story Recall task (daily memory; van der Molen, 2007). The participant is asked to recall details of a story that is read to him or her. The amount of details correctly recalled serves as the outcome measure, ranging from 0 to 58.	The total score on the Behaviour Rating Inventory of Executive Functioning (BRIEF; Smidts & Huizinga, 2009). There are two separate versions of the questionnaire to be completed by the parents or the teacher, to gain insight into the child's executive function problems (experienced daily) at home and at school. Both versions contain 75 behaviours that are rated in terms of frequency of occurrence in the last six months on a 3-point Likert scale (1 = never, 2 = sometimes, 3 = often), resulting in a possible total score between 75 and 225.
5	Backward Digit Recall (verbal WM; Pickering & Gathercole, 2001). A sequence of up to 7 digits is presented verbally to the participants and they are asked to recall this sequence in reverse order. The outcome measure is the amount of correctly recalled sequences, ranging from 0 to 36.	A Dutch arithmetic task named "Arithmetic Speed test" (de Vos, 1992) assesses arithmetic automation as a measure of academic achievement. Participants are asked five times (add, subtract, multiply, divide, mixed) to correctly answer as many as possible and up to 200 written out automation of mathematics questions of increasing difficulty within one minute. The amount of total correctly answered questions serves as the outcome measure, ranging from 0 to 200.	
6	Listening Recall task (verbal WM; Pickering & Gathercole, 2001). Participants are asked to judge the veracity of a series of short sentences, and to recall the last word of that sentence (or sequence of last words of sentences in case of multiple items). Outcome measure is the amount of correctly recalled sequences of last words, ranging from 0 to 36.	A Dutch reading task named "Reading Speed test" (Brus & Voeten, 1999) measures reading automation as a measure of academic achievement. Children are asked to read as many as possible words of increasing difficulty out loud within one minute. The amount of words correctly read out serves as the outcome measure, ranging from 0 to 116.	

STM = Short Term Memory; WM = Working Memory

Spatial Span task (i.e., the dependent variable) is the result of the interaction between the between-subjects factor Treatment condition (Experimental / Placebo) and the within-subjects factor Time. A similar Repeated Measures ANOVA was conducted for each of the secondary (n = 14) and tertiary (n = 6) outcomes. Each model contained the same within-subjects factor (Time) and a between-subjects factor (Treatment condition; Experimental / Placebo). The Repeated Measures ANOVA approach was deemed most suitable to address the study's objective of comparing the levels of improvement in the two treatment conditions rather than comparing the post-WMT scores in the two conditions while adjusting for baseline scores.

For the behavioural measures of ADHD (ADHD rating scale, ADHD-Vragenlijst (AVL) parents and AVL teacher), only participants with a diagnosis of ADHD or ASD with comorbid ADHD were included in the analyses (n = 51) and not the participants with ASD only. For the behavioural measure of ASD (ASD rating scale), only participants with a diagnosis of ASD and ASD with comorbid ADHD were included in the analysis (n = 35) and not the participants with ADHD only. For the remaining measures, all participants were included in the analyses.

Statistical assumptions inherent to the Repeated Measures ANOVA were checked for each dependent variable. The scores for Listening Recall, Visual Patterns Test, reaction time of Sustained Attention Dots, and the error scores of both Sustained Attention Dots and Go-NoGo did not adhere to the assumption of normality. Applying a log transformation to these variables adjusted their distribution sufficiently for all but the reaction time for Sustained Attention Dots and the error score of Go-NoGo. Analyses for the Listening Recall score, Visual Patterns Test score and Sustained Attention Dots error score were performed with the log-transformed version of the variable to retain as much statistical power as possible.

A total of 15 outliers (> 3 SD from the mean for the respective time point) were identified across all tests and time points. They were retained in the dataset due to insufficient clinical reason to remove them. In total, 4% of the data were missing. Little's MCAR test showed that no specific patterns could be identified for the primary outcome measure (Spatial Span; χ^2 = 2.367, df = 2, p = .306) and list-wise deletion was applied across all analyses. The significance level was set at the threshold of p = .050, and a Bonferroni correction was performed to evaluate the impact of multiple comparisons on the same sample for the neurocognitive as well as for the AVL and Behaviour Rating Inventory of Executive Functioning (BRIEF) scores (n = 19, p = .003). Post hoc pairwise comparisons were conducted with a Bonferroni correction as well.

Results

Study Population

A total of 375 children were screened for eligibility and 295 met eligibility criteria (Figure 1). Although eligible, candidates often refused to participate (66% of screened and eligible candidates). Other reasons for not enrolling are described in Figure 1. Finally, a total of 76 children enrolled in the study. Four dropped out before completing a minimum of 60% of the training (after 0, 6, 10 and 13 sessions out of 25) and refused to participate in post-measurements. These participants were excluded, resulting in a total sample size of 72. Eight out of these participants also did not complete all 25 sessions because of motivational problems, but did reach the minimum of 60% (between 15- 24 sessions). The fidelity of the coaching assessed was 100%. All participants received the agreed five coaching sessions (once a week) by the licensed Cogmed coach by telephone. Attrition rate was low (4%) and did not significantly differ between the experimental and placebo conditions. In total, 97% of the participants in the experimental condition and 95% of the participants in the placebo condition completed all three measurements. Controlling for the initial AVL return rate of 68% for parents and 63% for teachers at T0, we achieved a subsequent 98% and 92% return rate for parents at T1 and T2, respectively, and a 100% and 89% return rate for teachers. Controlling for the initial BRIEF return rate of 97% for parents and 93% for teachers at T0, we achieved a subsequent 96% and 93% return rate for parents at T1 and T2, respectively, and a 93% and 82% return rate for teachers.

Table 2 shows descriptive statistics of the experimental and placebo conditions. While the two treatment conditions were mostly comparable, mean treatment duration in the experimental condition (M = 714.3, SD =199.7) was longer than in the placebo condition (M = 564.7, SD =99.3), a statistically significant difference of M = 149.6 minutes, t(69) = 4.05, p = <.001. Subsequent Pearson correlations showed that treatment duration was not significantly related to any of the dependent variables, indicating limited necessity to control for the difference in training duration in the subsequent main analyses. Descriptive statistics for all outcome measures per condition and per time point can be found in Appendix B.

Visuo-Spatial WM

A significant time effect (p < .003) was found on the score of the Spatial Span task at T1. As is illustrated in Figure 2, the scores significantly improved over time and the improvement was similar for both the experimental and placebo conditions. No other main and interaction effects were found. All model statistics can be found in Appendix C and post-hoc comparisons of the significant time effects can be found in Appendix D.

Table 2 Descriptive statistics of IQ, age, treatment duration, sex and diagnosis per treatment condition.

		Experimental Condition (N = 35)	Placebo Condition (N = 37)	p-value[a]
		$M \pm$ SD	$M \pm$ SD	
IQ		76.63 ± 4.74	76.86 ± 4.96	.837
Age (in years)		11.69 ± 1.32	11.76 ± 1.09	.804
Treatment Duration (in minutes)		714.32 ± 199.65	564.70 ± 99.31	<.001
		n (%)	*n (%)*	p-value[b]
Sex	male	25 (71.6%)	28 (75.7%)	.683
	female	10 (28.6%)	9 (24.3%)	
Diagnosis	ADHD	17 (48.6%)	20 (54.1%)	.771
	ASD	10 (28.6%)	11 (29.8%)	
	both	8 (22.9%)	6 (16.2%)	

Note. [a] Independent samples t-test; [b] Chi-square test

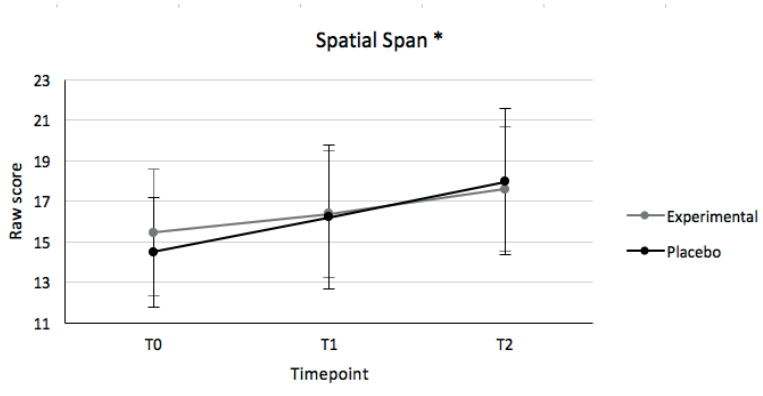

Figure 2: Line graphs for the primary outcome measure of visuo-spatial working memory.

Note. * Measure for which a significant main effect of time (p < .003) was found.

Near and Far-Transfer Tasks

A significant time effect (p < .003) was found on the scores of Block Recall, Digit Recall, Non-Word List, Backwards Digit Recall, the Raven Standard Progressive Matrices, Story Recall, Arithmetic Speed test, Reading Speed test, and both the reaction times of Sustained Attention Dots and the Go-No Go task. As illustrated in Figure 3 and Figure 4, these measures significantly improved over time. No other main and interaction effects were found for any of the near and far-transfer measures. All model statistics can be found in Appendix C and post-hoc comparisons of the significant time effects can be found in Appendix D.

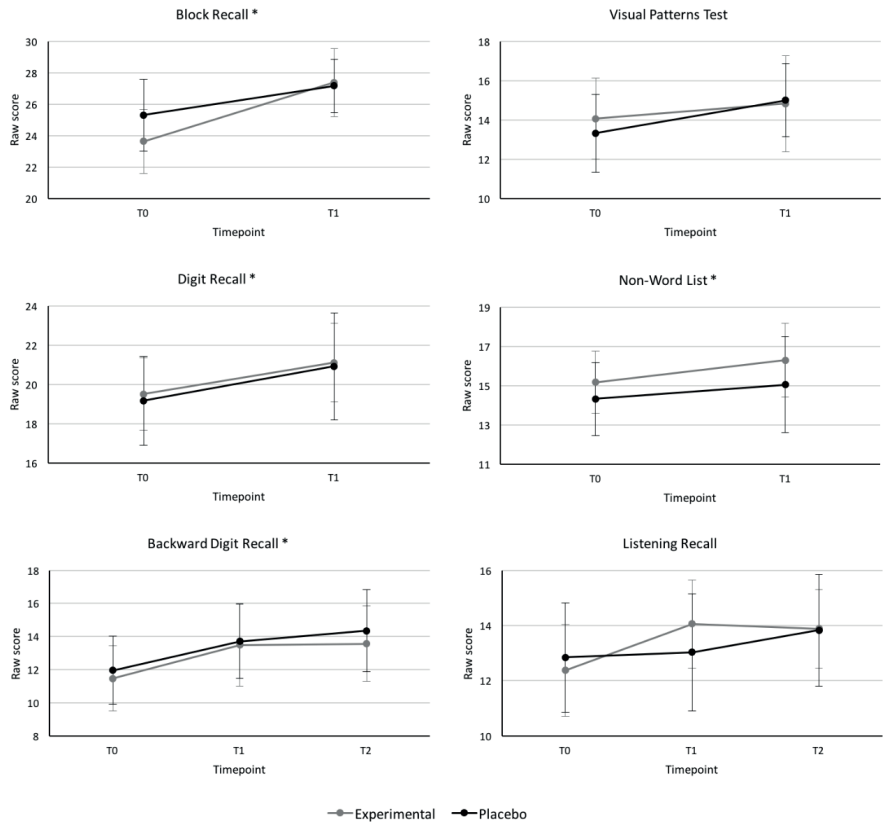

Figure 3: Line graphs for the secondary near-transfer outcome measures.

Note. * Measure for which a significant main effect of time (p < .003) was found.

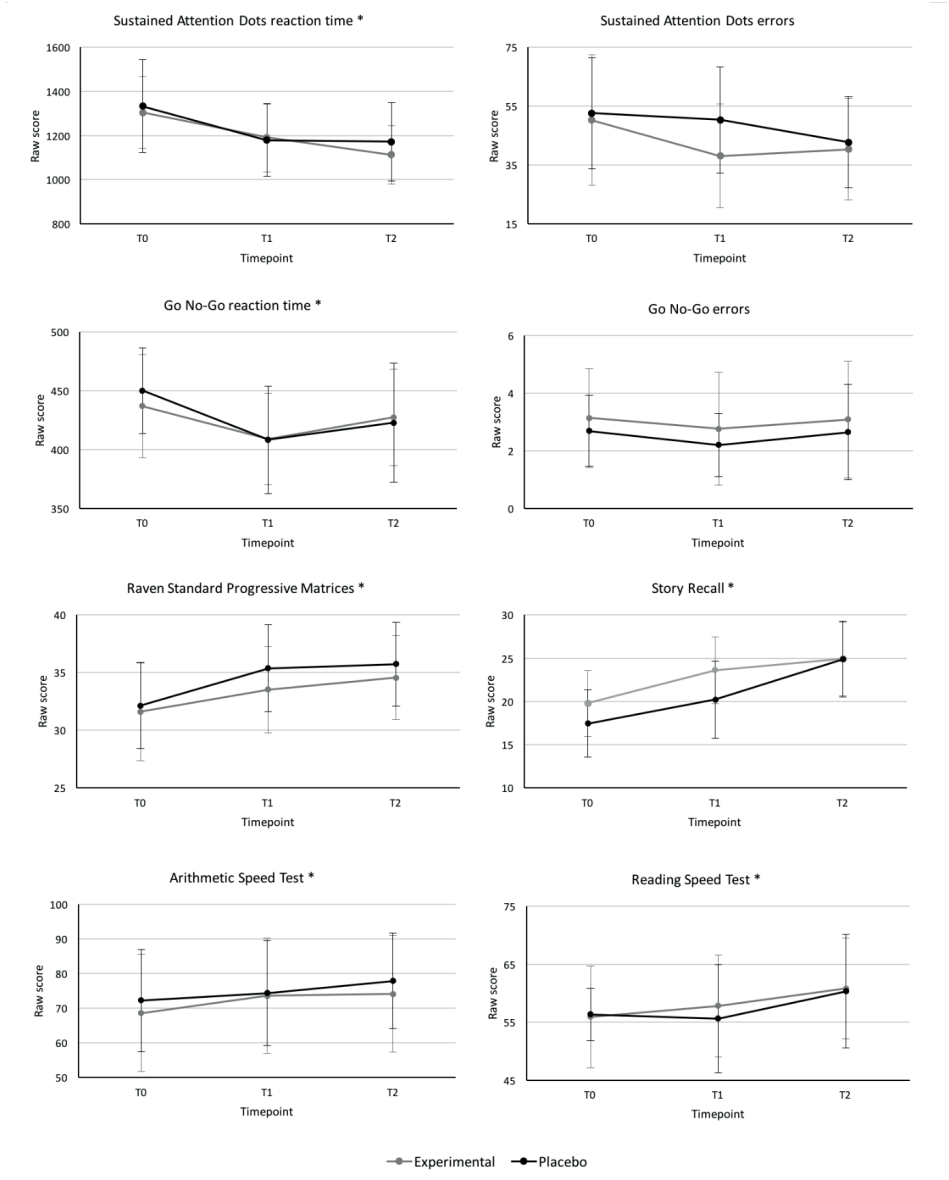

Figure 4: Line graphs for the secondary far-transfer outcome measures.

Note. * Measure for which a significant main effect of time ($p < .003$) was found.

Behavioural Measures

A significant time effect was found on the ADHD ratings by the investigator ($p < .05$), the ASD ratings by the investigator ($p < .05$), the AVL filled out by parents ($p < .003$) and the BRIEF filled out by parents ($p < .003$). As is illustrated in Figure 5, these measures significantly improved over time and these improvements were similar for both the experimental and placebo conditions. No other main and interaction effects were found for the behavioural measures. All model statistics can be found in Appendix C and post-hoc comparisons of the significant time effects can be found in Appendix D.

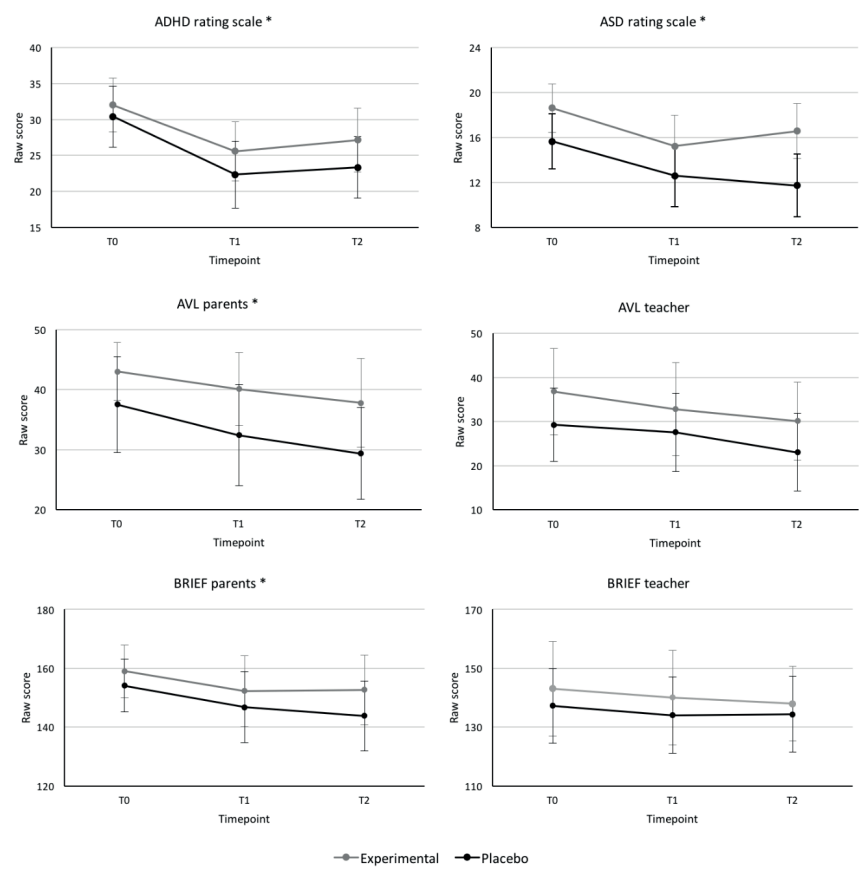

Figure 5: Line graphs for the tertiary behavioural outcome measures.

Note. * Measure for which a significant main effect of time ($p < .05$ for ADHD and ASD rating scales; $p < .003$ for AVL and BRIEF) was found.
Abbreviation: AVL = ADHD vragenlijst (ADHD questionnaire); BRIEF = Behaviour Rating Inventory of Executive Functioning.

Discussion

In contrast to our hypothesis, the results of this triple-blind randomised placebo-controlled study in children with BIF and neuropsychiatric disorders did not show significant larger improvement over time on our primary outcome measure (visuospatial WM) in the experimental WMT group compared to the placebo control WMT. Furthermore, no additional effects in favour of the experimental WMT were found on any of the secondary (near and far-transfer tasks) or tertiary (behavioural measures) outcomes. These findings are consistent with the outcome of several meta-analyses and reviews on Cogmed WMT (Shipstead et al., 2012; Chacko et al., 2013; Melby-Lervag & Hulme, 2013; Rapport et al., 2013; Sonuga-Barke et al., 2013; Cortese et al., 2015) and a recent study in youth with ADHD under pharmacological treatment (Dentz et al., 2020).

However, this study did show improvements over time for both the experimental and non-adaptive control condition on objectively measured non-trained visuo-spatial WM as well as on near and far-transfer neurocognitive measures and on behavioural measures (ADHD and ASD ratings by the investigator, AVL-parents and BRIEF-parents). Though no significantly higher levels of improvement over time were found in the experimental group compared to the control group, the results may suggest that these vulnerable children seem to be able to improve their WM capacity in a relatively short amount of time with (non)adaptive training.

The Cogmed WM improvement-index, provided by the training software to quantify compliance and performance in the adaptive version of the training, was 26.20 points (*SD* = 14.88) in our study. This is much higher than most improvement-indices reported in other studies. For example, Berger and colleagues (2020) reported an improvement-index of 20.76 points in children functioning at a lower or average neurocognitive level. Furthermore, they found that training effects did not differ significantly between children functioning at a lower neurocognitive level and those who had an average level (Berger et al., 2020), which seems to be in line with the findings in our study.

An explanation for the lack of difference in effectiveness between the experimental and placebo training group might be found in our study design. Van der Molen and colleagues (2010) studied a group of children that was quite similar to our patient group and found significant positive training-effects on (non-trained) neurocognitive measures. However, in this study, a third group, a waiting list control group was used. Positive effects of training were only seen in the active training group compared to the waiting list control group and not compared to a placebo (non-adaptive training) control group. The positive results in both groups in our study were not controlled for specific conditional factors common to both the experimental as well as the control group, which may have resulted in improvements in both groups. Both interventions required continued perseverance, sustained attention, inhibition skills and frustration tolerance and may have trained specific coping skills or even increased the sense of self-efficacy and self-esteem. Yet, the positive training results in our study might be of greater significance when compared to a waiting list control group.

A second explanation for the lack of difference in effectiveness between the experimental and placebo training group might be found in the intensity of WM training, the only difference between the experimental and placebo condition. The treatment condition (adaptive training) had an automatically adjusted level of difficulty implemented for each task on a trial-by-trial basis to match the WM span of the child. Perhaps the experimental condition did not meet the high intensity needed to accomplish significant training effects, despite the adaptive factor. Maybe a higher intensity training, more training minutes a day, or a prolonged training period in the experimental condition would lead to significant differences with the placebo condition. In contrast, the difficulty level of the tasks in the placebo condition (non-adaptive control training) never exceeded the starting level of three items. This way, the placebo condition encompassed a lower WM load (i.e., a low number of items to remember). However, in our study 8% of the participating children started with a particularly low verbal WM baseline (Backwards Digit Recall and Listening Recall; < 3 items) at pre-treatment, and did improve to a score of ≥ 3 after training was completed, which means that in this study some of the children in the placebo condition trained their verbal WM capacity up to a capacity of three. Besides the lower intensity in WM load in the placebo condition, there is also a significant lower intensity in total training minutes a day (see Table 2). Both factors might be of positive influence on the participating children's motivation for training. Training is, in general, more difficult for this population. A pilot study indicated that Cogmed WMT protocols containing more training days with shorter training durations per day, may lead to similar or even better training effects compared to the standard protocol, even with less total training time (Mawjee et al., 2014). This is consistent with the general treatment approach for children with mild intellectual disabilities. These children may have a shorter attention span and need shorter duration per each session (Dutch Knowledge Centre on MID/Landelijk Kenniscentrum LVB, 2012). Therefore, in these cases the placebo condition may represent a low intensive experimental condition. A third explanation for the lack of significant difference between the two training groups may be a lack of active coaching in the experimental condition. Due to the triple-blind design, coaching was limited to generic

encouragement and motivation, and – in contrast to Cogmed in clinical practice – coaching could not be based on individual training results since the coach was blinded to group assignment. The active weekly coaching is found to be one of the most important components in a training program with the aim of improving ADHD symptoms (Sonuga-Barke et al., 2001). Future studies should pay more attention to non-specific therapeutic effects and may consider coaching based on real training results and an active role for the (unblended) coach (e.g., weekly face-to-face contacts).

Despite the absence of significant superior trainings effects, our findings may suggest that this particular patient group may benefit from WMT, whether adaptive or non-adaptive, since the WM capacity of all children improved. Improvement of WM capacity is found to be associated with changes in the dopaminergic system (McNab et al., 2009). These changes enable more efficient general information processing in daily life since WM and attention and other executive functions are closely related (McNab et al., 2009). This association on neurobiological level illustrates how WM capacity, attention, daily functioning and academic achievement are linked. Furthermore, the cognitive training provides a structured learning environment in which neurocognitive functioning may ameliorate and children may pick up coping strategies such as perseverance and frustration tolerance. This may increase the sense of self-efficacy and self-esteem.

This study had some limitations. As noted before, our sample size was limited due to a large number of refusals to participate. A selection bias could therefore not be ruled out. Second, a waiting list control group was lacking, with the result that we could not control for specific conditional factors common to both groups. Third, the training was not embedded in daily life. Diamond & Lee (2011) demonstrated that isolated neurocognitive training may not be adequate to improve executive functioning in daily life. Further research is recommended to find out if an extended WMT including individualised coaching and embedded in daily life may be an effective intervention for children with BIF and neuropsychiatric disorders.

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Appendix A. Autism Spectrum Disorder rating scale.

To what extent is this behaviour applicable in the **last 2 weeks**;

1. Marked impairment in the use of multiple nonverbal behaviours, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction.
   Never / Sometimes / Often / Very often
2. Failure to develop peer relationships appropriate to developmental level.
   Never / Sometimes / Often / Very often
3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest).
   Never / Sometimes / Often / Very often
4. Lack of social or emotional reciprocity.
   Never / Sometimes / Often / Very often
5. Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime).
   Never / Sometimes / Often / Very often
6. When adequate speech, marked impairment in the ability to initiate or sustain a conversation with others.
   Never / Sometimes / Often / Very often
7. Stereotyped and repetitive use of language or idiosyncratic language.
   Never / Sometimes / Often / Very often
8. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level.
   Never / Sometimes / Often / Very often
9. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus.
   Never / Sometimes / Often / Very often
10. Apparently inflexible adherence to specific, nonfunctional routines or rituals.
    Never / Sometimes / Often / Very often
11. Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting or complex whole-body movements).
    Never / Sometimes / Often / Very often
12. Persistent preoccupation with parts of objects.
    Never / Sometimes / Often / Very often

Appendix B. Descriptive Statistics per Condition and Time Point.

Table B.1 reports some of the descriptive statistics for each outcome measure per condition and per time point.

Table B.1 Descriptive statistics per condition and time point for all (non-transformed) outcome measures.

	Experimental Condition (*N* = 35)							Placebo Condition (*N* = 37)					
	T0		T1		T2			T0		T1		T2	
	M ± SD	N	M ± SD	N	M ± SD	N		M ± SD	N	M ± SD	N	M ± SD	N
SS	15.46 ± 6.29	35	16.37 ± 6.23	35	17.59 ± 6.16	34	SS	14.49 ± 5.43	37	16.22 ± 7.13	37	17.97 ± 7.19	35
BR	23.63 ± 4.08	35	27.37 ± 4.32	35	-	-	BR	25.30 ± 4.58	37	27.16 ± 3.36	37	-	-
VPT	14.06 ± 4.14	34	14.82 ± 4.88	34	-	-	VPT	13.32 ± 3.98	37	15.00 ± 3.70	37	-	-
DR	19.51 ± 3.67	35	21.11 ± 4.013	35	-	-	DR	19.16 ± 4.54	37	20.92 ± 5.44	37	-	-
NWL	15.17 ± 3.15	35	16.29 ± 3.76	34	-	-	NWL	14.32 ± 3.71	37	15.05 ± 4.88	37	-	-
BDR	11.46 ± 3.94	35	13.49 ± 5.00	35	13.56 ± 4.55	34	BDR	11.95 ± 4.12	37	13.70 ± 4.49	37	14.34 ± 4.96	35
LR	12.37 ± 3.31	35	14.06 ± 3.19	34	13.88 ± 2.86	34	LR	12.84 ± 3.98	37	13.03 ± 4.25	37	13.83 ± 4.05	35
SAD errorscore	50.26 ± 44.32	35	38.12 ± 35.38	34	40.38 ± 34.42	32	SAD errorscore	52.64 ± 37.74	36	50.37 ± 36.10	35	42.73 ± 30.95	33
SAD reaction time	1304.68 ± 323.88	34	1191.32 ± 309.30	34	1112.63 ± 263.60	32	SAD reaction time	1333.06 ± 420.22	36	1179.83 ± 325.31	35	1172.88 ± 355.23	33
GNG errorscore	3.14 ± 3.42	35	2.76 ± 3.91	34	3.09 ± 4.04	32	GNG errorscore	2.69 ± 2.47	35	2.20 ± 2.18	35	2.65 ± 3.31	34
GNG reaction time	437.11 ± 87.66	35	409.06 ± 76.92	34	427.56 ± 82.09	32	GNG reaction time	450.31 ± 72.78	35	408.31 ± 91.01	35	423.00 ± 100.96	35
Raven SPM	31.60 ± 8.43	35	33.53 ± 7.46	34	34.56 ± 7.27	34	Raven SPM	32.14 ± 7.47	37	35.38 ± 7.51	37	35.74 ± 7.26	35
SR	19.80 ± 7.67	35	23.59 ± 7.74	34	24.91 ± 8.51	34	SR	17.46 ± 7.74	37	20.22 ± 8.92	37	24.89 ± 8.72	35
AST	68.63 ± 33.76	35	73.57 ± 33.31	35	74.15 ± 33.74	34	AST	72.30 ± 29.46	37	74.43 ± 30.19	37	77.94 ± 27.55	35
RST	55.94 ± 17.63	35	57.79 ± 17.66	34	60.82 ± 17.44	34	RST	56.32 ± 8.92	37	55.59 ± 18.58	37	60.34 ± 19.57	35
ADHD rating scale	32.00 ± 7.49	25	25.56 ± 8.24	25	27.13 ± 8.93	23	ADHD rating scale	30.38 ± 8.50	26	22.31 ± 9.35	26	23.33 ± 8.59	24
ASD rating scale	18.61 ± 4.34	18	15.22 ± 5.55	18	16.56 ± 4.90	18	ASD rating scale	15.65 ± 4.92	17	12.59 ± 5.49	17	11.73 ± 5.60	15
AVL parents	43.04 ± 9.70	24	40.13 ± 12.22	24	37.78 ± 14.78	23	AVL parents	37.52 ± 16.01	25	32.42 ± 16.84	24	29.36 ± 15.31	22
AVL teacher	36.86 ± 19.60	22	32.86 ± 21.12	22	30.14 ± 17.71	22	AVL teacher	29.30 ± 16.65	23	27.57 ± 17.71	23	23.06 ± 17.63	18
BRIEF parents	158.97 ±17.80	34	152.30 ± 24.17	33	152.67 ± 23.74	33	BRIEF parents	154.11 ± 23.07	36	146.79 ± 25.40	34	143.84 ± 26.52	32
BRIEF teacher	143.06 ± 32.18	32	140.03 ± 32.18	29	137.97 ± 25.42	29	BRIEF teacher	137.23 ± 25.27	35	134.03 ± 26.05	33	134.31 ± 25.79	26

Note. Abbreviation: BDR = Backward Digit Recall; LR = Listening Recall; BR = Block Recall; VPT = Visual Patterns Test; DR = Digit Recall; NWL = Non-Word List; SS = Spatial Span; SAD = Sustained Attention Dots; GNG = Go-No Go; Raven SPM = Raven Standard Progressive Matrices; SR = Story Recall; AST = Arithmetic Speed test; RST = Reading Speed test; ADHD rating scale = Severity of DSM-IV criteria for ADHD; ASD rating scale = Severity of DSM-IV criteria for ASD; AVL parents = Parents' reported severity of ADHD symptoms; AVL teacher = Teacher reported severity of ADHD symptoms; BRIEF parents = Parents' reported executive function behaviours; BRIEF teacher = Teacher reported executive function behaviours.

Appendix C. Model Statistics of Main Analyses.

This appendix contains tables with model statistics for all neurocognitive (Table C.1) and behavioural (Table C.2) outcome measures, as summarised in the main text. Please refer to Appendix D for post-hoc comparisons of the significant effects.

Table C.1 Model statistics of neurocognitive outcome measures.

Outcome Measure [a]	Effect	F	df	p	η^2	CI
SS [b]	Time	8.21	(2, 134)	.001	.11	[.03 - .19]
	Treatment	0.02	(1, 67)	.878	.00	[.00 - .01]
	Time*Treatment	0.29	(2, 134)	.740	.00	[.00 - .03]
BR	Time	31.10	(1, 70)	<.001	.31	[.16 - .43]
	Treatment	0.78	(1, 70)	.381	.01	[.00 - .08]
	Time*Treatment	3.49	(1, 70)	.066	.05	[.00 - .15]
VPT	Time	6.58	(1, 68)	.013 [c]	.09	[.01 - .20]
	Treatment	0.01	(1, 68)	.944	.00	[.00 - .01]
	Time*Treatment	4.33	(1, 68)	.041 [c]	.06	[.00 - .17]
DR	Time	17.80	(1, 70)	<.001	.20	[.08 - .33]
	Treatment	0.08	(1, 70)	.781	.00	[.00 - .04]
	Time*Treatment	0.04	(1, 70)	.844	.00	[.00 - .02]
NWL	Time	9.65	(1, 69)	.003	.12	[.03 - .25]
	Treatment	1.31	(1, 69)	.256	.02	[.00 - .10]
	Time*Treatment	0.53	(1, 69)	.469	.01	[.00 - .07]
BDR	Time	13.40	(2, 134)	<.001	.17	[.07 - .25]
	Treatment	0.55	(1, 67)	.461	.01	[.00 - .08]
	Time*Treatment	0.07	(2, 134)	.929	.00	[.00 - .00]
LR [b]	Time	4.79	(2, 132)	.012 [c]	.07	[.01 - .14]
	Treatment	0.74	(1, 66)	.392	.01	[.00 - .08]
	Time*Treatment	1.03	(2, 132)	.354	.02	[.00 - .06]
SAD errorscore	Time	3.65	(2, 124)	.031 [c]	.06	[.00 - .12]
	Treatment	0.48	(1, 62)	.493	.01	[.00 - .08]
	Time*Treatment	0.52	(2, 124)	.587	.01	[.00 - .04]
SAD reaction time [b]	Time	26.55	(2, 124)	<.001	.30	[.19 - .39]
	Treatment	0.04	(1, 62)	.837	.00	[.00 - .03]
	Time*Treatment	1.00	(2, 124)	.367	.02	[.00 - .06]
GNG errorscore [b]	Time	0.39	(2, 122)	.627	.01	[.00 - .03]
	Treatment	1.09	(1, 61)	.301	.02	[.00 - .10]
	Time*Treatment	0.01	(2, 122)	.979	.00	[.00 - .00]
GNG reaction time [b]	Time	6.73	(2, 124)	.002	.10	[.02 - .18]
	Treatment	0.03	(1, 62)	.872	.00	[.00 - .02]
	Time*Treatment	0.33	(2, 124)	.696	.01	[.00 - .03]

Table C.1 Continued.

Outcome Measure [a]	Effect	F	df	p	η^2	CI
Raven SPM	Time	16.33	(2, 132)	<.001	.20	[.10 - .29]
	Treatment	0.57	(1, 66)	.454	.01	[.00 - .08]
	Time*Treatment	0.32	(2, 132)	.729	.01	[.00 - .03]
SR	Time	25.62	(2, 132)	<.001	.28	[.17 - .37]
	Treatment	1.21	(1, 66)	.275	.02	[.00 - .10]
	Time*Treatment	1.33	(2, 132)	.268	.02	[.00 - .06]
AST [b]	Time	8.25	(2, 134)	.001	.11	[.04 - .19]
	Treatment	0.31	(1, 67)	.583	.01	[.00 - .06]
	Time*Treatment	0.67	(2, 134)	.485	.01	[.00 - .04]
RST	Time	18.44	(2, 132)	<.001	.22	[.12 - .31]
	Treatment	0.11	(1, 66)	.745	.00	[.00 - .05]
	Time*Treatment	1.00	(2, 132)	.370	.02	[.00 - .06]

Note. [a] Abbreviation: SS = Spatial Span; BR = Block Recall; VPT = Visual Patterns Test; DR = Digit Recall; NWL = Non-Word List; BDR = Backward Digit Recall; LR = Listening Recall; SAD = Sustained Attention Dots; GNG = Go-No Go; Raven SPM = Raven Standard Progressive Matrices; SR = Story Recall; AST = Arithmetic Speed test; RST = Reading Speed test.

[b] Mauchly's test indicated that the assumption of sphericity is violated for this measure. In accordance with Field (2013), Huynh-Feldt parameters are still reported as the Greenhouse-Geisser Epsilon is higher than .750.

[c] Significant effect did not survive the Bonferroni correction.

Table C.2 Model statistics of behavioural outcome measures.

Outcome Measure [a]	Effect	F	df	p	η^2	90% CI
ADHD rating scale	Time	27.60	(2, 90)	< .001	.38	[.24 - .48]
	Treatment	1.39	(1, 45)	.244	.03	[.00 - .15]
	Time*Treatment	0.86	(2, 90)	.425	.02	[.00 - .07]
ASD rating scale	Time	8.08	(2, 62)	.001	.21	[.06 - .33]
	Treatment	5.03	(1, 31)	.032	.14	[.01 - .32]
	Time*Treatment	1.08	(2, 62)	.345	.03	[.00 - .11]
AVL parents	Time	6.66	(2, 82)	.002	.14	[.03 - .24]
	Treatment	2.59	(1, 41)	.115	.06	[.00 - .20]
	Time*Treatment	0.84	(2, 82)	.437	.02	[.00 - .08]
AVL teacher	Time	1.72	(2, 68)	.189	.05	[.00 - .13]
	Treatment	2.29	(1, 34)	.139	.06	[.00 - .22]
	Time*Treatment	0.91	(2, 68)	.404	.03	[.00 - .10]
BRIEF parents	Time	7.45	(2, 118)	.001	.11	[.03 - .20]
	Treatment	0.82	(1, 59)	.370	.01	[.00 - .10]
	Time*Treatment	0.56	(2, 118)	.571	.01	[.00 - .04]
BRIEF teacher	Time	0.44	(2, 90)	.620	.01	[.00 - .05]
	Treatment	0.75	(1, 45)	.390	.02	[.00 - .12]
	Time*Treatment	0.11	(2, 90)	.873	.00	[.00 - .02]

Note. [a]Abbreviation: ADHD rating scale = Severity of DSM-IV criteria for ADHD; ASD rating scale = Severity of DSM-IV criteria for ASD; AVL parents = Parents' reported severity of ADHD symptoms; AVL teacher = Teacher reported severity of ADHD symptoms; BRIEF parents = Parents' reported executive function behaviours; BRIEF teacher = Teacher reported executive function behaviours.

Appendix D. Results of Post-Hoc Comparisons.

As mentioned in the main text, certain outcome measures showed a significant effect of time. While a subset of these only had two time points to compare (T0 and T1), post hoc comparisons were performed on the variables that were assessed at three time points across both conditions: T0 (baseline, before training), T1 (immediately after training), T2 (6 months after training). The descriptive statistics and post-hoc results are described in Table D.1.

Table D.1 Descriptive statistics and post hoc comparisons for the outcome measures with a significant main effect of Time.

Outcome measure	T0	T1	T2	T0 vs T1		T0 vs T2		T1 vs T2	
	M ± SD	M ± SD	M ± SD	Mean difference	Significance	Mean difference	Significance	Mean difference	Significance
SS	14.96 ± 5.84	16.29 ± 6.66	17.78 ± 6.66	+1.33	$p = .162$	+2.82	$p = .001$	+1.49	$p = .089$
BR	24.49 ± 4.39	27.26 ± 3.83	-	-	-	-	-	-	-
DR	19.33 ± 4.12	21.01 ± 4.77	-	-	-	-	-	-	-
NWL	14.74 ± 3.45	15.65 ± 4.40	-	-	-	-	-	-	-
BDR	11.71 ± 4.01	13.60 ± 4.71	13.96 ± 4.75	+1.89	$p < .001$	+2.25	$p < .001$	+0.36	$p = 1.000$
SAD reaction time	1319.27 ± 374.09	1185.49 ± 315.24	1143.22 ± 312.53	-133.78	$p < .001$	-176.05	$p < .001$	- 42.27	$p = .108$
GNG reaction time	443.71 ± 80.26	408.68 ± 83.74	425.18 ± 91.77	-35.03	$p = .002$	-18.53	$p = .702$	+16.50	$p = .090$
Raven SPM	31.88 ± 7.90	34.49 ± 7.49	35.16 ± 7.24	+2.61	$p < .001$	+3.28	$p < .001$	+0.67	$p = .532$
SR	18.60 ± 7.74	21.83 ± 8.49	24.90 ± 8.55	+3.23	$p = .001$	+6.30	$p < .001$	+3.07	$p = .002$
AST	70.51 ± 31.45	74.01 ± 31.52	76.07 ± 30.59	+3.50	$p = .001$	+5.56	$p = .002$	+2.06	$p = .662$
RST	56.14 ± 18.18	56.65 ± 18.05	60.58 ± 18.42	+0.51	$p = 1.00$	+4.44	$p < .001$	+3.93	$p < .001$
ADHD rating scale	31.18 ± 7.98	23.90 ± 8.89	25.19 ± 8.87	-7.28	$p < .001$	-5.99	$p < .001$	+1.29	$p = .409$
ASD rating scale	17.17 ± 4.81	13.94 ± 5.60	14.36 ± 5.69	-3.76	$p = .002$	-2.81	$p = .003$	+0.42	$p = 1.000$
AVL parents	40.22 ± 13.46	36.27 ± 15.07	33.67 ± 15.47	-3.95	$p = .025$	-6.55	$p = .002$	-2.60	$p = 1.000$
BRIEF parents	156.47 ± 20.67	149.51 ± 24.77	148.32 ± 25.34	-6.96	$p = .009$	-8.15	$p = .002$	-1.19	$p = 1.000$

Note. Abbreviation: SS = Spatial Span; BR = Block Recall; DR = Digit Recall; NWL = Non-Word List; BDR = Backward Digit Recall; SAD = Sustained Attention Dots; GNG = Go-No Go; Raven SPM = Raven Standard Progressive Matrices; SR = Story Recall; AST = Arithmetic Speed test; RST = Reading Speed test; ADHD rating scale = Severity of DSM-IV criteria for ADHD; ASD rating scale = Severity of DSM-IV criteria for ASD; AVL parents = Parents' reported severity of ADHD symptoms; BRIEF parents = Parents' reported executive function behaviours.

6

Working memory training in children with neurodevelopmental disorders and intellectual disabilities, the role of coaching; a double-blind randomised controlled trial

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Abstract

Background: Working memory training (WMT) can offer therapeutic benefits to patients with neurodevelopmental disorders (NDD) and mild to borderline intellectual disability (MBID). However, consistent evidence for treatment benefits of WMT over placebo training is missing. So far, participants in double-blind research designs did receive non-specific coaching, whereas active coaching based on individual training results might increase the efficacy of WMT. Furthermore, the intensity and duration of WMT is often too stressful for these children. This study therefore investigated whether a less intensive but more prolonged WMT, with active personalised coaching and feedback, would reduce behavioural symptoms and improve neurocognitive functioning and academic achievements in children with NDD and MBID.

Method: A double-blind randomised controlled trial in children (aged 10;0–13;11) with MBID (60 < IQ < 85) and ADHD and/or ASD evaluated the effects of a less intensive but prolonged version of the original Cogmed WMT (30 min a day, 4 days a week, 8 weeks in total). Eighteen participants received active, personalised coaching and feedback, based on their actual individual performance during training. Twenty-two received general non-personalised coaching for the same amount of time. Executive functioning, academic achievements and several behavioural measurements were administered, before and after training, with a 6-months follow-up.

Results: We observed a significant effect of time on both primary and secondary outcome measures, indicating that all children improved in working memory performance and other neurocognitive and academic outcomes. The interaction between time and group was not significant.

Discussion: This study was unable to document superior effects of active personalised coaching and feedback compared with general non-personalised coaching and no feedback in an adaptive WMT in children with MBID and NDD. The objectively documented changes over time suggest that for these vulnerable children, a regular, structured and structural contact with a coach and adapted exercises is enough to develop therapy fidelity, boost motivation and improve neurodevelopmental task performance. Further research is needed to examine which possible subgroups within this heterogenic group of children profit more from WMT compared with other subgroups.

Introduction

Mild to borderline intellectual disability (MBID) is defined as functioning at a lower intellectual level (IQ: 50–85) with evident deficits in adaptive functioning (American Psychiatric Association 2013). Approximately 33% of the children with MIBD have a comorbid neurodevelopmental disorder (NDD) like attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD; Strømme & Diseth 2000). In clinical practice, patients with these comorbidities often present with a wide range of behavioural, practical, and academic difficulties and represent a significant burden on the mental health care system. There is a lack of evidence-based interventions for these vulnerable patients. Interventions developed for cognitively abled children are often too complex, due to their limited cognitive and adaptive skills. Therefore, it is essential to search for alternatives.

Poor working memory (WM) is a core deficit in many children with MBID and comorbid NDD (Roording-Ragetlie *et al*. 2018; Santegoeds *et al*. 2021). WM impairments are related to poor adaptive behaviour (Gilotty *et al*. 2002) and increased risks of academic and social impairments (Cornish *et al*. 2012). Randomised controlled trials in children with MBID have shown that WM training (WMT) is associated with improved short-term memory (STM) (Van der Molen *et al*. 2010) and larger WM capacity on non-trained WM tasks (Söderqvist *et al*. 2012a). This aligns with reviews and meta-analyses showing positive effects on trained WM performance. Nevertheless, despite improving WM performance reviews and meta-analyses found no evidence for improvement of ADHD symptoms and academic achievement after WMT (Hodgson *et al*. 2012; Melby-Lervag & Hulme 2013; Sonuga-Barke *et al*. 2013; Cortese *et al*. 2015). Furthermore, our triple-blind placebo controlled randomised clinical trial in children with borderline intellectual functioning (IQ: 70–85) and neuropsychiatric disorders was unable to document superior training effects of an adaptive WMT, compared with a placebo (non-adaptive) WMT (Roording-Ragetlie *et al*. 2021). The non-adaptive WMT was associated with significant clinical effects, suggesting that this patient group with persistent impairments in WM may benefit from a structured learning environment associated with the improvement of neurocognitive functioning and coping strategies.

In most studies, a blinded form of coaching is used to meet the criteria of the randomised controlled design, which does not allow the coach to track progress or adjust the training program based on actual performance. However, active coaching involves real-time data and tailors the training program to meet specific needs, which may improve the effectiveness of cognitive training. Research by Foster (2019) contributes to evidence for the effectiveness of

cognitive training programs that involve coaching, showing effect sizes that are generally larger than those of similar studies that did not include coaching. For instance, Melby-Lervag & Hulme (2013) found that most studies on cognitive training that used a WM outcome variable reported an effect size less than 1.0, while Foster's study yielded effect sizes of 1.76, 1.28, and 1.45. These results indicate that the coaching component of the program may have played a significant role in the participants' performance. Although the far-transfer effects of active coaching have not yet been studied, this type of coaching may help participants to understand tasks better and apply effective learning strategies, which may result in improvements in WM performance and in other cognitive or daily skills.

Furthermore, Nelwan *et al*. (2018) showed that after WMT, a highly coached group of children with mathematic and attentional difficulties performed better on visual WM and mathematics compared with a similar group that received less coaching. They suggest that motivation and proper coaching might be crucial for ensuring compliance and the effects of WMT. Especially for children with MBID and comorbid NDD, motivational problems can occur during a highly demanding WMT. These children have more trouble motivating themselves compared with typically developing children, except when they really enjoy the activity (Cuskelly & Gilmore 2014). Active personalised coaching and feedback might increase motivation through personal support and small reward systems making WMT more appealing. Furthermore, it helps strengthen the parent–child relationship through spending more time with each other and working towards a common goal (Roeters *et al*. 2010), leading to a decrease in behavioural problems in children with MBID (Schuiringa *et al*. 2015). To our knowledge, there are currently no studies examining the role of coaching in WMT in children with MBID and NDDs.

Children with MBID learn slower compared with children with average intelligence and need shorter, but more treatment sessions to bring about cognitive and behavioural change (Dutch Knowledge Centre on MID/Landelijk Kenniscentrum LVB 2022). Therefore, the WMT used in this study was changed to less intensive but prolonged training (4 instead of 5 days per week training and 5 instead of 8 exercises per day for a period of 8 instead of 5 weeks).

The aim of this study was to investigate the role of coaching in a less intensive but prolonged WMT in children with MBID and NDD. We tested the hypothesis that active personalised coaching and feedback will be associated with greater improvement in neurocognitive functioning, academic achievements and behaviour problems, directly after training and at 6-month follow-up, compared with general non-personalised coaching and no feedback.

Methods

Study design

Children with MBID and ADHD and/or ASD were recruited between January 2018 and July 2021 from an outpatient facility for child and adolescent psychiatry in the Netherlands. Care providers were asked to inform eligible children and their legal representatives about the study. In addition, they were asked for written consent to share contact details with the research team. A member of the research team then contacted the legal representatives providing them with more information about the study and answering questions. In case of consent to participate in the study, the representatives were asked for written informed consent, and children provided oral consent (or written consent ≥12 years). The ethics approval was obtained from the Medical Ethical Committee (NL52647.091.15/METC2015–1618) at Radboud Academic Medical Centre in Nijmegen, the Netherlands. This trial is registered in the Dutch Trial Register, number NTR:5223, and the study protocol is published (Roording-Ragetlie *et al*. 2017). After inclusion and exclusion criteria were checked (see section Participants), parents were asked for demographic and background information such as previous care and medication use. Parents were also asked to complete the Diagnostic Interview Schedule for Children (DISC-IV), a highly structured diagnostic instrument designed for use by non-clinicians (Shaffer *et al*. 2000) to assess the presence of ADHD and to exclude other comorbid psychiatric disorders. The Social Communication Questionnaire (SCQ) was filled in to assess symptoms of ASD (Berument *et al*. 1999). These results were checked against DSM-IV criteria by an experienced mental health psychologist. If the results of an IQ test were >2 years old a shortened Wechsler intelligence test was taken (Kort *et al*. 2005).

Eligible children were individually randomised into two groups: (1) A less intensive and prolonged version of Cogmed WM training with active coaching and personalised feedback or (2) a less intensive and prolonged version of Cogmed WM training without active coaching and personalised feedback, only general non-personalised coaching. In both conditions, a Cogmed coach followed a strict protocol. This double-blind controlled clinical trial was characterised as double-blind because participants (children, parents, and teachers) and investigators were all blind to group allocation.

The study consisted of four phases (see Figure 1). In the first phase (baseline; T0), the children underwent a neuropsychological assessment, and parents and teachers filled out questionnaires about the child's behavioural symptoms. Second, children performed the training either at home and/or at school. Third, approximately 1 week after the training (post-treatment; T1), the neurocognitive

assessment was repeated. Parents and teachers again filled out the same questionnaires as at T0. Finally (follow-up; T2), the same neurocognitive assessment and questionnaires were administered once more approximately 6 months after completion of the training.

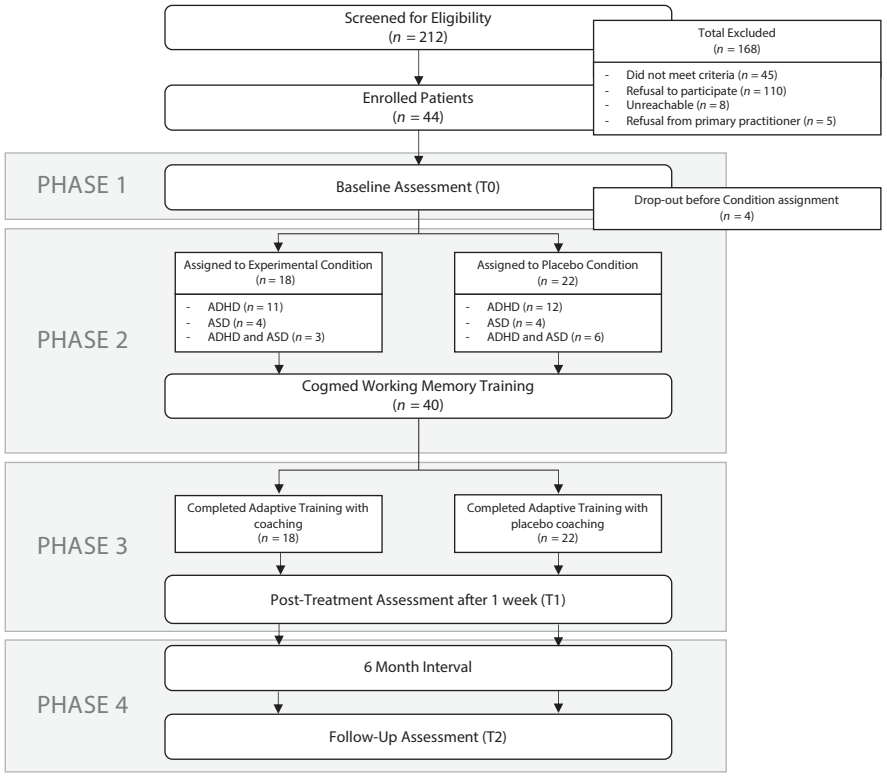

Figure 1: Study flow chart.

Note: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder.

Participants

Children participating in this study were between 10 years 0 months and 13 years 11 months (mean 11.3 ± 1.1 *SD*) old, with an IQ score between 60 and 85 (mean IQ 71.3 ± 7.8 *SD*). They also had ADHD (57%), ASD (20%), or both disorders (23%) in line with the DSM-IV/DSM-5 criteria (American Psychiatric Association 2000; 2013). Computer access with an internet connection and speakers was required for the training. Children on medication were included if there was 'room for improvement' with respect to ADHD symptoms and medication

dosages remained stable during study participation (ADHD medication *n* = 9, antipsychotic *n* = 1, no medication *n* = 20). Exclusion criteria were (1) treatment at an inpatient or day treatment clinic, (2) regular use of other medication than for ADHD, (3) psychiatric diagnoses other than ADHD, ASD or ODD, (4) neurological disorders (e.g. epilepsy) in the last 2 years, (5) current or a history of cardiovascular disease, (6) severe motor and/or visual impairment, (7), current participation in another clinical trial, (8) insufficient motivation or time to pursue training [child, parent(s), or aid(es) are too busy or not motivated to participate] and (9) medical illness requiring medical treatment.

Study Interventions

The original Dutch version of the Cogmed WMT (version R/M; Klingberg *et al.* 2002) consists of 13 verbal and visual STM and WM tasks, which are implemented using a computer program (Cogmed Cognitive Medical Systems AB Stockholm, Sweden). A child completes five different tasks in each training session. An example of a verbal WM task is Decoder. Letters are read out and lights flash at the same time. When solicited, the child must recall the letter associated with a given light. The program is provided online and used by the child on a personal computer at home and/or school, supervised by a parent and/or teacher. Responses are made by clicking on displays using the computer mouse. The difficulty level is automatically adjusted, in each trial, to match the WM span of the child on each task. In the original version, children trained for 5 weeks (25 days and 200 exercises in total), with an estimated time spent per day between 35 and 45 min (≈1000 min in total). The version used in this study had a duration of 8 weeks (30 days and 160 exercises in total), with an estimated time spent per day between 25 and 35 min (≈900 min in total).

A licensed Cogmed coach provides detailed personalised coaching and feedback based on the child's actual performance during the training following a strict protocol, by telephone with the parent or aide and the child every one and a half weeks. A more detailed description of the Cogmed coaching protocol can be found in the Cogmed Coaching Guide, which is available through Pearson Clinical Assessment (2021).

Condition 1: A less intensive and prolonged version of Cogmed working memory training with active coaching and personalised feedback

According to the protocol, the coach started with a demonstration of the training and determination of specific goals, with a focus on ecologically valid goals that were pertinent and useful to the child's daily life. These objectives were specifically related to WMT in children and aimed to improve attention, concentration (e.g. longer periods of independent homework completion),

executive functioning (e.g. organising one's room) or academic performance (reading attentively for 10 min). The goals were tailored to accommodate the individual circumstances of each child and aimed to help them comprehend the purpose of the training. Consequently, they were not standardised for all children.

Furthermore, training schedules were discussed, and agreements about who acts as aid (es) were made. Tailor-made advice was given about motivating the child in their specific home or school situation, and a reward system was agreed on. In an active form of coaching, real-time data are used to be able to give personalised feedback and address individual needs. This may potentially enhance the efficacy of cognitive training. Before every coaching contact, the coach studies the individual training graphs. This may help to evaluate the training progress or barriers to perform well. For example, the coach sees whether the child is following the schedule (day and time), whether the child is training to the limits of his/her abilities, whether there are significant differences in performance on the exercises, whether the child takes many breaks, makes many mistakes or shows a lot of variability. During the contact, the Cogmed coach reviews the graphs with the parent(s)/aide(s) and child and explains the highlights. The coach asks about their experiences, helps to find solutions for problems for example if motivation drops or if it is difficult to follow the schedule, or if conflicts may arise between the child and parent(s)/aide(s). The coach also uses the findings from the graphs and reports of the child or aides to make adjustments and check whether the agreements are being followed (such as training earlier in the day).

Because the WMT is adaptive, there may always be room for improvement for the child. If the child reaches his/her maximum performance, the coach can discuss strategies to stretch his/her capacity. Examples of strategies are chunking (breaking down information into smaller chunks to make it easier to remember), rehearsal (repeating information aloud or silently to oneself to help commit it to memory), visualisation (creating mental images or visualising the information to help remember it), verbalisation (encouraging children to talk through the steps of a task or problem-solving process to help improve WM) or association (associating new information with something already familiar to the child). Also meta-cognitive strategies, such as helping the child to reflect on their own thinking and learning processes and memory strategies, can be taught by the coach to help the child to improve his/her performances.

Condition 2: A less intensive and prolonged version of Cogmed working memory training with only general non-personalised coaching.
This condition was exactly the same as the active condition, except for the personalised coaching and feedback. The general non-personalised coaching condition also started with standardised training instruction with the same topics, except for the determination of the specific goals and the use of a rewarding system. In these weekly coaching sessions, no adjustments were made, nor were strategies for maintaining motivation and engagement were taught. The coach spent the same amount of time with the parents/aid (es) and child on the telephone, but did not log in on the Cogmed server to see the child's performances. No content-related interventions were made, only training time, training minutes and breaks during the training were checked, without giving personalised feedback. The coaches in the general coaching condition did not give advice to parents on how to deal with the situation that their child was unwilling to train. Rather, they recognised the difficulty but avoided giving direct recommendations to solve the problem.

In our study, two licensed Cogmed coaches were present during training and provided both active and general coaching as required. We did not measure the fidelity with which the two different coaching conditions were delivered. Nevertheless, we consider it unlikely that contamination occurred because both types of coaching were standardised, and the therapists followed a strict written protocol for both forms of coaching to ensure consistency in what was conveyed.

Measurements

The Backward Block recall task (Working Memory Test battery for Children; Pickering & Gathercole 2001) was used as the primary outcome measure to assess visual WM. This task has been used in previous research to identify low WM and academic disabilities in children with borderline intellectual functioning (Stefanelli & Alloway 2020) and to estimate baseline and outcome WM performance in WMT studies in children MBID (Van der Molen *et al*. 2010; Roording-Ragetlie *et al*. 2021).

Secondary outcome measures were (1) the scores on several non-trained near- and far-transfer tests capturing verbal and visual WM, sustained attention, response inhibition and goal-directed behaviour; and (2) the scores on a speed-reading test and a speed math test (academic achievement). As tertiary outcomes, several behavioural measures were collected (see Table 1).

Table 1 Secondary and Tertiary Outcome Measures.

	Secondary Outcome Measures		Tertiary Outcome Measures
	Near-Transfer Measures	**Far-Transfer Measures**	**Behavioural Measures**
1	The Spatial Span task (visuo-spatial WM; Automated Working Memory Assessment [AWMA; Alloway 2007]). The child views a picture of two arbitrary shapes, where the shape on the right has a red dot on it. The child identifies whether the shape on the right is the same as or opposite to the shape on the left. The shape with the red dot may also be rotated. At the end of each trial, the child has to recall the location of each red dot on the shape in sequence, by pointing to a picture with three compass points. Scores are given for every correct answer and can vary from 0 to 36 (6 items 6 trials).	Sustained Attention Dots reaction time and errors (Amsterdamse Neuropsychologische Taken [ANT; de Sonneville, 2009]) Participants should discriminate between patterns consisting of 3, 4 (target signal) or 5 dots. The probability of a yes vs no response is 1:2. As a consequence, with time-on-task a response bias (for the no-response key) is induced.	The total score on the ADHD-Vragenlijst (AVL; Scholte and van der Ploeg, 2005), as filled out by parents, to determine behavioural symptoms of ADHD. It contains 18 behaviours that are rated by the child's parents in terms of frequency of occurrence in the last six months on a 5-point Likert scale (0 = Never, 1 = Sometimes, 2 = Average, 3 = Often, 4 = Very often), resulting in a possible total score range from 0 to 72.
2	Listening Recall task (verbal WM; Pickering and Gathercole, 2001). Participants are asked to judge the veracity of a series of short sentences, and to recall the last word of that sentence (or sequence of last words of sentences in case of multiple items). Outcome measure is the amount of correctly recalled sequences of last words, ranging from 0 to 36.	Go-NoGo reaction time and errors (inhibitory control, ANT; de Sonneville, 2009). It contains a presentation of Go and NoGo signals in the centre of the screen to indicate whether or not the child should press a button.	The total score on the Vragenlijst voor Inventarisatie van Sociaal gedrag van Kinderen (VISK, Social Behaviour Inventory, Luteijn *et al.*, 2002), as filled out by parents, to determine social behaviour. It contains 49 behaviours that are rated by the child's parents in terms of frequency of occurrence in the last two months on a 3-point Likert scale (0 = never, 1 = sometimes, 2 = often), resulting in a possible total score between 0 and 98.
3	Backward Digit Recall (verbal WM; Pickering and Gathercole, 2001). A sequence of up to 7 digits is presented verbally to the participants and they are asked to recall this sequence in reverse order. The outcome measure is the amount of correctly recalled sequences, ranging from 0 to 36.	Comprehension of instruction: subtest from Nepsy-II-nl (Zijlstra *et al.*, 2010), measures the ability to receive, process and execute oral instruction of increasing syntactic complexity. It contains 33 questions. The amount of total correctly answered questions serves as the outcome measure, ranging from 0 to 33.	The total score on the Behaviour Rating Inventory of Executive Functioning (BRIEF; Smidts and Huizinga, 2009). There are two separate versions of the questionnaire to be completed by the parents or the teacher, to gain insight into the child's executive function problems (experienced daily) at home. It contains 75 behaviours that are rated in terms of frequency of occurrence in the last six months on a 3-point Likert scale (1 = never, 2 = sometimes, 3 = often), resulting in a possible total score between 75 and 225.
4		A Dutch arithmetic task named "Arithmetic Speed test" (de Vos, 1992) assesses arithmetic automation as a measure of academic achievement. Participants are asked five times (add, subtract, multiply, divide, mixed) to correctly answer as many as possible and up to 200 written out automation of mathematics questions of increasing difficulty within one minute. The amount of total correctly answered questions serves as the outcome measure, ranging from 0 to 200.	
5		A Dutch reading task named "Reading Speed test" (Brus and Voeten, 1999) measures reading automation as a measure of academic achievement. Children are asked to read as many as possible words of increasing difficulty out loud within one minute. The amount of words correctly read out serves as the outcome measure, ranging from 0 to 116.	

ADHD = attention-deficit hyperactivity disorder; WM = Working Memory

Randomisation

The randomisation, performed by an independent person not involved in this research project, was provided in sealed envelopes. Four strata were constructed based on sex and diagnosis, to enable important prognostic characteristics (the stratification factors) to be balanced between the treatment groups. A block randomisation schedule with varying block sizes was performed separately within each stratum to reduce the possibility of selection bias.

Professionals involved in the pre-assessment, post-assessment, and follow-up assessment were not informed about the coaching method. Professionals involved in the coaching were not involved in the pre–post and follow-up assessment. Parents/aide(s) and children were informed about the weekly contact with their coach by telephone but were not informed about coaching-content specifics beforehand.

Sample size

Data from the Klingberg *et al*. (2005) study were used for the population estimates. In this study, subjects were randomised to either high-intensity training or low-intensity training. After training the mean improvement on the main outcome measure (the span-board task) was 0.82 (*SD* = 1.01) in the high-intensity group and 0.15 (*SD* = 0.81) in the low-intensity group. The span-board task (a subtest of the WAIS-RNI used in Sweden) in the Klingberg *et al*. (2005) study was comparable with the Backward Block Recall task in this study and has been developed for children. Because our study is unique in terms of the two randomised training conditions for receiving active personalised coaching and feedback versus only passive coaching, we had to make an estimation about the expected difference in effectiveness based on the above-mentioned study in combination with our own clinical experience. Based on the Klingberg *et al*. (2005) study, a large effect size would have been a viable input parameter for a power analysis. However, we opted for a slightly more conservative small to medium effect size as input for our power analysis, partly based on the guidelines by Cohen (1988). The results of a power analysis using GPower (*f* = .20, α = .05, and power of .80) revealed a required sample size of *N* = 42 (*n* = 21 per group).

Statistical analysis

First, independent *t*-tests were performed to test group (personalised vs. non-personalised coaching) differences in age and IQ, at baseline. Further, χ^2 tests were used to examine the association between group and diagnosis (ADHD, ASD, ADHD + ASD) and group and sex. Next, descriptive statistics were calculated for all outcome measures, at all time points.

A Repeated Measures ANOVA with group (personalised vs. non-personalised coaching), time (pretest, posttest and follow-up), and the interaction between group and time as independent variables and WM as the dependent variable was performed to examine the effect of coaching on WM. Further, several additional Repeated Measures ANOVAs were conducted with the other academic, behavioural and neurocognitive scales as the dependent variables, group (personalised and non-personalised coaching) as the between-subject variable, and time (pre-assessment, post-assessment and follow-up assessment) as the within-subject factor. Given the relatively small sample size, confidence intervals around the estimated marginal means were calculated as well.

Statistical assumptions inherent to the repeated measures ANOVA were not violated. A total of 15 outliers (>3 *SD* from the mean for the respective time point) were identified across all tests and time points. They were retained in the dataset due to insufficient clinical reasons to remove them. Exploratory analyses without outliers did not change the results.

For the primary outcome measure (Backward Block recall task), the percentage of missing values was 12.5%. For the secondary measures, the percentage of missing values ranged from 12.5% to 27.5%. Missingness on the behavioural measures was higher (~40%). We explored the association between study variables at baseline and drop-out at follow-up. None of the baseline variables were related to drop-out at follow-up. Little's missing completely at random (MCAR) test showed that no specific patterns could be identified for the primary outcome measure (Backward Block Recall; χ^2 (3, *n* = 40) = 3.050, *P* = 0.384), and listwise deletion was applied across all analyses. The significance level was set at $\alpha < .05$, and a Bonferroni correction was performed (i.e., alpha divided by 14 tests: $\alpha = .004$). Post-hoc pairwise comparisons were also conducted with a Bonferroni correction.

The analysis regarding the behavioural scores measured with the VISK (measuring ASD symptoms) and the AVL (measuring ADHD symptoms) only included participants with a corresponding diagnosis. The VISK data were available for 17 participants (with ASD or ASD + ADHD), and the AVL data were available for 32 participants (with ADHD and ADHD + ASD). Because of these (very small) subsamples of children with an ADHD (or ADHD + ASD) classification or an ASD (or ADHD + ASD) classification, no univariate follow-up analyses were applied on these behavioural measures.

Results

Baseline differences

Independent sample *t*-tests showed that at baseline (T0), children in the personalised coaching condition did not differ, on average, from children in the non-personalised coaching condition with respect to age [$t(38) = .41$, $P = .684$] or TIQ [$t(37) = –1.66$, $P = .106$]. χ^2 tests of independence showed that group and sex were not associated [$\chi^2 (1) = .64$, $P = .424$] and that group was not related to diagnosis [$\chi^2 (2) = .65$, $P = .723$]. In sum, there were no group differences in these variables before the intervention was administered. Baseline (T0) scores on the neurocognitive and academic tasks were also compared between the two groups to examine whether groups differed before the intervention was administered. Except for the reaction time on the sustained attention task ($t(38) = 2.33$, $P = .025$), baseline scores did not significantly differ between the two groups. At baseline, children in the personalised coaching condition on average were faster ($M = 1292.11$, $SD = 389.78$) compared with children in the non-personalised condition ($M = 1615.91$, $SD=472.01$).

The effect of coaching on primary and secondary outcomes

A repeated measures ANOVA was used to investigate the effect of coaching within Cogmed WMT on visual WM as measured with the Block Recall Task (i.e., primary outcome measure). The main effect of the group was borderline significant (Wilks' $F_{1,33} = 3.33$, $P = .08$, $\eta^2 = .09$). Children in the active coaching condition, on average, performed better ($M = 24.31$, $SD = 1.17$) compared with children in the passive coaching condition ($M = 21.48$, $SD = 1.01$) on a visual WM task. A significant main effect for time was found ($F_{2,32} = 11.41$, $P < .001$, $\eta^2 = .42$). Univariate follow-up tests showed that visual WM improved over time between T0 ($M = 20.76$, $SD = .84$) and T1 ($M = 23.95$, $SD = .90$; $F_{2, 33} = 17.75$, $P < .001$, $\eta^2 = .35$) and between T0 and T2 ($M = 23.98$, $SD = .92$; $F_{1,33} = 17.91$, $P < .001$, $\eta^2 = .35$). No significant change in visual WM was found between T1 and T2 ($F_{1,33} = .00$, $P = .965$, $\eta^2 = .00$). The interaction between group and time was not significant ($F_{2,32} = .05$, $P = .955$, $\eta^2 = .00$), indicating that changes in WM over time were not significantly different for both groups (see Figure 2).

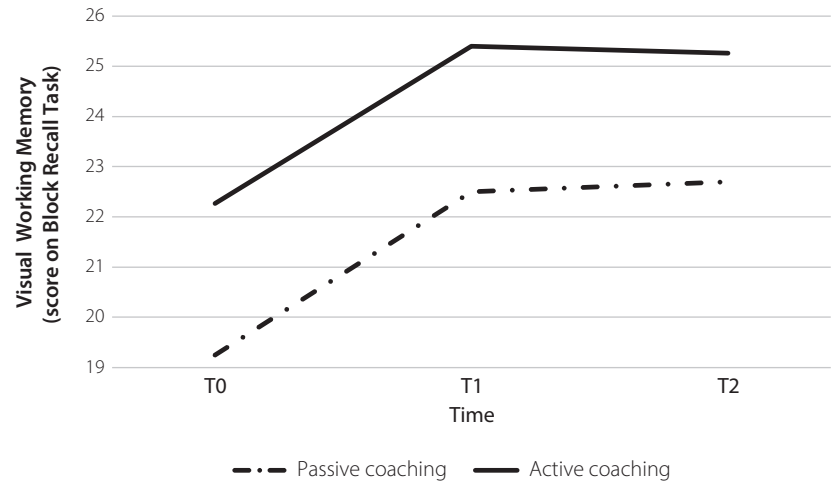

Figure 2: Effect of Coaching on Visual Working Memory over Time

Note. Changes over time regarding visual working memory (measured with the Block Recall Task) are shown for both conditions.

A series of repeated measures ANOVAs was performed to examine the effect of coaching on secondary outcomes (near and far transfer tasks and behavioural measures). Results are shown in Table 2, estimated marginal means are shown in Table 3. The main effect of group was not significant in any of the analyses. Also, no significant interaction between group and time was detected in any of the analyses, suggesting that changes over time in the specific (secondary) outcome were not significantly different between the two groups.

A main effect of time was found for several outcome measures, including visuo-spatial WM (SST), sustained attention (reaction time), inhibitory control (errors), arithmetic speed and reading speed. Univariate follow-up analyses are shown in Table 4. Regarding visuo-spatial WM, an increase in performance was found from T0 to T1 and from T0 to T2, for both groups. Furthermore, a decrease in reaction time over time, from T0 to T1, from T1 to T2 and from T0 to T2, was found for the sustained attention measure, suggesting that participants in both conditions became faster on that specific measure over time. In addition, the number of errors made on the inhibitory control measure decreased over time, from T0 to T2. With regard to reading speed, scores were higher (indicating better performance) at T2 compared with T0 and at T2 compared with T1. For arithmetic speed, an increase in performance was

Table 2 Effect of Coaching on Secondary Outcomes over Time

Outcomes		Effect		
		Time	Interaction	Group
Near Transfer	Visuo-spatial WM (SST)	$F(2, 30) = 9.14$ $p < .001$ $\eta^2 = .38$	$F(2, 30) = 1.10$ $p = .347$ $\eta^2 = .07$	$F(1, 31) = 1.08$ $p = .306$ $\eta^2 = .03$
	Verbal WM (LRT)	$F(2, 32) = .74$ $p = .484$ $\eta^2 = .04$	$F(2, 32) = 1.32$ $p = .282$ $\eta^2 = .08$	$F(1, 33) = 1.01$ $p = .323$ $\eta^2 = .03$
	Verbal WM (BDR)	$F(2, 32) = 3.64$ $p = .038$ $\eta^2 = .19$	$F(2, 32) = 1.00$ $p = .381$ $\eta^2 = .06$	$F(1, 33) = .28$ $p = .603$ $\eta^2 = .01$
Far transfer	Sustained Attention (errors)	$F(2, 27) = .22$ $p = .805$ $\eta^2 = .02$	$F(2, 27) = 1.28$ $p = .295$ $\eta^2 = .09$	$F(1, 28) = 1.22$ $p = .279$ $\eta^2 = .04$
	Sustained Attention (reaction time)	$F(2, 27) = 7.65$ $p = .002$ $\eta^2 = .36$	$F(2, 27) = .48$ $p = .624$ $\eta^2 = .03$	$F(1, 28) = 2.89$ $p = .100$ $\eta^2 = .09$
	Inhibitory control (errors)	$F(2, 26) = 7.94$ $p = .002$ $\eta^2 = .38$	$F(2, 26) = 3.05$ $p = .064$ $\eta^2 = .19$	$F(1, 27) = .00$ $p = .958$ $\eta^2 = .00$
	Inhibitory control (reaction time)	$F(2, 26) = 4.82$ $p = .017$ $\eta^2 = .27$	$F(2, 26) = .58$ $p = .567$ $\eta^2 = .04$	$F(1, 27) = .00$ $p = .960$ $\eta^2 = .00$
	Comprehension of instruction	$F(2, 32) = 2.82$ $p = .074$ $\eta^2 = .15$	$F(2, 32) = .07$ $p = .929$ $\eta^2 = .01$	$F(1, 33) = .80$ $p = .378$ $\eta^2 = .02$
	Arithmetic speed	$F(2, 31) = 18.35$ $p < .001$ $\eta^2 = .54$	$F(2, 31) = .40$ $p = .677$ $\eta^2 = .03$	$F(1, 32) = .13$ $p = .718$ $\eta^2 = .00$
	Reading speed	$F(2, 32) = 8.60$ $p = .001$ $\eta^2 = .35$	$F(2, 32) = .25$ $p = .778$ $\eta^2 = .02$	$F(1, 33) = .20$ $p = .660$ $\eta^2 = .01$
Behaviour	ADHD symptoms*	$F(2, 12) = 2.31$ $p = .141$ $\eta^2 = .28$	$F(2, 12) = 6.90$ $p = .01$ $\eta^2 = .54$	$F(1, 13) = .1.11$ $p = .312$ $\eta^2 = .08$
	Social behaviour*	$F(2, 4) = 4.52$ $p = .094$ $\eta^2 = .69$	$F(2, 4) = 2.57$ $p = .192$ $\eta^2 = .56$	$F(1, 5) = 68$ $p = .447$ $\eta^2 = .12$
	Executive functioning*	$F(2, 15) = .53$ $p = .602$ $\eta^2 = .07$	$F(2, 15) = .02$ $p = .979$ $\eta^2 = .00$	$F(1, 16) = .03$ $p = .862$ $\eta^2 = .00$

Note. * as perceived by parents. ADHD symptoms were only tested in a subsample of children with an ADHD (or ADHD and ASD) classification. Social behaviour was only tested in a (very small) subsample of children with an ASD (or ADHD + ASD) classification.

found over time from T0 to T1, from T0 to T2 and from T1 to T2. All post-hoc comparisons of the significant time effects can be found in Table 4.

Repeated measures ANOVAs were repeated, adjusted for sex and diagnosis. The results for all outcome variables but one did not change substantially. Only the group * time interaction for inhibitory control errors (GNG) was significant when adjusting for sex and diagnosis ($F_{2,18} = 6.90$, $P = .006$, $\eta^2 = .43$). Follow-up analyses showed a significant decrease in errors from T0 ($M = 4.71$, $SD = .85$) to T1 ($M = 2.50$, $SD = .73$; $F_{1,14} = 4.80$, $P = .046$, $\eta^2 = .26$) and from T0 to T2 ($M = 2.02$, $SD = .53$; $F_{1, 11} = 18.85$, $P = .001$, $\eta^2 = .63$) only for the passive coaching condition ($F_{1,14} = 4.80$, $P = .046$, $\eta^2 = .26$). Other simple effects were not significant. However, given the small sample size, these results should be taken with caution.

Table 3 Estimated Marginal Means

Group		Personalised coaching (*N* = 18)								
		T0			T1			T2		
Outcomes		*M (SD)*	*N*	*95% CI*	*M (SD)*	*N*	*95% CI*	*M (SD)*	*N*	*95% CI*
Primary	1. Visual WM (BBRT)	22.27 (1.27)	18	[19.68-24.85]	25.40 (1.36)	17	[22.63-28.17	25.27 (1.40)	15	[22.43-28.11]
Near transfer	2. Visuo-spatial WM (SST)	13.87 (1.72)	18	[10.36-17.37]	16.40 (1.66)	17	[13.02-19.78]	19.13 (1.90)	15	[15.26-23.00]
	3. Verbal WM (LRT)	11.07 (.94)	18	[9.16-12.97]	12.07 (1.22)	17	[9.58-14.55]	13.07 (.95)	15	[11.13-15.01]
	4. Verbal WM (BDR)	10.80 (.95)	18	[8.88-12.72]	13.00 (1.25)	17	[10.46-15.54]	11.53 (1.14)	15	[9.21-13.86]
Far transfer	5. Sustained Attention (errors)	59.25 (13.51)	18	[31.58-86.92]	60.17 (12.28)	17	[35.01-85.32]	69.25 (13.11)	12	[42.40-96.11]
	6. Sustained Attention (RT)	1333.25 (130.40)	18	[1066.15-1600.35]	1230.58 (145.24)	17	[933.06-1528.10]	1060.08 (134.90)	12	[783.76-1336.41]
	7. Inhibitory Control (errors)	3.25 (.79)	17	[1.64-4.86]	3.25 (.76)	16	[1.70-4.80]	2.50 (.62)	12	[1.24-3.76]
	8. Inhibitory control (RT)	494.17 (27.79)	17	[437.16-551.18]	460.42 (24.27)	16	[410.61-510.22]	445.58 (22.18)	12	[400.08-491.09]
	9. Comprehension of instruction	24.20 (.60)	18	[22.99-25.42]	25.47 (.69)	17	[24.07-26.87]	25.33 (.62)	15	[24.07-26.60]
	10. Arithmetic Speed	51.67 (9.10)	18	[33.14-70.20]	56.13 (9.02)	17	[37.77-74.50]	63.00 (8.69)	15	[43.27-82.73]
	11. Reading Speed	48.40 (6.31)	18	[35.57-61.23]	49.33 (6.03)	17	[37.07-61.60]	53.13 (6.69)	15	[39.53-66.74]
Behaviour	12. ADHD symptoms	43.38 (4.89)	14	[32.82-53.93]	43.88 (4.82)	9	[33.47-54.29]	40.63 (5.33)	9	[29.11-52.14]
	13. Social behaviour	49.00 (10.43)	5	[22.18-75.82]	44.00 (9.10)	4	[25.75-62.25]	37.33 (8.87)	4	[14.54-60.13]
	14. Executive functioning	147.33 (12.92)	16	[119.95-174.72]	153.89 (5.71)	12	[141.79-165.99]	145.33 (13.39)	10	[116.94-173.73]

Group		Non personalised coaching (*N* = 22)								
		T0			T1			T2		
Outcomes		*M (SD)*	*N*	*95% CI*	*M (SD)*	*N*	*95% CI*	*M (SD)*	*N*	*95% CI*
Primary	1. Visual WM (BBRT)	19.25 (1.10)	22	[17.01-21.29]	22.50 (1.18)	22	[20.10-24.90]	22.70 (1.21)	20	[20.24-25.16]
Near transfer	2. Visuo-spatial WM (SST)	11.33 (1.57)	21	[8.13-14.53]	15.89 (1.51)	20	[12.80-18.98]	15.94 (1.73)	18	[12.41-19.48]
	3. Verbal WM (LRT)	10.90 (.81)	22	[9.25-12.55]	11.45 (1.06)	22	[9.30-13.60]	10.65 (.83)	20	[8.97-12.33]
	4. Verbal WM (BDR)	10.20 (.82)	22	[8.54-11.86]	11.55 (1.08)	22	[9.35-13.75]	11.50 (.99)	20	[9.49-13.51]
Far transfer	5. Sustained Attention (errors)	51.83 (11.03)	22	[29.24-74.43]	44.17 (10.03)	22	[23.63-64.71]	42.78 (10.70)	18	[20.85-64.71]
	6. Sustained Attention (RT)	1606.22 (106.47)	22	[1388.13-1824.31]	1479.06 (118.59)	22	[1236.13-1721.98]	1388.83 (110.14)	18	[1163.22-1614.45]
	7. Inhibitory Control (errors)	4.65 (.66)	22	[3.29-6.00]	2.82 (.63)	20	[1.52-4.13]	1.65 (.52)	17	[.59-2.71]
	8. Inhibitory control (RT)	476.94 (23.34)	22	[429.04-524.84]	468.82 (20.39)	20	[426.98-510.67]	449.88 (18.63)	17	[411.65-488.11]
	9. Comprehension of instruction	25.00 (.52)	22	[23.95-26.05]	25.95 (.60)	22	[24.74-27.16]	25.80 (.54)	20	[24.71-26.89]
	10. Arithmetic Speed	48.68 (8.08)	21	[32.22-65.15]	51.58 (8.01)	22	[35.26-67.90]	57.11 (8.61)	20	[39.57-74.64]
	11. Reading Speed	45.45 (5.46)	22	[34.34-56.56]	44.65 (5.22)	22	[34.03-55.27]	49.75 (5.79)	20	[37.97-61.53]
Behaviour	12. ADHD symptoms	42.00 (5.22)	17	[30.71-53.29]	29.00 (5.15)	10	[17.87-40.13]	36.86 (5.70)	10	[24.55-49.17]
	13. Social behaviour	55.25 (9.04)	9	[32.02-78.48]	51.00 (6.15)	6	[35.20-66.80]	52.25 (7.68)	5	[32.51-71.99]
	14. Executive functioning	150.78 (12.92)	19	[123.39-178.16]	155.67 (5.71)	12	[143.57-167.76]	147.00 (13.39)	12	[118.61-175.39]

Note. WM = working memory, BBRT = Backward Block Recall Task, SST = Spatial Span Task, LRT = Listening Recall Task, BDR = Backward Digit Recall. ADHD symptoms were only tested in a subsample of children with an ADHD (or ADHD and ASD) classification. Social behavior was only tested in a (very small) subsample of children with an ASD (or ADHD + ASD) classification.

Table 4 Changes over Time: Univariate Follow-Up Tests for Secondary Outcome Measures

Outcome	Contrast	Test		
		F	p	*Partial* χ^2
Visuo-spatial WM (SST)	T0 vs. T1	$F(1, 31) = 15.17$	$p < .001$	$\eta^2 = .33$
	T0 vs. T2	$F(1, 31) = 13.99$	$p < .001$	$\eta^2 = .31$
	T1 vs. T2	$F(1, 31) = 1.54$	$p = .224$	$\eta^2 = .05$
Verbal WM (BDR)	T0 vs. T1	$F(1, 33) = 7.51$	$p = .010$	$\eta^2 = .19$
	T0 vs. T2	$F(1, 33) = 3.19$	$p = .083$	$\eta^2 = .09$
	T1 vs. T2	$F(1, 33) = 2.34$	$p = .136$	$\eta^2 = .07$
Sustained Attention (rt)	T0 vs. T1	$F(1, 28) = 6.27$	$p = .018$	$\eta^2 = .18$
	T0 vs. T2	$F(1, 28) = 15.49$	$p < .001$	$\eta^2 = .36$
	T1 vs. T2	$F(1, 28) = 9.70$	$p = .004$	$\eta^2 = .26$
Inhibitory control (errors)	T0 vs. T1	$F(1, 27) = 2.76$	$p = .108$	$\eta^2 = .09$
	T0 vs. T2	$F(1, 27) = 16.46$	$p < .001$	$\eta^2 = .38$
	T1 vs. T2	$F(1, 27) = 3.22$	$p = .084$	$\eta^2 = .11$
Inhibitory control (rt)	T0 vs. T1	$F(1, 27) = 3.21$	$p = .084$	$\eta^2 = .11$
	T0 vs. T2	$F(1, 27) = 9.15$	$p = .005$	$\eta^2 = .25$
	T1 vs. T2	$F(1, 27) = 4.47$	$p = .044$	$\eta^2 = .14$
Artihmetic speed	T0 vs. T1	$F(1, 32) = 8.84$	$p = .006$	$\eta^2 = .22$
	T0 vs. T2	$F(1, 32) = 36.99$	$p < .001$	$\eta^2 = .54$
	T1 vs. T2	$F(1, 32) = 22.43$	$p < .001$	$\eta^2 = .41$
Reading Speed	T0 vs. T1	$F(1, 33) = .00$	$p = .958$	$\eta^2 = .00$
	T0 vs. T2	$F(1, 33) = 13.62$	$p < .001$	$\eta^2 = .29$
	T1 vs. T2	$F(1, 33) = 12.82$	$p = .001$	$\eta^2 = .28$

Note. Univariate follow-up tests are shown for the outcomes for which a significant main effect of time (multivariate) emerged in the Repeated Measures ANOVA. Means are shown in Table 3.

Discussion

This study examined the effects of different types of coaching WMT in children with MBID and NDD. In contrast to our hypothesis, the results of this double-blind, randomised controlled trial did not show any differences between the effects of active, personalised coaching and feedback and general non-personalised coaching and no feedback on changes over time regarding the primary outcome measures. Furthermore, no additional effects in favour of the active coaching group were found on changes over time regarding any of the secondary (visual and verbal WM, sustained attention, response inhibition and goal-directed behaviour, arithmetic and reading) or tertiary (behavioural measures) outcomes. Results did show a main effect of time for several of the outcomes, suggesting an increase in performance for both groups, probably reflecting learning effects.

These findings are not in line with research that showed that (the amount of) coaching positively influenced the effects of WMT (Nelwan *et al*. 2018). An explanation could be that Nelwan *et al*. (2018) studied children with relatively mild neurocognitive problems, who possibly may have more abilities to apply to feedback, because they experience less persistent impairments in WM and most likely grow up in more favourable circumstances compared with our vulnerable patient group. Also, Nelwan *et al*. (2018) studied the frequency of coaching to differences in study outcomes.

However, this study did show improvements over time on several neurocognitive measures (visuo-spatial WM, sustained attention and inhibitory control) and academic achievement (arithmetic speed and reading speed) for both groups. An explanation for these improvements in both groups might be found in isolated training effects because both groups underwent an adaptive WMT (with a difference in coaching quality during training). However, this is not in line with our prior study, showing no superior training effects over time of an adaptive WMT in a similar patient group, compared with a placebo (non-adaptive) WMT (Roording-Ragetlie *et al*. 2021). Because no waiting list control group was added to this study, we could not control for specific conditional factors common to both groups, such as brain maturation, acquired underlying cognitive abilities, and/or practice effects. However, it is worth noting that the training software used in the study provided a measure of performance in training, known as the Cogmed WM improvement index, which was found to be 17.13 points ($SD = 7.4$) in the total population of this study. This index calculates the difference between the best successful trials at the start of the program and the best trials on the two overall best training days. Previous research has identified an improvement index score of 17 as a

threshold to represent successful improvement after finishing training Cogmed WMT (Gray *et al*. 2012; Chacko *et al*. 2014). Although the lack of a control group limits the generalisability of the findings, the use of the Improvement Index provides some indication of the effectiveness of the Cogmed WMT program in improving WM in both coaching groups.

No significantly higher levels of improvement over time were found in the group with active coaching and feedback compared with the group receiving only general coaching and no feedback. Hereby, it could be argued that setting specific goals to improve understanding of the training's purpose or implementing a reward system to boost motivation may not have been beneficial for these children, as this was a primary distinction between the active and general coaching groups. However, it is also possible that the child, parents or aides were capable of implementing these interventions independently without any coaching. Furthermore, these results may suggest that for these vulnerable children a regular, structured and structural contact with a coach is sufficient to develop therapy fidelity resulting in progress. This is consistent with the general treatment approach for children with MBID in which a 'keep it simple' and trusted therapeutic relationship is of great value (Dutch Knowledge Centre on MID/Landelijk Kenniscentrum LVB 2022). Perhaps, the general but trusted coaching might have given parents and children the opportunity to reflect on what may motivate the child to succeed in the training and how the child learns and behaves. This may reinforce the child's feeling of competence, which may improve self-confidence and self-esteem of the child. Children with MBID in general have the feeling of being incompetent compared with similar-age peers without intellectual disabilities (Li & Morris, 2007). The importance of motivation is underlined by research on the impact of feedback and motivational style on WMT in youth with ADHD (Sadeghi *et al*. 2020). The unusually low drop-out rate (0% drop-out) lends support to the feasibility and suitability of this type of intervention in a vulnerable and disadvantaged population. A study in a similar patient group, in which coaching was limited due to the triple-blind design, had a much higher drop-out rate of 15% (Söderqvist *et al*. 2012a).

This study showed no significant interaction or group effects on social behavioural difficulties, daily experienced executive functioning or ADHD-related behaviour as rated by parents after WMT (neither with active nor with general coaching). Although these results are based on very small subsamples, this is in line with previous research and suggests that coaching in WMT does not contribute to far-transfer effects on behavioural level (Shipstead *et al*. 2012; Rapport *et al*. 2013; Melby-Lervag *et al*. 2016). An alternative rationale is that despite an increase (but still a vulnerability) in WM capacity after training,

behavioural difficulties may continue to exist because of a mismatch between the support needs of these children and the inability of the environment to meet these needs in daily live (Santegoeds *et al*. 2021).

There were some limitations in this study. First, the rather small sample size (n = 40), and the unwillingness or low interest of this specific patient group in participating in research, makes it difficult to rule out a selection bias. The high rate of refusal to participate in this study may be due to great care needs and low coping abilities of this population. Often MIBD and neurodevelopmental problems run in families, making participation in studies an additional burden. These families are often unaware of the added value of scientific research and/or unable to meet the extra requirements of the study. Furthermore, our inability to fully meet the needs and preferences of this patient group may also have contributed to low participation rates. This highlights the importance of designing feasible study designs for children with MBID and their families to enhance participation rates. Above, it is important to ensure that research findings are applicable and meaningful to this population. Furthermore, the results of our study may have been impacted/influenced by methodological limitations such as low power. This may have limited the study's ability to detect a small but meaningful effect of the intervention. Therefore, we also reported confidence intervals around the means. However, the results should be interpreted cautiously.

This study may provide evidence that children with MBID and NDD can engage and make progress in a less intensive and prolonged Cogmed WMT. However, the active coaching aspects of the intervention did not result in significantly larger effects of training compared with generalised coaching and far transfer effects of WMT failed to appear. Future studies of cognitive training should take into consideration if and how different coaching styles and inter-individual differences in training progress may influence transfer effects. Söderqvist *et al*. (2012a) found that girls with MBID and without an additional diagnosis and with higher baseline performance on verbal WM showed greater training progress. To understand differences in training progress a person-centred latent profile approach may help to identify subgroups within this heterogenic patient group that is homogeneous at a demographic and/or neurocognitive level. Furthermore, it would be of interest to collect qualitative data on the acceptability of WMT, to provide valuable insights into participants' perceptions of the intervention, which is useful for future research and intervention development.

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7

General Discussion

Introduction

Working memory (WM) plays a crucial role in daily functioning and learning. The objective of this thesis was to study the role of WM characteristics in children with mild to borderline intellectual disability (MBID)[1], both with and without coexisting neurodevelopmental disorders such as attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and/or learning disorders (LD)s. Two main topics were addressed in four clinical studies and a systematic review: (1) the neurocognitive functioning of children with MBID and/or neurodevelopmental disorders in relation to behavioral correlates, and (2) the trainability of WM in children with neurodevelopmental disorders, with or without MBID, and the influence of coaching during treatment.

This concluding chapter will provide a summary of the main findings. The conclusions and clinical implications will be discussed. Additionally, the strengths and limitations will be examined, and potential areas for future research will be explored.

Neurocognitive functioning

In **chapter 2**, a systematic literature review was conducted to gain a better understanding of WM strengths and weaknesses in children with MBID. This review compared the WM performance of children with MBID aged 4 to 18 years with that of typically developing children of the same chronological age and of younger, typically developing children with the same mental age (MA). The results indicated that children with MBID had lower verbal and visuospatial WM spans compared to typically developing children in the same age range. Lower functioning children with MBID (IQ < 70) had poorer scores on both verbal and visuospatial WM tasks compared to relatively higher functioning children with MBID (IQ 70-85). Verbal WM was a weakness for both higher and lower functioning children with MBID when compared to their chronologically age-matched peers, while visuospatial WM appeared to be a strength for the relatively higher functioning children with MBID, as it may be related to intellectual functioning. Additionally, children with MBID demonstrated differences in verbal WM performance compared to younger, typically developing children with the same MA. When the MA of children with MBID was lower than 7 years (irrespective of the chronological age), they scored

1 In the Netherlands, children with Borderline Intellectual Functioning (BIF), who also experience (serious) additional problems, can access care intended for children with Mild Intellectual Disability (MID). Therefore, although this isn't an official DSM-5 classification, we use the term MBID in this thesis when referring to the entire group of children with MID and BIF.

worse on verbal WM tasks compared to a MA-matched control group. However, when their MA was above 7 years, their verbal WM performance was in line with typically developing seven-year-old children. In contrast to verbal WM, visuospatial WM in children with MBID appeared to be consistent with their MA and was a relative strength.

In **chapter 3**, the results of a latent profile analysis in a clinical sample of children with MBID and neurodevelopmental disorders (ADHD and/or ASD) found a solution that identified three cognitive profiles characterized by differences in the speed–accuracy trade-off and cognitive performance. Profile 1, which comprised 70% of the participants, was described as a "high accuracy–high speed" subgroup, characterized by a relatively high trade-off between speed and accuracy, as well as relatively high scores on both cognitive and academic achievement tasks. Profile 2, which comprised 21% of the sample, was described as a "high accuracy–low speed" subgroup and was characterized by a low speed and relatively high accuracy trade-off, as well as middling scores on cognitive and academic achievement tasks. Finally, profile 3, which constituted 9% of the sample, was described as an "instable accuracy/speed" subgroup. This subgroup had an unstable trade-off between speed and accuracy, along with low scores on both cognitive and academic achievement tasks. Despite these unique cognitive profiles with varying levels of performance on both cognitive and academic achievement tasks, they did not differ in the severity of ADHD symptoms, social behavior, or in their daily experience of executive functioning problems.

Taken together, it can be inferred that visual WM represents a relative strength in children with MBID as a group, when compared to typically developing children of the same (mental) age. This advantage may stem from their proficient use of more advanced visual coding strategies, including the storage of meaningful visual imagery. It is plausible that children with MBID rely heavily on their superior visual WM abilities at an earlier stage of development to tackle problem-solving tasks, thereby exacerbating the discrepancy in their verbal WM abilities as they continue to mature (see chapter 2). Moreover, there is additional evidence suggesting that verbal WM constitutes a core deficit in the entire group of children with MBID, when compared to typically developing children of the same (mental) age. These children display an inability to automatically rehearse incoming information (Hasselhorn & Mähler, 2007; Henry & Conners, 2008; Rosenquist, Conners & Roskos-Ewoldsen, 2003; Russel, Jarrold & Henry, 1996), indicating a deficiency in coping mechanisms to prevent the rapid decay of information from their short-term memory (see chapter 2). This finding aligns with prior research on children with MBID and

neuropsychiatric disorders, concluding that WM remains a fundamental deficit in these children, even when considering their slower processing speed, as compared to typically developing children of the same age (Santegoeds et al., 2022).

However, upon closer examination within the cohort of children with MBID and neurodevelopmental disorders, we identified three distinct cognitive subgroups characterized by different trade-offs in processing speed, which appear to be associated with variations in WM performance. The largest subgroup (70%) of children with MBID and neurodevelopmental disorders exhibits a high accuracy–high speed trade-off with relatively minor WM challenges. This suggests that these children possess adequate foundational cognitive skills and coping strategies, enabling them to perform comparatively well on cognitive and academic tasks. The high accuracy–low speed subgroup (21%) demonstrates the ability to employ coping strategies when confronting cognitive challenges by moderating their working pace to maintain task accuracy, particularly in WM-related tasks. However, when the cognitive complexity intensifies or time becomes a critical factor for performance, these children may still encounter difficulties in adapting, resulting in lower WM scores. The subgroup of children with an unstable accuracy/speed trade-off (9%) exhibits notably low scores in verbal WM and slightly better but still limited scores in visual WM tasks.
Thus, it appears that a combination of processing speed and the ability (or inability) to employ effective coping strategies contributes to the variation in WM difficulties. Importantly, the three identified cognitive subgroups did not show significant differences in the severity of ADHD behavior problems, social behavior problems, or in their daily experience of executive functioning problems. This observation suggests that these challenges might arise from a mismatch between the support and adaptations needed due to their cognitive problems and the insufficient support or compensation provided by their environment. Consequently, conducting a neuropsychological assessment to determine the relevant subgroup applicable to each child could be beneficial in making appropriate treatment adjustments.

Trainability

Chapter 4 detailed a naturalistic, open-label, non-randomized, controlled intervention study that investigated the effects of WMT in different groups of children aged between 7 and 17 years with neurodevelopmental problems, including ADHD, LDs, or learning problems. This study found a significant main effect with small to moderate effect sizes on inattention symptoms, hyperactivity/impulsivity symptoms, overall executive function problems, and

a large effect size for WM capacity. These results suggest that all groups (ADHD, LDs, and learning problems) benefited from training. Additionally, significant interaction effects with small effect sizes revealed that children with LDs benefited less from training in respect to hyperactivity/impulsivity symptoms and overall executive function problems, compared to children with ADHD. Finally, all groups benefited equally from training with regards to behavioral attention and WM capacity.

In **chapter 5**, the results of a triple-blind, placebo-controlled, randomized clinical trial were presented. This study aimed to investigate whether adaptive computerized WMT resulted in greater improvements on a non-trained visuospatial WM task compared to a non-adaptive control WMT (placebo) in children with BIF (70< IQ <85) and neuropsychiatric disorders (ADHD and/or ASD). The analysis showed no superior training effects over time of an adaptive WMT compared to a placebo (non-adaptive) WMT on WM performance. There were also no effects on the secondary (near and far-transfer tasks) or tertiary (behavioral measures) outcome measures. Similar within-subject changes over time were observed for these measurements for both the experimental and placebo condition, suggesting that these children with persistent impairments in WM may benefit from a structured learning environment that is associated with the improvement of neurocognitive functioning and coping strategies.

Chapter 6 reported the results of a double-blind, randomized controlled trial on the effectiveness of a less intensive version of Cogmed WMT with personalized coaching and feedback in children with neurodevelopmental disorders and MBID, compared to a similar version without personalized coaching and feedback. Both versions led to an improvement in WM and other outcomes (executive functioning, academic achievements, and behavioral measurements), but there was no significant difference between the two, suggesting that a regular, structured, and consistent contact with a coach and adapted exercises was enough to develop therapy fidelity, boost motivation and improve neurodevelopmental task performance in these vulnerable children.

General discussion

Taken together, the evidence regarding the effectiveness of WMT in improving cognitive, academic, and behavioral outcomes for children with MBID and/or neurodevelopmental disorders remains inconclusive. However, a more nuanced approach is needed to decisively conclude that WMT should not be conducted in children with MBID and/or neurodevelopmental disorders solely

based on the lack of significant difference in training outcomes over time between an adaptive WMT and a placebo (non-adaptive / non-coaching) WMT. The fact that all three intervention studies showed an improvement in WM capacity in children, reflected by a WM Improvement Index score above the threshold for successful improvement after completing the Cogmed WMT (Gray et al., 2012; Chacko et al., 2014), may suggest that these vulnerable children are able to improve their WM capacity through training.

Considering these three studies collectively, several things stand out regarding the effectiveness of WMT. Children with MBID and neurodevelopmental disorders can benefit from low-intensity WMT, as indicated by WM improvement after a placebo (non-adaptive) training that turned out to be an intervention training for some of the included children, because their baseline WM capacity was lower than the training level (WM span < 3 items) (chapter 5). As well as the lower intensity in WM load in the placebo condition, there is also a significantly lower intensity in total training minutes per day with the same WM improvement after training (chapter 5), which is also the case with the implementation of a less intense but prolonged WMT (chapter 6).

Another point to consider is the difference in coaching intensity between the groups. Children with MBID and co-morbid neurodevelopmental disorders can benefit from low-intensity (regular, structured and structural) coaching during WMT, resulting in high therapy fidelity and low dropout rates (chapters 5 and 6). In contrast, high-intensity coaching, such as setting specific goals or implementing reward systems to boost motivation, on top of more general coaching, has not been proven to be of added value in WMT for these children (chapter 6). It should be noted that these children are particularly vulnerable during cognitively demanding situations, due to quicker feelings of inadequacy compared to typically developing peers (Li & Morris, 2007). Therefore, it is important to exercise caution with intensive intervention programs like WMT as overburdening is a risk. Enabling a structured learning environment with an established therapeutic alliance can improve their neurocognitive functioning and may help these children to develop coping strategies, such as perseverance and frustration tolerance (chapters 5 and 6).

Another important factor to consider is the heterogeneity in our study population and the potential influence of the individual severity of and/or co-morbidity with neurodevelopmental disorder(s) on the effectiveness of WMT. Our studies might suggest that WMT may be particularly useful for children who have relatively mild or subthreshold psychiatric disorders or learning disabilities and are 'at risk' for developing a more severe psychiatric disorder. Training may even prevent the development of a full psychiatric disorder or severe academic achievement problems (as discussed in Chapter 4).

In addition, it is possible that among the more severely affected group of children with MBID and co-morbid neurodevelopmental disorders, different cognitive subgroups (as described in Chapter 3) may benefit differently from WMT. Specifically, cognitive subgroups characterized by "high accuracy–high speed" or "high accuracy–low speed" thresholds may derive greater benefits from WMT. These subgroups exhibited relatively mild cognitive difficulties and demonstrated sufficient flexibility in adjusting their cognitive strategies to meet the demands of WMT effectively. In contrast, the smaller subgroup characterized by "instable accuracy/speed" has greater struggles with various cognitive tasks. It appears that the information processing ability of this subgroup is compromised, resulting in prolonged decision-making times and frequent errors. These children are particularly vulnerable and exhibited limited flexibility in adapting their cognitive strategies to meet the cognitive demands. Consequently, it is worth considering whether these children might benefit more from compensation strategies rather than training interventions to reduce the risk of drop-out.

Finally, our results align with prior studies (Melby-Lervag et al., 2016; Rapport et al., 2013; Shipstead et al., 2012), indicating that WMT does not result in long-term, far-transfer effects at a behavioral level as only time-effects occurred in both (experimental and placebo) groups. One explanation could be that even though WM capacity increases, it may still be vulnerable after training, and the persistence of behavioral difficulties could be due to a discrepancy between the support requirements of these children and the environment's incapacity to fulfill those needs in everyday life, as noted by Santegoeds and colleagues (2022).

General conclusions

In answer to the research questions posed in Chapter 1:

1. **Are there differences in WM abilities between children with MBID and typically developing children of the same chronological age, or younger typically developing children with the same mental age?**

Yes, as a group, children with MBID demonstrated weaker WM abilities compared to typically developing children of the same chronological age. Specifically, verbal WM appeared to represent a core deficit in children with MBID, often being weaker than their mental age, while visual WM aligns more closely with their mental age.

2. **Do subgroups exist within the heterogeneous group of children with MBID and comorbid neurodevelopmental disorders at a cognitive level in relation to behavioral correlates?**

Yes, within the group of children with MBID and neurodevelopmental disorders, our data allowed for the distinction of three subgroups based on cognitive performance. The first group demonstrated a relatively high trade-off between speed and accuracy, as well as relatively high scores on both cognitive and academic achievement tasks. The second group exhibited a low speed and relatively high accuracy trade-off, along with middling scores on cognitive and academic achievement tasks. The third group displayed an unstable trade-off between speed and accuracy, accompanied by low scores on both cognitive and academic achievement tasks. Notably, these three groups did not differ significantly in terms of ADHD behavior symptoms, social behavior, or their daily experience of executive functioning problems.

3. **Can WM be effectively trained in children with neurodevelopmental disorders with or without MBID, and if so, does this affect other cognitive abilities and/or behavior?**

No, our analyses did not find a significant difference in training outcomes between an adaptive WMT and a placebo (non-adaptive) WMT in children with MBID and neurodevelopmental disorders. However, children with neurodevelopmental disorders, with or without MBID, all demonstrated a WM Improvement Index score above the threshold for successful improvement after completing the Cogmed WMT (Gray et al., 2012; Chacko et al., 2014). This may suggest that these vulnerable children are capable of improving their WM capacity through training. Furthermore, these results do not impact long-term, far-transfer effects at a behavioral level, as only time effects occurred for both (experimental and placebo) groups.

4. **What is the role of coaching on WMT in children with MBID and neurodevelopmental disorders?**

Our studies did not find a significant difference in the effectiveness of training between a less intensive version of Cogmed WMT with personalized coaching and feedback compared to a similar version without personalized coaching and feedback in children with neurodevelopmental disorders and MBID. However, both groups did show improvement on WM performance and other neurocognitive and academic outcomes, suggesting that regular, structured, and consistent contact with a coach and the completion of adapted exercises was enough to develop therapy fidelity, boost motivation, and improve neurodevelopmental task performance for these vulnerable children.

Strengths and limitations

Children with MBID exhibit significant diversity in terms of background and psychosocial characteristics. Moreover, the etiology of the disability can vary widely among children. This diversity, along with a lack of clarity surrounding the underlying causes of IDs, may explain the hesitance among researchers to investigate children with MBID, resulting in a lack of knowledge regarding their neurocognitive abilities and no tailored treatment options. One of the main strengths of this thesis lies in its focus on such a heterogeneous co-morbid patient population, which is highly relevant in clinical practice. This approach helps to fill the gap in the scientific literature on children with MBID and enhances the applicability of the findings to this diverse patient population. By recognizing the importance of studying this population, this thesis aims to improve our understanding of their neurocognitive strengths and weaknesses, the potential benefits of training and the influence of coaching within WMT, which has not been done before in this way. By exploring the impact of coaching on the success of WMT, this thesis offers valuable insights and new perspectives for the practice of WMT in children with MBID and/or neurodevelopmental disorders. Another strength in this thesis lies in its novel approach to understanding similarities within a heterogeneous group. By examining shared underlying neurocognitive differences among children with similar co-morbid diagnoses, rather than focusing solely on clinical observations of their behavior, we gained deeper insights into the underlying causes and shared characteristics of their conditions. This may help to develop more targeted and effective interventions that address the root causes of these conditions, rather than just treating the symptoms.

It is important to consider the limitations of the studies presented in this thesis. First, one of our inclusion criteria was solely based on IQ and did not include adaptive functioning, as the new DSM-V criteria for IDs were released during our research. This limitation means that the full range of (dis)abilities that individuals with MBID possess may not have been fully captured. By relying only on IQ as a criterion for inclusion, some children with slightly above borderline IQ scores but weak adaptive functioning skills may have been wrongfully excluded, while others with low IQ scores but no objectively measured WM difficulties may have been incorrectly included. Another limitation in this thesis is the overall high refusal rate of participation, which lead to restricted sample sizes. The care needs and burdens on families of this patient group may have contributed to this low participation rate, as well as our inability to fully address the needs and preferences of this patient group. Consequently, the possibility of selection bias cannot be dismissed. Also, the

absence of a waiting list control group in the intervention studies is a limitation in this thesis, making it challenging to derive conclusions about the efficacy of the intervention and increasing the likelihood of obtaining false positive results. Van der Molen and colleagues (2010) studied a group of children that was quite similar to our patient group and found only positive effects of WMT in the active training group compared to the waiting list control group, but not compared to a placebo (non-adaptive training) control group.

Directions for future research

It is recommended, based on the findings in this thesis, that future research may clarify what types of children with MBID and co-morbid neurodevelopmental disorders may benefit from individual training. To find out, subtyping can be based on neurocognitive performance, and methods such as multiple N=1 studies can be used (Gagnier et al., 2013). Also, efforts should be made to investigate the impact of individual differences, such as etiology of the disability, environmental and psychosocial determinants and gender, on the effectiveness of training interventions for children with MBID. It is possible that certain subgroups within this heterogeneous population may benefit more from WMT than others, which could help tailor interventions to better meet their needs. Ultimately, this may lead to more effective interventions and improved outcomes for these children.

Future research should also explore how to effectively integrate training into the daily lives of children with MBID and co-morbid neurodevelopmental disorders. For example, the training program could be enhanced with training-related exercises to be performed at home that could improve transfer and generalization effects (Diamond & Lee, 2011). Incorporation of WM tasks in daily life could improve executive functioning and academic performance. Additionally, it would be beneficial to investigate how involving other stakeholders (parents/teachers) and different coaching styles can lead to the implementation of skills learnt from training to daily practice. It is important to note that isolated WM training may not be sufficient for improving executive functioning in daily life. Research suggests that training WM is necessary, but incorporating emotional, social, and physical support, such as through sports, nutrition, and mindfulness, is crucial in creating a healthy and stimulating environment for learning how to deal with daily life events (Diamond & Ling, 2016).

Moreover, it would be of considerable interest to investigate whether processing speed is amenable to training in children with MBID and/or neuro-

developmental disorders and, if so, whether such training yields positive outcomes in terms of long-term cognitive abilities, academic achievements, and/or behavioral improvements. This interest stems from the observation that speed training has been found to impact neural mechanisms and the performance of untrained cognitive measures in adults (Takeuchi & Kawashima, 2012).

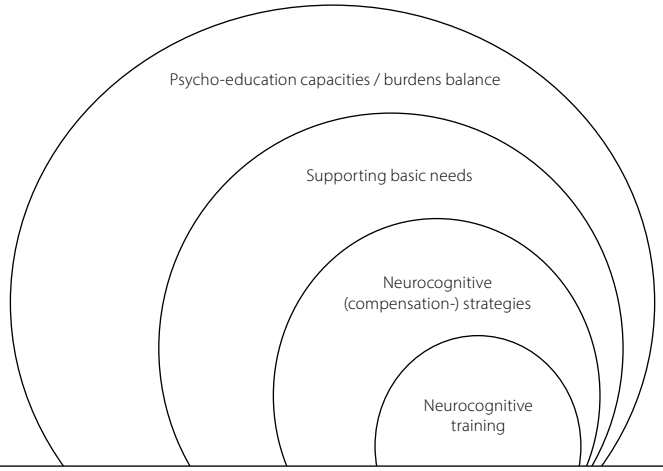
Finally, the cognitive measures utilized in this study are limited and do not encompass all of the cognitive domains that are sensitive to disorder-specific difficulties as noted by Danielsson et al. (2012). Therefore, future studies should consider including additional cognitive measurements to supplement the findings of this study.

Clinical implications

The results of this thesis may have significant implications for clinical practice. One important implication is the need to conduct neuropsychological assessments of children with MBID and co-occurring neurodevelopmental disorders to better understand their learning and behavior problems and to provide tailored intervention recommendations. The present results regarding the cognitive functioning of these children showed that neurocognitive profiles are unique and not necessarily related to IQ or a specific DSM-5 classification. In a sense, behavioral issues act as feedback indicating a discrepancy between the necessary support and adaptations these children require due to their cognitive problems, and the insufficient resources provided by their environment. A more transdiagnostic approach considering neurocognitive strengths and weaknesses serves to illuminate more precisely where the burdens lie. The 'zone of proximal development' by Vygotsky & Cole (1978) is often used to describe what is necessary to effectively assess a child, taking into account their strengths and avoiding overburdening them with tasks that rely too heavily on their weaknesses. By considering a neuropsychological profile of strengths and weaknesses, along with relevant background information and current child and environmental factors, intervention recommendations can be provided.

Layered approach to neuropsychological treatment

Based on the results presented in this thesis and extensive clinical experience, we firmly believe that WMT should never be considered as a standalone intervention in children with MBID and neurodevelopmental disorders. Instead, it should be viewed as an integral part of a "layered" approach to neuropsychological treatment embedded in daily life (see Figure 1). Within each neuropsychological treatment, the central focus revolves around the balance between the child's capacities and burdens. Psychoeducation for the child, parents, and/or school is given related to the child's strengths and weaknesses in neurocognitive functioning, and it is made clear which factors contribute to overburdening and the symptoms (i.e., behavioral manifestations) exhibited by the child when overwhelmed. Concrete strategies should be provided on how to account for a child's weaker neurocognitive skills, such as providing more processing time and less verbal information at once, while maximizing the utilization of their stronger skills, such as reliance on the relatively strong visuospatial aspect, to optimize the learning ability of children with MBID.



In a neuropsychological treatment, there exists a certain layering or hierarchy.
1. Psycho-education capacities / burdens balance. Explanation to parents, teachers, and/or the child regarding the relationship between complaints or behavioural issues in relation to neurocognitive profiles and the call to respond from the environment, providing tools to reduce overburdening.
2. Supporting basic needs. These often involve child-related factors on a somatic level (such as addressing visual and/or hearing problems, conducting diagnostics, and possibly treating illnesses, adjusting medication usage, changing lifestyle habits (sleep quality, nutrition, exercise, screen time), and temporarily eliminating or compensating for environmental stressors (for example, modifying the level, amount, or pace of schoolwork; providing support to the child in carrying out tasks at home).
3. Neurocognitive (compensation-) strategies. Teaching parents, teachers, and/or the child neurocognitive (compensation) strategies to improve functioning and well-being.
4. Neurocognitive training. Repeated and prolonged (often 20 weeks or more) training, e.g. working memory training.

Figure 1: "layered" approach to neuropsychological treatment

In addition, key child and environmental factors that contribute to improvements in the disrupted overburdened balance in the child should be determined. Priority should be given to factors that have the potential to significantly enhance functioning and well-being. These factors may include somatic aspects related to the child, such as addressing vision and/or hearing issues, diagnosing and potentially treating co-occurring somatic problems, adjusting medication use and/or improving lifestyle factors, such as sleep quality, nutrition, physical activity, and screen time. They can also involve eliminating or compensating for environmental stressors, for example, adjusting educational settings (modifying level, amount, and/or pace of schoolwork) or providing more support in the home environment for specific tasks (Dawson & Guare, 2019).

Subsequently, the consideration is given to whether teaching neuro-cognitive (compensatory) strategies, either alone or in combination with strengthening specific neurocognitive skills through training, e.g., WMT, can improve functioning and well-being and prevent any possible further asymmetrical development. The preferences and abilities of the child, parents/care takers, and/or teachers should be taken into account in this process.

Considering all of the aforementioned points, it is crucial to incorporate interventions that target basic neurocognitive skills in an easily accessible and low-threshold way to empower the potential of children with MBID. Creating a positive learning environment, for example through WMT with low-intensity (regular, structured and structural) coaching that fosters engagement, motivation, and self-regulation is of the utmost importance. Through repeated practice and mastery of these tasks, these children may develop a sense of their own capabilities and foster a growth mindset based on the experience of perseverance (Verberg et al., 2019), ultimately empowering the child's sense of capability and enhancing their self-confidence and self-esteem.

It may be advantageous for special education schools to place greater emphasis on the underlying factors of learning difficulties, such as WM problems and WMT, as such programs can support the conditions for learning and empower these vulnerable children, potentially leading to greater progress during their educational journey.

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Nederlandse samenvatting

Kinderen met een licht verstandelijke beperking (LVB) vertonen vaak een heterogeen beeld wat betreft gedragsproblemen en praktische- en neurocognitieve vaardigheden. Sinds de invoering van de DSM-5 is bij de classificatie van een LVB het belang van het klinisch oordeel toegenomen, wat het classificeren ervan complex en uitdagend maakt. Volgens de DSM-5 wordt een verstandelijke beperking gekenmerkt door een IQ-score lager dan 70, in combinatie met adaptieve problemen. Het ernstniveau (licht, matig, ernstig) van een verstandelijke beperking wordt bepaald aan de hand van het adaptief vermogen en is niet langer meer uitsluitend gebaseerd op de IQ-score. Dit komt doordat het niveau van ondersteuning bepaalt wat nodig is in het dagelijks functioneren en/of de vereiste zorg. Hierdoor is de afhankelijkheid van IQ-scores verminderd, en wordt het belang van het klinisch oordeel benadrukt. Adaptieve problemen omvatten: (1) conceptuele vaardigheden, zoals lezen, schrijven en rekenen, (2) sociale vaardigheden, zoals communicatie en het aangaan van vriendschappen, en (3) praktische vaardigheden, zoals persoonlijke verzorging en gebruik van openbaar vervoer.

In Nederland kunnen zwakbegaafde kinderen met een IQ-score tussen 70 en 85, die ook te maken hebben met (ernstige) bijkomende problemen, gebruikmaken van zorg voor kinderen met een LVB. Dit beleid is ingesteld omdat deze vorm van zorg vaak de meest passende ondersteuning biedt. Derhalve hanteren we in dit proefschrift een bredere definitie voor LVB, waarbij kinderen met een IQ lager dan 85 met bijkomende adaptieve problemen worden opgenomen (LVB en zwakbegaafdheid samen). In Nederland wordt geschat dat er meer dan 1 miljoen mensen zijn met een IQ tussen 50 en 85 en bijkomende problemen, waarvan ongeveer 11.000 kinderen en jongeren die zich in ernstige situaties bevinden, zoals schooluitval, slachtoffer zijn van seksuele en criminele uitbuiting, (gedwongen) opnames, veelal met ernstige gedragsproblemen tot gevolg.

Bij kinderen met een LVB manifesteren zich diverse tekortkomingen in het neurocognitief functioneren. Dit fenomeen wordt deels verklaard doordat de oorzaken van de verstandelijke beperking sterk verschillen tussen individuen. Sommige kinderen met een LVB hebben onderliggend genetische aandoeningen die invloed uitoefenen op hun neurocognitieve ontwikkeling, terwijl anderen hersenletsel hebben opgelopen of infecties tijdens hun ontwikkeling hebben doorgemaakt. Daarnaast worden omgevings- en psychosociale factoren beschouwd als significante risicofactoren voor een LVB.

Gezien de complexiteit en variabiliteit van de factoren die bijdragen aan een LVB is het niet verrassend dat kinderen met een LVB, ondanks vergelijkbare IQ-scores, uiteenlopende neurocognitieve profielen vertonen en een verhoogd

risico lopen op het ontwikkelen van bijkomende neurobiologische ontwikkelingsstoornissen. De diversiteit in neurocognitieve beperkingen en symptoommanifestatie maakt het uitdagend om gedeelde onderliggende factoren binnen deze klinisch heterogene groep te identificeren. Desondanks zou het identificeren van gedeelde factoren kunnen bijdragen aan beter begrip van het gedrag van deze kinderen.

In de klinische praktijk vertonen kinderen met een LVB, al dan niet in combinatie met een bijkomende neurobiologische ontwikkelingsstoornis, vaak een breed scala aan gedragsmatige, adaptieve en onderwijsproblemen. Zij vormen een aanzienlijke belasting voor het geestelijke gezondheidszorgsysteem.

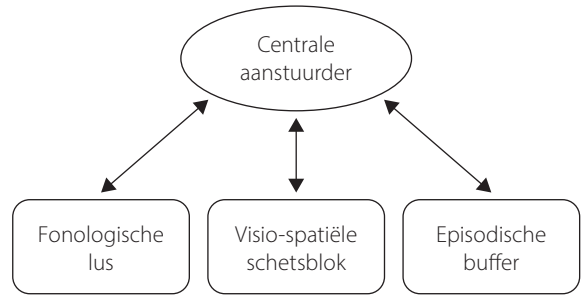
Dit proefschrift beschrijft onderzoek naar neurocognitieve kenmerken van kinderen met een LVB, al dan niet in combinatie met een ontwikkelingsstoornis. Meer specifiek richt het onderzoek zich op werkgeheugencapaciteiten en de trainbaarheid hiervan bij kinderen met een LVB en aandachtstekortstoornissen met hyperactiviteit (ADHD), een autisme spectrum stoornis (ASS) en/of leerstoornissen zoals dyslexie. Hierbij is ook onderzocht hoe de neurocognitieve kenmerken zich verhouden tot gedrag en wat de invloed is van coaching tijdens werkgeheugentraining.

Werkgeheugen

Het werkgeheugen wordt vaak geïdentificeerd als een neurocognitieve zwakte bij kinderen met diverse neurobiologische ontwikkelingsstoornissen, zoals een verstandelijke beperking, ADHD, ASS en/of specifieke leerstoornissen zoals dyslexie. Deze tekorten worden geassocieerd met problemen in adaptief gedrag, schoolse- en sociale vaardigheden. Hoewel er meerdere werkgeheugenmodellen bestaan, is dat van Baddeley het meest gangbaar in wetenschappelijk onderzoek (zie Figuur 1).

Volgens dit model is het werkgeheugen opgedeeld in vier componenten: (1) Het visuo-spatiële schetsblok en (2) de fonologische lus zijn respectievelijk verantwoordelijk voor de tijdelijke opslag van visuo-spatiële en verbale informatie, ook wel visuo-spatieel kortetermijngeheugen en verbale kortetermijngeheugen genoemd. De fonologische lus heeft tevens als functie om binnengekomen informatie automatisch te herhalen om verlies te voorkomen. Beide van deze 'slaafsystemen' worden aangestuurd door (3) de centrale aanstuurder, een aandachts- en controlesysteem. Taken die zowel het kortetermijngeheugen als de centrale aanstuurder aanspreken, worden werkgeheugentaken genoemd.

De episodische buffer (4), ook aangestuurd door de centrale aanstuurder, kan geïntegreerde informatie uit verschillende modaliteiten (zowel verbaal als visueel), afkomstig van zowel het langetermijngeheugen als het kortetermijngeheugen, opslaan.



Figuur 1: Baddeley's werkgeheugenmodel (Baddeley, 2000a)

Resultaten

Neurocognitief functioneren

In de eerste studie, zoals beschreven in hoofdstuk 2, is een systematische literatuurreview uitgevoerd om een dieper inzicht te verkrijgen in de sterke en zwakke kanten van het werkgeheugen bij kinderen met een LVB. Deze review vergeleek de werkgeheugenprestaties van kinderen met een LVB in de leeftijd van 4 tot 18 jaar met die van gemiddeld ontwikkelende kinderen van dezelfde chronologische leeftijd en met die van gemiddeld ontwikkelende jongere kinderen met dezelfde mentale leeftijd.

De bevindingen tonen aan dat kinderen met een LVB een lagere verbale en visueel-ruimtelijke capaciteit van het werkgeheugen hebben in vergelijking met gemiddeld ontwikkelende kinderen van dezelfde chronologische leeftijd. Bij kinderen met een IQ lager dan 70 waren de scores op zowel verbale als visueel-ruimtelijke werkgeheugentaken zwakker dan bij zwakbegaafde kinderen (IQ 70 – 85). Zowel kinderen met een IQ lager dan 70 als zwakbegaafde kinderen laten een zwakte zien op het gebied van verbaal werkgeheugen in vergelijking met hun leeftijdsgenoten, terwijl visueel-ruimtelijk werkgeheugen een sterkte lijkt te zijn voor zwakbegaafde kinderen, mogelijk gerelateerd aan hun intellectuele functioneren.

Bovendien vertonen kinderen met een LVB verschillen in verbale werkgeheugenprestaties in vergelijking met jongere, gemiddeld ontwikkelende

kinderen met dezelfde mentale leeftijd. Als de mentale leeftijd van kinderen met een LVB lager is dan 7 jaar (ongeacht de chronologische leeftijd), presteren ze zwakker op verbale werkgeheugentaken in vergelijking met een controlegroep met dezelfde mentale leeftijd. Echter, wanneer hun mentale leeftijd boven de 7 jaar ligt, is hun verbale werkgeheugenprestatie vergelijkbaar met die van gemiddeld ontwikkelende kinderen van zeven jaar. In tegenstelling tot het verbale werkgeheugen lijkt visueel-ruimtelijk werkgeheugen bij kinderen met een LVB consistent met hun mentale leeftijd en is het een relatieve sterkte.

In de tweede studie, beschreven in hoofdstuk 3, worden de resultaten van een latente profielanalyse onderzocht in een klinische steekproef van kinderen tussen de 10 en 14 jaar oud met een LVB en een neurobiologische ontwikkelingsstoornis (ADHD en/of ASD). Deze analyse levert een oplossing op waarin drie cognitieve profielen worden geïdentificeerd, gekenmerkt door verschillen in de snelheid-nauwkeurigheidsverhouding en cognitieve prestaties.

Profiel 1, bestaande uit 70% van de deelnemers, wordt omschreven als een "hoge nauwkeurigheid-hoge snelheid" subgroep, gekenmerkt door een relatief evenwichtige verhouding tussen snelheid en nauwkeurigheid, evenals relatief hoge scores op zowel cognitieve als schoolse prestatietaken. Profiel 2, dat 21% van de steekproef vertegenwoordigt, wordt omschreven als een "hoge nauwkeurigheid-lage snelheid" subgroep en kenmerkt zich door een lage snelheid en een relatief hoge nauwkeurigheid, evenals middelmatige scores op cognitieve en schoolse prestatietaken. Tenslotte wordt profiel 3, dat 9% van de steekproef omvat, omschreven als een "instabiele nauwkeurigheid/snelheid" subgroep. Deze subgroep heeft een instabiele balans tussen snelheid en nauwkeurigheid van werken, samen met lage scores op zowel cognitieve als schoolse prestatietaken.
Ondanks deze unieke cognitieve profielen met variërende niveaus van prestaties op zowel cognitieve als schoolse prestatietaken, vertonen de groepen geen verschillen in de ernst van ADHD-symptomen, sociaal gedrag of dagelijkse ervaren problemen met de uitvoerende functies.

Trainbaarheid

Hoofdstuk 4 beschrijft een naturalistische, open-label, niet-gerandomiseerde gecontroleerde interventiestudie die de effecten van werkgeheugentraining onderzoekt bij verschillende groepen kinderen in de leeftijd van 7 tot 17 jaar met neurobiologische ontwikkelingsproblemen, waaronder ADHD, leerstoornissen (zoals dyslexie) of leerproblemen. Deze studie toont een significant hoofdeffect met kleine tot matige effectgroottes op symptomen van onoplettendheid, symptomen van hyperactiviteit/impulsiviteit, algemene problemen met de uitvoerende functie, en een grote effectgrootte voor werkgeheugencapaciteit. De resultaten suggereren dat alle groepen (ADHD, leerstoornissen en

leerproblemen) baat hebben bij de training. Ook laten significante interactie-effecten met kleine effectgroottes zien dat kinderen met leerstoornissen minder profiteren van de training wat betreft symptomen van hyperactiviteit/impulsiviteit en algemene problemen met de uitvoerende functie, in vergelijking met kinderen met ADHD. Ten slotte profiteren alle groepen in gelijke mate van de training met betrekking tot aandachtsproblemen en werkgeheugencapaciteit.

In hoofdstuk 5 worden de resultaten gepresenteerd van een triple-blinde, placebo-gecontroleerde, gerandomiseerde klinische studie. Het doel van deze studie is om te onderzoeken of adaptieve werkgeheugentraining leidt tot significantere verbeteringen op een niet-getrainde visueel-ruimtelijke werkgeheugentaak in vergelijking met een niet-adaptieve (placebo) werkgeheugentraining bij zwakbegaafde kinderen (10-14 jaar; 70 < IQ < 85) en neuropsychiatrische stoornissen (ADHD en/of ASD). De analyse levert geen superieure trainingsresultaten op over de tijd voor adaptieve werkgeheugentraining in vergelijking met placebo (niet-adaptieve) werkgeheugentraining wat betreft werkgeheugenprestaties of gedragsmaten. Ook worden geen verschillen gezien op taken die sterk verwant zijn aan de oorspronkelijke trainingstaken, of taken die een beroep doen op het vermogen om de geleerde vaardigheden toe te passen op taken die minder direct verwant zijn aan de oorspronkelijke trainingstaken. Wel worden tijdseffecten waargenomen voor zowel de experimentele als de placebogroep, wat suggereert dat kinderen met aanhoudende beperkingen in het werkgeheugen mogelijk baat hebben bij een gestructureerde leeromgeving, geassocieerd met verbetering van neurocognitieve functies en copingstrategieën.

Hoofdstuk 6 rapporteert de resultaten van een dubbelblinde, gerandomiseerde gecontroleerde studie naar de effectiviteit van een minder intensieve versie van Cogmed werkgeheugentraining met gepersonaliseerde coaching en feedback in vergelijking met een vergelijkbare versie zonder gepersonaliseerde coaching en feedback bij kinderen (10-14 jaar) met neurobiologische ontwikkelingsstoornissen (ADHD en/of ASS) en een LVB (60 < IQ < 85). Uit de resultaten blijkt dat beide groepen verbeteringen laten zien in werkgeheugencapaciteit en andere uitkomsten (uitvoerende functies, schoolse prestatietaken en gedragsmaten). Er is geen significant verschil tussen beide groepen. Dit suggereert dat regelmatig, gestructureerd en consistent contact met een coach en aangepaste oefeningen voldoende zijn om therapietrouw te ontwikkelen, motivatie te stimuleren en de uitvoering van neurocognitieve taakprestaties te verbeteren bij deze kwetsbare kinderen.

Algemene conclusies van dit proefschrift

Het visueel werkgeheugen is over het algemeen een relatief sterke kant bij de gehele groep kinderen met een LVB, wanneer ze worden vergeleken met gemiddeld ontwikkelende kinderen met dezelfde (mentale) leeftijd. Het verbaal werkgeheugen vormt daarentegen een kernprobleem bij deze kinderen. Echter, binnen de groep kinderen met een LVB en neurobiologische ontwikkelingsstoornissen (ADHD en/of ASS), kunnen drie verschillende cognitieve subgroepen worden geïdentificeerd. Hierbij draagt een combinatie van verschillen in balans tussen snelheid en nauwkeurigheid van werken en het vermogen (of onvermogen) om effectieve copingstrategieën toe te passen bij aan de variatie in werkgeheugenproblemen, maar niet aan de ernst van gedragsproblemen.

Het bewijs voor de effectiviteit van werkgeheugentraining ter verbetering van cognitieve, schoolse en gedragsmaten bij kinderen met een LVB en/of neurobiologische ontwikkelingsstoornissen is nog niet overtuigend. Desalniettemin moet niet direct de conclusie worden getrokken dat werkgeheugentraining niet moet worden toegepast bij deze kinderen. Alle drie de interventiestudies hebben een verbetering in werkgeheugencapaciteit laten zien, wat suggereert dat deze kwetsbare kinderen in staat zijn hun werkgeheugencapaciteit te verbeteren door training. Belangrijk is om factoren zoals de intensiteit van de training en coaching mee te nemen, omdat een hogere intensiteit (van training en/of coaching) niet significant bijdraagt aan de effectiviteit van werkgeheugentraining. Hierbij moet rekening worden gehouden met het feit dat deze kinderen bijzonder kwetsbaar zijn in situaties met een hoge cognitieve belasting, omdat ze sneller gevoelens van onbekwaamheid ervaren in vergelijking met gemiddeld ontwikkelende leeftijdsgenoten en er een risico op overbelasting bestaat.

Het creëren van een gestructureerde leeromgeving en een goede werkrelatie met de behandelaar kan het neurocognitief functioneren van deze kinderen verbeteren en hen helpen bij het ontwikkelen van copingstrategieën zoals doorzettingsvermogen en frustratietolerantie. Daarnaast kunnen de heterogeniteit binnen de onderzoekspopulatie en de mogelijke invloed van de individuele ernst en/of co-morbiditeit van de neurobiologische ontwikkelingsstoornis(sen) invloed hebben op de effectiviteit van werkgeheugentraining. Met name kinderen met mildere stoornissen lijken meer baat te hebben bij de training. Tenslotte lijken er geen langdurige effecten van werkgeheugentraining op te treden op gedragsniveau. Dit kan wijzen op een discrepantie tussen de ondersteuning en aanpassingen die nodig zijn vanwege neurocognitieve problemen en de onvoldoende ondersteuning of compensatie die wordt geboden door de omgeving. Daarom kan het uitvoeren van neuropsychologisch onderzoek nuttig zijn bij het maken van passende behandelaanpassingen op basis van de individuele behoeften van het kind.

Gebaseerd op de resultaten in dit proefschrift en uitgebreide klinische ervaring, is de sterke overtuiging dat werkgeheugentraining nooit als een op zichzelf staande interventie moet worden beschouwd voor kinderen met een LVB, al dan niet met bijkomende neurobiologische ontwikkelingsstoornissen. Het moet worden gezien als een integraal onderdeel van een "gelaagde" benadering van neuropsychologische behandeling die is geïntegreerd in het dagelijks leven. Hierbij moet steeds opnieuw worden overwogen of het aanleren van neurocognitieve (compenserende) strategieën, alleen, of in combinatie met het versterken van specifieke neurocognitieve vaardigheden door training, de functie en het welzijn kan verbeteren en verdere asymmetrische ontwikkeling kan beperken.

Appendix I: Research data management

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles and we adhered to CONSORT guidelines. The paragraphs below specify in detail how this was achieved.

Ethics

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. All participants were tested with research protocols that were approved by the local ethics committee CMO Arnhem-Nijmegen, registered under NL32435.091.10. and NL52647.091.15 and are also registered in the Dutch Trial Register, numbers NL2798 and NTR5223.

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Findable, Accessible

Electronic data of the studies is stored at the secure servers/network drives of Karakter. Informed consent was obtained on paper following the procedures of the Ethics Committee. Paper data is stored at the central archive of Karakter. All research data remains available for at least 10 years after termination of the studies.

Interoperable, reusable

A description of the intervention protocol can be found in the published protocol paper in *BMC Psychiatry* (Roording-Ragetlie et al., 2017). The raw data and the analysis scripts are stored on the secure Karakter server. The final dataset will not be available to other researchers at the end of the study.

Privacy

The privacy of the participants in this thesis has been warranted using encrypted and unique individual subject codes. This code corresponds with the code used in the patient report forms. Code lists are stored separately from the research data. Documents are stored at the secure directory networks of Karakter and are only accessible to members of the project.

Appendix II: Curriculum vitae

Sammy Roording-Ragetlie was born on December 26, 1977, in Doorn, The Netherlands. She completed her pre-university education at St. Willibrordus Gymnasium, Deurne (1996) and obtained a Bachelor's degree in child psychology at Leiden University (1998). In addition, she enrolled in a Honours Class in Cognitive Neuroscience at Leiden University and completed a Master's degree in child neuropsychology at the Free University in Amsterdam (2001). During this period, she conducted a clinical internship at the Psychosocial Department of the Emma Children's Hospital, Academic Medical Center, Amsterdam. Her master's thesis examined the effect of Methylphenidate on the inhibitory capacity and behavior of children with ADHD, for which she won the Professor Dr. D.J. Bakker Master Thesis Prize in Clinical Neuropsychology in 2001. After a 4-month work experience opportunity at the School Support Service (Sentro pa Guia Edukashonal) in Curaçao, followed by a backpacking adventure for 7 months through South America, she worked as a neuropsychologist at Stichting Kinder- en Jeugd Psychiatrie Oost-Nederland (SKJPON), now known as Karakter. Her specialization involved neuropsychological assessment and treatment of children with intellectual disabilities and psychiatric disorders. In 2005 and 2006, she obtained her post-master's degree as a healthcare psychologist at Karakter. In 2008, she enrolled in a specialized postgraduate residency in clinical neuropsychology. As part of this education program, she conducted a scientific study that formed the basis of her present thesis. She was registered as a certified clinical neuropsychologist in 2013. In 2015, Sammy officially started her PhD research at Karakter in collaboration with Radboud University Medical Center. During this time, she combined research with clinical work, innovative projects and was involved as a supervisor practitioner in various postgraduate education programs. She became co-author of an online blended psycho-education module for adolescents and their parents called "Straatwijzer" (Streetwise) about intellectual disability and psychiatric disorders. This module was nominated for the Jan van der Kruis Innovation Award in 2017 and won the Karakter Knowledge Award in 2018. In 2022, Sammy's work expanded as a project leader at the Academic Workplace Kajak, bridging between the knowledge center for child and adolescent psychiatry and the knowledge center for people with intellectual disabilities.

Appendix III: Publications

International papers

Roording-Ragetlie S., Pieters, S., Wennekers, E., Klip H., Buitelaar J., Slaats-Willemse D. (2023). Working memory training in children with neurodevelopmental disorders and intellectual disabilities, the role of coaching; a double-blind randomized controlled trial, *Journal of Intellectual Disabilities Research*, *67* (842-859).

Roording-Ragetlie S., Spaltman M., de Groot E., Klip H., Buitelaar J., Slaats-Willemse D. (2022). Working memory training in children with borderline intellectual functioning and neuropsychiatric disorders: a triple-blind randomised controlled trial. *Journal of Intellectual Disabilities Research*, *66* (178-194).

Santegoeds E., van der Schoot E., **Roording-Ragetlie S.**, Klip H., Rommelse N. (2021). Neurocognitive functioning of children with mild to borderline intellectual disabilities and psychiatric disorders: profile characteristics and predictors of behavioural problems. *Journal of Intellectual Disabilities Research*, *66* (162-177).

Roording-Ragetlie S., Slaats-Willemse D., Buitelaar J., Van der Molen M.J. (2018). Working memory in children with mild to borderline intellectual disabilities: A systematic review of strengths and weaknesses. *Journal of Child Psychology*, 2 (16-22).

Roording-Ragetlie S., Klip H., Buitelaar J., Slaats-Willemse D. (2017). Working memory training in children with neuropsychiatric disorders and mild to borderline intellectual functioning, the role of coaching; a double-blind randomized controlled trial (study protocol). *BMC Psychiatry 17*:114.

Roording-Ragetlie, S., Klip, H., Buitelaar, J., Slaats-Willemse, D. (2016). Working Memory Training in Children with Neurodevelopmental Disorders. *Psychology, 7,* (310-325).

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Roording, S. (2023). De onzichtbare beperking. Waarom het (her)kennen van het onbekende cruciaal is. Column in; *LVB Onderzoek en Praktijk, 1* (24-25).

Spaltman, M., Mulder, M. A., van 't Hof, C., Slot, D., Jeunet, N., **Roording-Ragetlie, S.** (2021). Psycho-educatie bij mensen met een licht verstandelijke beperking: Het digitale spectrum. *Tijdschrift Onderzoek en Praktijk / Publicatieplatform LVB en de digitale wereld, Landelijk Kenniscentrum LVB*.

Roording-Ragetlie, S., Groen, W., de Bildt, A (2020). Rosa en de verandering in denken over een verstandelijke beperking. *Kind en Adolescent, 41* (254-257).

Spaltman M., & **Roording-Ragetlie, S.** (2019). LVB jongeren met stoornis aan meer zelfinzicht helpen. Studie naar blended psycho-educatie module "Straatwijzer". *Kind & Adolescent Praktijk, 4 (*6-14).

Book (chapters)

Rommelse, N., Slaats, D., Ponsioen, A., **Roording, S.**, Oostrom, K., Hendriks, M., Tjeenk-Kalff, A. (Red.), (in press). *Casusboek kinderneuropsychologie*. Uitgeverij Boom.

Rommelse, N., Hendriks, M., Slaats, D., Ponsioen, A., **Roording, S.**, Oostrom, K., Tjeenk-Kalff, A. (in press). Hoofdstuk 1: Klinisch neuropsychologische diagnostiek en behandeling bij kinderen en jeugdigen. *Casusboek kinder-neuropsychologie*. Uitgeverij Boom.

Van der Waa, A. **Roording, S.** (in press). Hoofdstuk 19: Jayden: hoe kunnen we de regressie in functioneren snappen en wat heeft hij nodig? *Casusboek kinderneuropsychologie*. Uitgeverij Boom.

Rommelse, N., Tjeenk-Kalff, A**., Roording-Ragetlie, S.**, Luman, M., (2021). Hoofdstuk 32: Focus op neurocognitieve processen. Indicaties voor klinisch neuropsychologisch onderzoek binnen de specialistische jeugd GGZ. *Handboek Kinder- en Jeugdpsychiatrie: Probleemgeoriënteerd werken met kinderen, adolescenten en ouders (Staal e.a.).* Uitgeverij Boom

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Online modules

Van den Bogaart, M., Appelboom, K., Sauter, F., Boven, S., van Wijk, M. Groen, W., **Roording-Ragetlie S.** (2023): E-learning CGT bij jeugdigen met een LVB en een psychische stoornis. Academische werkplaats Kajak, Utrecht. https://ggzecademy.nl/product/cgt-bij-jeugdigen-met-een-LVB-en-een-psychische-stoornis

Roording-Ragetlie S., van der Waa, A., Verlinden, D., Zwaanswijk, M., Kok, L. (2015). Straatwijzer: Blended psycho-educatie module over LVB en psychiatrische stoornissen voor jongeren en hun ouders. Jouw Omgeving, Utrecht. https://www.jouwomgeving.nl/nieuws/2015/8/13/wijzer-de-straat-op/

Appendix IV: Portfolio

Presentaties congressen

Roording-Ragetlie, S. Herkennen van problematiek. Spreker Landelijke studiedag LVB en Psychiatrie, Leids Congres Bureau, 18 juni 2024, Aristo Amsterdam.

Santegoeds, E., van der Waa, A., **Roording-Ragetlie, S.** De rol van de neuropsychologie bij kinderen en jongeren met LVB: diagnostiek en behandeling op maat vanuit een neuropsychologisch perspectief. Symposium Jaarcongres Klinisch Psychologen en Klinisch Neuropsychologen (Stichting WKK), 18-19 april 2024, Hotel Zuiderduin, Egmond aan zee.

Oostrom, K., Tjeenk, A., Lambregts-Rommelse, N., Ponsioen, A., **Roording-Ragetlie, S**. Wat nou … neuropsychologische behandeling voor kind of jongere? Symposium Jaarcongres Klinisch Psychologen en Klinisch Neuropsychologen (Stichting WKK), 18-19 april 2024, Hotel Zuiderduin, Egmond aan zee.

Roording-Ragetlie, S. Herkennen van een licht verstandelijke beperking (LVB). Spreker Op de Sofa; omgaan met dilemma's in de kinder- en jeugdpsychiatrie, 23 september 2023, Carlton President, Utrecht.

Heinemann, A., Santegoeds, E., Bouwman, S., Hochstenbach, B., **Roording-Ragetlie, S.** Transdiagnostic factors in mental health care for youth with MBID. Round table discussion European Association for Mental Health in Intellectual Disability (EAMHID), 21-23 september 2023, Helsinki, Finland.

Roording-Ragetlie, S., Wolthuis, K., Jeunet, N., Ezendam, M. De (on)zin van psycho-educatie over LVB bij jongeren, hun ouders en (jong)volwassenen. Workshop Studiedag Academische Werkplaats Kajak, 8 juni 2023, Postillion Hotel, Bunnik.

Roording-Ragetlie, S. Blik op recente ontwikkelingen. Spreker Landelijke studiedag LVB en Psychiatrie, Leids Congres Bureau, 8 maart 2022, Aristo Amsterdam.

Roording-Ragetlie, S. Digitale psycho-educatie voor jongeren met een licht verstandelijke beperking en bijkomende psychiatrische problemen en voor hun ouders. Spreker Congres Jeugd in Onderzoek, 8 april 2021, Online Congres.

Roording-Ragetlie, S. Executieve functies bij kinderen en jongeren met LVB**.** Spreker congres kinderen met bijzondere breinen, 11 Congressen 2021, Online congres.

Roording-Ragetlie, S. Sterkte- en zwakteprofielen bij LVB. Spreker congres kinderen met bijzondere breinen 11 Congressen 2020, Beatrix theater Utrecht.

Roording-Ragetlie, S. ADHD bij LVB. Workshop congres psychiatrie en LVB, Werken aan samenspel, Academische werkplaats Kajak, 17 mei, 2018, Muntgebouw Utrecht.

Roording-Ragetlie, S., van der Waa, A., Zwaanswijk, M. Straatwijzer, een online psycho-educatie module voor jongeren (>12 jaar) en hun ouders over een licht verstandelijke beperking en psychiatrische stoornissen. Workshop congres van Wijk tot Wetenschap, 23 november 2017, Den Bosch.

Roording-Ragetlie, S., Klip, H., Buitelaar, D. Slaats-Willemse. Working memory training in children with neuropsychiatric disorders with or without borderline intellectual disabilities. Symposium European Society for Child and Adolescent Psychiatry (ESCAP)**,** 20-24 June 2015, Madrid.

Hochstenbach, B., Schuur, M., **Roording-Ragetlie, S.**, de Bourgraaf, A., Simons, M. Treatment of Mental Disorders in Children and Adolescents With Mild to Moderate Learning Disability. Workshop European Association for Mental Health in Intellectual Disability (EAMHID) 12-14 september 2013, Lisbon.

Geaccrediteerde bijscholing (127 uur)

08-06-2023: AW Kajak Studiedag Kinder- en jeugdpsychiatrie & LVB: Passende Perspectieven (ID nummer: 508827, 6 punten).

26-04-2023: Scientific Integrity Course, Donders Graduate School (7 punten).

08-11-2022: Seminar Kinder- en Jeugdpsychiatrie Karakter (ID nummer: 486717, 4 punten).

24-10-2022: (Be)handelen volgens de Wet verplichte ggz (ID nummer: 476291, 4 punten).

16-02-2022: Nascholing psychiatrie 16 februari 2022 (ID nummer: 456498, 2 punten).

22-06-2021: Seminar Kinder- en Jeugdpsychiatrie Karakter (ID nummer: 432730, 6 punten).

06-11-2020: Symposium Gedragsneurologie van het kind in ontwikkeling (ID nummer: 404284, 6 punten).

18-03-2020: Privacy en informatieveiligheid (ID nummer: 343083, 1 punt).

14-11-2019: Kinderen met bijzondere breinen 2019 (ID nummer: 375135, 7 punten).

07-11-2019: Seminar Kinder- en Jeugdpsychiatrie Karakter (ID nummer: 377839, 6 punten).

26-09-2019: COTAPP 1-daagse workshop basisrapportage (ID nummer: 370839, 7 punten).

02-07-2019: ESCAP Congres, Oostenrijk (27 punten).

25-06-2019: Seminar Kinder- en Jeugdpsychiatrie Karakter (ID nummer: 365781, 6 punten).

12-04-2019: 11e Jaarcongres voor klin. psychologen en klin. neuropsychologen: Thema: "Seksualiteit" (ID nummer: 354503, 6 punten).

05-04-2019: Voorjaarsconferentie 2019 Nederlandse Vereniging voor Neuropsychologie (NvN) (ID nummer: 357185, 7 punten).

23-11-2018: Seminar Kinder- en Jeugdpsychiatrie Karakter (ID nummer: 340100, 5 punten).

28-09-2018: Dag van Intelligentie (ID nummer: 331780, 4 punten).

03-09-2018: Gegeven bij- en nascholing, Lesgeven aan de KNP opleiding (ontwikkelingsstoornissen – LVB, 9 punten).

28-06-2018: Seminar Kinder- en Jeugdpsychiatrie Karakter (ID nummer: 325349, 4 punten).

17-05-2018: Congres Psychiatrie en LVB: werken aan samenspel (ID nummer: 317652, 3 punten).

Appendix V: Acknowledgements (dankwoord)

En dan... is het afgerond. Met lichte verbazing en een vleugje ongeloof, begin ik dit dankwoord. Het is een enorm leerzaam, uitdagend maar vooral ook leuk traject geweest om dit proefschrift te schrijven. Vastberadenheid, een overdosis doorzettingsvermogen en een lange adem hebben tot dit eindresultaat geleid. Zonder de steun van velen om mij heen zou ik deze taak echter nooit hebben kunnen volbrengen. Mijn oprechte dank gaat dan ook uit naar eenieder die deel uitmaakte van deze academische achtbaan. Jullie hebben mijn leven verrijkt met kennis en wijsheid, mijn koffieconsumptie verveelvoudigd en een mentale meltdown voorkomen.

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Appendix V: Acknowledgements (dankwoord)

Appendix VI: Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

The DGCN tracks the career of PhD graduates carefully. More than 50% of PhD alumni show a continuation in academia with postdoc positions at top institutes worldwide, e.g. Stanford University, University of Oxford, University of Cambridge, UCL London, MPI Leipzig, Hanyang University in South Korea, NTNU Norway, University of Illinois, North Western University, Northeastern University in Boston, ETH Zürich, University of Vienna etc.. Positions outside academia spread among the following sectors: specialists in a medical environment, mainly in genetics, geriatrics, psychiatry and neurology. Specialists in a psychological environment, e.g. as specialist in neuropsychology, psychological diagnostics or therapy. Positions in higher education as coordinators or lecturers. A smaller percentage enters business as research consultants, analysts or head of research and development. Fewer graduates stay in a research environment as lab coordinators, technical support or policy advisors. Upcoming possibilities are positions in the IT sector and management position in pharmaceutical industry. In general, the PhDs graduates almost invariably continue with high-quality positions that play an important role in our knowledge economy.

For more information on the DGCN as well as past and upcoming defenses please visit: **http://www.ru.nl/donders/graduate-school/phd/**