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Review article

Cognitive mechanisms underlying depressive disorders in ADHD: A systematic review

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ABSTRACT

The risk for major depressive disorder (MDD) is considerably increased in young adults with attention-deficit/hyperactivity disorder (ADHD) but underlying mechanisms are poorly understood. This review explores ADHD-specific neurocognitive impairments as possible underlying mechanisms for ADHD-depression comorbidity. Two systematic literature searches were conducted in EBSCOhost, PubMed, and Cochrane Reviews databases according to PRISMA guidelines. The first search identified 18 meta-analyses of cross-sectional and longitudinal studies on cognitive dysfunctions in MDD across the lifespan. The second search identified six original studies on reaction time variability in MDD. During acute depression, children and adults showed cognitive deficits that overlapped with some of the ADHD-related impairments. Findings from remitted patients, high-risk individuals, and few prospective studies suggest that a subset of these shared impairments, specifically executive dysfunctions (selective attention, verbal fluency, working memory) and long-term memory problems, are candidate pre-existing risk markers of depression. We discuss if and how these specific neurocognitive mechanisms may mediate developmental pathways from ADHD to depression. If replicated by longitudinal studies, these findings may guide future prevention strategies.

1. Introduction

1.1. ADHD across the lifespan

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition defined by a persistent and cross-situational pattern of age-inappropriate inattention and/or hyperactivity-impulsivity that leads to functional impairment (American Psychiatric Association, 2013). About 5 % of children and adolescents worldwide meet the diagnostic criteria of ADHD (Polanczyk et al., 2015, 2014; Polanczyk et al., 2007). ADHD typically starts during childhood but shows a high rate of persistence into adulthood calling for a lifespan perspective of the disorder (Franke et al., 2018). Longitudinal studies suggest that at least 15 % of individuals diagnosed with ADHD during childhood will continue to meet full diagnostic criteria as young adults, whereas an additional 50 % will continue to have subthreshold

symptoms (Agnew-Blais et al., 2016; Faraone et al., 2006). During childhood, ADHD is associated with severe functional impairments in academic (Frazier et al., 2007) and social aspects of life (Bunford et al., 2018; Ros and Graziano, 2018; Ruiz-Goikotxea et al., 2018), and many children go on to have psychosocial problems as young adults (Wilens et al., 2018) even when the core ADHD symptoms are remitted (Hechtman et al., 2016). Adult ADHD is associated with poor academic, occupational, and social outcomes such as less academic and professional success (Biederman et al., 2006; Erskine et al., 2016; Hechtman et al., 2016; Klein et al., 2012), high rates of changing jobs (Biederman et al., 2006), unemployment (Biederman et al., 2006; Erskine et al., 2016; Klein et al., 2012), accidents (Chang et al., 2014; Valero et al., 2017), criminal behavior (Biederman et al., 2006; Erskine et al., 2016) and spousal separation and divorce (Biederman et al., 2006; Klein et al., 2012). Across the lifespan, the clinical phenotype of ADHD may change, with inattentive symptoms rather than overt hyperactivity-impulsivity

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persisting into adulthood (Adler et al., 2017; Francx et al., 2015; Gibbins et al., 2010; Wilens et al., 2009; Willcutt et al., 2012). The clinical phenotype however remains a significant risk for severe functional impairment that likely increases the risk of mortality among patients (Dalsgaard et al., 2015).

Neurocognitive impairments are a key component of the ADHD phenotype (Barkley, 1997; Sergeant, 2000; Sonuga-Barke, 2003), and substantial deficits in various neurocognitive functions have been reliably identified in children (Coghill et al., 2014; Huang-Pollock et al., 2012; Karalunas et al., 2014; Marx et al., 2018; Noreika et al., 2013; Willcutt et al., 2005) and adults with ADHD (Boonstra et al., 2005; Hervey et al., 2004; Mostert et al., 2015; Mowinckel et al., 2015; Schoechlin and Engel, 2005) using cross-sectional designs. In addition, longitudinal studies also suggest that the neurocognitive deficits observed during childhood persist into adulthood (Biederman et al., 2009; Cheung et al., 2016; McAuley et al., 2014). Focusing on “cool” cognitive functions that are elicited under relatively abstract, non-affective contexts, a recent meta-analysis of 34 meta-analyses including cross-sectional case-control studies in children, adolescents, and adults revealed group differences with medium effects regarding reduced executive and non-executive neurocognitive performance, with the largest effects in relation to intra-individual reaction time (RT) variability (SMD = 0.66, number of studies: $k = 433$) and global cognitive ability, i.e. measured by standardised intelligence tests (SMD = 0.60, $k = 339$), followed by vigilance/sustained attention (SMD = 0.56, $k = 282$), working memory (SMD = 0.54, $k = 156$), and response inhibition (SMD = 0.52, $k = 438$) (Pievsky and McGrath, 2018). Consistent with findings from longitudinal studies (Roy et al., 2017), between-group differences were lower among adolescents than among children and adults, which likely is caused by increased intra- and interindividual variability due to variable stages of puberty and related brain development (Pievsky and McGrath, 2018). Importantly, independent from the specific developmental stage, individuals with ADHD differ greatly in the type of cognitive impairments they may have and there is no unique cognitive profile that defines ADHD similarly across patients (Coghill et al., 2014; Mostert et al., 2015; Nigg et al., 2005b); rather, mean cognitive impairment might be similar to other mental disorders.

1.2. Comorbidity as a hallmark of ADHD

Being a prevalent neurodevelopmental disorder with childhood onset, ADHD is also often the entry point into a trajectory defined by a high risk for co-morbid psychiatric and somatic disorders that typically develop after ADHD onset (Fayyad et al., 2017; Franke et al., 2018; Taurines et al., 2010). Over the lifespan these co-morbid disorders become major disease burden determinants (Dalsgaard et al., 2015; Hakkaart-van Roijen et al., 2007; Libutzki et al., 2019). About 50 % of children with ADHD experience at least one co-morbid psychiatric disorder, the most common being other externalizing disorders, such as oppositional defiant disorder and conduct disorder, as well as autism spectrum disorder, specific learning disorders, and intellectual disability (Jensen and Steinhausen, 2015). In adulthood, the comorbidity rate is estimated to be higher, up to about 85 % (Jacob et al., 2007; Kessler et al., 2006; Kooij et al., 2012; Miller et al., 2007; Yoshimasu et al., 2018). The most frequent disorders are mood (~ 60 %), anxiety (~ 30 %), substance use (~ 45 %) and personality disorders (~ 35 %) as well as many somatic conditions (Chen et al., 2018; Cortese et al., 2016; Instanes et al., 2018; Libutzki et al., 2019; Solberg et al., 2018). The changes in patterns and rates of comorbidities suggest that the period of transition from adolescence into young adulthood may represent a particularly sensitive phase in the development of new co-occurring disorders, especially from the internalizing spectrum (Libutzki et al., 2019; Wilens et al., 2018). However, the mechanisms of increased risk for developing co-morbid conditions at this developmental stage remain poorly understood.

Mood disorders such as Major Depressive Disorder (MDD) or dysthymia are among the most common comorbidities of ADHD in adulthood (Chen et al., 2018; Kooij et al., 2012; Solberg et al., 2018) with prevalence rates considerably increasing when patients transition from childhood into adulthood. The administrative prevalence rate of mood disorders in ADHD increases from ~3 % in children (OR ~ 7), to ~8 % in youth (OR ~ 5), to ~25 % in young adults (OR ~ 6) and ~70 % in adults over 30 years (OR ~ 13.5) as indicated by a recent report from a sample with approximately 4 million member-records available from a German Statutory Health Insurance database (Libutzki et al., 2019). Epidemiologically confirmed prevalence rates of MDD are also considerably higher in adolescents (OR ~ 5.5) (Angold et al., 1999) and adults with ADHD (OR ~ 3) (Fayyad et al., 2017; Kessler et al., 2006) than in the general population, with lifetime prevalence rates in ADHD of up to 55 % (Jacob et al., 2007; Sobanski et al., 2007; Torgersen et al., 2006). Albeit less frequent (~13 %), adult patients with ADHD are also seven times more likely to develop dysthymia as shown by the National Comorbidity Survey Replication study (Kessler et al., 2006). In addition, ADHD is found frequently in adults with a mood disorder (Bron et al., 2016; Kessler et al., 2006; McIntosh et al., 2009; Roy et al., 2017). Importantly, longitudinal studies suggest that children and adolescents with ADHD are at increased risk of developing depression when they reach adulthood (Biederman et al., 2008; Meinzer et al., 2016, 2013; Roy et al., 2014; Yoshimasu et al., 2018, 2012). The co-occurrence of depression significantly worsens health outcomes (including the risk for completing suicide), causes psychosocial impairment and increases medical costs compared to those resulting from either disorder alone (Biederman et al., 2008; Daviss, 2008; Libutzki et al., 2019; McIntyre et al., 2010; Miller et al., 2007). Therefore, a better understanding of the factors that contribute to the increased risk for depressive disorders among patients with ADHD that also takes developmental trajectories into account is needed and may provide new opportunities in the development of early intervention and prevention strategies.

Because depression typically emerges after the onset of ADHD (Fayyad et al., 2017), the presence of ADHD may directly increase the risk for MDD. In this context, a demoralization model has been proposed in which depression results from the academic and/or social failures associated with ADHD (Biederman et al., 1998; Herman et al., 2007; Humphreys et al., 2013). However, this model may not be fully sufficient to explain the large increase of co-morbid depression that specifically occurs during young adulthood (Biederman et al., 1998; Eadeh et al., 2017; Meinzer et al., 2013). Alternatively, the pathway from ADHD to depression may be mediated by shared risk factors that contribute to the development of both disorders. Both disorders are highly heritable, and the high co-occurrence of ADHD and depression may be explained by a common genetic etiology (Cole et al., 2009; Faraone and Biederman, 1997; Faraone and Larsson, 2019) and shared psychosocial factors probably interacting with the individual genetic background (Hoogman et al., 2013). Genetic risk however manifests via brain mechanisms. Low reward responsivity (Meinzer et al., 2012), poor emotion regulation (Anastopoulos et al., 2011; Eyre et al., 2019, 2017; Seymour et al., 2014, 2012), and anxiety and disruptive behavior (Roy et al., 2014) have been proposed as candidate intermediate psychological risk factors.

Neurocognitive impairments however have been largely neglected in the study of common risk factors mediating the developmental pathway from ADHD to depression. This is surprising given that neurocognitive dysfunctions, specifically in terms of impairments in “cold” cognitive functions, are considered as an integral part of both, ADHD and depression. Cognitive symptoms such as reduced ability to concentrate and indecisiveness are included in the diagnostic criteria for MDD (American Psychiatric Association, 2013). In line with these cognitive symptoms, empirical research on neurocognitive impairment in depression has focused on cognitive tasks with emotionally neutral material highly similar to those used in ADHD research and compared performance across various non-executive and executive functions in

patients with MDD versus healthy controls (McIntyre et al., 2013). The findings, mostly from adult patients, suggest that widespread impairments across executive and non-executive domains are common during acute depression (McIntyre et al., 2013). Moreover, neurocognitive impairments including problems in long-term memory, attention, psychomotor speed, and executive functioning may have significant consequences on functional outcome (Lee et al., 2013; Woo et al., 2016) and predict treatment response in patients with MDD (Bruder et al., 2014; Maalouf et al., 2018; McIntyre et al., 2013). As suggested by theoretical models on cognitive reserve (Barnett et al., 2006), impairment in general cognitive function, as indicated by low IQ and/or reduced performance in the various cognitive tasks that correlate with measurements of IQ, may not only be associated with the acute state of depression but could also reflect a predisposition for depression (Watson and Joyce, 2015) or influence disease progression, especially during the highly vulnerable period of adolescence and young adulthood (Allott et al., 2016).

Few studies exist that directly assessed the effect of co-morbid depression on cognitive functioning in ADHD by either covarying MDD (Nigg et al., 2005a; Silva et al., 2013) or comparing performance between patients with ADHD with and without co-morbid depression in cognitive tasks with emotionally neutral material (Knouse et al., 2013b; Larochette et al., 2011; Mostert et al., 2015; Murphy et al., 2001; Riordan et al., 1999; Roy et al., 2017). These studies were predominantly conducted in adolescents and adults, in line with the relative rareness of depression in childhood. One study reported an additive deficit in the areas of executive functioning, processing speed, and contextual memory when depression was comorbid with ADHD (Larochette et al., 2011). This study also found highly similar cognitive profiles for patients with either depression or ADHD. However, the majority of studies did not find an effect of depression comorbidity on cognitive task performance either in terms of a current diagnosis of MDD (Katz et al., 1998; Riordan et al., 1999; Roy et al., 2017; Silva et al., 2013) or a history of MDD (Mostert et al., 2015; Nigg et al., 2005a). Interestingly, in a sample of adults referred for assessment of ADHD, neurocognitive impairment measured via self-reports predicted current and lifetime depression (Knouse et al., 2013a). However, very few prospective studies followed adolescents into early adulthood and the findings from one study did not suggest that poor cognitive functioning precedes the onset of depression in patients with ADHD (Roy et al., 2017).

1.3. Aims and outline

In summary, ADHD increases the risk for depression especially during adolescence and young adulthood, however it is not well understood why ADHD increases the risk for depression at this developmental stage. Neurocognitive dysfunctions across executive and non-executive domains are a central feature of ADHD – persisting from childhood into adulthood (Pievsky and McGrath, 2018). Impairments in these neurocognitive functions are also common in MDD (McIntyre et al., 2013) – probably increasing an individual's vulnerability to develop depression during adolescence and early adulthood (Allott et al., 2016; Barnett et al., 2006; Watson and Joyce, 2015). Therefore, we hypothesize that neurocognitive impairments from executive and non-executive domains frequently observed in ADHD may increase the risk to develop co-morbid depression, especially at the transition from adolescence into adulthood. So far, neurocognitive impairments of ADHD and depression have been largely studied in isolation. To test our hypothesis, the main goal of the present paper is to provide a systematic review of the published literature on neurocognitive impairment in patients with MDD with a focus on those functions that are most consistently and most severely impaired in ADHD (Pievsky and McGrath, 2018), and to determine the degree of overlap between the disorders at different developmental stages (childhood, adolescence, early adulthood, adulthood). Especially, we will review prospective, longitudinal studies that

assessed the association between cognitive functioning determined at baseline and later onset of depression. We argue that the lifespan approach of cross-sectional and longitudinal studies can provide new insights into the role of neurocognitive dysfunctions in mediating the pathway from ADHD to depression.

There is robust evidence from a meta-analysis of 34 meta-analyses in ADHD for deficits of executive and non-executive cognitive functions that are elicited under relatively abstract, non-affective contexts (“cold cognitive functions”) (Pievsky and McGrath, 2018). Taking these ADHD-related impairments as a starting point, and in order to avoid confounding of altered emotion processing with neurocognitive impairment, we focused the literature search only on tasks based on emotionally neutral material. A large number of studies have assessed executive and non-executive functions based on performance in neurocognitive tasks in individuals with depression compared to healthy controls. Most findings have been quantitatively summarized and therefore, we systematically searched and reviewed meta-analytic evidence. With regard to intra-individual RT variability, meta-analytic evidence for MDD was not available and therefore, a second systematic search was conducted specifically for this domain.

2. Methods

A two-part systematic review was conducted. Part 1 examined meta-analyses of cross-sectional and longitudinal studies on cognitive task performance in patients with MDD including children, adolescents and adults. We focused on neurocognitive functions that are consistently impaired in patients with ADHD as revealed by meta-analytic evidence from 34 meta-analyses (Pievsky and McGrath, 2018). These fell into the categories of executive (verbal fluency, planning, response inhibition, selective attention/cognitive flexibility, set shifting, working memory) and non-executive functions (reaction time/processing speed, intra-individual RT variability, vigilance/sustained attention, learning and memory, intelligence) (Pievsky and McGrath, 2018). Because there was a lack of meta-analyses on intra-individual RT variability in the depression literature as revealed in part 1, part 2 reviewed original research studies on RT variability in patients with MDD relative to healthy controls as well as prospective studies. PRISMA guidelines for conducting and reporting systematic reviews and meta-analyses were followed (Moher et al., 2009). The search strategies, inclusion and exclusion criteria were defined in advance.

The electronic databases EBSCOhost (PsynINFO and PsycArticles), PubMed, and Cochrane Reviews were searched for articles published in a peer-reviewed academic journal in English between January, 1st 1992 [the year when the diagnostic criteria for major depression were published in the ICD-10 Classification of Mental and Behavioural Disorders (World Health Organization, 1992)] to May 31st 2020. The search terms used for part 1 included meta-analysis and variations of depression (depression OR depressed OR “major depressive disorder” OR “major depressive episode” OR “affective disorder” OR “mood disorder”) paired with any term from a list describing general and specific cognitive functions (cognit* OR neurocognit* OR neuropsych* OR “cognitive test*” OR intelligence OR “intellectual functioning” OR memory OR “working memory” OR “verbal memory” OR “visual memory” OR attention OR “sustained attention” OR “controlled attention” OR “executive function” OR “cognitive flexibility” OR learning OR “visual processing” OR motor OR “verbal fluency” OR “psychomotor speed” OR “processing speed” OR orientation OR perception OR language OR verbal OR visual OR reasoning OR vigilance OR visuospatial OR “problem solving” OR “intra-individual variability” OR “reaction time variability” OR “response time variability” OR “reaction time distribution” OR “response time distribution” OR “drift rate” OR “reaction time standard deviation” OR “reaction time standard error” OR “RT variability” OR “coefficient of variation” OR RTCV OR SDRT) or neurocognitive tests often used in ADHD research following the list used by a previous meta-analysis (Pievsky and McGrath, 2018) (see Appendix A for a full set of search

terms).

For part 2 we used the following search terms: (depression OR depressed OR "major depressive disorder" OR "major depressive episode" OR "affective disorder" OR "mood disorder") AND ("intra-individual variability" OR "reaction time variability" OR "response time variability" OR "reaction time distribution" OR "response time distribution" OR "drift rate" OR "reaction time standard deviation" OR "reaction time standard error" OR "RT variability" OR "coefficient of variation" OR RTCV OR SDRT).

Figs. 1 and 2 present PRISMA flow diagrams depicting a summary of our selection procedures. The searches were done by two independent raters (JSM and NF). After duplicates were removed, all remaining

articles were checked by the two reviewers in a first (title, abstract, keywords) and second (whole article) screening. Any discrepancies were resolved via consensus. References from identified meta-analyses and articles were hand-searched to find additional studies.

Studies were required to include a patient group with a diagnosis of unipolar MDD according to DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-9, or ICD-10 criteria, and a healthy control group with no diagnosed psychopathology. Patients could be currently experiencing an episode of depression or be in remission at the time of testing. Any comorbid psychiatric conditions were allowed. Studies were excluded if they reported on patients with bipolar disorder or only mixed diagnostic groups (e.g., all mood disorders), or if depression was secondary to a

Fig. 1. PRISMA flow diagram for identifying meta-analyses of cross-sectional and longitudinal studies on cognitive impairment associated with MDD. MDD = Major Depressive Disorder.

Fig. 2. PRISMA flow diagram for identifying cross-sectional and longitudinal studies on intra-individual reaction time variability associated with MDD. ADHD = Attention-deficit/hyperactivity disorder, MDD = Major Depressive Disorder, RTV = intra-individual reaction time variability.

neurologic (e.g., traumatic brain injury, Alzheimer's disease) or a medical condition (e.g., heart failure). Because cognitive impairment is discussed as a risk factor for MDD, we included longitudinal studies that compared individuals developing or not developing a depressive disorder as well as studies assessing neurocognitive functioning in unaffected first-degree relatives of patients with MDD under the assumption of a shared genetic vulnerability. For part 1, studies needed to report on at least one objective neurocognitive task. For part 2, studies needed to report on at least one parameter of intra-individual RT variability derived from a neurocognitive task. To avoid confounding of altered emotion processing and neurocognitive impairment, as stated above, only tasks with emotionally neutral material were included. For

instance, we excluded studies including tasks on emotion processing, reward processing, social cognition, autobiographical memory elicited by negative or positive cues, implicit cognitive biases, and delay discounting. Reviews and studies focusing on neuroimaging measures or electroencephalography were also excluded. Intervention studies were excluded unless baseline behavioral case-control data were reported.

Table 1
Characteristics of included studies (part 1).

Study	Research aim	Design	Inclusion criteria ¹			Exclusion criteria	Quality of included studies	# studies/# samples sample size (N) and specific characteristics	Mean age (SD)	Sex (% female)	Cognitive domains
			Years	Participants/Specific study characteristics	Age (years)						
Adults Veiel, 1997	To determine the pattern of neuro-cognitive deficits in neurologically unimpaired individuals with MDD	CS	1975–1992	Adult patients with MDD vs. healthy controls Diagnosis of MDD according to research diagnostic criteria or DSM-III criteria Patient and controls carefully matched on age and IQ	Mean age < 60	Organic brain damage (e. g., Parkinson's disease), uncertain neuropsychological status (e.g., psychopaths), bipolar disorder, depressed sample selected on cognitive ability	NA	13/NR Patients: N = 302 Patients: N = 364	Patients: 39.8 (8.1) range: 33–56 Controls: 40.9 (8.9) range: 31–56	Patients: 54 % Controls: 60 %	2 executive and 5 non-executive domains Composite effect sizes ²
Kindermann and Brown, 1997	To determine the pattern and severity of memory impairments in elderly currently depressed individuals	CS	1973–1994	Currently depressed individuals vs. nondepressed controls	Mean age > = 55	Depression associated with another medical illness (e. g., vascular disease, Parkinson's disease), dementia	NA	40/NR Patients: NR Controls: NR unipolar depression: k = 33 mixed groups (unipolar and bipolar): k = 6	Patients: NR (NR) Controls: NR (NR)	Patients: NR Controls: NR	Tasks on learning and memory and working memory Composite effect sizes
Zakzanis et al., 1998	To determine the severity and pattern of neuro-cognitive impairment in patients with MDD	CS	1980–1997	Patients with MDD vs. healthy controls Diagnosis of unipolar MDD according to DSM-III criteria	No restriction	Dysthymia, bipolar I and bipolar II disorder	NA	22/NR Patients: N = 726 Controls: N = 795	Patients: 55.5 (11) range: 34–72 Controls: NR	Patients: 56 % Controls: NR	3 executive and 4 non-executive domains Task-specific effect sizes
Stefanopoulou et al., 2009 ³	To determine the extend and severity of cognitive impairment across schizophrenia, bipolar disorder, and major depression	CS	1980–2005	Adult patients with MDD vs. healthy controls Diagnosis of MDD according to research diagnostic criteria, DSM or ICD criteria Information about patients' symptom levels at the time of assessment is provided	16–65	NR	NA	NR/NR Patients: N = 197 Controls: N = 992	NR NR	NR	2 executive and 5 non-executive domains Task-specific effect sizes
Epp et al., 2012 ⁴	To systematically assess performance in the emotional and classic Stroop task in patients with MDD	CS	Until 2010	Clinically depressed adults vs. healthy controls Inpatients and outpatients with a current primary diagnosis of unipolar depression or research participants who met Structural	>17	Other psychiatric comorbidities than anxiety (e.g., schizophrenia)	NA	14/NR Patients and controls: N = 1065	NR	NR	Classic Stroop interference task Task-specific effect sizes

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Table 1 (continued)

Study	Research aim	Design	Inclusion criteria ¹			Exclusion criteria	Quality of included studies	# studies/# samples sample size (N) and specific characteristics	Mean age (SD)	Sex (% female)	Cognitive domains
			Years	Participants/Specific study characteristics	Age (years)						
Wagner et al., 2012	To determine the extend of executive dysfunctions in adult patients with MDD and their course during antidepressant treatment	CS	NR	Clinical Interview for Diagnosis criteria for current unipolar depression (MDD, major depressive episode, dysthymia, minor depression) Study employed a classic Stroop task (with incongruent color stimuli) Any stimulus presentation format allowed Patients with a diagnosis of unipolar, non-psychotic MDD vs. healthy controls Diagnosis of MDD according to DSM-IV Information on depression severity reported	Mean age < 61	NR	Reviewed by two reviewers	15/NR Patients: N = 375 Controls: N = 481	Patients: 42.3 (NR) range: 35.6–53.4 Controls: 41.3 (NR) range: 30.0–52.9	Patients: 67 % Controls: 60 %	4 executive domains Task-specific effects sizes
Lim et al., 2013	To determine the severity of cognitive deficits in adults with MDD including samples of elderly	CS	1997–2011	Patients with a diagnosis of MDD vs. healthy controls Diagnosis of MDD according to DSM Assessment of depression severity using rating scale or self-report Moderate or severe depression according to rating scale used Case-control studies, cohort studies, randomized-controlled trials	No restriction	Delirium, any neurodegenerative disorder, active substance abuse, unstable medical disease, current or past diagnosis of psychotic disorder, bipolar disorder or other mood disorder except for MDD, treatment with electroconvulsive therapy	NA	22/NR Patients: N = 955 Controls: N = 7664	Patients: 46.9 (13.6) range: 33–74 Controls: 45.1 (14.6) range: 26–74	Patients: NR Controls: NR	4 executive and 3 non-executive domains Task-specific effects sizes
Snyder, 2013	To determine if executive functions are reliably impaired in patients with MDD	CS	Until 2011	Patients with a diagnosis of MDD or major depressive episode vs. healthy controls Diagnosis of MDD according to DSM or ICD criteria Patients with an acute episode of	No restriction	Mixed diagnostic groups (all mood disorders), depression secondary to organic brain damage or a medical condition	NA	113/NR Patients: N = 3936 Controls: N = 3771 Severity of depressive symptoms: severe: k = 52, moderate: k = 25, mild: k = 10, in remission: k = 19	Patients: 46.0 (NR) Controls: 45.0 (NR)	Patients: 61 % Controls: 60 %	7 executive domains, 2 non-executive domains Task-specific effects sizes and composite effect sizes

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Table 1 (continued)

Study	Research aim	Design	Inclusion criteria ¹			Exclusion criteria	Quality of included studies	# studies/# samples sample size (N) and specific characteristics	Mean age (SD)	Sex (% female)	Cognitive domains
			Years	Participants/Specific study characteristics	Age (years)						
Rock et al., 2014	To determine the degree of cognitive impairment in patients with depression during symptomatic and remitted states	CS	1980–2012	depression or in remission At least one objective cognitive test on cold executive functions is used Part 1: Currently depressed patients vs. healthy controls Part 2: Remitted depressed patients vs. healthy controls Diagnosis of MDD according to DSM or ICD criteria Use of CANTAB to assess cognitive function	No restriction	NR	NA	Part 1: 24/NR Patients: N = 784 Controls: N = 727 Part 2: 6/NR Patients: N = 168 Controls: N = 178	Part 1: Patients: 40.7 (14.5) Controls: 39.4 (15.2) Part 2: Patients: 43.0 (24.0) Controls: 47.5 (25.9)	Part 1: Patients: 71 % Controls: 70 % Part 2: Patients: 75 % Controls: 66 %	3 executive and 3 non-executive domains Task-specific effect sizes
First-episode of depression Lee et al., 2012	To determine the pattern and severity of cognitive dysfunctions in adult patients with a first-episode of MDD	CS	1990–2011	Patients with a first-episode of MDD vs. healthy controls MDD diagnosis according to DSM or ICD criteria Adult samples (mean age > 18)	16–65	Electroconvulsive therapy in the preceding 12 months, co-morbid substance use disorder, samples with greater than 50 % of patients < 16 years or > 65 years old, mixed samples (single episode and recurrent depression) if additional episodes had a dose-dependent effect on cognitive functioning	NA	13/15 Patients: N = 644 Controls: N = 570	Patients: 39.4 (10.2) Controls: NR	NR	4 executive domains, 2 non-executive domains Composite effect sizes
Ahern and Semkovska, 2017	To determine the pattern and extent of cognitive deficits during a first episode of depression and their persistence following remission	Part 1: CS Part 2: LS Mean follow-up period = 17.68 months	Part 1 & 2: 1980–2015	Part 1 & 2: Patients in remission from a first-episode of MDD vs. healthy controls MDD diagnosis according to DSM or ICD criteria Participants must not have previously been diagnosed with a major depressive episode Part 2: Participants were followed to remission using a	Mean age < 55	Part 1 & 2: redundant reports, case series	NA	Part 1: 30/NR Patients: N = 994 Controls: N = 1471 Part 2: 2/NR Patients: N = 92	Part 1: Patients: 27.4 (NR) Controls: 29.99 (NR) Part 2: Patients: 40.29 (NR)	Part 1: Patients: 59 % Controls: 52 % Part 2: Patients: 35 %	41 standardized tests from 12 domains Task-specific effect sizes and composite effect sizes

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Table 1 (continued)

Study	Research aim	Design	Inclusion criteria ¹			Exclusion criteria	Quality of included studies	# studies/# samples sample size (N) and specific characteristics	Mean age (SD)	Sex (% female)	Cognitive domains
			Years	Participants/Specific study characteristics	Age (years)						
Adolescents & young adults Goodall et al., 2018	To determine the pattern and severity of cognitive dysfunctions in young people with MDD at the transition to adulthood	CS	until Jan. 2016	repeated-measures design Patients with MDD vs. healthy controls Diagnosis of MDD according to DSM or ICD criteria or reaching a cutoff threshold using a self-report or clinician-rated depression symptom scale Minimum sample size of 5 participants	Mean age: 12–25	Diagnosis of bipolar disorder, any psychotic disorder, intellectual disability	Overall poor quality according to ratings on Newcastle-Ottawa Scale (mean rating of 4.87, SD = 1.47, range 1–8)	23/NR Patients: N = NR range: 10–125 Controls: N = NR range 13–605	Patients: NR (NR) range 12.8–22.8 Controls: NR (NR) range 12.8–22.2	NR	13 cognitive domains Composite effect sizes
Lipszyc and Schachar, 2010 ⁵	To determine the severity and generality of response inhibition deficits across psychiatric disorders	CS	1966–2009	Patients with MDD vs. healthy controls SSRT task or change task to measure response inhibition	No restriction	Studies that provided feedback to participants, atypical SSRT paradigms (e.g., Selective SST)	NA	SSRT: 2/NR, N = NR MRT: 4/NR, N = NR SDRT: 0/NR	Patients: 26.6 (11.7) range: 16–39 Controls: NR (NR)	Patients: 63 % Controls: NR	Response inhibition Task-specific effects sizes
Children Wagner et al., 2015	To determine the pattern and severity of cognitive dysfunctions in children and adolescents with MDD	CS	until 2014	Children and adolescents with acute episode of MDD vs. healthy controls Diagnosis of MDD according to DSM or ICD criteria	<19	Diagnoses of bipolar disorder, MDD with psychotic features, co-morbid ADHD, co-morbid substance abuse	High quality of all studies according to ratings on Newcastle-Ottawa Scale (mean rating of 7.18, SD = 0.39, range: 7–8)	17/NR Patients: N = 447 Controls: N = 1347	Patients: 13.6 (NR) range: 9–15.3 Controls: 13.7 (NR) range 9–15.8	NR	6 executive and 3 non-executive domains Task-specific effect sizes and composite effect sizes
Remitted depression Bora et al., 2013	To identify the most consistent cognitive impairments of patients with euthymic MDD and their relationship with clinical factors	CS	1980–2011	Patients in remission from a major depressive episode vs. healthy controls MDD diagnosis according to DSM or ICD criteria. Definition of remission either with regard to cut-off scores on depression scales and/or a	> 17	Redundant reports, non-published studies, Patients with co-morbid physical illness	NA	27/NR Patients: N = 895 Controls: N = 993 unipolar: 13 samples mixture of unipolar and single-episode MDD diagnosis: 17 samples late onset: 10 samples early onset: 18 samples	NR	Patients: 61 % Controls: 60 %	7 domains Task-specific effects sizes and composite effect sizes

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Table 1 (continued)

Study	Research aim	Design	Inclusion criteria ¹			Exclusion criteria	Quality of included studies	# studies/# samples sample size (N) and specific characteristics	Mean age (SD)	Sex (% female)	Cognitive domains
			Years	Participants/Specific study characteristics	Age (years)						
Semkovska et al., 2019	To specify the pattern and severity of persistent cognitive dysfunctions following a major depressive episode	CS	1972–2018	minimum temporal duration Patients in remission from a major depressive episode vs. healthy controls Diagnosis of one or more major depressive episodes according to DSM or ICD criteria Details on mood disorder's polarity and on how remission was assessed reported	> 17	Redundant reports, case series, subjective cognitive assessment, severe psychiatric co-morbidity, neurological disorders, electroconvulsive treatment in the previous 6 months, assessment following from a manic or mixed episode, intellectual disability, non published studies	Quality rating according to the major depressive episode remission criterion used Excellent: k = 194, good: k = 55, sufficient: k = 22, low quality: k = 32	252/NR Patients: N = 11,882 Controls: N = 8533 unipolar: 82 %, bipolar 8 %, mixed samples: 11 %	Patients: NR (NR) range: 20.9–77.6 Controls: NR (NR)	Patients: NR Controls: NR	75 cognitive variables from 18 cognitive domains Task-specific effect sizes
High-risk population MacKenzie et al., 2019	To compare cognitive performance between individuals with and without family history of MDD	CS	1980–2018	Unaffected first-degree relatives of individuals with vs. without MDD MDD diagnosis based on clinically validated measures	< 70	Controls with a first-degree relative diagnosed with MDD, bipolar disorder, or schizophrenia, samples matched on cognitive performance, studies using test without clear direction of better vs. worse performance, redundant reports	NA	90/54 first-degree relatives of patients with MDD: N = 3246 first-degree relatives of controls: N = 5222	first-degree relatives of patients with MDD: 15.38 (13.66) first-degree relatives of controls: 14.70 (12.37)	first-degree relatives of MDD patients: 58 % first-degree relatives of controls: 56 %	11 domains Composite effect sizes
Prospective studies Scul et al., 2017	To determine whether cognitive function acts as a predictor of later MDD diagnosis or change in depressive symptoms	LS	until 2016	Population-based Assessment of cognitive function at baseline and depression assessment at follow up unipolar depression diagnosis or symptoms rated by investigator or self-report	< 65	Studies not specifying how depression was measured, no unique measure of depression, baseline and protocol studies without follow-up data	Assessed by two raters according to checklist High quality studies: 41 % Medium quality studies: 59 %	29/34 121,749 participants Most common types of samples: 9 school samples, 8 communitysamples, 7 birth cohorts	at baseline: 14.4 (10.2) range: 5–59	52 %	General cognitive impairment mainly assessed via tests on IQ

¹Criteria that applied to all meta-analyses: including at least one standardized neurocognitive task, providing sufficient statistical data (e.g., mean, SD, SE, number of participants, F or t statistics) which could be converted into effect sizes. ²Composite effects sizes were calculated by pooling across tasks belonging to one domain and/or pooling across domains. ³Only data for subgroups analysis on performance in patients with MDD vs. controls are reported. ⁴Only data for subgroups analysis on performance in the Classical Stroop task in depressed patients vs. controls are reported. ⁵Only data for subgroups analysis on performance in patients with MDD vs. controls are reported. CANTAB = Cambridge Neuropsychological Test Automated Battery, CS = cross-sectional design, k = number of studies, LS = longitudinal design, MDD = Major depressive disorder, MRT = mean reaction time, N = number of participants, NA = not assessed, NR = not reported, SD = standard deviation, SDRT = within-subject standard deviation of reaction time, SSRT = stop signal reaction time.

3. Results

3.1. Part 1: Systematic review of meta-analyses of neurocognitive dysfunctions in MDD

The search identified 4603 articles (see Fig. 1). After deleting duplicates (988), 3615 potentially relevant articles were identified from which 3516 were removed after title and abstract screening against the selection criteria. The remaining 99 articles were reviewed in full, resulting in 18 articles eligible for the review. In summary, 12 meta-analyses of cross-sectional studies were found reporting information on cognitive dysfunctions in patients with depression, in patients in remission from a depressive episode (2), or in both (2). Of these, 12 meta-analyses included mainly adults (range of mean age: 27–55 years) and one study focused on older adults (mean age ≥ 55 years). One meta-analysis reported on children/adolescents, and two studies included young adults (mean age < 27 years old). One meta-analysis focused on studies assessing cognitive dysfunctions in individuals with high-risk to develop depression. Furthermore, we identified one meta-analysis including only longitudinal studies with baseline measures of cognitive functioning and subsequent risk for depression (see Table 1, Fig. 3).

3.1.1. Current depression

The majority of the meta-analyses assessing cognitive functioning in patients with a current diagnosis of unipolar MDD compared to demographically matched healthy controls included middle-aged patients (mean age of the samples ranging from 40 to 55 years) with some studies explicitly excluding elderly patients (e.g., mean age < 61 years) (Veiel, 1997; Wagner et al., 2012). One study included only samples with elderly individuals (mean age ≥ 55 years) (Kindermann and Brown, 1997). Seven meta-analyses were identified that assessed deficits across several executive and non-executive domains either reporting effect sizes pooled across different tasks that tap into the same domain (Snyder, 2013; Veiel, 1997) and/or task-specific effect sizes (Lim et al.,

2013; Rock et al., 2014; Snyder, 2013; Stefanopoulou et al., 2009; Wagner et al., 2012; Zakzanis et al., 1998). These meta-analyses provide consistent evidence for broad cognitive impairments in currently depressed middle-aged adult patients compared to healthy controls including executive (Lim et al., 2013; Rock et al., 2014; Snyder, 2013; Stefanopoulou et al., 2009; Veiel, 1997; Wagner et al., 2012; Zakzanis et al., 1998) and non-executive dysfunctions (Rock et al., 2014; Snyder, 2013; Veiel, 1997; Zakzanis et al., 1998). Highly consistent findings have also been reported for younger adults specifically in their first-episode of depression (mean age of the samples ranging from 27 to 40 years) as revealed by two meta-analyses (Ahern and Semkova, 2017; Lee et al., 2012) (see Table 2a).

Deficits in executive functions most often fell into the domains of verbal fluency, working memory, planning, set shifting, and selective attention/cognitive flexibility as assessed with the Stroop interference task (note, the latter domain is most often termed inhibition or interference control in the depression literature, assuming that the Stroop task measures interference control as one component of inhibition). Impairments in non-executive functions included most often learning and episodic memory functions, processing speed, vigilance (most often termed sustained attention in the depression literature) as well as measures on general cognitive functioning (i.e., full scale IQ). However, effect size estimates for individual functions considerably varied between meta-analyses (small to large effect sizes) which might be explained by the small number of studies especially in earlier meta-analyses and/or the heterogeneity of the included patient samples in terms of age, sex, medication, age of onset of depression, duration of illness, and remission status. For instance, including older patients (mean age of the samples: 55 years, number of studies: $k = 22$), Zakzanis et al. (1998) found the largest effect on measures of encoding and retrieval from episodic memory, in contrast to the findings of Veiel (1997), that demonstrated a large effect size for performance deficits in executive functioning. However, the latter finding was based on only three studies and the composite effect size was pooled across tasks on set shifting (TMT-B) and selective attention/cognitive flexibility (Stroop

ADHD											
Verbal fluency/ language development	Intelligence/ Achievement	Long-term memory	Planning	RT/ psychomotor speed	Intra-individual RT variability	Response inhibition ¹	Selective attention/ interference control ²	Set shifting	Vigilance/ sustained attention	Working memory	Number of meta-analyses
Current episode - adults					-	- / ?					
Current episode - adolescents					-						
Current episode - children				-	-						
Remitted MDD - adults					-	-					
High-risk individuals			-		-	-					
Prospective studies	-		-	-	-	-	-	-	-	-	

Fig. 3. Summary of meta-analytic findings of cross-sectional and longitudinal studies on neurocognitive impairments associated with MDD across the lifespan compared to the neurocognitive profile of ADHD according to Pievsky and McGrath (2018).

Legend: ADHD = Attention-deficit/hyperactivity disorder, MDD = Major Depressive Disorder. Green: consistently impaired/associated with MDD and overlapping with ADHD; light green: impaired/associated with MDD and overlapping with ADHD but poorly documented, ambiguous, very mild or variable evidence; grey: consistently not impaired/not associated with MDD; light grey: not impaired in MDD but small number of studies; -: no meta-analytic evidence available; ? : Findings on response inhibition in adults (Snyder, 2013) were inconclusive due to the use of composite scores calculated across tasks from different domains. ¹The domain of response inhibition as defined by Pievsky and McGrath (2018) refers to inhibition of an initial pre-potent response to an event and the stopping of an ongoing response as assessed with tasks such as CPT (i.e. commission errors), stop-signal reaction time and the go/no-go task. ²The domain of selective attention as defined by Pievsky and McGrath (2018) refers to inhibition of cognitive interference based on the Stroop interference task.

Table 2a

Meta-analytic findings of cross-sectional studies assessing cognitive functioning in patients with depression vs. healthy controls compared to neurocognitive profile of ADHD.

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
ADHD¹ <i>Veiel, 1997</i>	0.49 Verbal fluency (COWAT) SMD = 0.55 (SD = 0.25), k = 3	0.60 NA	0.49 Verbal learning- Aquisition (composite score: Paired-association Task, RAVLT, CVLT, immediate story recall) SMD = 0.90 (SD = 0.48), k = 10 Verbal learning- Retention/ Recognition (composite score: paired-association task, RAVLT, CVLT, delayed story recall, Logical Memory II) SMD = 0.91 (SD = 0.80), k = 6 Nonverbal learning- Aquisition (composite score: ROCF, recognition of recurring figures) SMD = 0.97 (SD = 0.49), k = 7 Nonverbal learning- Retention/ Recognition (composite score: ROCF, delayed picture recognition, visuo-spatial learning task) SMD = 0.83 (SD = 0.26), k = 4	0.49 NA	0.35 Scanning and visuo-motor tracking (composite score: TMT-A, digit symbol coding) SMD = 0.93 (SD = 0.25), k = 3	0.66 NA	0.52 NA	0.46 Mental flexibility and control (composite score: TMT-B, Stroop test) SMD = 2.0 (SD = 0.41), k = 3	0.35 Mental flexibility and control (composite score: TMT-B, Stroop test) SMD = 2.0 (SD = 0.41), k = 3	0.56 NA	0.54 Attention and Concentration (composite score: digit span forward, digit span backward, block span) SMD = 0.18 (SD = 0.06), k = 3
<i>Kindermann and Brown, 1997</i>	NA	NA	Memory Composite score: tasks on immediate and delayed memory, recognition and recall, digit span forward, digit span backward, supraspan tasks with and without delay) d = -0.60, p < .00001, k = 40 unipolar depression:	NA	NA	NA	NA	NA	NA	NA	Memory Composite score: tasks on immediate and delayed memory, recognition and recall, digit span forward, digit span backward, supraspan tasks with and without delay) d = -0.60, p < .00001, k = 40 unipolar

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Table 2a (continued)

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
			d = −0.58, k = 33 tasks with delays d = −0.74, k = 13 immediate recall: d = −0.59, k = 36								depression: d = −0.58, k = 33
Zakzanis et al., 1998 ²	Semantic fluency d = −0.97 (SD = 0.45) k = 2 COWAT d = −0.61 (SD = 0.26) k = 7	WAIS-R Arithmetic d = −0.89 (SD = 1.21) k = 3 WAIS-R Comprehension d = −0.63 (SD = 0.75) k = 3 WAIS-R Performance IQ d = −0.52 (SD = 0.25) k = 6 WAIS-R Full scale IQ d = −0.22 (SD = 0.13) k = 6 WAIS-R Verbal IQ d = 0.10 (SD = 0.16) k = 8 NART d = −0.42 (SD = 0.02) k = 2	RAVLT list A total d = −1.43 (SD = 0.23) k = 2 WMS-R Verbal Paired Associates d = −0.80 (SD = 0.93) k = 2 CVLT long delay free recall d = −0.77 (SD = 0.14) k = 2 WMS-R Visual reproduction I d = −0.71 (SD = 0.43) k = 3 WMS-R Visual reproduction II d = −0.67 (SD = 0.25) k = 2 CVLT discriminability d = −0.66 (SD = 0.40) k = 2 CVLT list A trial 5 d = −0.62 (SD = 0.35) k = 3 ROCF delayed reproduction d = −0.63 (SD = 0.40) k = 2 WMS-R Logical memory II d = −0.60 (SD = 0.70) k = 7	NA	Stroop word reading d = 0.66 (SD = 0.56) k = 3 Digit symbol coding d = −0.63 (SD = 0.49) k = 7 TMT-A d = 0.18 (SD = 0.47) k = 3	NA	NA	Stroop interference d = 0.69 (SD = 0.15) k = 2	TMT-B d = 0.77 (SD = 0.70) k = 5 WCST Categories d = −0.44 (SD = 0.36) k = 2 WCST Perseverations d = 0.32 (SD = 0.23) k = 3	Paced auditory serial addition test d = −0.31 (SD = 0.15) k = 3	Digit span forward d = −0.43 (SD = 0.55) k = 10 Digit span backward d = −0.31 (SD = 0.35) k = 10
Stefanopoulou et al., 2009	NA	General IQ (WAIS-R) SMD = 0.09 (−0.17 to 1.35), p = .50, k = NR	NA	NA	TMT-A SMD = −0.82 (−1.47 to −0.16), p = .01, k = NR	NA	NA	Stroop Colour Word Test SMD = 0.96 (0.30–1.61), p = .0041, k = NR	TMT-B SMD = −1.38 (−2.47 to −0.68), p < .0001, k = NR	NA	NA
Epp et al., 2012	NA	NA	NA	NA	NA	NA	NA	Classical Stroop interference task, g = 0.86 (0.47–1.25), p < .001, k = 14	NA	NA	NA
Wagner et al., 2012	Phonemic verbal fluency (letter)	NA	NA	NA	NA	NA	NA	Stroop interference task SMD = 1.18	WCST SMD = 0.44 (0.20 to 0.68),	NA	NA

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Table 2a (continued)

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
Lim et al., 2013	SMD = 0.72 (0.55 to 0.90), p = .000, k = 10 Semantic verbal fluency (category) SMD = 0.92 (0.66–1.19), p = .000, k = 9							(0.72–1.64), p = .000, k = 7	p = .000, k = 5 TMT-B SMD = 1.11 (0.86–1.35), p = .000, k = 5		
	Verbal fluency SMD = −0.57 (−0.82 to −0.33), p < .00001, n = 12		Memory (composite score: RAVLT, Luria Verbal Learning Test, CVLT, WMS) Immediate Verbal Memory SMD = −0.67 (−1.15 to −0.18), p < .0001, k = 6 Delayed Verbal Memory SMD = −0.39 (−1.13 to 0.34), p = .29, k = 5 Immediate Visual Memory SMD = −0.18 (−0.70 to 0.34), p = .49, k = 4 Delayed Visual Memory SMD = −0.13 (−0.78 to 0.52), p = .70, k = 4 NA		TMT-A SMD = 0.48 (0.17 to 0.79), p = .002, k = 9 Digit symbol test SMD = −0.53 (−0.90 to 0.15), p = .006, k = 9 Finger tapping SMD = −0.34 (−0.72 to 0.04), p = .08, k = 2			Stroop test SMD = 0.84 (0.51–1.17), p < .00001, k = 6	TMT-B SMD = 0.3 (−0.49 to 2.16), p = .22, k = 10 WCST SMD = −0.40 (−0.55 to −0.24), p < .00001, k = 8	CPT SMD = −0.69 (−1.24 to −0.15), p = .01, k = 2	Digit span backward SMD = −0.50 (−0.72 to −0.27), p < .0001, k = 10
Snyder, 2013	Verbal fluency (Composite score: phonemic and semantic verbal fluency) d = 0.55, (0.44 to 0.66), p < .001, k = 46 Phonemic verbal fluency (letter) d = 0.46 (0.34 to 0.57), p < .001, k = 37 Semantic	Vocabulary (Composite score: NART, WAIS-R, Stanford-Binet, Binois-Pichot, Ammons Quick Test, British picture vocabulary test, Mill Hill vocabulary test, German vocabulary test) d = 0.14 (0.04 to 0.25), p = .007, k = 36	NA	Planning (Compo-site score: ToL, SoC) d = 0.38 (0.22 to 0.53), p < .001, k = 17	Psychomotor speed (composite score: RT, choice RT, finger- tapping, grooved pegboard) d = 0.33 (0.15 to 0.50), p < .001, k = 23 Digit-symbol substitution task d = 0.55 (0.34–.75), p < .001, k = 22 TMT-A d = 0.52	NA	Inhibition (Compo-site score: Stroop task, Hayling task, Go/-Nogo task, SST, Simon task, Flanker task) d = 0.58 (0.47 to 0.69), p < .001, k = 48	Inhibition Stroop interference task d = 0.39 (0.23 to 0.54), p < .001, k = 20 Stroop accuracy in incongruent condition d = 0.70 (0.46 to 0.93), p < .001, k = 10 Hayling task d = 0.97 (0.54–1.40), p < .001, k = 5	Shifting composite (WCST, ID/ED, TMT-B) d = 0.47 (0.39 to 0.55), p < .001, k = 69 WCST d = 0.47 (0.32 to 0.61), p < .001, k = 25 ID/ED d = 0.46 (0.31 to 0.61), p < .001, k = 15	NA	Verbal WM composite (digit span forward and backward) d = 0.45 (0.34 to 0.56), p < .001, k = 39 Digit span forward d = 0.39 (0.25 to 0.53), p < .001, k = 27 Digit span backward d = 0.55 (0.39 to 0.71), p < .001, k = 23 Verbal WM maintenance

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Table 2a (continued)

Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
verbal fluency (category) d = 0.70 (0.52 to 0.88), p < .001, k = 24				(0.38 to 0.66), p < .001, k = 32				TMT-B d = 0.59 (0.45 to 0.73), p < .001, k = 35		composite (CVLT, Sternberg and letter maintenance, reading span) d = 0.39 (0.27 to 0.51), p < .001, k = 31 Verbal WM manipulation composite (digit or letter sequencing task, letter-number sequencing) d = 0.53 (0.38 to 0.66), p < .001, k = 28 Visual WM composite (DMTS, self-ordered pointing, spatial span) d = 0.45 (0.30 to 0.59), p < .001, k = 23 DMTS d = 0.32 (0.15 to 0.48), p < .001, k = 10 Self-ordered pointing d = 0.37 (0.16 to 0.50), p = .001, k = 10 Spatial span forward d = 0.36 (0.17 to 0.55), p < .001, k = 17 Spatial span backward d = 0.72 (0.35–1.09), p < .001, k = 9 WM updating composite d = 0.57 (0.20 to 0.94), p = .003, k = 10 n-back task d = 0.63 (0.11–1.15), p = .018, k = 7

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Table 2a (continued)

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
Rock et al., 2014 ³ Part 1: acute depressed patients vs. healthy controls	NA	NA	DMS d=−0.46 (−0.62 to −0.29), p < .00001, k = 12 Paired Associates Learning d=−0.50 (−0.73 to −0.26), p < .0001, k = 9 Pattern Recognition Memory d=−0.46 (−0.69 to −0.23), p < .0001, k = 12 Spatial Recognition Memory d=−0.41 (−0.61 to −0.22), p < .0001, k = 13	SoC d=−0.43 (−0.63 to −0.24), p < .0001, k = 16	RT d=−0.07 (−0.61 to 0.46), p = .79, k = 4	NA	NA	NA	ID/ED d=−0.44 (−0.65 to −0.23), p < .0001, k = 16	RVP d=−0.65 (−0.83 to −0.46), p < .00001, k = 7	Spatial WM d=−0.54 (−0.75 to −0.33), p < .00001, k = 15 Spatial span d=−0.34 (−0.70 to 0.01), p = .06, k = 8
Lee et al., 2012	Verbal fluency (composite score: letter and semantic fluency) g = 0.59 (0.13 to 0.59), p < .05, k = 4	NA	Visual learning and memory (composite score: Visual Reproduction, ROCF, Wechsler Memory Scale Visual Memory Index): g = 0.53 (−0.05 to 1.11), p = .07, k = 7 Verbal learning and memory (composite score: Logical Memory, RAVLT, CVLT-II, HVL, Buschke's Selective Reminding Test): g = 0.13 (−0.18 to 0.45), p = .040, k = 12	NA	Psychomotor speed (composite score: TMT-A, digit symbol, Symbol Digit Modalities Test): g = 0.48 (0.21 to 0.75), p < .001, k = 10	NA	NA	NA	Attentional switching: TMT-B g = 0.22 (0.00 to 0.44), p = .05, k = 6 Cognitive flexibility (composite score: WCST, MCST, CANTAB ID/ ED g = 0.53 (0.23 to 0.83), p < .001, k = 7	NA	WM (composite score: digit span backwards, spatial span backwards) g = 0.16 (−0.20 to 0.51), p < .38, k = 6 Attention (composite score: digit span forwards, spatial span forwards) g = 0.36 (0.13 to 0.59), p < .005, k = 5
Ahern and Semkovska, 2017 Part 1: acute depressed patients vs. healthy controls	Verbal fluency (composite score: letter and semantic fluency) g = 0.64 (0.43 to 0.58),	Intelligence (composite score: WAIS, WISC, Raven's Standard Progressive Matrices and Coloured Matrices)	Visual learning (composite score: Visual Reproduction I, Penn Face Memory) g = 0.64 (0.25–1.03), p = .001, k = 5	NA	Processing speed (composite score: TMT-A, number coding, DSST, SDMT, Stroop color/ word reading g = 0.63	NA	NA	Inhibition (composite score: Stroop Colour Word Test, Affective Go/No Go test visuo-spatial WM) g = 0.76	Shifting (composite score: TMT-B, WCST, MCST, D-KEFS, CANTAB ID/ ED) g = 0.51	Sustained visual attention, RT (composite score: Complex Tracking, several unstandar- dized tests)	WM (composite scores) visuo-spatial WM g = 0.74 (0.23–1.25), p = .005, k = 7 auditory WM g = 0.39

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Table 2a (continued)

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
	p < .00001, k = 7	g = 0.26 (0.08 to 0.44), p = .005, k = 10	Visual memory (composite score: Visual Reproduction II, Penn Face Memory, ROCF, DMS) g = 0.43 (0.22 to 0.64), p < .0001, k = 12 Verbal recognition (composite score: CVLT, RVLt, Process Dissociation Task) g = 0.37 (−0.13 to 0.88), p = .15, k = 3 Verbal learning (composite score: word list, CVLT, RVLt, Buschke's Selective Reminding Test, Story telling, Logical Memory I) g = 0.31 (0.00 to 0.62), p = .05, k = 10 Verbal memory (composite score: word list, CVLT, RVLt, Buschke's Selective Reminding Test, HVLt, Story telling, Logical Memory II) g = 0.43 (0.22 to 0.64), p < .0001, k = 12		(0.35 to 0.92), p < .0001, k = 11 Motor skills g = 0.39 (0.06 to 0.72), p = .02, k = 2			(0.33–1.18), p = .0005, k = 5	(0.31 to 0.72), p < .00001, k = 16	g = 0.06 (−0.35 to 0.47), p = .87, k = 4 Sustained visual attention, accuracy (composite score: CPT, RVP, Visual Detection Task, unstandar- dized tests) g = 0.43 (0.15 to 0.71), p < .003, k = 6	(0.20 to 0.58), p < .0001, k = 7 Spatial span forward g = 0.32 (0.04 to 0.60), p = .02, k = 3 Digit span forward g = 0.35 (0.04 to 0.65), p = .03, k = 3
Wagner et al., 2015	Phonemic verbal fluency (letter) SMD = 0.76 (0.39–1.12), p = .0001, k = 3 Semantic verbal fluency (category) SMD = 0.23 (0.004 to 0.44), p = .29, k = 4	Full scale IQ (composite score: WISC, Raven's standard progressive matrices) SMD = 0.36 (0.21 to 0.50), p < .0001, k = 10 Verbal IQ (WISC) SMD = 0.43 (0.19 to 0.68), p < .001, k = 6 Performance IQ (WISC)	Verbal memory, learning trial (composite score: AVLT, CVLT) SMD = 0.22 (−0.021 to 0.42), p = .03, k = 5 Verbal memory, delayed recall (composite score: AVLT, CVLT) SMD = 0.52 (0.21 to 0.62), p = .03, k = 5	Planning (compo-site score: Tower of Hanoi, SoC) SMD = 0.51 (0.10 to 0.92), p = .014, k = 3	NA	NA	Selective attention (Go/ Nogo task) SMD = 0.19 (−0.06 to 0.45), p = .13, k = 3	Inhibition (Stroop task RT) SMD = 0.77 (0.28–1.60), p = .002, k = 3	Shifting (composite score: TMT-B, ID/ED, SAS, SAT) SMD = 0.44 (0.27 to 0.62), p = .000, k = 6	Sustained attention SMD = 0.52 (0.32 to 0.73), p = .000, k = 6	WM (composite score: digit span forward, n-back task, symbol digit coding, spatial WM) SMD = 0.49 (0.28 to 0.69), p = .000, k = 6

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Table 2b

Meta-analytic findings of cross-sectional studies assessing cognitive functioning in patients remitted from depression vs. healthy controls compared to neurocognitive profile of ADHD.

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response Inhibition	Selective attention	Set shifting	Vigilance	WM
ADHD¹	0.49	0.60	0.49	0.49	0.35	0.66	0.52	0.46	0.35	0.56	0.54
Bora et al., 2013	Phonetic fluency d = 0.34 (−0.08 to 0.76), p = .11, k = 6 Semantic fluency d = 0.57 (0.28 to 0.85), p < .001, k = 5	NA	Verbal memory (composite score: RAVLT, CVLT, other list learning tasks, logical memory) d = 0.48 (0.23 to 0.73), p < .001, k = 15 Visual memory (composite score: visual reproduction/WMS visual memory, ROCFT, pattern recognition, spatial recognition, paired associate learning, Rey design learning) d = 0.54 (0.33 to 0.76), p < .001, k = 12	Planning (composite score: WCST, ToL, Hanoi tower, IDED, BADs) d = 0.64 (0.37 to 0.91), p < .001, k = 17	Processing speed (composite score: TMT-A, digit symbol, letter fluency, category fluency, reaction time) d = 0.47 (0.31 to 0.64), p < .001, k = 20 TMT-A d = 0.39 (0.14 to 0.69), p = .002, k = 7	NA	NA	Stroop task d = 0.74 (0.52 to 0.96), p < .001, k = 7	TMT-B d = 0.48 (0.14 to 0.81), p = .005, k = 5 WCST perseveration d = 0.18 (−0.10 to 0.46), p = .21, k = 6	Attention (composite score: CPT, tests of attentional performance, continuous concentration, cancellation test, time test of selective attention) d = 0.53 (0.33 to 0.72), p < .001, k = 10	WM (composite score: digit span, letter number sequencing, DMTS, reading span, digit sequencing) d = 0.39 (0.20 to 0.57), p < .001, k = 14
Rock et al., 2014² Part 2: remitted patients vs. healthy controls	NA	NA	Delayed Matching to Sample d = −0.22 (−0.60 to 0.15), p = .24, k = 3 Pattern Recognition Memory d = −0.54 (−1.08 to 0.01), p = .05, k = 3	Stockings of Cambridge d = −0.61 (−0.88 to −0.34), p < .001, k = 4	NA	NA	NA	NA	Intra-Extra Dimensional Set Shift d = −0.53 (−0.88 to −0.18), p = .003, k = 3	Rapid Visual Information Processing d = −0.52 (−0.83 to −0.21), p = .0009, k = 4	Spatial WM d = −0.53 (−0.98 to −0.07), p = .02, k = 3
Semkovska et al., 2019	Letter fluency g = −0.30 (−0.41 to −0.19), p < .0001, k = 63 Semantic fluency g = −0.38 (−0.54 to −0.22), p < .0001, k = 49	WAIS IQ g = −0.16 (−0.24 to −0.08), p < .001, k = 66 NART IQ g = 0.062 (−0.16 to 0.30), p = .61, k = 21 Vocabulary g = −0.063 (−0.19 to 0.06), p = .35, k = 22 Raven matrices g = −0.064 (−0.23 to	Verbal memory: Logical memory immediate recall g = −0.81 (−1.01 to −.61), p < .0001, k = 24 Logical memory delayed recall g = −0.88 (−1.19 to −.57), p < .0001, k = 22 Verbal immediate recognition g = −0.30 (−0.45 to −.14), p < .0001, k = 9 RAVLT, first learning attempt g = −0.37 (−0.47 to −.27), p < .0001, k = 24 RAVLT, last learning	ToL g = −0.35 (−0.46 to −.24), p < .0001, k = 19 ROCF copy g = −0.24 (−0.43 to −.05), p = .013, k = 11 Bloc design g = −0.29 (−0.43 to −.15), p < .0001, k = 13	Simple reaction time g = −0.37 (−0.63 to −.11), p < .01, k = 29 Finger tapping g = −0.44 (−0.84 to −.04), p = .031, k = 9 pegboard g = −0.56 (−0.78 to −.33), p < .0001, k = 4 Digit symbol g = −0.54 (−0.63 to −.44), p < .0001, k = 73 TMT-A g = −0.54 (−0.63 to −.44),	NA	NA	Stroop accuracy g = −0.50 (−0.70 to −0.30), p < .0001, k = 19 Stroop completion time g = −0.46 (−0.64 to −0.27), p < .0001, k = 48	TMT-B g = −0.60 (−0.72 to −.48), p < .0001, k = 73 WCST total g = −0.048 (−0.37 to 0.27), p = .76, k = 8 WCST number of categories completed g = −0.30 (−0.38 to −.21), p < .0001, k = 30 WCST number of perseverations g = −0.32	d2 test of attention g = −0.79 (−0.88 to −.69), p < .0001, k = 7 Visual selective attention: Reaction time g = −0.38 (−0.51 to −.24), p < .0001, k = 25 Accuracy g = −0.38 (−0.51 to −.25), p < .0001, k = 31 Omission errors g = −0.55 (−0.77 to −.34), p < .0001, k = 7 Commission errors g = −0.52 (−0.75 to	Digit span forward g = −0.13 (−0.27 to 0.02), p = .079, k = 46 Digit span backward g = −0.23 (−0.34 to −0.12), p < .0001 k = 48 Digit span total g = −0.53 (−0.71 to −0.35), p < .0001 k = 23 Mental short-term manipulation task g = −0.30 (−0.46 to −0.13), p < .001 k = 34 Spatial span

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Table 2b (continued)

Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response Inhibition	Selective attention	Set shifting	Vigilance	WM
	0.10), p = .48, k = 6 Information g = −0.15 (−0.30 to 0.036), p = .051, k = 9 Similarities g = 0.008 (−0.20 to 0.22), p = .93, k = 5 Picture completion g = −0.33 (−0.66 to −0.01), p = .047, k = 5	attempt g = −0.57 (−0.75 to −.38), p < .0001, k = 8 Word lists learning total g = −0.33 (−0.49 to −.17), p < .0001, k = 56 Word lists delayed recall g = −0.41 (−0.53 to −.29), p < .0001, k = 71 Word lists delayed recognition g = −0.21 (−0.37 to −.05), p = .01, k = 32 Visual memory: CANTAB pattern recognition latency g = −0.84 (−1.18 to −.50), p < .0001, k = 4 CANTAB pattern recognition accuracy g = −0.31 (−0.54 to −.08), p = .008, k = 6 Spatial design learning g = −0.29 (−0.97 to 0.40) p = .41, k = 4 CANTAB delayed matching latency g = −1.05 (−2.21 to .11), p = .076, k = 3 CANTAB delayed matching accuracy g = −0.50 (−0.78 to −.19), p = .0021, k = 7 ROCF immediate recall g = −0.75 (−0.94 to −.57), p < .0001, k = 9 ROCF delayed recall g = −0.50 (−0.66 to −.35), p < .0001, k = 30 Visual reproduction immediate recall g = −0.51 (−0.66 to −.36),		p < .0001, k = 73				(−0.47 to −.17), p < .0001, k = 35 Brixton test g = 0.07 (−0.17 to 0.31), p = .57, k = 55	−0.28), p < .001, k = 7	forward g = −0.28 (−0.43 to −0.13), p < .001 k = 11 Spatial span backward g = −0.35 (−0.50 to −0.21), p < .001 k = 10 CANTAB visuo- spatial strategy g = −0.59 (−0.80 to −0.37), p < .001 k = 5

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Table 2a (continued)

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
Goodale et al., 2018	Verbal fluency (composite score: COWAT, words, animals) SMD = 0.27 (−0.08 to 0.63), p = .13, k = 3	SMD = 0.43 (0.23 to 0.62), p = .0000, k = 6 Full scale IQ (composite score: WISC III full scale and vocabulary reasoning subtests, WASI full scale) SMD = 0.32 (0.21 to 0.56), p = .01, k = 5 Verbal reasoning/ knowledge (composite score: vocabulary, similarities, comprehension) SMD = 0.46 (0.14 to 0.79), p = .00, k = 6 Nonverbal reasoning/ knowledge (composite score: vocabulary, similarities, comprehension) SMD = 0.22 (−0.01 to 0.46), p = .07, k = 5	Verbal learning (composite score: RAVLT, CVLT) SMD = 0.51 (0.10 to 0.93), p = .02, k = 5 Verbal memory (composite score: AVLT, CVLT, LM, VPA) SMD = 0.78 (0.50–1.06), p = .00, k = 6 Visual memory (composite score: DMS, visual PAL, VR, ROCF) SMD = 0.65 (0.30–.99), p = .00, k = 6	Planning/ Organi- zation (compo-site score: ToL Tower of Hanoi, WISC III mazes, ROCF, SoC) SMD = 0.13 (−0.58 to 0.84), p = .72, k = 6	Processing speed/RT (composite score: e.g., TMT- A, ID/ED RT, RVPT, ITT, PSI, MRT) SMD = 0.27 (0.02 to 0.52), p = .03, k = 16	NA	Response inhibition (composite score: Stroop task, COWAT, Go/ Nogo task, divided attention, CANTAB response inhibition, TEA- Ch, Simon task, SST, Serial choice RT, word task) SMD = 0.06 (−0.24 to 0.36), p = .68, k = 11	Response inhibition (composite score: Stroop task, COWAT, Go/Nogo task, divided attention, CANTAB response inhibition, TEA- Ch, Simon task, SST, Serial choice RT, word task) SMD = 0.06 (−0.24 to 0.36), p = .68, k = 11	Shifting (composite score: TMT-B, ID/ED, SAS, SAT) SMD = 0.35 (−0.18 to 0.89), p = .20, k = 14	Attention (composite score: CPT, RVPT, FDI, spatial span, digit span forward) SMD = 0.50 (0.18 to 0.83), p = .002, k = 11	WM (composite score: spatial span, mental counting task, digit span, visual memory letter test, mental control, n-back, CANTAB spatial WM) SMD = −0.04 (−0.90 to 0.82), p = .92, k = 11
Lipszyc and Schachar, 2010	NA	NA	NA	NA	SST mean reaction time g = −0.09 (−0.67 to 0.49), p = .76, k = 4	SST RT SD: no study	SST RT g = 0.25 (−0.13 to 0.62), p = .2, k = 2	NA	NA	NA	NA

Effect sizes in terms of standardized mean difference (SMD), d, or Hedges' g (95 % confidence interval of lower to upper bound) are reported. ¹Standardized mean difference weighted by number of studies calculated across children, adolescents and adults from Pievsky and McGrath (2018) are reported. Note, the domain termed selective attention by Pievsky and McGrath (2018) is most often termed inhibition in the depression literature, assuming that the Stroop task measures interference control as one component of inhibition. ²Neurocognitive tests that were above the median effect size (−0.52) and below the median effect size are reported. ³Included studies used the CANTAB. AVLT = Adaptive Verbal Learning Test, CANTAB = Cambridge Neuropsychological Test, Automated Battery, COWAT = Controlled Oral Word Association Test, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, d-KEFS = Delis Kaplan Executive Function System, DMTS = Delayed Matching to Sample, DSST = Digit Symbol Substitution Test, FDI = Freedom from Distractibility Index, HVLIT = Hopkins Verbal Learning Test, IDIED = intra-dimensional/extra-dimensional, ITT = Inspection time task, k = number of studies, LM = Logical Memory Task, MCST = Modified Card Sorting Test, MRT = Manual reaction Time, NA = not assessed, NART = Natioanl Adult Reading Test PAL = Visual Paired Associates, PSI = Processing Speed Index, RAVLT = Rey Auditory Verbal Learning Test, ROCFT = Rey-Osterrieth Complex Figure Test, RT = reaction time, RTV = reaction time variability, RVPT = Rapid Visual Processing Test, SAS = Supervisory Attention System, SAT = Shifting Attention Test, SD = standard deviation, SDMT = Symbol Digit Modalities Test, SoC = Stockings of Cambridge, SST = Stop Singnal Task, TEA-Ch = Test of Everyday Attention for Children, TMT-A/B = Trial-Making-Test A/B, ToL = Tower of London, VPA = Verbal Paired Associates, VR = Visual Reproductions, WAIS-R = Wechsler Adult Intelligence Scale - revised, WASI = Wechsler Abbreviated Scale of Intelligence, WCST = Wisconsin Card Sorting Test, WISC = Wechsler Intelligence Scale for Children, WM = working memory, WMS = Wechsler Memory Scale.

Table 2b (continued)

	Fluency	Intelligence/ achievement	Memory	Planning	RT	RTV	Response Inhibition	Selective attention	Set shifting	Vigilance	WM
			p < .0001, k = 20 Visual reproduction delayed recall g = −0.64 (−0.85 to −.43), p < .0001, k = 7								
Ahern and Semkovska, 2017 Part 2: repeated-measures design ³	Letter fluency g = 0.06 (−0.26 to 0.38), p = .70, k = 2 Semantic fluency g = 0.03 (−0.60 to 0.67), p = .67, k = 2	NA	NA	NA	Processing speed TMT-A g = 0.68 (0.31 to 1.05), p < .001, k = 2 Stroop color naming and word reading g = 0.11 (−0.81 to 1.02, p = .82, k = 2	NA	NA	Stroop inhibition g = 0.33 (−0.38 to 1.059, p = .36, k = 2	Stroop switching g = 0.29 (−0.12 to 0.70), p = .17, k = 2 TMT-B: g = 0.45 (0.12 to 0.79), p = .008, k = 2	NA	NA

Effect sizes in terms of standardized mean difference (SMD), d, or Hedges' g (95 % confidence interval of lower to upper bound) are reported. ¹Standardized mean difference calculated across children, adolescents and adults from Pievsky and McGrath (2018) are reported. Note, the domain termed selective attention by Pievsky and McGrath (2018) is most often termed inhibition in the depression literature, assuming that the Stroop task measures interference control as one component of inhibition. ²Included studies used the CANTAB. ³Comparison between acute episode and remission: A non-significant difference indicates persistence of cognitive deficit. BADS = Behavioral Assessment of Dysexecutive Syndrome, CANTAB = Cambridge Neuropsychological Test, Automated Battery, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, DMTS = Delayed Matching to Sample, IDED = intra-dimensional/extra-dimensional, k = number of studies, NA = not assessed, NART = National Adult Reading Test, RAVLT = Rey Auditory Verbal Learning Test, ROCFT = Rey-Osterrieth Complex Figure Test, ROCF = RT = reaction time, RTV = reaction time variability, TMT-A/B = Trial-Making-Test A/B, ToL = Tower of London, WCST = Wisconsin Card Sorting Test, WM = working memory, WMS = Wechsler Memory Scale.

Table 2c

Meta-analytic findings of cross-sectional studies assessing cognitive functioning in first-degree relatives of individuals with vs. without MDD compared to neurocognitive profile of ADHD.

	Fluency	Intelligence/ achievement	Memory	PL	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
ADHD¹	0.49	0.60	0.49	0.49	0.35	0.66	0.52	0.46	0.35	0.56	0.54
MacKenzie ² et al., 2019	Language ³ SMD=-.29 (-.55 to -0.04), p = .03, k = 6	Full-scale IQ ⁴ : SMD=-0.19 (-0.31 to -0.08), p = .001, k = 32 Verbal IQ: SMD=-0.29 (-0.56 to -0.03), p = .03, k = 11 Perceptual IQ: SMD=-0.23 (-0.41 to -0.05), p = .02, k = 9 Academic performance ⁵ : SMD=-0.40 (-0.66 to -0.14), p = .02, k = 4	Memory ⁶ SMD=- .20 (-0.35 to -.05), p = .02, k = 8	NA	Processing speed ⁷ SMD=-0.14 (-0.38 to 0.10), p = .22, k = 8	NA	NA	Executive function ⁸ SMD=-0.22 (-0.49 to 0.05), p = .10, k = 9	Executive function ⁸ SMD=-0.22 (-0.49 to 0.05), p = .10, k = 9	Attention ⁹ SMD=-0.20 (-0.49 to 0.09), p = .13, k = 6	Executive function ⁸ SMD=-0.22 (-0.49 to 0.05), p = .10, k = 9

¹Standardized mean difference calculated across children, adolescents and adults from [Pievsky and McGrath \(2018\)](#) are reported. Note, the domain termed selective attention by [Pievsky and McGrath \(2018\)](#) is most often termed inhibition in the depression literature, assuming that the Stroop task measures interference control as one component of inhibition. ²Pooled effect sizes in terms of standardized mean difference (SMD) and 95 % confidence interval of lower to upper bound are reported. ³Pooled across Bayley scales of infant development, the early screening profiles (expressive language and receptive language), Reynell developmental language scales (expressive language and receptive language), and Word communication task. ⁴For full-scale, verbal, and perceptual IQ, effect sizes were pooled across different types of standardized tests (e.g., Wechsler Adult Intelligence Scale, Wechsler Intelligence Scale for Children, National Adult Reading Scale). ⁵measured with the Wechsler Individual Achievement Test, ⁶Pooled effect size across tests of verbal memory, visual memory, and autobiographical memory, ⁷Pooled across Trail Making Test A and Digit Symbol Coding from the Wechsler Preschool and Primary Scale of Intelligence, Wechsler Adult Intelligence Scale, Wechsler Intelligence Scale for Children, ⁸Pooled effect size across cognitive flexibility (Stroop Color-Word Interference), set shifting (Trail Making Test B, Wisconsin Card Sorting Test, Intra/Extra dimensional Set Shifting), working memory (Digit Span, Letter Number Sequencing, Letter N-Back), and hot executive function (e.g., emotional stroop, affective go/no-go), ⁹measured with the Continuous Performance Test, k = number of studies, NA = not assessed, PL = planning, RT = reaction time, RTV = reaction time variability, WM = working memory.

interference task).

With regard to executive functions, the most comprehensive meta-analysis was based on a large dataset from 113 studies (3936 patients, mean age = 46.0 and 3771 healthy controls, mean age = 45.0) analyzing performance across a wide range of individual tasks ([Snyder, 2013](#)). The findings on individual task performance as well as composite domain scores point to widespread deficits in executive functions

(verbal fluency, planning, selective attention/cognitive flexibility, set shifting, working memory) with effect sizes mostly in the small to medium range ($d = 0.38-0.72$, $k = 8-69$; $d = 0.97$, $k = 5$ for the Hayling task). These deficits were not influenced by age, which indicates depression related neurocognitive deficits that are comparable during the course of adulthood.

The Stroop interference task has been widely used to assess the

Table 2d

Meta-analytic findings of longitudinal studies on the association of cognitive functioning and subsequent depression compared to neurocognitive profile of ADHD.

	Fluency	Intelligence/ achievement	Memory	PL	RT	RTV	Response inhibition	Selective attention	Set shifting	Vigilance	WM
ADHD¹ Scully et al., 2017 Mean time between baseline and follow-up assessment (years): 12.65 (SD = 11.83) (range = 0.14–36 years)	0.49 NA	0.60 General cognitive function² overall analysis: $r = -0.088$ (95 % CI: -0.121 to -0.054), $p < 0.001$, $k = 34$ adjusted for baseline depression: $r = -0.032$ (95 % CI: -0.078 to 0.014), $p = 0.169$, $k = 9$	0.49 NA	0.49 NA	0.35 NA	0.66 NA	0.52 NA	0.46 NA	0.35 NA	0.56 NA	0.54 NA

¹Standardized mean difference calculated across children, adolescents and adults from [Pievsky and McGrath \(2018\)](#) are reported. Note, the domain termed selective attention by [Pievsky and McGrath \(2018\)](#) is most often termed inhibition in the depression literature, assuming that the Stroop task measures interference control as one component of inhibition. ²General cognitive function was assessed by standard IQ tests. If no measure captured broad cognitive functioning, the measure that was most closely aligned with constructs on a standard IQ test was used (working memory, processing speed, verbal comprehension, perceptual reasoning). Correlation coefficients (r) and 95 % confidence interval of lower to upper bound are reported. No differences were observed between studies that used standard IQ tests vs. specific cognitive tasks ($p = 0.57$), k = number of studies, NA = not assessed, PL = planning, RT = reaction time, RTV = reaction time variability, WM = working memory.

Table 3
Characteristics of included studies (part 2).

Study	Research aim	Design	Task	Inclusion criteria		Exclusion criteria	Sample size	Mean age (SD)	Sex (% female)	Mean IQ (SD)
				Participants	Age (years)					
Gallagher et al., 2015	To characterize neurocognitive variability among patients with mood disorders	CS	Double-stimulus CPT with letters	Adult patients with BP disorder vs. MDD vs. healthy controls matched for age, sex, IQ Diagnosis of BP disorder (euthymic or currently depressed) or MDD (single episode or recurrent) according to DSM-IV criteria based on clinical interview For BP cohort: stable medication for at least 4 weeks before recruitment For MDD cohort: psychotropic medication-free for at least 6 weeks before recruitment	18–65	For BP cohort: Any other current Axis I disorder (except anxiety) or substance dependence/abuse For MDD cohort: Any co-morbid medical/psychiatric diagnosis, recent substance misuse	MDD: N = 39 Controls: N = 138 Matched controls: N = 39 Euthymic BP: N = 86 Depressed BP: N = 33	MDD: 32.3 (10.1) All controls: 40.5 (12.5) Matched controls: 32.5 (10.4) Euthymic BP: 44.0 (9.7) Depressed BP: 47.0 (8.6)	MDD: 62 % All controls: 56 % Matched controls: NR Euthymic BP: 52 % Depressed BP: 42 %	MDD: 108.2 (11.0) All controls: 111.1 (8.6) Matched controls: 109.1 (9.2) Euthymic BP: 110.9 (10.3) Depressed BP: 109.0 (10.2)
Kaiser et al., 2008	To characterize intra-individual reaction time variability in neuropsychological task performance across psychiatric disorders	CS	Go/Nogo task	Adult patients with SZ vs. MDD vs. BPD vs. healthy controls Diagnoses according to DSM-IV criteria based on clinical interview Control subjects scoring less than 10 points on Beck Depression Inventory	17–58	Less than 9 years of education, IQ < 80, hearing deficit or neurological disease	MDD: N = 22 Controls: N = 25 SZ: N = 27 BPD: N = 16	MDD: 41.6 (9.2) Controls: 31.4 (8.8) SZ: 26.7 (9.4) BPD: 23.5 (5.2)	MDD: 64 % Controls: 52 % SZ: 48 % BPD: 100 %	MDD: 108 (13.1) Controls: 113 (13.2) SZ: 116 (11.0) BPD: 105 (12.4)
Vallesi et al., 2015	To determine cognitive flexibility deficits in major depression	CS	Perceptual decision-making task with speed/accuracy instructions	Adult MDD patients vs. healthy controls matched for age and education MDD diagnosis (current or past) according to DSM-IV criteria based on clinical interview	23–73	Any other Axis I disorder including history of substance abuse	Patients: N = 20 Controls: N = 28	Patients: 47.0 (NR) Controls: 48.0 (NR)	Patients: 75 % Controls: 54 %	NR
Van den Bosch et al., 1996	To determine the cognitive mechanisms that contribute to impaired performance in the CPT in patients with schizophrenia and depression	CS	Double-stimulus CPT with numbers	Adult patients with SZ vs. MDD vs. patient controls (nonpsychotic/nondepressed patients comprising diagnoses of somatoform, anxiety, adjustment, and personality disorder) vs. healthy controls Diagnoses according to DSM-III-R criteria based on clinical interview	> 18	Organic brain dysfunction and substance abuse	MDD: N = 16 Patient Controls: N = 19 Healthy Controls: N = 20 SZ: N = 21	MDD: 39.9 (12.7) Patient Controls: 29.5 (8.1) Healthy Controls: 32.2 (8.3) SZ: 28.7 (8.2)	MDD: 50 % Patient Controls: 63 % Healthy Controls: 55 % SZ: 33 %	NR
Roy et al., 2017	To assess cognitive functioning among adolescents with retrospectively self-reported ADHD and onset of depression, only ADHD, only	CS & LS base-line and follow-up (W4): 6–9 years later	Sustained attention - dots task from the Amsterdam Neuropsychological Task Program	Adolescents with primary school participation providing informed consent from both parent and child to participate in the study ADHD and depression diagnoses according to DSM-	10–12 onwards	NR	Baseline: N = 2230 W4: N = 1584 ADHD: N = 35 ADHD + Depression: N = 21 Only Depression: N = 282	Baseline 11.1 (NR) W4: 19.1 (NR)	Baseline: 50.8 % W4: 52.3 % ADHD: 37 % ADHD + Depression: 52 % Only Depression: 73 %	NR

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Table 3 (continued)

Study	Research aim	Design	Task	Inclusion criteria		Exclusion criteria	Sample size	Mean age (SD)	Sex (% female)	Mean IQ (SD)
				Participants	Age (years)					
Van Deuren et al., 2012	To assess the longitudinal association between neurocognitive functioning and affective problems in a large unselected cohort of adolescents	LS base-line and two follow-ups: W2: 2.5 years later, W3: 5 years later	Sustained attention - dots task from the Amsterdam Neuropsychological Task Program	IV criteria based on clinical interview	10–12 onwards	NR	Neither ADHD nor Depression: = 1211	Baseline: 11.1 (NR) W2: 13.6 (NR) W3: 16.3 (NR)	Neither ADHD nor Depression: 50 %	NR
				Lifetime diagnosis of major depressive episode, dysthymia, or minor depressive disorder with onset after baseline assessment						
				Adolescents with primary school participation providing informed consent from both parent and child to participate in the study						
				Data on neurocognitive tasks and on the affective problems scale of the Youth Self Report available at all assessment time-points			Baseline: N = 2230 W2: N = 2087 W3: N = 1819		Baseline: 50.7 % W2: 51.2 % W3: 52.3 %	

BP = bipolar, BPD = Borderline personality disorder, CPT = Continuous performance task, CS = cross-sectional design, MDD = major depressive disorder, LS = longitudinal design, SZ = schizophrenia, NR = not reported, W = wave of assessment.

severity of deficits in interference control in patients with MDD ($k = 20$ in the meta-analysis of Snyder, 2013). In contrast, performance in other tasks tapping into the domain of response inhibition, such as the stop signal task, the go/no-go task, and the flanker task widely implemented in ADHD research (Pievsky and McGrath, 2018) have rarely been implemented in MDD research. Snyder (2013) reported a composite score combining findings from the Stroop task with findings from the stop signal task ($k = 1$), the go/no-go task ($k = 4$), the flanker task ($k = 1$), the Hayling task ($k = 5$), and the Simon task ($k = 1$), pointing to impaired response inhibition in patients with MDD ($d = 0.58$). Other meta-analyses did not report on response inhibition in adult patients with MDD.

Compared with executive functions, non-executive functions have less often been studied during episodes of depression, and findings are more variable. With regard to the domain of learning and memory (most often assessed with list learning tasks), performance deficits have been reported in middle-age (Lim et al., 2013; Rock et al., 2014; Veiel, 1997; Zakzanis et al., 1998) and elderly adults with depression (Kindermann and Brown, 1997), but also in younger adults with a first-episode of depression (Ahern and Semkovska, 2017; Lee et al., 2012) with medium to large effect sizes. However, the number of studies included in the respective meta-analyses was overall small (range: 2–12) except for one meta-analysis including elderly adults [$k = 13–44$, (Kindermann and Brown, 1997)]. Also, the meta-analysis by Lim et al. (2013) revealed deficits in immediate verbal memory in depressed patients whereas delayed verbal and visual memory was not impaired.

Three meta-analyses summarizing findings from up to 7 studies reported deficits in visual (Lim et al., 2013; Rock et al., 2014) and auditory (Zakzanis et al., 1998) sustained attention with small to medium effect sizes. Sustained visual attention was also found to be impaired during the first-episode of depression (Ahern and Semkovska, 2017). Reduced processing speed is another deficit observed in depressed patients with effect sizes ranging from none to small, medium and large effects (Ahern and Semkovska, 2017; Lee et al., 2012; Lim et al., 2013; Rock et al., 2014; Snyder, 2013; Stefanopoulou et al., 2009; Veiel, 1997). Snyder (2013) reported a pooled effect size across several different types of RT tasks of $d = 0.33$ ($k = 23$) which increased marginally with mean patient age. Meta-analytic evidence also suggests that adult patients with MDD during an acute episode have lower scores on standard IQ tests compared with healthy controls (Snyder, 2013; Zakzanis et al., 1998) with effect sizes increasing with patient age (Snyder, 2013). However, overall effect sizes were small ($d = 0.14$, $k = 36$, composite score for vocabulary tests reported by Snyder, 2013; $g = 0.26$, $k = 10$, composite score for full scale IQ reported by Ahern et al., 2017).

Few studies exist that assessed the pattern and severity of neurocognitive dysfunctions in children with depression. One meta-analysis (Wagner et al., 2015) reported on studies that included children and adolescents with MDD (mean age: 13.6, range = 9–15) and demographically matched healthy controls and investigated performance differences across a wide range of executive and non-executive tasks known to be relevant from the literature in adults. The analysis was based on data from 447 patients and 1347 controls from 17 studies with high methodological quality as assessed by two independent reviewers using a standardized rating scale. Studies including patients with co-morbid ADHD were excluded. The findings revealed lower performance for patients vs. controls across several tasks on executive functioning (i.e., verbal fluency, planning, set shifting, Stroop interference, working memory) with effect sizes in the medium range ($SMD = 0.44–0.77$, $k = 3–6$). Semantic fluency ($SMD = 0.23$, $p = .29$, $k = 4$) and performance in the go/nogo task ($SMD = 0.19$, $p = .13$, $k = 3$) did not differ between groups. Patients' performance was also reduced in non-executive tasks on verbal learning and memory and sustained attention ($SMD = 0.22–0.52$, $k = 5–6$). Furthermore, scores on verbal, visual, and full scale IQ were significantly lower in patients compared to healthy controls with low to medium effect sizes ($SMD = 0.36–0.43$, $k = 6–10$).

Table 4

Findings on intra-individual RT variability from cross-sectional studies of patients with MDD vs. healthy controls and from prospective cohort studies.

Study	Design	Task	Group differences in parameters of intra-individual RT variability (Mean, SD)			
			Standard deviation of all RTs for each individual (=iSD)	Coefficient of variation (iSD/mean RT)	Ex-Gaussian decomposition: μ , σ , τ	Diffusion model decomposition: drift rate (v), non-decision time (T_{er}), boundary separation (a)
Gallagher et al., 2015	CS	Double-stimulus CPT with letters	MDD: 104.8 (50.28), CO: 83.1 (26.53) $F(1,76) = 5.66$, $p = 0.02$, $d = 0.54$, 95 % CI: 0.08 to 0.99	MDD: 0.27 (0.09) CO: 0.23 (0.09) $F(1,76) = 3.55$, $p = 0.06$, $d = 0.43$, 95 % CI: -0.02 to 0.87	μ : MDD: 298.5 (78.66), CO: 309.4 (95.24) $F(1,76) = 0.301$, $p = 0.59$, $d = -0.12$, 95 % CI: -0.57 to 0.32 σ : MDD: 40.8 (39.62), CO: 31.2 (17.97) $F(1,76) = 1.90$, $p = 0.17$, $d = 0.31$, 95 % CI: -0.14 to 0.76 τ : MDD: 84.5 (47.67), CO: 68.9 (28.71) $F(1,76) = 3.03$, $p = 0.09$, $d = 0.39$, 95 % CI: -0.06 to 0.84	NA
Kaiser et al., 2008	CS	Go/Nogo task	Go task: MDD: 0.12 (0.05), CO: 0.12 (0.04), $p = 0.96$ Nogo task: MDD: 0.17 (0.06), CO: 0.14 (0.05), $p = 0.15$	Go task: MDD: 0.24 (0.08), CO: 0.212 (0.06), $p = 0.29$ Nogo task: MDD: 0.36 (0.114), CO: 0.274 (0.09), $p = 0.026$	NA	NA
Vallesi et al., 2015	CS	Perceptual decision-making task	NA	NA	NA	Drift rate: MDD < CO, $F(1,46) = 10.49$, $p = .0022$ Non-decision time: MDD = CO, $p = .72$
Van den Bosch et al., 1996	CS	Double-stimulus CPT with numbers	Target stimuli: MDD: 138 (60.0), Control patients: 107 (36.0), Healthy CO: 101 (23.0), SZ: 140 (64.0) Group effect: $F = 3.4$, $p = 0.05$	NA	NA	NA
Roy et al., 2017	CS & LS	Sustained attention - dots task	Baseline: D: 1688 (828), CO: 1652 (810), ADHD: 2095 (762) D v/s CO: Mean difference: 16.51, $SE = 35.78$, $p = 0.64$ ADHD v/s D: Mean difference: 258.74, $SE = 96.71$, $p = 0.008$ Follow-up/W4: D: 862 (366), CO: 858 (366), ADHD: 916 (365) D v/s CO: ns, ADHD v/s D: ns	NA	NA	NA
Van Deurzen et al., 2012	LS	Sustained attention - dots task	Baseline: girls: 1.66 (0.86), boys: 1.86 (0.97) Increased iSD of mean RTs at baseline predicts affective problems in girls at wave 2 ($\beta = 0.09$, $p = 0.005$, unadjusted for baseline affective problems) and wave 3 ($\beta = 0.08$, $p = 0.015$, unadjusted for baseline affective problems). No significant association when adjusted for baseline affective problems ($\beta = 0.03$, $p = 0.29$ at wave 2, $\beta = 0.05$, $p = 0.09$ at wave 3). No significant associations in boys at wave 2 and wave 3 (all p -values > 0.11)	NA	NA	NA

ADHD = attention-deficit/hyperactivity disorder, CPT = Continuous performance task, CS = cross-sectional design, D = participants with an onset of depression between baseline and wave 4, MDD = major depressive disorder, LS = longitudinal design, NA = not assessed, RT = reaction time, SZ = schizophrenia, W = wave of assessment.

Several studies on neurocognitive deficits in current depression have focused specifically on young people at the transition from childhood into adulthood (between the ages of 12 and 25 years) and the findings have been recently synthesized in a meta-analysis (Goodall et al., 2018). The meta-analysis included 23 studies reporting on patients with MDD (range of mean age: 12.8–22.8 years) and pooled effect sizes were reported for executive and non-executive cognitive domains. The findings revealed small to moderate deficits in general cognitive functioning as measured by standardized IQ tests (full scale IQ and subtests on vocabulary and comprehension, $SMD = 0.32$ – 0.46 , $k = 5$ – 6), moderate

deficits in learning and memory functions ($SMD = 0.51$ – 0.78 , $k = 5$ – 6), as well as small to moderate deficits in processing speed ($SMD = 0.27$, $k = 16$) and sustained attention ($SMD = 0.50$, $k = 11$). These deficits remained significant when omitting low quality studies, except for the domains of processing speed and verbal learning. In contrast, no significant differences were found between groups on measures of executive functions including domains of verbal fluency ($SMD = 0.27$, $p = 0.13$, $k = 3$), working memory ($SMD = -0.04$, $p = 0.13$, $k = 3$), planning ($SMD = 0.13$, $p = 0.72$, $k = 6$), set-shifting ($SMD = 0.35$, $p = 0.20$, $k = 14$), and response inhibition ($SMD = 0.06$, $p = 0.68$,

$k = 11$) (note, performance in the Stroop interference task contributed to the response inhibition composite score), and these findings did not change when the analysis was restricted to high quality studies. Moderator analyses revealed lower set-shifting performance in patients younger than 15 vs. patients older than 15 years old ($SMD = .71$, $CI: .00–1.41$, $p = 0.05$, $k = 7$). The effect of age could not be analyzed for the other domains. Focusing specifically on performance in the stop signal task as measure of response inhibition, another meta-analysis (Lipszyc and Schachar, 2010) also found no performance deficit in executive functioning in young adults with MDD (mean age: 24, range: 16–39) compared to healthy controls (stop signal mean RT: $g = -0.09$, $p = 0.76$, $k = 4$; stop signal RT: $g = 0.25$, $p = 0.20$, $k = 2$).

3.1.2. Remitted depression

In order to determine the persistence of cognitive dysfunctions following remission of depressive symptoms, three meta-analyses reported on cross-sectional studies that compared neurocognitive task performance between patients in remission from a major depressive episode and healthy controls (Bora et al., 2013; Rock et al., 2014; Semkovska et al., 2019), and one meta-analysis reported on studies following patients to remission using a longitudinal design (Ahern and Semkovska, 2017). All meta-analyses included mainly adult samples (see Tables 1 and 2b).

Bora et al. (2013) included 895 remitted adult patients and 997 controls from 27 studies and found cognitive impairments in the majority of studied functions including executive (selective attention/cognitive flexibility, set shifting, working memory, planning, and semantic fluency) and non-executive domains (sustained attention, processing speed, verbal and visual memory) with small to medium effect sizes ($d = 0.39–0.74$; composite score including all domains: $d = 0.47$). The magnitude of observed deficits, with the exception of performance in the Stroop task ($d = .82$), were generally modest when patients with a late onset of depression (after 50–65 years) were excluded ($d = 0.21–0.54$). Another meta-analysis that included a small number of studies focusing on tasks from the Cambridge Neuropsychological Test Automated Battery (range of number of aggregated studies: 3–4) (Rock et al., 2014) also reported moderate deficits in executive functions (planning, set shifting, and working memory), sustained attention, and visual memory in patients remitted from depression compared to healthy controls.

The most comprehensive meta-analysis on cognitive functioning after a major depressive episode synthesized data on 75 cognitive tests tapping into 18 executive and non-executive domains derived from 252 studies including 11,882 remitters and 8533 healthy controls (Semkovska et al., 2019). In the meta-analysis, the quality of the remission criterion was rated, and analyses were provided based on high quality studies. Significant impairments were observed for 73 % of the 75 cognitive constructs. In terms of executive functions, consistent deficits, generally small or medium in size ($g = -0.23$ to -0.59 , $k = 5–63$), were found in tasks on verbal fluency, selective attention as assessed with the Stroop task, planning, and working memory (except for digit span forward, $g = -0.13$, $p = .08$, $k = 46$). Set-shifting was not consistently impaired in patients, with effect sizes ranging from small and non-significant to medium depending on the specific implemented task ($g = 0.07$ to -0.60 , $k = 8–73$). Deficits in the small to medium range were also found in tasks on non-executive functions (i.e., processing speed, sustained attention) ($g = -0.37$ to -0.79 , $k = 4–73$), with large impairments observed only for some of the long-term memory variables (logical and visual memory tasks, $g = -0.81$ to -0.88 , $k = 4–24$). Measures on full scale IQ were significantly lower in remitters compared to controls (WAIS, $g = -0.16$, $k = 66$), however intellectual functioning unconstrained by speed did not differ between groups. These findings point to widespread cognitive impairments that persist into remission of a major depressive episode. Importantly, performance worsened with increasing numbers of previous depressive episodes, especially in the domains of processing speed, verbal fluency, and set shifting when using

time constrained tasks, and full scale IQ.

Only few studies have used longitudinal designs assessing cognitive performance during the acute phase of depression and again during remission in the same patients. Two studies that included adolescents and adults with a first-episode of depression have been included in a meta-analysis (Ahern and Semkovska, 2017) which found persistent impairments in verbal fluency and performance in the Stroop interference task while processing speed (TMT-A) and set-shifting performance (TMT-B) were significantly improved following remission (see Table 2b).

3.1.3. High-risk populations

A considerable amount of studies have compared cognitive task performance between unaffected first-degree relatives of individuals with MDD and first-degree relatives of individuals without MDD. The findings have been quantitatively summarized in a recent meta-analysis (MacKenzie et al., 2019) including 54 unique samples from 90 studies (in total 3246 first-degree relatives and 5222 control relatives) (see Tables 1 and 2c). The samples were offsprings of parents with MDD (72.2 %), any first-degree relatives (22.2 %), or siblings/twins (5.6 %) and included infants, children, adolescents, and adults (mean age: 15.38 years [$SD = 13.66$] for relatives of individuals with MDD and 14.70 years [$SD = 12.37$] for control relatives). Eligible studies assessed broad cognitive abilities (i.e., IQ and academic achievement) as well as specific executive and non-executive functions from various domains. When pooling across all domains, the meta-analysis found robust evidence for cognitive impairment in the unaffected first-degree relatives of individuals with MDD vs. first-degree relatives of controls ($SMD = -0.19$, $n = 54$). However, when analyzing task performance for individual domains, significant effect sizes were found only for a subset of non-executive functions (measures on full scale IQ, verbal IQ, and perceptual IQ: $SMD = -0.19$ to -0.29 , $k = 9–32$; academic achievement: $SMD = -0.40$, $k = 4$; memory: $SMD = -0.20$, $k = 8$, language: $SMD = -0.29$, $k = 6$) and were relatively small compared to estimates derived from case-control studies of patients with MDD. Performance on tasks tapping into the domains of executive functions (pooled across tasks on working memory, set-shifting, and selective attention as assessed by the Stroop interference task, and “hot” executive functions), sustained attention, processing speed, psychomotor skills, and cognitive-emotional processing, was also lower in first-degree relatives of individuals with vs. without MDD ($d = -0.14$ to -0.30 , $k = 6–9$), however differences were not statistically significant. Cognitive impairment was not affected by participant’s age and other sample characteristics (e.g., socioeconomic status, geographic region, type of sample).

3.1.4. Prospective studies

In order to test the hypothesis that neurocognitive deficits may reflect a risk factor for developing depression, population-based prospective studies have been conducted assessing the association between cognitive functioning determined at baseline and depression determined at a follow-up time-point. Our search identified one meta-analysis of longitudinal datasets including large cohorts (Scult et al., 2017) which focused on general cognitive ability rather than exploring specific subtypes of neurocognitive function. The meta-analysis included 29 studies reporting on 121,749 participants from 34 unique samples (predominantly school samples, community samples, and birth cohorts) including children, adolescents, and adults under the age of 65 (mean age at baseline: 14.41 years [$SD = 10.22$]) (see Tables 1 and 2d). General cognitive ability was mainly assessed by standard IQ tests in the included studies, but specific cognitive tasks that were closely aligned with constructs on a standard IQ test (e.g., working memory, processing speed, verbal comprehension, perceptual reasoning) were also allowed when standard IQ tests had not been conducted. The overall analysis revealed a weak correlation ($r = -0.088$, 95 % $CI -0.121$ to -0.054 , $p < 0.001$, $k = 34$) between general cognitive impairment at baseline and subsequent depression (mean time between baseline and follow-up

assessment: 12.65 years, SD = 11.83), especially when depression was determined by a clinical diagnosis of depression ($r = -0.035$, 95 % CI -0.054 to -0.017 , $p < 0.001$, $k = 12$) rather than symptom severity ($r = -0.121$, 95 % CI -0.168 to -0.073 , $p < 0.001$, $k = 22$). Importantly, this correlation was not significant after accounting for depressive symptoms at the time of cognitive assessment ($r = -0.032$, 95 % CI -0.078 to 0.014 , $p = 0.169$, $k = 9$). Neither age at baseline nor age at follow-up assessment as well as other factors such as time between assessments, IQ, percent of sample that was female, percent of the sample that was white, and study quality changed the observed null effect.

3.2. Part 2. Systematic review of individual studies on intra-individual RT variability in depression

The search identified 561 articles (see Fig. 2). After deleting duplicates (85), 476 potentially relevant articles were identified from which 445 were removed after title and abstract screening against the selection criteria. The remaining 31 articles were reviewed in full, resulting in 6 articles eligible for the review. Four cross-sectional studies were found that reported on intra-individual RT variability derived from neurocognitive tasks from the domains of response inhibition, sustained attention, and perceptual decision making in adult patients with a current diagnosis of MDD compared to healthy controls (Gallagher et al., 2015; Kaiser et al., 2008; Vallesi et al., 2015; van den Bosch et al., 1996). Three of these studies also included other patients groups (e.g., patients with schizophrenia, bipolar disorder, or Borderline personality disorder) (Gallagher et al., 2015; Kaiser et al., 2008; van den Bosch et al., 1996). Furthermore, two prospective cohort studies were identified that assessed neurocognitive functioning including RT variability during early adolescence while affective problems were followed up into late adolescence/early adulthood (Roy et al., 2017; van Deurzen et al., 2012) (see Tables 3 and 4).

Two studies assessed performance in the continuous performance task and reported that the individual RT standard deviation (i.e., the standard deviation of item-by-item RT for each individual) - which is the most common method to quantify intra-individual RT variability in cognitive and clinical research (Karalunas et al., 2014) - was increased in patients with MDD compared to demographically matched healthy controls (Gallagher et al., 2015; van den Bosch et al., 1996). With the majority of patients in their first depressive episode, patients with MDD (number of patients: $N = 39$) were medication-free in the study by Gallagher et al. (2015), whereas medication status was not reported by van den Bosch et al. (1996). Furthermore, Gallagher et al. (2015) used additional estimates of intra-individual variability (i.e., the coefficient of variation and ex-Gaussian analyses to decompose RT distributions: parameters μ , σ , τ), but did not reveal significant differences between patients with MDD and controls in any of these parameters (Gallagher et al., 2015) (however, the coefficient of variation and tau were increased at a trend level in patients vs. controls, see Table 4). Another study compared two parameters of intra-individual RT variability obtained from a go/nogo task between a sample of 22 patients with MDD who were all medicated and 25 demographically matched healthy controls. The individual RT standard deviation did not differ between groups. However, when taking differences in mean RT into account by calculating the coefficient of variation, patients with MDD showed higher intra-individual RT variability than controls in the nogo task condition that requires the inhibition of a prepotent response. In contrast, there was no group difference in the go task condition. Furthermore, another study (Vallesi et al., 2015) that was conducted to assess cognitive flexibility in MDD by implementing a perceptual decision-making task with instructions to stress either speed or accuracy, analyzed RT data by means of a diffusion model (Ratcliff and Rouder, 1998). The findings revealed that the drift rate parameter (v), an indicator of the rate at which information is accumulated in favor of one of the response criterion, was generally lower in patients with MDD

($N = 20$, medicated) than controls ($N = 28$) and was negatively correlated with ratings of depression severity in the patient group ($r = -0.52$, $p = 0.018$). The non-decision time parameter (Ter), reflecting processes that are not directly related to the response decision, did not differ between groups.

With regard to intra-individual RT variability and its association with depression, the literature search revealed two reports on the same prospective cohort study (i.e., the Tracking Adolescents 'Individual Lives Survey) that followed children and adolescents into young adulthood (Roy et al., 2017; van Deurzen et al., 2012). Individual RT standard deviation was obtained from the Sustained Attention Dots task and over the course of ten years participants reported affective problems using the Youth Self Report at the baseline wave (mean age: 11.1), the second wave (mean age: 13.6), the third wave (mean age: 16.3), and the fourth wave (mean age: 19.1) of assessment. The longitudinal analysis (van Deurzen et al., 2012) revealed that increased intra-individual RT variability assessed at baseline predicted self-reported affective problems after 2.5 years and after 5 years in girls but not in boys. However, after adjustment for baseline affective problems, the predictive effects of intra-individual RT variability disappeared ($\beta = 0.03$, $p = 0.29$ after 2.5 years, $\beta = 0.05$, $p = 0.09$ after 5 years). In a second study, Roy et al. (2017) compared intra-individual RT standard deviation from the Sustained Attention Dots task between participants with an onset of depression after wave 1 (which was retrospectively assessed at wave 4 based on a clinical interview) and control participants with neither ADHD nor an onset of depression. Both, at baseline and at wave 4, intra-individual RT variability did not differ between participants with an onset of depression and controls (see Table 4).

4. Discussion

The present systematic review aimed at studying the role of ADHD-related neurocognitive impairments in the development of MDD or clinically relevant depressive symptoms to elicit possible neurocognitive risk factors explaining an increased rate of depression in individuals with a diagnosis of ADHD. To this end, we provided a systematic review of meta-analyses of cross-sectional and longitudinal studies on neurocognitive dysfunctions in depression taking different developmental stages into account with a focus on executive (verbal fluency, planning, response inhibition, selective attention/cognitive flexibility, set shifting, working memory) and non-executive functions (reaction time/processing speed, intra-individual RT variability, vigilance/sustained attention, learning and memory, intelligence) that are known to be impaired in ADHD (Pievsky and McGrath, 2018). The majority of identified meta-analyses ($k = 14$) reported on cross-sectional studies comparing neurocognitive functioning among patients with current depression versus healthy controls (range of number of aggregated studies between 2 and 69 across domains) and patients in remission from a depressive episode ($k = 4$, range of number of aggregated studies between 2 and 73 across domains). These studies predominantly included middle-aged adults, whereas considerably less reports were found on neurocognitive functioning in depressed children and adolescents ($k = 1$, range of number of aggregated studies between 3 and 10 across domains) as well as young adults at the phase of transition from adolescence into adulthood ($k = 2$, range of number of aggregated studies between 2 and 16 across domains) (see Fig. 3). This is in contrast to the ADHD literature where the overall number of studies on neurocognitive dyfunctions is much higher (i.e., range of number of aggregated studies between 37 and 497 across domains in the meta-analysis of Pievsky and McGrath, 2018) and which include most often children (85 %) (Pievsky and McGrath, 2018) rather than adolescents and adults. This is one of many important caveats that need to be taken into account when comparing the results of our extensive two systematic literature searches. Comparing the neurocognitive profiles of depression and ADHD across several executive and non-executive functions (Fig. 3), one prominent finding was the lack of studies with respect to

intra-individual RT variability in depression. Only one meta-analysis which focused specifically on performance in the stop signal task in young adults, searched for reports on this domain in patients with MDD but did not reveal any studies (Lipszyc and Schachar, 2010). All other identified meta-analyses did not report on this domain. Because intra-individual RT variability is central to ADHD (Karalunas et al., 2014; Pievsky and McGrath, 2018; Vainieri et al., 2020), we performed an additional literature search on individual studies assessing intra-individual RT variability from neurocognitive tasks on “cold” cognitive functions in MDD revealing four cross-sectional and two longitudinal studies.

Besides these studies on neurocognitive impairment in patients with depression compared to healthy controls, the search identified one meta-analysis that included studies comparing neurocognitive functioning between first-degree relatives of individuals with vs. without MDD (MacKenzie et al., 2019). However, the number of aggregated studies in this meta-analysis was limited for most domains (between 4 and 11 studies, with the highest number of aggregated studies of 32 for full scale IQ). Most importantly with respect to our hypothesis that ADHD-related neurocognitive impairment might reflect a risk factor for developing subsequent depression, the search revealed only one meta-analysis that reported on findings from 34 prospective studies assessing the association between neurocognitive functioning determined at baseline and depression determined at a follow-up time-point (Scully et al., 2017). This study focused on only one domain, i.e. general cognitive function as assessed by standard IQ tests.

Before we discuss these findings in more detail, we turn to several important methodological constraints related to the chosen search strategy or due to the quality of the reviewed studies, that complicate the comparison of the neurocognitive profiles of MDD and ADHD. While the present study followed the standard PRISMA guidelines of systematic literature searches (Moher et al., 2009) and was conducted by two independent raters, the selection of electronic databases (EBSCOhost, PubMed, and Cochrane Reviews), the definition of search criteria (i.e., including filters of time and language), and the evaluation of those criteria are subject to some degree of subjectivity which can bias the final set of included studies. For example, the search was restricted to articles published in English starting with the year 1992 [the year when the diagnostic criteria for major depression were published in the ICD-10 Classification of Mental and Behavioural Disorders (World Health Organization, 1992)]. Also, the identified meta-analyses reported predominantly on samples from North America, Europe, and Australia. We cannot fully exclude that potentially eligible studies have been omitted in the search process. Given the large number of primary data studies, especially reporting on adults with acute depression, we decided to focus on meta-analytic evidence, disregarding findings from primary data studies which have not been synthesized by meta-analyses. Meta-analyses were not available especially for the domain of intra-individual RT variability, and therefore a second search was done on primary studies for this domain. Also, we chose to base our review on an earlier meta-analysis reporting on “cold” neurocognitive impairment in ADHD (Pievsky and McGrath, 2018) and explicitly excluded studies that reported only on performance in “hot” cognitive tasks, which test responses to positively or negatively valenced stimuli. This was done in order to avoid confounding of altered emotion processing and neurocognitive impairment. However, emotion dysregulation has been increasingly recognized as an important part of ADHD throughout the lifespan (Faraone et al., 2019; Graziano and Garcia, 2016; Shaw et al., 2014). Impairments in the processing of emotional stimuli both at the level of non-executive and executive functions (Graziano and Garcia, 2016; Shaw et al., 2014) as well as abnormalities in the appraisal of reward and punishment (Marx et al., 2018) have been reported in children and adults with ADHD. Conceptualizing depression as a disorder of emotion regulation (Nolen-Hoeksema et al., 2008; Visted et al., 2018), numerous studies in patients with MDD have demonstrated biases in the processing of emotional information at different levels

including attention, memory, and interpretation of ambiguous stimuli (Joormann and Stanton, 2016; LeMoult and Gotlib, 2019; Mathews and MacLeod, 2005), abnormalities in reinforcement processing (Eshel and Roiser, 2010), and impairments in executive functions in the context of negative mood-eliciting situations (Etkin et al., 2013; Joormann and Stanton, 2016; LeMoult and Gotlib, 2019). Therefore, alterations in emotional processing and abnormalities in the usage of affective information to guide behavior not included in our review may also constitute an important facet of the neurocognitive profiles of ADHD and MDD, but may also overlap with frequent ADHD comorbidities, such as conduct disorder (Fairchild et al., 2019) and autism spectrum disorder (Waddington et al., 2018). Additional efforts are needed to characterize the similarities and differences between the disorders with regard to performance in tasks on “hot” cognitive functions which was beyond the scope of the present review.

With regard to the reviewed studies, there were some inconsistencies in the definition and assignment of tasks to cognitive domains among the ADHD and depression literature. This was most evident for the Stroop interference task which has been most often assigned to the domain of inhibition/interference control rather than selective attention/cognitive flexibility as suggested by Pievsky and McGrath (2018). In order to clarify, according to Barkley (1997) impaired response inhibition, which has been suggested as the central deficit in ADHD, comprises three components, i.e., inhibition of the initial prepotent response to an event, stopping of an ongoing response, and interference control. The domain of response inhibition as defined by Pievsky and McGrath (2018) most likely reflects the first two of these components which have been widely assessed with tasks such as continuous performance task (i.e. commission errors), stop-signal reaction time and the go/nogo task in ADHD research. The domain of selective attention/cognitive flexibility according to Pievsky and McGrath (2018) rather refers to the inhibition of cognitive interference which has been widely operationalized through the Stroop interference task but also the Flanker task. Also, whereas working memory span tasks forward (e.g., digit or visual span) have been assigned to the domain of working memory in the ADHD literature, the categorization of performance in this task was more variable in the depression literature (assignment to the domains of either working memory or sustained attention). In addition, the domain vigilance according to Pievsky and McGrath (2018) is often termed sustained attention in the depression literature. Acknowledging these conflicting definitions, in this review we followed the definitions of cognitive domains proposed by Pievsky and McGrath (2018) to allow cross-diagnostic comparisons. Furthermore, whereas some studies reported effect sizes for specific tasks, other meta-analyses reported composite scores on data from tasks tapping into the same domain. While this approach can increase statistical power and reduces problems of multiple comparisons when assessing a large number of cognitive functions, it is problematic when tasks are grouped differentially across studies. Differential effects on specific neurocognitive functions cannot be parsed out making group comparisons of specific neurocognitive functions difficult. This methodological problem was found especially for the meta-analysis by MacKenzie et al. (2019) where the domain of executive function included tasks on set shifting, selective attention (Stroop task) and working memory as well as tasks on “hot” executive functions such as for example the emotional Stroop task, the affective go/nogo task, and the monetary incentive delay task. In addition, composite inhibition scores including Stroop interference performance as well as performance in tasks on response inhibition have been reported (Goodall et al., 2018; Snyder, 2013).

Whereas organic brain damage and other co-occurring medical and neurological conditions were exclusion criteria in some of the identified meta-analyses (Bora et al., 2013; Kindermann and Brown, 1997; Lim et al., 2013; Semkowska et al., 2019; Snyder, 2013; Veiel, 1997), most studies did not take psychiatric comorbidities into account. Few of the meta-analyses excluded patients with MDD with psychotic symptoms or disorders (Epp et al., 2012; Goodall et al., 2018; Lim et al., 2013;

Semkovska et al., 2019) and/or substance abuse (Lee et al., 2012; Lim et al., 2013; Wagner et al., 2015) – conditions that likely increase the severity of cognitive impairment in depression (Baune et al., 2009; Bora et al., 2009; Zaninotto et al., 2015). Furthermore, only one meta-analysis restricted the analysis to studies that excluded patients with co-morbid anxiety disorders, another common comorbidity of depression, which did not impact effect sizes (Snyder, 2013). With regard to ADHD, only the meta-analysis on neurocognitive dysfunctions in children and adolescents with depression (Wagner et al., 2015) explicitly excluded patients with this comorbidity suggesting that the observed group differences were not confounded by ADHD-related impairments. However, co-morbid ADHD was neglected in studies including adults. Given that ADHD occurs frequently in adults with a mood disorder (Alpert et al., 1996; Kessler et al., 2006; McIntosh et al., 2009), we cannot exclude that the pattern and/or severity of the neurocognitive impairments observed in adults with depression are driven, at least partially, by neurocognitive impairments associated with co-morbid ADHD.

4.1. Current depression

Acknowledging these limitations, the results of this systematic review revealed widespread impairments across executive and non-executive functions with effect sizes mostly in the small to medium range, both in adults and children with acute depression (Ahern and Semkovska, 2017; Lee et al., 2012; Lim et al., 2013; Rock et al., 2014; Snyder, 2013; Stefanopoulou et al., 2009; Veiel, 1997; Wagner et al., 2012; Zakzanis et al., 1998). Whereas the severity of executive dysfunctions seems to persist during the course of adulthood (Snyder, 2013), impairments in non-executive functions including psychomotor speed, memory, and general cognitive functioning might further increase (Snyder, 2013; Zakzanis et al., 1998). Importantly, a different pattern of cognitive dysfunction emerged during the transition stage from adolescence to adulthood. Youths and young adults with current depression showed impairments in non-executive functions including learning and memory, sustained attention, processing speed, and IQ, while executive functions from the domains of verbal fluency, working memory, planning, shifting, selective attention/cognitive flexibility, and response inhibition were largely intact (Goodall et al., 2018; Lipszyc and Schachar, 2010). Preliminary evidence from a moderator analysis revealed larger set-shifting deficits in patients younger than 15 vs. patients older than 15 years old (Goodall et al., 2018).

When comparing the neurocognitive profile associated with acute depression with the neurocognitive profile of ADHD taking different developmental stages into account (Pievsky and McGrath, 2018), the results point to two important similarities: First, in line with the age-dependent pattern of neurocognitive impairment in ADHD (Pievsky and McGrath, 2018), impairments were most evident in adults and children with MDD whereas less impairment was found in emerging adults. On the one side, methodological constraints in terms of the low number of studies including children/adolescents as well as young adults, and because primary studies exclusively used cross-sectional rather than longitudinal designs, might explain this pattern. On the other side, these age-dependent trajectories of neurocognitive impairment observed across disorders might be attributable to increased intra- and interindividual variability in onset and speed of developmental changes in brain structure (Blakemore and Choudhury, 2006; Fuhrmann et al., 2015; Shaw et al., 2007; Straub et al., 2019) and maturation of associated cognitive functions due to variable stages of puberty. Specifically, maturation of executive functions that rely on frontal structures continues into adolescence (Luna et al., 2004) and young adulthood (Luca et al., 2003). Consistent with this assumption, deficits in non-executive but not in executive functions were reported for adolescents and young adults with MDD in the meta-analysis by Goodall et al. (2018).

Second and more important with regard to our research question,

there was some degree of overlap between disorders, both in terms of the pattern (i.e., both patients with MDD and patients with ADHD show reduced performance in tasks on executive and non-executive functions) and the severity of neurocognitive dysfunctions (i.e., small to moderate effect sizes in MDD and ADHD). Specifically, in line with the widespread impairments observed across executive and non-executive functions in patients with ADHD (Pievsky and McGrath, 2018), adults and children with MDD showed lower performance in several tasks on executive functions including verbal fluency, planning, selective attention/cognitive flexibility, set shifting and working memory with small to moderate effects. In addition, impairments in non-executive functions included verbal memory, sustained attention, and processing speed (note, processing speed was only assessed in adults), again with small to moderate effects. Also, IQ was lower in patients with MDD but this effect seemed to be stronger in children than adults. With regard to non-executive functions, adolescents with MDD showed a similar pattern of impairment (i.e., verbal memory, sustained attention, processing speed, and IQ with small to moderate effect sizes), however executive functions were not impaired. Besides this cross-diagnostic overlap in the reported wide-spread impairment in executive and non-executive functions in childhood and adulthood, the systematic review revealed no consistent evidence for an overlap with regard to response inhibition and intra-individual RT variability – two domains that have been extensively studied in patients with ADHD (Pievsky and McGrath, 2018) and that may be central to ADHD etiology (Barkley, 1997; Karalunas et al., 2014; Nigg et al., 2005b).

Meta-analysis of findings from three studies including the go/nogo task, reported no performance deficit in children with acute MDD (Wagner et al., 2015). In addition, response inhibition as assessed with the stop signal task was not impaired in adolescents and young adults with MDD (Lipszyc and Schachar, 2010). The few findings from adults were inconclusive due to the use of composite scores calculated across performance in the Stroop task and several response inhibition tasks (Snyder, 2013). In addition, the meta-analyses of studies including patients with MDD in remission, high-risk samples, or prospective designs, did not include studies with tasks tapping into this domain. Thus, while tentative based on the small number of studies and the use of cross-sectional designs, the findings point to intact response inhibition in children and adolescents with acute MDD and therefore do not provide reasonable evidence to suggest that deficits in response inhibition may contribute to the increased risk for co-morbid depression among adolescents and young adults with ADHD.

In addition, meta-analytic evidence on intra-individual RT variability was lacking in the depression literature, and therefore a second search on individual studies was conducted which identified few cross-sectional and longitudinal studies in adults and adolescents. Although different methodological approaches were used, the findings of studies in adults revealed increased RT variability in adults with MDD (Gallagher et al., 2015; Kaiser et al., 2008; Vallesi et al., 2015; van den Bosch et al., 1996). While this pattern resembles the increase in intra-individual RT variability observed in patients with ADHD (Karalunas et al., 2014; Pievsky and McGrath, 2018; Vainieri et al., 2020), it cannot be ruled out that this overlap was due to ADHD-related impairments given that this comorbidity was not taken into account in the adult samples. In contrast, intra-individual RT variability was not impaired in a sample of adolescents and young adults with MDD with no co-morbid ADHD and the same patients did not show any alterations in intra-individual RT variability when assessed during childhood before they had developed MDD (Roy et al., 2017). Furthermore, the same study found a significant increase in intra-individual RT variability in a sample of children who were later diagnosed with ADHD but not MDD pointing to an ADHD-specific impairment. In the same cohort, intra-individual RT variability assessed during childhood was not found to be predictive of self-reported affective problems during early and late adolescence when baseline affective problems were taken into account (van Deurzen et al., 2012). These findings from cross-sectional and

longitudinal studies do not suggest that intra-individual RT variability represents a candidate cognitive risk factor for the development of co-morbid depression in ADHD.

In conclusion, the systematic review of studies reporting on patients with acute depression revealed that their pattern and severity of cognitive dysfunctions observed across executive and non-executive domains shows some overlap with the neurocognitive profile of ADHD at different developmental stages across the lifespan. Given that general cognitive impairment, reflected by low IQ and/or specific cognitive dysfunctions that partially overlap with measures of IQ, may increase the vulnerability to depression and other forms of psychopathology (Barnett et al., 2006; Watson and Joyce, 2015), the overlap of impairments in executive functions (i.e., verbal fluency, planning, selective attention, set shifting, and working memory) and non-executive functions (i.e., verbal memory, sustained attention, processing speed, and IQ) may point to a developmental pathway from ADHD to depression that is mediated by ADHD-related neurocognitive impairments. Still, for some clearly ADHD-related impairments, i.e. response inhibition and response time variability, at least for depression in childhood, adolescence, and early adulthood, this might be excluded.

To determine the role of neurocognitive dysfunctions for the development of co-morbid depression in ADHD, an important question is to what extent impairments in executive and non-executive functions in patients with MDD reflect a trait-based impairment increasing the vulnerability to develop depression. However, the evidence from cross-sectional studies in patients with acute depression is limited with regard to answering this question. Even though neurocognitive dysfunctions that occur during a first-episode of acute depression and that are sensitive to the specific symptomatology of depression likely reflect state-dependent impairments (McDermott and Ebmeier, 2009; Snyder, 2013), the existence of trait-related impairments cannot be ruled out. To be considered a possible trait or risk marker, neurocognitive impairment need to be persistent, being present despite clinical recovery and, most importantly, occur prior to depression onset (Allott et al., 2016). Therefore, the investigation of neurocognitive functioning in patients in remission from MDD as well as prospective studies that can determine whether impaired cognition predates the onset of MDD are of particular importance. In addition, given the known familial risk for depression (Rasic et al., 2014), the assessment of neurocognitive functioning in unaffected first-degree relatives of individuals with vs. without MDD can help to clarify the role of neurocognitive impairment as part of a pre-existing disposition to depression. Findings from studies implementing these approaches are discussed next.

4.2. Remitted depression

Several meta-analyses have synthesized findings from cross-sectional studies on cognitive impairments in adult patients following remission of depressive symptoms compared to healthy controls. The findings consistently suggest that the executive and non-executive functions that are known to be impaired during acute depression are also impaired during remission with mostly small to moderate effect sizes (Bora et al., 2013; Rock et al., 2014; Semkovska et al., 2019). Thus, broad neurocognitive impairment persists despite clinical recovery and may reflect a trait marker for the onset or recurrence of depression. However, neurocognitive impairments may also persist as a consequence of the illness and therefore should worsen with repeated episodes (Allott et al., 2016). In line with the scarring hypothesis, it has been shown that a subset of the impairments observed in remitted patients including the domains of processing speed, verbal and visual memory, verbal fluency, set shifting when using time constrained tasks, and full scale IQ, increased as a function of the number of previous depressive episodes (Semkovska et al., 2019). In contrast, the number of previous episodes had no effect on performance in tasks on logical memory, working memory (digit span backward), set-shifting (WCST), and selective attention (Stroop interference task) in remitters versus controls and therefore are more likely to

be trait-related. For the domain of planning this was not tested (Semkovska et al., 2019). The existing evidence has been largely derived from cross-sectional studies. Preliminary evidence from the few longitudinal studies assessing cognitive performance during the acute phase of a first episode of depression and again during remission in the same patients are partly consistent with the cross-sectional results and also point to executive impairments (verbal fluency and performance in the Stroop interference task but not set-shifting) rather non-executive impairments (i.e., processing speed) as candidate neurocognitive trait markers of the disease (Ahern and Semkovska, 2017). Taken together, the findings from remitted patients with MDD indicate that discrete cognitive dysfunctions, potentially from executive domains (i.e., selective attention, verbal fluency, and working memory) and long-term memory, rather than broad cognitive impairments reflect a pre-existing trait marker of depression. Because impairments of these functions are associated with ADHD as well, these deficits might specifically contribute to the increased risk for co-morbid depression in ADHD. Still, this hypothesis needs to be tested by well-controlled longitudinal studies that assess neurocognitive performance during the acute phase and again during remission in the same patients and which take the comorbidity of ADHD and depression during development into account. In addition, to be considered as a cognitive vulnerability marker of depression, longitudinal studies are needed to test if these candidate dysfunctions (selective attention, verbal fluency, working memory, and long-term memory) precede the onset of depression

4.3. High-risk populations

A familial risk for depression has been well established (Flint and Kendler, 2014; Howard et al., 2019; Kwong et al., 2019; Wray et al., 2018) with unaffected first-degree relatives of individuals with MDD being more likely to develop depression themselves (Rasic et al., 2014). Therefore, the assessment of neurocognitive functioning in unaffected first-degree relatives of individuals with vs. without MDD can also help to clarify the role of neurocognitive impairment as part of a pre-existing vulnerability of depression. A considerable amount of studies have used this approach and findings from 54 samples including children, adolescents, and adults have been recently synthesized by a meta-analysis (MacKenzie et al., 2019). When pooling across all executive and non-executive domains that were assessed in individual studies, the meta-analysis revealed robust evidence for cognitive impairment in the unaffected first-degree relatives of individuals with MDD vs. first-degree relatives of controls. This finding suggests that general neurocognitive impairment may be associated with a familial liability to MDD. However, effect sizes for individual domains considerably varied and were relatively small with significant effect sizes observed only for the domains of general cognitive functioning (IQ and achievement), long-term memory, and language development. Effect sizes were not significant for the domains of executive function ($k = 9$), sustained attention ($k = 6$) and processing speed ($k = 8$), “hot” cognition ($k = 9$), and psychomotor skills ($k = 6$). This may be due to a lack of power to detect relatively small effect sizes or other reasons. Moreover, a composite score for the domain of executive function was calculated by pooling set sizes across tasks on set shifting, selective attention, working memory, and “hot” executive functions. As a consequence, differential effects on specific executive functions could not be parsed out. Therefore, the degree of overlap between the neurocognitive profiles associated with a familial high risk for MDD and ADHD is inconclusive unless the exact neurocognitive deficits that are part of the familial disposition to depression are determined in more detail. Despite these caveats, the findings of the meta-analysis point to neurocognitive impairments most consistently observed in terms of IQ, long-term memory, and language development as pre-existing trait markers for depression. Given that these domains largely overlap with the neurocognitive profile of ADHD, these findings support the hypothesis that ADHD-related impairments in these cognitive abilities may contribute to the increased risk to develop co-morbid

depression among patients with ADHD. Longitudinal designs are clearly needed to determine which of the neurocognitive dysfunctions observed in high-risk individuals increase their risk to develop depression themselves. Taken the reported findings from remitted patients with MDD into account, it can be suggested that these studies should focus on executive functions (including selective attention, verbal fluency, and working memory) as well as long-term memory.

4.4. Prospective studies

The systematic review revealed only one meta-analysis that reported on studies using longitudinal designs that are most informative in order to determine whether impaired neurocognition predates the onset of MDD and thus can be regarded as a pre-existing risk factor for depression. The identified meta-analysis (Scully et al., 2017) reported on 29 large cohort studies that examined general cognitive function in terms of IQ in children, adolescents, and mainly young adults before they experienced the first onset of depression. The results revealed only a weak association between impairment in general cognitive function and subsequent depression both in terms of clinically relevant depressive symptoms and MDD diagnosis. Given that substantial heterogeneity occurred across the included samples, these findings need to be interpreted with some caution. While several possible confounding factors (e. g. age at baseline, time between assessments) were ruled out based on meta-regression analyses, baseline ADHD symptoms were not taken into account. Most importantly, a subgroup analysis including nine studies that provided information on baseline depressive symptoms revealed that the association between impairment in general cognitive function and subsequent depression was not significant after accounting for baseline depressive symptoms. Thus, contrary to the hypothesis that reduced cognitive function represents a risk marker for MDD, variability in general cognitive function was not predictive of subsequent depression. Since the majority of included studies reported on cognitive performance in young people, these findings do not suggest that general cognitive impairment at a critical period of brain development (Blake-more and Choudhury, 2006; Fuhrmann et al., 2015) and cognitive maturation (Luca et al., 2003; Luna et al., 2004) predisposes to the onset of depression. While this conclusion is in line with the finding in remitted patients with MDD that impairments in full scale IQ increased as a function of the number of previous depressive episodes pointing to a scar-related impairment (Semkovska et al., 2019), it seems to be at odds with the lower IQ consistently found in individuals at high-risk for depression (MacKenzie et al., 2019) – which has been interpreted in terms of a heritable trait marker of MDD. This discrepancy, however, can likely be explained by the need to account for subclinical depressive symptoms, which was neglected in the meta-analysis of the studies on high-risk samples. In addition, because MacKenzie et al. (2019) included only cross-sectional studies, it was not known whether the lower IQ observed in first-degree relatives of people with MDD increased their risk to develop MDD themselves. Although cognitive reserve as indicated by premorbid IQ has been proposed as an important etiologic factor in the development of neuropsychiatric disorders (Barnett et al., 2006; Watson and Joyce, 2015), the present findings do not suggest that ADHD-related general cognitive impairment in terms of low IQ can be considered a cognitive risk factor for the development of co-morbid depression in ADHD.

4.5. Summary of cognitive mechanisms of ADHD and depression comorbidity

The findings of this systematic review revealed that the neurocognitive profile of adults but also children with acute depression showed some overlap with the neurocognitive profile of ADHD in terms of executive dysfunctions (i.e., verbal fluency, planning, selective attention, set shifting, and working memory) and non-executive dysfunctions (i.e., verbal memory, sustained attention, processing speed,

and IQ) (Fig. 3). In contrast, impairments in intra-individual RT variability and response inhibition did not show cross-diagnostic overlap at least with regard to childhood, adolescence, and early adulthood and may be specific to ADHD. One important caveat that emerged mostly from studies in adults with MDD is that they did not control for ADHD symptoms, and therefore a confounding effect on the pattern and/or severity of the observed neurocognitive deficits cannot be excluded. Consistent with this hypothesis, the few studies taking ADHD-depression comorbidity explicitly into account, have shown a detrimental effect of ADHD comorbidity on neurocognitive impairments of patients with MDD, for example with regard to processing speed, verbal memory, and working memory (Larochette et al., 2011; Roy et al., 2017). Importantly, the findings from remitted patients with MDD indicated that only a subset of these overlapping impairments, most likely from the domains of executive functions (i.e., selective attention, verbal fluency, and working memory) and long-term memory can be regarded as trait-related suggesting that discrete neurocognitive dysfunctions may represent cognitive vulnerability markers of depression. The presence of neurocognitive impairments in healthy first-degree relatives of people with MDD mostly found in tasks measuring IQ, long-term memory, and language development also indicates that these neurocognitive deficits may reflect a trait-related precursor of MDD (MacKenzie et al., 2019). However, MacKenzie et al. (2019) did not control for subthreshold depressive symptoms as potential confounding factor. In addition, the meta-analysis (MacKenzie et al., 2019) was not conclusive with regard to impairments in other domains, specifically executive functions, due to methodological constraints or a lack of power. Prospective studies which are most suitable to determine whether impaired neurocognitive functioning predates the onset of MDD have been synthesized in one meta-analysis which reported that variability in general cognitive function was not associated with subsequent depression taken depressive symptoms at baseline into account. However, the meta-analysis focused only on general cognitive function mainly assessed via IQ and the findings do not exclude that specific neurocognitive functions are more predictive of later depression. In line with this hypothesis and partly consistent with the findings in remitted patients with MDD pointing to executive dysfunctions (selective attention, verbal fluency, and working memory) and long-term memory as candidate cognitive risk mechanisms, preliminary findings from prospective studies in adults and adolescents have found an association between reduced working memory (Evans et al., 2016) as well as reduced long-term memory (Airaksinen et al., 2007; Simons et al., 2009) measured at baseline and the later development of depression. Importantly, while these studies controlled for potential effects of current subclinical depressive symptoms or past depressive symptoms on task performance at baseline, ADHD co-morbidity was not taken into account.

In conclusion, the findings of this systematic review suggest that shared neurocognitive mechanisms in terms of impairments in specific neurocognitive functions most likely from the domains of executive function (i.e., selective attention, verbal fluency, and working memory) and long-term memory rather than general cognitive impairment in terms of low IQ may mediate developmental pathways from ADHD to depression. As only very few of such studies exist (Roy et al., 2017), the major challenge remains to test whether these specific impairments predate the onset of depression specifically in children, adolescents and young adults using longitudinal designs which take the comorbidity of ADHD and depression during development into account. In addition, longitudinal designs that repeatedly assess cognitive functions in individual at high risk for depression (including relatives of patients with MDD and most importantly adolescents and young adults with ADHD) are needed to specify the neurocognitive risk factors for the development of co-morbid depression in ADHD.

4.6. Possible developmental pathways from ADHD to depression

The findings of this review point to ADHD-related impairments in

executive functions (i.e., selective attention, verbal fluency, and working memory) as well as long-term memory problems as possible underlying mechanisms for the development of co-morbid depression in ADHD. In order to guide future research, we discuss several possibilities how these neurocognitive dysfunctions may confer the risk to develop depression among patients with ADHD, especially during adolescence and young adulthood.

Because depression typically emerges after the onset of ADHD (Fayyad et al., 2017), the presence of neurocognitive impairments in patients with ADHD may directly increase the risk for MDD. As revealed by this systematic review, and if this hypothesis would be confirmed, these impairments most likely refer to specific dysfunctions from the domains of executive functions (i.e., selective attention, verbal fluency, and working memory) and long-term memory. This is in contrast to the hypothesis of the cognitive reserve theory (Barnett et al., 2006) which suggests that broad cognitive impairment represents a risk factor for developing depression and several other common psychiatric disorders (Koenen et al., 2009; Watson and Joyce, 2015). However, lower cognitive reserve has been largely operationalized through IQ measures that reflect composite scores that are calculated across performance in a variety of tasks that tap into different executive and non-executive domains. Using this global measure, differential effects with regard to individual neurocognitive domains might not be detected.

Why might deficits specifically in executive functions increase the risk for co-morbid depression among patients with ADHD? Given that “cold” executive functions as assessed in this review may strongly interact with emotional processing in the aetiology of depression and depression risk (Nord et al., 2020; Roiser et al., 2012), biases in emotional processing and poor emotion regulation, which critically depends on self-regulatory skills (Gyurak et al., 2011), may be candidate mechanisms mediating this association. However, the present review did not assess performance in tasks on “hot” cognitive functions in patients with depression, and therefore we can only speculate about the role of such cognition-emotion interactions in the development of ADHD-depression comorbidity. Previous findings suggest that the effective usage of explicit cognitive emotion regulation strategies such as reappraisal is associated with better performance on tasks measuring executive functions, in particular working memory (McRae et al., 2012; Schmeichel et al., 2008) and verbal fluency (Gyurak et al., 2012). Deficits in these cognitive functions in turn may render the use of adaptive strategies more difficult and increase the use of maladaptive strategies such as rumination and avoidance which are characteristic for depression and have been associated with depression risk (Nolen-Hoeksema et al., 2008; Visted et al., 2018). In line with this hypothesis, rumination has been associated with impaired cognitive inhibition in “hot” cognitive tasks (Joormann and Gotlib, 2010; Whitmer and Banich, 2007) as well as in tasks without an affective component in patients with depression (Yang et al., 2017).

Furthermore, cognitive maturation, specifically maturation of executive functions continues into adolescence (Luna et al., 2004) and young adulthood (Luca et al., 2003) and relies on brain development, especially prefrontal cortex (Blakemore and Choudhury, 2006; Fuhrmann et al., 2015). ADHD has been characterized by a prolonged delay in brain development during adolescence, specifically prefrontal cortex (Shaw et al., 2007). Some evidence suggests that delays in brain maturation and its impact on associated neurocognitive functions not only characterizes ADHD (Shaw et al., 2007) but may also increase vulnerability to depression during the highly sensitive phase of transition from adolescence into young adulthood (Straub et al., 2019). Although tentative, given the lack of prospective evidence, the present findings therefore suggest that delayed maturation of prefrontal cortex and its impact, specifically on selective attention, verbal fluency, and working memory, which are candidate pre-existing risk markers of depression onset, may make adolescents and young adults with ADHD more susceptible to develop co-morbid depression.

Besides these executive dysfunctions, another line of research points

to the importance of long-term memory abnormalities for depression risk during the critical window of adolescence and young adulthood (Barch et al., 2019). Memory functions critically rely on hippocampal function (Cohen et al., 1999) and reduced hippocampal volume has been consistently linked to MDD (Schmaal et al., 2016). Therefore, impairments in long-term memory may be a marker of structural brain abnormalities that increase vulnerability to depression in patients with ADHD. Furthermore, stressful life events, which occur more often in patients with ADHD (Shapero et al., 2018), are a risk factor for MDD (Liu and Alloy, 2010; Stroud et al., 2008) and co-morbid depression in patients with ADHD (Hartman et al., 2019), and have been linked to memory and hippocampal abnormalities and reduced emotion regulation in adolescents with MDD (Barch et al., 2019). As revealed by this review, adolescents with current MDD show memory impairments rather than executive dysfunctions which might point to a unique role of long-term memory deficits in explaining the increased depression risk during the particular sensitive phase of transition from adolescence into adulthood (Barch et al., 2019). However, some findings derived from community rather than clinical samples suggest that the risk for developing internalizing pathologies during adolescence may be also associated with executive dysfunctions (Snyder et al., 2019; Snyder and Hankin, 2016). Also, there were several methodological constraints with regard to the reviewed studies on adolescents with depression (i.e., low number of studies including adolescents/young adults; inclusion of cross-sectional rather than longitudinal designs; increased intra- and interindividual variability in onset and speed of developmental changes in brain structure and maturation of associated executive functions due to variable stages of puberty). Therefore, a potential unique contribution of deficits in long-term memory to the depression risk among adolescents with ADHD warrants future clarification.

Furthermore, neurocognitive impairments of patients with ADHD might not have a direct effect on the development of depression at all. Rather it might be proposed that the developmental pathway from ADHD to depression is mediated, at least partially, by shared cognitive risk factors that contribute to the development of both disorders (Bloemen et al., 2018). Both disorders have been associated with an increased familial risk (Faraone and Larsson, 2019; Rasic et al., 2014). More specifically, the findings from this systematic review indicate that ADHD-related neurocognitive impairment (i.e., IQ, long-term memory, and language processing) may be associated with a familial liability to MDD (MacKenzie et al., 2019). Neurocognitive impairments, from the domain of executive functions and IQ, have been also discussed as endophenotype of ADHD (Boxhoorn et al., 2019; Rommelse et al., 2008). Increased familial liability might be driven by common genetic and/or environmental factors. Recently, the genetic association between ADHD and MDD has been well established by large scale genome-wide association studies and polygenic risk score analyses (Anttila et al., 2018; Demontis et al., 2019; Howard et al., 2019; Rice et al., 2019; Wray et al., 2018). Moreover, an overlap in genetic influences on psychopathology and cognitive functioning - as indexed by broad cognitive function in terms of IQ but also impairments in specific neurocognitive functions such as response inhibition and working memory - has been reported in separate studies for ADHD (Anttila et al., 2018; Kuntsi et al., 2014; Nigg et al., 2018; Stergiakouli et al., 2017) and MDD (Anttila et al., 2018; Hagenaars et al., 2016; Wray et al., 2018). Specifically, some evidence suggests that reduced general cognitive ability in terms of measurements of IQ and achievement may be associated with greater genetic liability to both ADHD and MDD (Anttila et al., 2018; Davies et al., 2018; Stergiakouli et al., 2017; Wray et al., 2018). It is also possible that specific neurocognitive impairments are genetically linked to both disorders (Chang et al., 2020; Hagenaars et al., 2016) and the present findings suggest that selective attention, verbal fluency, working memory and long term memory may have strongest genetic sharing with both ADHD and depression. However, few studies have tested this hypothesis (Chang et al., 2020; Hagenaars et al., 2016). One study that included long-term memory (Hagenaars et al., 2016), reported a genetic

correlation between memory performance and MDD but not ADHD. A recent study that examined polygenic risk scores for different psychiatric disorders in a sample of children and adolescents with ADHD found that the genetic risk for both ADHD and depression was associated with lower performance in the Stroop interference task (Chang et al., 2020). However, polygenic risk scores for ADHD and MDD were not associated with reduced working memory in this study (Chang et al., 2020). Additional research is clearly needed, given these conflicting results. Besides these genetic factors, environmental factors [e.g., home environment and parental style (Stein et al., 2008)] may influence cognitive development and thus might contribute to the shared familial liability as well.

Based on the present findings, it is not known whether the shared neurocognitive mechanisms suggested by this review are specific to the ADHD-depression comorbidity or rather reflect transdiagnostic neurocognitive dysfunctions (Millan et al., 2012) that may increase the risk for developing psychopathology of many forms [as captured by the general p factor, (Caspi and Moffitt, 2018)]. Several studies in adolescents suggest that impairments in executive functions such as working memory, cognitive inhibition and flexibility, are associated with general psychopathology (Bloemen et al., 2018; Castellanos-Ryan et al., 2016; Shanmugan et al., 2016; Snyder et al., 2019; White et al., 2017) which points to transdiagnostic risk factors that may account for various ADHD comorbidities from internalizing and externalizing domains (Jacob et al., 2007; Kessler et al., 2006; Kooij et al., 2012; Miller et al., 2007; Yoshimasu et al., 2018). These findings, however, do not exclude that different problem domains may additionally be associated with specific patterns of executive dysfunctions (Bloemen et al., 2018; Shanmugan et al., 2016; White et al., 2017). The contribution of common and domain-specific executive impairments to the increased risk for depression as well as other comorbidities among adolescents and young adults with ADHD remains to be determined by future studies using longitudinal designs.

4.7. Conclusions

Comorbidity has been increasingly recognized as a hallmark of ADHD, but underlying mechanisms and developmental pathways are poorly understood. This systematic review explored neurocognitive impairments as seen in ADHD as possible underlying mechanisms for the development of co-morbid depression in ADHD, especially during adolescence and young adulthood. To this end, we conducted two systematic literature searches, one on meta-analyses of cross-sectional and longitudinal studies on cognitive dysfunctions associated with depression across the lifespan, and one on original research studies on intra-individual RT variability in patients with MDD relative to healthy controls. The findings suggest that shared neurocognitive mechanisms, specifically impairments in executive functions (selective attention, verbal fluency, and working memory) and long-term memory problems, may mediate developmental pathways from ADHD to depression. These identified mechanisms may not be exhaustive and may be extended based on new research findings from future studies. In particular, well-controlled prospective studies in individuals with and without ADHD, in multiple assessments of neurocognitive functioning during development, and taking the potential presence or increase in subthreshold depression and ADHD symptoms into account, are strongly needed to specify the neurocognitive risk factors of the comorbidity of ADHD with depression. Our review has indicated that selective attention, verbal fluency, working memory, and long term memory should be part of the neurocognitive tasks evaluated in such studies. Such studies may guide the development of early intervention and prevention strategies in the future.

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Declaration of Competing Interest

Christine Freitag receives royalties for books on Autism Spectrum Disorder, ADHD, and depressive disorder. Andreas Reif has received speakers' honoraria and/or served on advisory boards from Shire/Takeda, Janssen, Medice, SAGE and Servier. All other authors declare no competing interests.

Appendix A

Search terms used in the search on meta-analyses of cross-sectional and longitudinal studies on cognitive impairment associated with MDD (part 1). We followed the list used by the meta-analysis of (Pievsky and McGrath, 2018).

Meta-analysis AND (depression OR depressed OR "major depressive disorder" OR "major depressive episode" OR "affective disorder" OR "mood disorder") AND (cognit* OR neurocognit* OR neuropsych* OR "cognitive test*" OR intelligence OR "intellectual functioning" OR memory OR "working memory" OR "verbal memory" OR "visual memory" OR attention OR "sustained attention" OR "controlled attention" OR "executive function" OR "cognitive flexibility" OR learning OR "visual processing" OR motor OR "verbal fluency" OR "psychomotor speed" OR "processing speed" OR orientation OR perception OR language OR verbal OR visual OR reasoning OR vigilance OR visuospatial OR "problem solving" OR "intra-individual variability" OR "reaction time variability" OR "response time variability" OR "reaction time distribution" OR "response time distribution" OR "drift rate" OR "reaction time standard deviation" OR "reaction time standard error" OR "RT variability" OR "coefficient of variation" OR RTCV OR SDRT OR "go no go" OR "go/no-go" OR stopping OR saccade OR "conflict motor task" OR inhibition OR "continuous performance test" OR Conners OR CPT OR "stop signal*" OR SST OR SSRT OR "delayed oculomotor response*" OR "matching familiar figures*" OR trailmaking* OR "trail making*" OR "sustained attention to response task" OR "letter cancellation*" OR "paced auditory serial addition*" OR PASAT OR "shifting sets*" OR stroop OR colorword OR 3RT OR "finger tapping" OR "digit span*" OR "target orientation test" OR Wechsler OR Woodcock OR "digit symbol" OR GDS* OR TOAD OR "logical memory*" OR "reading span" OR 2-back OR n-back OR 1-back OR "auditory verbal learning*" OR "letter-number sequencing" OR "letter number sequencing" OR "cognitive activation*" OR "dichotic memory*" OR "whole report*" OR "continuous word recognition*" OR number-letter OR "visual reproduction*" OR CANTAB OR "spatial span*" OR "corsi block tapping*" OR LAMB OR Rey* OR Rey-Osterreith* OR "complex figure*" OR "visual memory span*" OR "simon game" OR "simon task" OR "design memory" OR "counting span" OR "sentence span" OR CML OR "numbers backward" OR "finger windows" OR arithmetic OR "auditory consonant trigrams" OR mazes OR "Tower of Hanoi" OR "Tower of London" OR "Delis Kaplan" OR "Porteus Mazes" OR "progressive planning*" OR "Wisconsin card sort*" OR "number letter sequencing" OR "number recall" OR "dot test" OR "spatial memory" OR "word order" OR "phonological memory test" OR "digit recall" OR "numbers forward" OR "missing digit" OR "California verbal learning test" OR "Kimura recurring figures test" OR "letter fluency" OR "category fluency" OR "Controlled Oral Word Association Test" OR COWAT OR "animal fluency*" OR "cookie theft test" OR "design fluency" OR similarities OR information OR vocabulary OR "reinforcement task" OR "Eriksen Flanker*" OR "attention network test" OR "fast track" OR "stop change task" OR "complex visual memory search" OR "visual orienting and detection task" OR "test of variables of attention" OR TOVA OR flicker OR "Delayed SRT" OR CRT OR "visual attention" OR KITAP OR "anterior network test" OR "perceptual discrimination task" OR "probabilistic learning" OR "divided attention" OR "focused attention" OR 0-back OR "Sternberg task" OR "visual search task" OR "word matching

task" OR "tracking task" OR "reversal task" OR "bilateral responding task" OR "response time" OR "SRT monetary incentive task" OR SCAT OR "motor inhibition" OR "cue-detection task" OR "Go-change task" OR ETC)

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