Cognition and comorbidity in ADHD: The role of methylphenidate and development
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CHAPTER 1

GENERAL INTRODUCTION
PREVALENCE AND IMPLICATIONS OF ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurobiological developmental disorder defined by age-inappropriate behavioural characteristics of inattention, hyperactivity and/or impulsivity, with childhood onset (Diagnostic and Statistical Manual of Mental Disorders [DSM-IV text rev.]; American Psychiatric Association [APA], 2000). In order to meet DSM-IV defined criteria for ADHD, at least six persistent symptoms of inattention and/or hyperactivity/impulsivity should be present before the age of seven years, occurring in multiple settings, and causing significant impairment in school/work or social situations. With approximately 5 to 9 percent of children meeting diagnostic criteria, ADHD is the most prevalent psychiatric disorder in childhood (Akinbami, Liu, Pastor, & Reuben, 2011; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007).

Studies on the outcome of individuals with ADHD have revealed a higher risk of academic underachievement, social and financial problems, self-esteem, psychiatric comorbidity, traffic accidents, drug abuse, and criminal activities (Barkley, Fischer, Smallish, & Fletcher, 2002; Faraone & Biederman, 2005; Frederiksen et al., 2014; Hesson & Fowler, 2015; Koisaari et al., 2015; Mannuzza, Gittelman Klein, & Addalli, 1991). Regarding psychiatric comorbidity, levels of depression and anxiety and the risk of a lifetime comorbid diagnosis are significantly higher in individuals with ADHD relative to typically developing (TD) individuals (Biederman et al., 2006; Blackman, Ostrander, & Herman, 2005; Chronis-Tuscano et al., 2010; Guttmann-Steinmetz, Gadow, DeVincent, & Crowell, 2010; Larson, Russ, Kahn, & Halfon, 2011; Roy, Oldehinkel, Verhulst, Ormell, & Hartman, 2014). As onset of internalizing problems generally follows onset of ADHD, depression and anxiety comorbidity is hypothesized to follow from both shared genetic components (Biederman et al., 1992; Cole, Ball, Martin, Scourfield, & McGuffin, 2009), and negative environmental interactions, as after a history of failure and punishment, more depressive symptoms develop (Ostrander & Herman 2006; Schatz & Rostain, 2006). Hence, individuals with ADHD may encounter functional challenges across many domains.

Whereas ADHD was once assumed to be a childhood disorder, persistence of ADHD into adulthood has consistently been addressed in the past two decades (Biederman et al., 1996a, Biederman, Petty, Clarke, Lomadico, & Faraone, 2011a; Faraone, Biederman, & Mick, 2006; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Simon, Bélint, Meszáros, & Bitter, 2009). The average cross-national prevalence of adult ADHD was estimated at 3.4 percent (1.2 - 7.3 percent; Fayyad et al., 2007), and at 2.8 percent in elderly up to 94 years of age (Michielsen et al., 2012). The high prevalence of ADHD in both children and adults, in combination with the association
between ADHD and negative outcomes, emphasizes the importance of effective treatment and the relevance of ADHD research across the lifespan.

STIMULANT TREATMENT IN ADHD

The first-line pharmacological treatment in Europe for both children and adults with ADHD is psychostimulant methylphenidate (MPH; Atkinson & Hollis, 2010; Kooij et al., 2010). MPH increases the availability of extracellular dopamine (DA) and norepinephrine (NE) in striatal and prefrontal brain areas, by blocking the reuptake of DA and NE by dopamine and norepinephrine transporters (DAT and NET; Koda, Ago, Cong, Takuma, & Matsuda, 2010; Volkow et al., 2012). Hypothetically, this increased availability of DA and NE amplifies DA and NE signalling, while it also reduces background firing rates through presynaptic D2 activation. The mechanism of action leading to the observed improvements in attention and distractibility may be this improvement of the signal-to-noise ratio (Wilens, 2008). In animals, the mechanism of action seems similar across ages, however, differences in response occur in accord with DAT availability (Andersen, 2005). Stimulants are effective by reducing behavioural symptoms in approximately 70 percent of individuals with ADHD (Goldman, Genel, Bezman, & Slanetz, 1998; Wigal et al., 1999). In addition, MPH improves cognitive functions that are compromised in ADHD (Coghill et al., 2013). Peak plasma concentrations of MPH (immediate release) occur within one to two hours after ingestion (Spencer et al., 2006a) and behavioural improvement lasts up to approximately four hours (elimination half-life of two to three hours; Kimko, Cross, & Abernethy, 1999). Thus, stimulant treatment is effective by managing the core behavioural symptoms of ADHD, but the observed behavioural response wanes with treatment cessation.

In Europe, approximately 80 percent of children with ADHD are treated with psychostimulants only, or with psychostimulants combined with behavioural therapy (Hodgkins et al., 2013). A common misconception is that the effects of stimulants in ADHD are “paradoxical”, which is stated since they would cause hyperactivity and inattention in TD and would have opposite effects in ADHD. Instead, the effects seem to be similar in people with and without ADHD (Agay, Yechiam, Carmel, & Levkovitz, 2010; Seifert, Scheuerpflug, Zillessen, Faggagner, & Warnke, 2003), therefore a positive medication response does not imply the presence of the disorder. Instead, a dose-dependent relationship of MPH may explain contradictory findings. Optimal effects are observed at low or moderate dosages, while higher dosages have an increased benefit in some (linear relationship), but detrimental effects in others (inverted U-shape relationship; Evans et al, 2001; Stein et al., 2003). Regarding cognition, an inverted U-shaped dose-response was observed in animals (Arnsten
& Dudley, 2005), but findings in humans are equivocal (an inverted U-shape dose response reported by Tannock, Schachar, & Logan, 1995; Bédard et al., 2003, but not by Bédard & Tannock, 2008; Cooper et al., 2005; McInnes, Bédard, Hogg-Johnson, & Tannock, 2007; Rapport & Kelly, 1991; Scheres et al., 2003).

COGNITION IN ADHD

In ADHD, cognitive impairment is observed on a group level in both children and adults, and concerns both executive and non-executive cognitive domains (Bálint et al., 2009; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Rhodes, Coghill, & Matthews, 2006). Executive function is an umbrella-term covering a set of higher order functions crucial for the regulation of cognition and behaviour, such as planning, inhibition, flexibility, and working memory (Benson, Stuss, & Bowen, 1989; Stuss, 2011). Non-executive function denotes lower-order processes, such as perception, processing speed, and motor skills. In ADHD, deficits in prepotent response inhibition, verbal and visual working memory, sustained attention, and planning are most consistently described (Doyle, 2006; Huang-Pollock, Karalunas, Tam, & More, 2012; Kasper, Alderson, & Hudec, 2012). However, a slower response speed and higher response variability is also described (Epstein et al., 2011a), as is poorer long-term memory (Skodzik, Holling, & Pedersen, 2013), and altered reward sensitivity (Luman, Tripp, & Scheres, 2010).

Whereas around the first half of the 20th century ADHD impairment was referred to as a form of brain damage arising from birth injury, the focus later shifted towards the terms of delayed development. Over the years, many cognitive and neurobiological theories have been proposed in order to explain the observed impairment in ADHD, on which more elaborate recent theories are based. In 1972 already, Douglas summarized theories of poor inhibitory control, of a lack of control of cortical over subcortical brain functions, of abnormally high or low levels of physiological arousal, and of variability in reaction to reward. In line with a self-regulatory deficit, Zentall and Zentall (1976) observed that hyperactivity appears in an understimulating environment, proposing overfiltering instead of oversensitivity to sensory information. However, Quay (1988; 1997) integrated Gray’s (1982) Behavioral Inhibition System (BIS) and Behavioural Activation System (BAS) in the theory of a BIS-BAS imbalance in ADHD. The BIS and BAS interact in relationship to rewarding and punishing stimuli and together control the response mechanism. The BIS would reflect a primarily noradrenergic system, which was thought to insufficiently control the extinction of behaviour in response to aversive situations in ADHD and improve following stimulant use. The BAS was less neurobiologically defined, however, it was thought to control the increase of action in response to rewarding situations. Barkley’s (1997) model also posed deficient inhibitory
control as the underlying deficit in ADHD, accounting for problems in working memory and regulation of attention, emotion and motivation. However, the concept of a motivational deficit as a consequence of inhibitory problems was challenged by a differential response pattern to delay in children with ADHD as opposed to TD. This response pattern was related to the duration of delay, instead of to reward or the inability to wait, and gave rise to the Delay Aversion Hypothesis (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). Since Solanto and colleagues (2001) observed that delay aversion and executive dysfunctions were dissociable concepts, Sonuga-Barke (2003) proposed the dual-pathway model of dissociable executive and motivational pathways. However, not all children with ADHD demonstrate executive or motivational deficits. Therefore, a third pathway of temporal processing deficits has been added to the model, which can be divided into the subcategories of time discrimination, time reproduction and motor synchronization (Sonuga-Barke, Bitsakou, & Thompson, 2010). Other well-established theories of ADHD, focusing more on neurobiology, concern the Dynamic Developmental Theory (DDT; Sagvolden, Johansen, Aase, & Russel, 2005), the Dopamine Transfer Deficit (DTD; Tripp, & Wickens, 2008), and the Cognitive Energetic Model (CEM; Sergeant, 2005). The DDT (Sagvolden et al., 2005) states that hypofunctioning DA systems could account for a diversity of deficits, which are non-static across development due to interactions between predisposition and environmental influences. The DTD (Tripp & Wickens, 2008) also focuses on the role of DA in motivational processes specifically, and suggests that the magnitude and timing of DA cell activity differs, leading to altered sensitivity to positive reward in ADHD. The CEM (Sergeant, 2005) follows through on arousal, and divides efficiency of information processing in three levels: computational mechanisms of attention, energetic state factors, and management/executive function. It emphasizes that energetic dysfunction may play a large role in the observed executive function deficits in ADHD, which should be investigated further. While the aetiology of ADHD remains to be fully determined, for now the focus on neurobiological systems, multiple cognitive pathways, and the non-static nature of ADHD all seem to account for the substantial amount of variability in the observed deficits.

Although deficits in similar cognitive domains have been described for children and adults, only few studies have directly compared the degree of cognitive dysfunction in children and adults with ADHD, with equivocal results. First of all, a study with children between the ages of 6 to 12 years revealed ongoing development of, but stability of deficits in, working memory in an ADHD relative to a TD group (Barnett et al., 2001). Second, compared to adults with ADHD, children with ADHD had larger deficits in working memory and time discrimination, and smaller deficits in time reproduction and delay aversion (Marx et al., 2010). Last, children and adults
with ADHD were comparable in inattentive and impulsive responding, but only adults responded slower on a sustained attention task than their TD counterparts (Tucha et al., 2009). Taken together, these findings suggest that the degree of cognitive dysfunctions in ADHD might be age-related.

However, the age-relatedness of cognitive dysfunctions in the discussed studies might be obscured by previous stimulant use. With normal development, the human brain continues to mature throughout childhood, adolescence and young adulthood (Giedd et al., 1999; Giedd & Rapoport, 2010; Shaw et al., 2007; Westlyle et al., 2010). Neurotransmitter systems change drastically from early postnatal time to early adulthood, with a peak of synaptogenesis and pruning in the prefrontal cortex around adolescence (Blakemore & Choudhury, 2006). During development, the human brain adapts to experience and environmental conditions (Fox, Levitt, & Nelson, 2010). It remains unknown whether stimulant use alters brain development in humans, however, alterations in brain structure and function were observed in rats receiving chronic MPH during development (Adriani, Canese, Podo, & Laviola, 2007; Bolaños et al., 2008; Carrey & Wilkinson, 2011; Marco et al., 2011; Vendruscolo, Izídio, Takahashi, & Ramos, 2008; Volkow et al., 2001; Wiley, Poveromo, Antapasis, Herrera, & Bolaños Guzmán, 2009). The discussed studies, offering a developmental perspective on cognition in ADHD, did not account for a possible influence of prior stimulant use. Consistent with the notion of potential long-term effects of stimulants, some studies included stimulant naïve children, and observed deficits of executive function mainly (Barnett et al., 2001; Epstein et al., 2011a, Johnson et al., 2008; Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2006; Rhodes, Coghill, & Matthews, 2004; Skogli, Teicher, Andersen, Hovik, & Øie, 2013; Yang et al., 2011). The few studies with medication-naïve adults also point at deficits in working memory, processing speed, and variability (Biederman et al., 2011b; Biederman et al., 2012). Still, in studies with stimulant naïve populations, a developmental perspective is lacking, and developmental studies do not take prior stimulant treatment into account, despite the potential long-term effects on the developing brain. For this reason, Chapter 2 focuses on cognition in stimulant treatment-naïve boys and men with ADHD.

**ACUTE EFFECTS OF MPH ON COGNITION**

In addition to the degree of cognitive dysfunction, it remains unknown whether the acute effects of MPH on cognition are age-dependent. As discussed, the brain changes drastically from early postnatal time to early adulthood. Given the age-related changes in the DA system (Haycock et al., 2003; Moll et al., 2000), the neurochemical effects of MPH, and thus the cognitive sensitivity to MPH, could differ depending of age. Animal studies indeed suggest that acute treatment effects of MPH depend on the mat-
urational level of the brain (Urban, Waterhouse, & Gao, 2012, Carrey & Wilkinson, 2011). Differential behavioural responses to stimulant administration were observed in juvenile as compared to adult animals, with some studies reporting a reduced (locomotion) sensitivity (Bolaños et al., 1998; Niculescu, Ehrlich, & Unterwald, 2005), and another suggesting a heightened sensitivity in young as compared to adult animals (Bizot et al., 2007). The question is whether an age-dependent effect of MPH is also present in humans.

Indeed, consistent with an age-dependent sensitivity to MPH, adolescents with ADHD seem to benefit equally from the same dosage of MPH as children with ADHD, regardless of their age-related increase of body weight (Smith et al., 1998; Findling, Short, & Manos, 2001). However, hardly any study has summarized the MPH effects in adults with ADHD, or has focused on the age-dependency of MPH effects on cognitive and behavioural responses, whereas multiple (meta-analytic) reviews have systematically tested or described the influence of MPH on cognitive functions in children with ADHD (Chamberlain et al., 2011; Coghill et al., 2013; Kavale, 1982; Losier, McGrath, & Klein., 1996; Pietrzak, Mollica, Maruff, & Snyder, 2006; Riccio, Waldrop, Reynolds, & Lowe, 2001; Solanto, 1984). One of these reviews, which is now dated, summarizes beneficial effects of MPH on a broader range of cognitive functions in children as compared to adults with ADHD (Solanto, 1984). Furthermore, a meta-analysis focusing on MPH effects on behaviour revealed that studies with children showed a larger positive response to MPH than studies with adolescents (Faraone & Buitelaar, 2010), whereas a study focusing on attention reported enhanced positive effects in younger as compared to older children (Hanisch, Konrad, Günther, & Herpertz-Dahlmann, 2004). A recent meta-analysis concluded positive acute effects of MPH relative to placebo on executive and non-executive memory, response speed and variability, and response inhibition, from studies with children aged 5 to 18 years (Coghill et al., 2013). However, adult studies were not considered, and the possibility of an age-dependency was not evaluated. Many results of trials with adults have been published in the last few years, offering the possibility to systematically address these issues. Therefore, Chapter 3 summarizes the acute effects of MPH on response inhibition, working memory and sustained attention, while evaluating the effect of prior stimulant use to determine the age-dependency of acute MPH effects.

**STIMULANTS AND DEVELOPMENT**

As mentioned, preclinical studies in ADHD suggest long-term effects of stimulants on behaviour and cognition. These animal studies often comprise normal rodents, or genetic rodent models of ADHD, such as the Spontaneous Hypertensive Rat (SHR), which displays inattentive behaviour, restlessness, and impulsiveness, but
also heightened sensitivity to delay of reinforcement and increased intra-individual variability in responding (Sagvolden et al., 2009). In prospective studies with SHR, exposure to stimulants during prepuberty and adolescence improved attentive and inhibitory behaviour in adulthood (Marco et al., 2011; Ruocco et al., 2010). However, impaired working memory was also observed (Sherill, Stanis, & Gulley, 2013), as well as altered learning (Bethancourt, Camarena, & Britton, 2009). Also, normal and SHR rats treated with MPH during adolescence showed more depressive- and anxiety-like behaviour in adulthood than saline vehicle-treated rats (the placebo condition), presumably due to cellular alterations in reward pathways (Bolaños et al., 2008; Carlezon, Mague, & Andersen, 2003; Vendruscolo et al., 2008; Wiley, Poveromo, Antapasis, Herrera, & Bolaños Guzmán, 2009). Thus, in animals, stimulant treatment during development seems to have both positive and negative long-term effects on behaviour, cognition and affect.

In humans, imaging studies suggest stimulant treatment-associated normalization of brain structure and function (Frodl & Skokauskas, 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Nakao, Radua, Rubia, & Mataix-Cols, 2011; Wang et al., 2013). Furthermore, cross-sectional comparisons of stimulant treated and untreated groups reveal superior attention and executive function in treated children (Semrud-Clikeman, Pliszka, & Liotti, 2008), but similar attention, working memory and learning in treated and untreated adults with childhood ADHD (Biederman et al., 2012; Stoy et al., 2011). Regarding depression, both detrimental and protective effects of MPH were reported, following findings of both negative and positive associations between duration of stimulant use and the risk of major depressive disorder (MDD; Jerrell, McIntyre, & Mark Park, 2014; Lee et al., 2015). In line with the protective effect, earlier initiation of stimulant use was related to a decreased risk of MDD (Daviss, Birmaher, Diler, & Mintz, 2008a). Together, these findings may imply that the effects of stimulants on cognition, depression, and anxiety extend beyond treatment. However, results are inconclusive due to a lack of randomization.

The most comprehensive study investigating long-term effects of stimulant treatment is the Multimodal Treatment Study of Children with ADHD (MTA). Children were randomly allocated to one of four treatment conditions lasting 14 months: medication only, behavioural treatment only, combined medication and behavioural treatment, or community care. After 14 months, randomization was terminated and the outcome evaluated. At this point, the medication conditions were superior to the behavioural treatment and community care conditions on symptoms of ADHD and comorbidity, and academic functioning (The MTA Cooperative Group, 1999). However, re-evaluation after 36 months revealed no superiority of the medication conditions over the behavioural treatment and community care conditions (Jensen et al., 2007). With
regard to homework problems, only the behavioural treatment conditions revealed positive effects at 10 months follow-up (Langberg et al., 2010). Furthermore, pharmacological treatment was associated with higher rates of anxiety and depression at six year follow-up, although this effect was not observed at later follow-up (Molina et al., 2009). It was concluded that medication treatment is not associated with beneficial or detrimental outcomes at 3-, 6- or 8-year follow-up (Jensen et al., 2007; Molina et al., 2009), thus, the initial superior effect of medication treatment over behavioural treatment wanes off soon after randomization ends. However, the question whether medication use influences cognitive development was not addressed in the MTA study.

To summarize, long-term effects of MPH in humans on behaviour, cognition, and affective comorbidity largely remain unclear, as the literature on long-term MPH effects mainly comprises cross-sectional, naturalistic human studies and randomized animal studies. The ideal way of determining long-term medication effects is by conducting a double-blind, randomized, placebo-controlled trial over a time period across developmental phases. However, since MPH is the most effective and first-line treatment according to the (inter)national guidelines for the treatment of children and adults with ADHD (Atkinson, & Hollis, 2010; Kooij et al., 2010), it is considered ethically unjustified to withhold this type of treatment for a long period of time. In the current dissertation, we will therefore focus on the short-term persistency of MPH on cognition and affect (Chapter 4 and 5).

AIMS AND OUTLINE OF THIS DISSERTATION

The general aim of this dissertation was to advance our understanding of the relationship between cognition, stimulant use, and development in ADHD, in order to improve informed-decision making in ADHD treatment. Specifically, the aim of this dissertation was threefold. A first aim was to determine the degree of cognitive dysfunctions (Chapter 2) and internalizing co-morbidity in ADHD (Chapter 4), while excluding the possible influence of prior stimulant treatment by including stimulant naïve participants. A second aim was to investigate whether MPH has acute (Chapter 3) and persistent (Chapter 4 and 5) effects on cognition and internalizing comorbidity. The third aim was to estimate the value of experimental tests used in the current studies and in ADHD research in general (Chapter 6). An age-perspective was central in each of these objectives. Given the persistent nature of ADHD, we directly compared children to adults, or included participants across developmental phases. Following from the initiation date of the studies, diagnostic DSM-IV criteria were applied for both children and adults with ADHD (APA, 2000). The difference between DSM-IV and DSM-5 (APA, 2013) criteria is that the DSM-IV is more strict with regard to the number of symptoms (≥ 6 in children and ≥ 5 in adults in the DSM-5 as opposed to
≥ 6 in the DSM-IV) and the reported age of symptom onset (< 12 years in the DSM-5 as opposed to < 7 years in the DSM-IV). In addition to the benefits of stringent criteria, this approach increased comparability between children and adults, which is favourable in studies directly comparing age groups.

As the extent to which cognitive dysfunctions described in the literature are moderated by stimulant use is unknown, we determined the actual cognitive performance in both child- and adulthood ADHD in Chapter 2, by including stimulant treatment-naïve children and adults. We cross-sectionally compared whether the degree of cognitive dysfunction differed between the young and adult age group. Performance of boys aged 10 to 12 years (n = 53) and adult men aged 23 to 40 years (n = 48) with ADHD was compared to TD performance on tests of visuo-spatial working memory, response speed, episodic memory, delay aversion and response inhibition.

Next, Chapter 3 presents a meta-regression analysis, which we conducted to test the hypothesis that the effects of MPH on response inhibition, working memory, and sustained attention are moderated by age. We also explored whether the percentage of medication naïve participants per study moderated the effects of MPH on cognition, as altered reward sensitivity was observed after stimulant exposure in preclinical studies (Carlezon, Mague, & Andersen, 2003).

Chapter 4 aimed at determining the impact of prior stimulant treatment on internalizing comorbidity in ADHD, and describes two studies. The first study evaluated the association between ADHD and self-reported symptoms of depression and anxiety respectively, without the influence of prior stimulant treatment, by establishing the predictive value of diagnosis with stimulant naïve ADHD (n = 58) and TD males (n = 74) aged 10 to 17 years. Cognitive performance of the children, aged 10 to 12 years, included in this first study was described in Chapter 2 and 5. The second study assessed the impact of prior MPH treatment on comorbid depressive and anxiety symptoms, by comparing stimulant naïve adolescent boys to prior medicated adolescent boys with ADHD (n = 30 and n = 51 respectively, aged 12 - 17 years) and determining whether medication status predicted depressive and anxiety symptoms. We expected more depression and anxiety in the stimulant naïve ADHD group as compared to the TD group, following the hypothesis that both shared genetic components and negative environmental interactions lead to comorbidity in ADHD (Daviss, 2008b). Given the conflicting evidence in the literature, we did not formulate specific expectations regarding the relationship between stimulant use and comorbidity.

In Chapter 5 the effects of Psychotropic drugs On the Developing brain (ePOD) study is presented: a randomized, placebo-controlled trial on the persistency of MPH effects. Cognitive functions of stimulant treatment-naïve children (n = 50) and adults
(n = 48) with ADHD (these samples overlap with those in Chapter 2) were assessed before and after 16 weeks of treatment with MPH or placebo, following a wash-out period of one week. The aim was to determine whether MPH treatment has persistent effects on neuropsychological functions, measured with tests of visuo-spatial working memory, response inhibition, response speed, episodic memory, and delay aversion. A larger difference between pre- and post-treatment functioning, in an active treatment as compared to a placebo group, would mark persistency of MPH effects, and larger non-acute effects in children than in adults would suggest developmentally driven adaptations.

Like most recent studies in the field of the developmental disorders, the present dissertation mainly contains studies using experimental cognitive tests as outcome measures, as opposed to established clinical neuropsychological tests with extensive norms and known psychometric properties. These experimental tasks are easy to administrate and adjust, and are often computerized, reducing potential inter-assessor differences. Most experimental tests, such as the Stop Signal Test (SST), Go/No-Go test (GNG), n-back and newly developed reaction speed tests have consistently shown treatment effects in the expected direction (Coghill et al., 2013). However, psychometric properties such as test-retest reliability remain largely unknown, while this information is crucial for interpreting change observed in studies with a repeated-measures design (such as a crossover design), and for determining the utility of these tests to evaluate individual change in the clinic. It is important to assess these characteristics in both children and adults, given the use of these tests in different stages of development.

For this reason, Chapter 6 presents the test-retest reliabilities and Reliable Change Indices (RCIs) in both children and young adults of tests of visuo-spatial working memory, response speed and variability, and compares these to a well-established episodic memory test. We provide test-retest reliabilities and RCI’s, computed with data from two normative TD samples, one including boys (aged 9 - 13 years, n = 37) and one including young male adults (22 - 40 years, n = 38), following repeated assessments after 8 and 16 weeks (data from the same TD children and adults was described in Chapter 2 and 4).

Finally, in Chapter 7, the findings and limitations of all studies are summarized, and implications for the scientific and clinical field are discussed.