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Review article

Neuropsychological functioning in adolescents and young adults with major depressive disorder – A review

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ABSTRACT

While neuropsychological dysfunction is a contributor to major depressive disorder (MDD) in adult MDD, little is known about neuropsychological function in MDD during adolescence and early adulthood. The aim of this review is to evaluate literature on neuropsychological function in this young age group. A database search of Medline, the Cochrane database and PsycInfo was conducted. Inclusion/exclusion criteria yielded seven case-control studies on neuropsychological functioning in MDD (12–25 years of age) published since 1995. Effect sizes were calculated. Results show a broader range of statistically significant neuropsychological deficits in MDD compared to controls in the cognitive domains of executive function (EF), working memory (WM), psychomotor and processing speed (PPS), verbal fluency (VF) and visual (-spatial) memory (VM). Most convincingly, three out of four studies investigating WM and three out of four studies investigating PPS found statistically significant impairments in MDD with varying effect sizes. EF deficits were reported only in three out of seven studies with small, medium and large effect sizes. While some evidence was found for impaired VM and VF, no evidence was observed for attention and verbal learning and memory; however, these domains have been less extensively studied. Further research is required to broaden the study base.

Contents

1. Introduction

Neuropsychological dysfunction in depression has been researched for more than 50 years and is regarded as a characteristic of depression indicating a broad profile of affected neuropsychological domains such as memory, concentration and decision-making (Madden et al., 1952; Kiloh and Ball, 1961). Studies in adults and elderly samples have demonstrated that depression is associated with a variety of neuropsychological impairments (Purcell et al., 1997; Austin et al., 2001; Fossati, 2002; Porter et al., 2003, 2007; Fossati et al., 2004; Harvey et al., 2004) such as in executive functioning, attention, memory, and

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psychomotor skills (Sobin and Sackeim, 1997; Fossati et al., 1999, 2004; Airaksinen et al., 2004; Gohier et al., 2009; Baune et al., 2010). In contrast, findings regarding the extent of impairments on neuropsychological tasks in samples of younger adults (21–38 years) with mild to moderate depression have been controversial suggesting a lack of such deficits in younger adults (Grant et al., 2001; Wang et al., 2006; Casteneda et al., 2008). However, limited data has been published in the even younger age groups such as adolescence and early adulthood.

Although the most consistently reported findings of neuropsychological impairments across age groups from younger adults to elderly include executive functioning (Purcell et al., 1997; Fossati et al., 1999; Grant et al., 2001; Harvey et al., 2004; Hill et al., 2004; Stordal et al., 2004; Smith and Muir, 2006; Taylor Tavares et al., 2007; Gohier et al., 2009), adult studies provide evidence to suggest that depression is associated with global cognitive deficits affecting various neuropsychological domains (Gualtieri et al., 2006).

In contrast, there is a paucity of research about the potential impact of depression on neuropsychological functioning in people during early adulthood and adolescence exposed to depression. This is important to note the consequences of early-onset depression are often more severe, far-reaching and show more frequent depressive episodes, possibly causing long-term social and mental disability as compared to later onset of depression in adulthood (Klein et al., 1999; Parker et al., 2003; Gollan et al., 2005a). In addition, research has shown that the psychological, social, physical and biological alterations occurring during adolescence are significant risk factors for the development of depression in young age groups, with a clear increase in prevalence from age 13 years onwards (Abela and Hakin, 2008; Lack and Green, 2009). Despite the prevalence of depression in adolescents and young adults being estimated similar to adults with 5.3% for a 12-month episode and 13.2% for a lifetime major depressive disorder (MDD) (Hasin et al., 2005), depressed young people are more likely to experience recurrent episodes of depression with increased likelihood of suicide, achieve lower educational attainment, and have a higher chance of unemployment and an increased risk of co-morbidities in adulthood (Berndt et al., 2000; Parker et al., 2003; Gollan et al., 2005b; Calles, 2007), which taken together, potentially result in severe long-term psychosocial impairment (Weissman et al., 1999; Dunn and Goodyer, 2006). Given this significant long-term impact of depression at early onset on various outcomes, it is important to better understand the nature of neuropsychological function and dysfunction in this younger age group.

Furthermore, since adult studies suggest a possible relevant functional relationship between neuropsychological function, employment status (Baune et al., 2010) and general function (Airaksinen et al., 2006; Jaeger et al., 2006) in depression, a better clinical description of neuropsychological function and dysfunction in young people with depression would be an important step forward to understand poor outcomes and help identify targets for intervention in depression. Moreover, whether adolescents and young adults are also prone to global cognitive deficits or are better characterised by domain-specific cognitive disturbance remains unclear, although some first evidence suggests domain-specific deficits such as in executive and working memory functioning (Baune et al., 2012) and executive functioning in younger depressed individuals with early onset of depression (Castaneda et al., 2008). Furthermore, studies in adults suggest that cognitive function may be present in a first episode of MDD (indicative of an early sign of MDD) (Lee et al., 2012) and may still be impaired at least in some domains of cognitive function during remission of depression (Hammar and Ardal, 2009) and importantly, that cognitive dysfunction may have a role as a prognostic marker of depression (Reppermund et al., 2009). These clinical observations on both cause and effects of cognitive dysfunction in depression are highly important for clinical prevention and are unknown in the younger age groups. The identification and treatment of cognitive deficits in depression may help both in improving clinical outcomes and possibly in identifying early signs of deterioration of mood states.

Since these clinical observations demonstrate a need to focus on neuropsychological function in younger age groups, namely adolescents and early adults, it is necessary to frame the review in a context of normative and disruptive brain developmental. The effects of depression in neuropsychological function may depend on the following briefly described important principles of brain development. First, while the developmental trajectory of grey matter (GM) volume follows an inverted U-shape, white matter (WM) volume increases steadily throughout childhood and adolescence and is likely to reflect improved connectivity and integration of disparate neural circuits (Giedd et al., 1999; Lee et al., 2012) and possibly influencing cognitive abilities (Tamnes et al., 2010). With various brain regions undergoing different patterns of maturation, neural consequences of stress-related conditions such as depression depend on the developmental stage at which the stress and depression occurred (Reppermund et al., 2009). Therefore, stress and stress-related depression may have a greater impact on cognitive and emotional function in childhood and adolescence as the brain experiences critical changes compared to adulthood.

Second, since it has been reported that higher-order association cortices develop only after lower-order sensorimotor cortices have matured in structure and function with the frontal lobe structures (e.g. dorsolateral prefrontal cortex (DLPFC)) involved in executive functioning, attention, motor coordination as well as heteromodal association regions the last areas to develop, it has been suggested that complex functions in higher-order structures are more susceptible to the effects of stress-related conditions including depression due to protracted earlier periods of postnatal development (Hammar and Ardal, 2009). Third, genetic and gender influences jointly contribute to individual differences in brain development. Based on these principles of normative brain development, it can be hypothesised that a pathological brain condition such as depression and related stressful experiences impact on neuropsychological function specifically in younger age groups during development.

In summary, given (a) the reported functional implications of neuropsychological deficits in depression, (b) the proposed differences in neuropsychological deficits between young age groups, older adulthood and the elderly, (c) the likely impact of depression on neuropsychological function during adolescence and younger adulthood, and (d) the above mentioned neurobiological normative developmental processes relevant to adolescence and young adulthood (e.g., brain maturation and PFC development), this review focuses on studies in this particular age group.

In this review we evaluate a range of cognitive domains of neuropsychological function as published in the original studies. These include the domains of executive functioning, verbal learning and memory, working memory, visual memory, attention and psychomotor speed. The method and the results sections will define the domains and list the individual cognitive test under each domain for review. In summary, the aim of this review is to characterise a variety of domains of neuropsychological function in depression among individuals between adolescence and young adulthood (12–25 years of age).

2. Methods

A literature search was performed using MEDLINE, the Cochrane Library, and PsycINFO databases covering publications from 1995 to 2014. The following

keywords were used to search for articles: youth OR adolescence AND major depressive disorder OR depression OR depressive OR depre* OR early onset depression AND cognitive function OR neuropsychological AND impairment OR deficit. The literature search was limited to English language and human studies. Additional articles were obtained by reviewing reference lists of research articles. Research articles conducting neuropsychological/neuropsychological assessment between adolescence and adults with unipolar depression were considered for inclusion in the review. Initially, a total of 194 studies were retrieved using these initial search terms. The following inclusion and exclusion criteria were applied to this pool of initial hits – inclusion criteria: (1) age groups between 12 and 25 years; (2) case-control study; (3) primary diagnosis of depression; (4) lifetime diagnosis of depression; (5) current and/or previous episodes (including euthymic mood states) of depression; Exclusion criteria: (1) the study focus was on medical disorders (e.g. diabetes type 1); or (2) other psychiatric disorders as primary diagnosis (e.g. bipolar disorder, schizophrenia); (3) depression was regarded as co-morbidity rather than as primary diagnosis of unipolar depression and (4) developmental disorders were present. In addition, studies primarily investigating participants with (5) psychotic depression or cognitive decline were excluded from this review. These criteria excluded also studies on participants with a simultaneous inclusion of an age range below and above 25 yrs of age (e.g. 17–70 years of age). Hence, the applied inclusion / exclusion criteria led to an age homogenous study base of participants between 12 and 25 years of age making comparisons between studies highly valid and not compounded by the simultaneous inclusion of older or younger groups. The inclusion and exclusion process of primary studies was performed independently by two reviewers (MF, BTB). Disagreements on inclusion/exclusion of studies were resolved by consensus. Finally, a total of seven articles met the inclusion and exclusion criteria and remained eligible for this review.

The retrieved studies investigated various cognitive domains and a large variety of individual neuropsychological tests was used across studies. The underlying theoretical construct of a neuropsychological domain was not consistently provided in each study. As an overview, Table 1 lists the cognitive domains and related individual neuropsychological tests as used in the original studies. This review presents the results based on neuropsychological constructs and individual tests of cognitive domains as reported in the original studies. The review focuses on executive function, verbal fluency, working memory, verbal learning and memory, visual (-spatial) memory, attention and psychomotor and processing speed as these domains have been reported to show impairments in adults with depression (Beblo et al., 2011; Rock et al., 2013). While we reported the individual tests and associated cognitive domains as shown in the original studies (see Table 3), we re-ordered individual tests under the most appropriate cognitive domain, which might have been different from the original study. Details of the alignment of individual tests and cognitive domains for the purpose of this review are shown in Table 1.

In order to place the observed differences in neuropsychological function between case and control groups across studies into a more meaningful context, effect sizes were included when reported in the original studies or calculation of effect sizes based on means and standard deviations or t values and d.f. were carried out for the purpose of this review. Calculation of the value of Cohen's d and the effect-size correlation, $r_Y l$, using the means and standard deviations of two groups (cases and controls) as follows:

$$\text{Cohen's } d = M_1 - M_2 / \sigma_{\text{pooled}} \text{ where } \sigma_{\text{pooled}} = \sqrt{[(\sigma_1^2 + \sigma_2^2)/2]}$$

$$r_Y \lambda = d / \wp(d^2 + 4)$$

or

calculation of the value of Cohen's d and the effect size correlation, $r_Y l$, using the t test value for a between subjects t test and the degrees of freedom as follows:

$$\text{Cohen's } d = 2t / \sqrt{(\text{d.f.})}$$

$$r_Y l = \sqrt{(t^2/(t^2 + \text{d.f.}))}$$

The Cohen convention for small and large effect sizes was used: small effect size ≤ 0.5; medium effect size > 0.5 and < 0.8; and large effect size ≥ 0.8 (Rock et al., 2013).

3. Results

For the purpose of this review, seven studies examining neuropsychological functions in adolescents and young adults between 12 and 25 years of age were identified fulfilling the inclusion and exclusion criteria. The selected studies employed case-control designs with generally small total sample sizes ranging from 97 of the largest study to the smallest with 28 participants. Two of the studies investigated female participants only (McClure et al., 1997; Matthews et al., 2008). In total across the seven studies, 431 participants were studied with $N=170$ MDD cases, $N=12$ cases of minor depression, $N=21$ cases of BSD and $N=228$ controls. A large variety of study methodologies such as the use of different neuropsychological batteries as well as differences in clinical sample characteristics (e.g., chronicity,

Table 1
Domain-specific individual neuropsychological tests used in studies on neuropsychological functioning in depressed adolescents and young adults.

Executive measures	Verbal learning and memory	Working memory	Visual (-spatial) memory	Attention	Psychomotor/processing/ cognitive speed
Wisconsin Card Sorting Test (WCST)	Rey Auditory Verbal Learning Test	n-Back	Pattern recognition	Behavioural inhibition tests (affective Go, No-Go task)	Inspection time task
Intra-dimensional, extra-dimensional set-shifting task of the WCST	California verbal learning test for children	Spatial span	Delayed matching to sample		Reaction and movement times under simple and multiple choice condition
Attention set-shifting task	Logical memory subtest	Spatial Working Memory (SWM)	Paired associated learning		Movement preparation time
Tower of London	List learning test	Paired associated learning	Rey Osterreith Complex Figure-Recall		Movement execution time
Tower of Hanoi	Complex figure test		Non-Verbal Selective Reminding Test		Trail Making Test A
Stockings of Cambridge	Verbal selective reminding task		Judgement of line orientation (visual spatial perception)		Reaction time
Trail Making Test B					Digit symbol substitution test and symbol digit
Stroop Colour and Word Test					
Brixton Spatial Anticipation Test					
Local–global task (set shifting task)					
Rey Osterreith Complex Figure-organisational score					
Verbal fluency					
Controlled oral word association test (verbal fluency)					
Clinical evaluation of language functions (verbal fluency)					

Table 2
Association between depression and neuropsychological function in adolescence and young adulthood (12–25 years of age).

Authors	Sample	Cognitive domains	Cognitive tests and measures	Results
Baune et al. (2012)	Sample size $N=97$ Depression $N=32$ Controls $N=65$ Age range 13–25 years	(A) Executive function (B) Attention and working memory (C) Verbal Memory	(A) Executive function (a) Wisconsin Card Sorting Test (WCST): perseverative, non-perseverative and total errors (b) Tower of London: number of excess moves (B) n-Back task: % accuracy (C) Rey Auditory Verbal Learning Test: number of correctly remembered words and total number of word remembered	(A) Participants with major depression demonstrated impairments in measures of executive function WCST: (a) total errors: $d=0.67$; $r=0.32$; (b) categories completed: $d=-0.41$; $r=-0.20$; (B, C) no diff. between cases and controls for planning & conceptual skills, attention & working memory and verbal memory;
Korhonen et al. (2002)	Sample size $N=41$ Depression $N=16$ Controls $N=25$ Age range 16–20 years	(A) Working memory (B) Executive function, flexibility control and motor speed (C) Subjective memory disturbance (D) General cognition	(A) Memory function (a) Wechsler memory scale Logical memory subtest List Learning Test Complex figure test (B) Executive function (a) Trail Making Tests A & B: difference in speed of performance in parts B and A (b) Stroop Colour-Word test: difference in speed of performance in parts B and A (C) Subjective memory disturbance (memory complaint questionnaire (MCQ)) (D) General cognitive function (a) 5 subscales of WAIS-R Similarities; vocabulary; digit span; digit symbol; block design	(A–D) No differences in any neuropsychological test performance between adolescents with MDD and controls;
Smith et al. (2006)	Sample size $N=96$ Euthymic state of both MDD and BSD; MDD $N=42$ BSD $N=21$ Controls $N=33$ Age: depression group: $M=21.3$ years Bipolar spectrum disorder group: $M=22.4$ years Controls: $M=22.2$	(A) Verbal memory (B) Executive function (C) Attention	(A) Verbal memory (a) California verbal learning test total recall trials 1–5 short delay recall long delay recall recognition hits (B) Executive function (a) Brixton spatial anticipation test (b) Trail-Making Test B (c) (c) Stroop Colour-Word test: number of correct words (C) Attention (a) Trail Making Test A	(B, C) MDD patients significantly differed from controls on Trail Making Test A ($d=1.01$; $r=0.45$) and Trail Making Test B ($d=0.76$; $r=0.35$); BSD patients showed worse performance than MDD group on CVLT total recall ($p=0.05$), short delay recall (p=0.009), recognition hits ($p=0.02$) and Trail Making Test B ($p=0.03$); BSD performed worse than MDD participants on short delay recall ($p=0.009$), recognition hits ($p=0.02$) and Trail Making Test B ($p=0.03$)
Klimkeit et al. (2011)	Sample size $N=67$ MDD $N=22$ Minor depression $N=12$ Controls $N=33$ Age range 12–18 years; Age: MDD Group: $M=15.3$ years Minor Depression Group: $M=15.6$ years Controls: M=15.8 yrs; first episode depression	(A) Verbal fluency (B) Cognitive speed (C) Motor speed (D) Executive function (E) Working memory	(A) Verbal fluency task (B) Cognitive speed Inspection time task a) Inspection time b) reaction time (C) Motor speed SCRT task involving motor reprogramming results	(A) (A, E) Adolescents with minor depression showed working memory deficits ($d=-1.06$;$r=-0.471$) and poorer verbal fluency ($d=-1.496$; $r=-0.599$); (B, C, E) Adolescents with MDD showed deficits in: (B) Cognitive speed deficits: (a) inspection time $d=0.786$; $r=0.366$ (b) reaction time: $d=0.627$; $r=0.299$

			a) movement preparation time b) movement execution time (D) Executive function Local–global tasks (a) Serial choice reaction time task (b) Set shifting task	(C) motor speed deficits (a) movement preparation time: MDD $d=1.678$; $r=0.642$ (b) movement execution time: MDD $d=5.844$;$r=0.946$ (D) Executive function deficits in MDD were found for: (a) SC reaction time task: $d=7.01$; $r=0.961$ (b) set shifting task: $d=6.595$; $r=0.956$
			(a) (E) Working memory (a) Digit span	(E) MDD working memory ($d=-0.527$;$r=-0.25$)
Kyte et al. (2005)	Sample size $N=79$ Major depression $N=30$ Controls $N=49$ Age: MDD group: $M=15.2$ years Controls: $M=15.2$ years; first episode depression	(A) Executive function/ attentional flexibility (B) Behavioural inhibition	CANTAB-battery: (A) Attentional flexibility: Wisconsin Card Sorting Test; Intra-dimensional; extra-dimensional set-shifting task (B) Behavioural inhibition – Affective Go, No-Go task (a) general ability to inhibit behavioural responses and focus attention by examining overall performance regardless of valence and shift condition; (b) ability to inhibit and reverse stimulus-reward associations by comparing shift and non-shift conditions;	no Executive function differences between cases vs controls; similar response time between cases and controls (Affective Go, No-Go task);
Matthews et al. (2008)	Sample size $N=28$ Depression $N=14$ Controls $N=14$ Age range: 12–16 years; girls only Depression Group: $M=14.5$ years Controls: $M=14.3$ years	(A) Working memory, planning/ executive function (B) Visual memory (C) Attention (D) Psychomotor skills	CANTAB-battery: (A) Working memory, planning/executive function (a) Spatial span (b) Spatial working memory (SWM) (c) Stockings of Cambridge (SOC) (B) Visual memory (a) Pattern recognition (b) Spatial recognition (c) Delayed matching to sample (DMtS) (d) Paired associated learning (PAL) (C) Attention (a) Attention set-shifting task (b) Reaction time (D) Psychomotor skills (a) Reaction and movement times under simple and multiple choice condition	(A) MDD group performed poorer on the spatial working memory task (SWM): (a) more search errors $d=1.17$; $r=0.5$ (b) poorer strategy score: $d=1.21$; $r=0.517$ (c) no impairment on SOC (B) MDD group performed poorer on DMtS, pattern recognition and PAL: (a) MDD had fewer correct responses on DMts during the delay conditions of the delayed matching on sample task: $d=1.01$; $r=0.45$; (b) less %-correct pattern recognition: $d=0.96$; $r=0.43$ (c) more errors on paired associates learning: $d=1.26$; $r=0.533$ (C) Attention: no sig. differences between groups; (D) MDD had slower movement times at simple condition: $d=1.2$; $r=0.51$
McClure et al. (1997)	Sample size $N=31$ Female only; depression $N=14$ Controls $N=17$ Age range: 12–17 years Depression group: $M=13.7$ years Controls: M=13.8 yrs	(A) Verbal learning and memory (B) Visual-Spatial Memory and Learning (C) Visual-spatial perception (D) Executive Function (fluency, organisation, problem solving)	(A) Verbal learning and memory (a) California verbal learning test for children (b) Verbal selective reminding task (B) Visual-spatial memory and learning (a) Rey Osterreith Complex Figure-Recall (b) Non-Verbal Selective Reminding Test (C) Motor-free measure of visual-spatial perception (a) Judgement of line orientation (D) Executive function (a) Planning and problem solving Tower of Hanoi	(A, B, D) No differences were apparent on any measures of memory (visual or verbal) or executive function; (C) Depressed females showed poorer motor-free visual-spatial perception (JLO) compared to controls: $d=-1.73$; $r=-0.655$

Table 2 (*continued*)

Authors	Sample	Cognitive domains	Cognitive tests and measures	Results
			(b) Visual-spatial organisation Rey Osterreith Complex Figure-organisational score (c) Fluency Controlled oral word association Clinical evaluation of language functions (CELF)	

Legend: *N*=sample size; *M*=mean; MDD=major depressive disorder; BSD=bipolar spectrum disorder; CANTB=Cambridge Neuropsychological Test automated Battery.

duration, subtype of depression, co-morbidity, medication use, and the age of the participants) are characteristic for this field of research. The results section presents the literature according to cognitive domains and individual test as used in the original studies (see Table 1). Results are presented based on effect sizes for differences of neuropsychological function between depressed and control groups (see Tables 2 and 3).

3.1. Cognitive domain-specific results

3.1.1. Executive function

Executive function (EF) is a neuropsychological construct to describe the regulation of cognitive processes including a variety of cognitive abilities such as working memory, flexibility, problem solving, planning, execution and reasoning (Chan et al., 2008). A large variety of individual tests as shown in Table 1 has been developed and is commonly used to measure EF. However, rarely has the same neuropsychological construct or individual test been employed to measure EF across studies reviewed.

All seven included studies employed at least one measure of executive function as defined in Table 1. In total, three out seven studies found impairments of individual measures of executive functioning with varying effect sizes (see Table 3). While one of these studies (Klimkeit et al., 2011) reported a large effect size for poorer results on a set-shifting task in MDD cases compared to controls, two others showed either medium (Smith et al., 2006) or small (Baune et al., 2012) effect sizes for worse performance on EF measures (Trail Making Test B; Wisconsin Card Sorting Test) in the depressed groups compared to healthy controls. Interestingly, two other single measures of EF (Brixton spatial anticipation test and Stroop Colour-Word test) employed in the study by Smith et al. (2006) showed no differences between depressed and control groups, suggesting that EF deficits in depressed individuals in their study were specific to measures on the Trail Making Test B. In contrast, four out of the seven studies found no significant difference in measures of EF (McClure et al., 1997; Korhonen et al., 2002; Kyte et al., 2005; Matthews et al., 2008). All of these four studies used different single tests for EF and the study by Matthews et al. (2008) investigated females only which might have contributed to the heterogeneous negative results. In total of the seven studies, only two studies used the same measure of EF, namely the Wisconsin Card Sorting Test (WCST), however, with opposing results. The positive study by Baune et al. (2012) used 'total errors' and 'categories completed' of the WCST as single measures of EF as compared to the negative study by Kyte et al. (2005), that emphasised on attentional flexibility by using the 'Intra-Dimensional, Extra-Dimensional Set-Shifting task' derived from the WCST. These results again suggest that results on the cognitive domain of EF across studies largely depend on the use of the individual tests. Since *verbal fluency* is frequently regarded as a measure of EF, the results reported here show two studies explicitly examining this domain as part of EF. It was found that participants with minor depression compared to controls had deficits in verbal fluency showing a large effect size, whereas MDD patients remained unaffected in the same study (Klimkeit et al., 2011). In a second study on verbal fluency studied as part of EF and investigating a similar age group between 12 and 17 years of age showed a contrasting result as the controlled oral word association test and the test of clinical evaluation of language functions (CELF) showed no impairments in verbal fluency in the depressed group compared to controls (McClure et al., 1997).

3.1.2. Memory

Memory is the process in which information is encoded, stored, and retrieved. The literature suggests several models of memory

Table 3
Statistically significant neuropsychological impairments in MDD showing effect size estimations in seven case-control studies among adolescents and young adults with MDD.[a]

Category of effect sizes[b]	Executive function (7 studies)[c]	Verbal fluency (1 study)[c]	Verbal learning and memory (3 studies)[c]	Working memory (4 studies)[c]	Visual (-spatial) memory (2 studies)[c]	Attention (1 study)[c]	Psychomotor/processing/ cognitive speed (4 studies)[c]
Small	+	–	–	–	–	–	–
Medium	+	–	–	+	–	–	++
Large	+	+	–	++	+	–	++

+ Denotes number of studies showing significant effect sizes in the respective neuropsychological domain.
– Denotes no significant differences between depression and controls.

[a] Effect sizes are reported for studies with statistically significant differences in neuropsychological performance between MDD and control subjects.

[b] Effect sizes for significant results on individual neuropsychological test differences between depressed participants and controls: small effect size ≤ 0.5; medium effect size > 0.5 and < 0.8; and large effect size ≥ 0.8 (Cohen, 1988).

[c] Number of studies that investigated this domain.

and indicates various ways to classify types of memory (e.g. declarative and procedural memory, retrospective and prospective memory). The types of memory investigated in studies on neuropsychological performance in adolescents and young adults included in this review include *working memory*, *verbal learning and memory*, and *visual (-spatial) memory*. The processing of verbal and visual (-spatial) stimuli within the working memory can be regarded as part of the storage process.

3.1.2.1. Working memory. Working memory (WM) is a model of active maintenance of information in the short-term storage formulated by Baddeley and Hitch that consists of three basic stores: the central executive, the phonological loop and the visuo-spatial sketchpad (Baddeley, 2000). Due to the executive component of this model, working memory is often, but not consistently, regarded as part of executive function. For the purpose of this review, working memory is listed under a broad memory domain. Four out of seven studies investigated working memory by using a variety of individual tests, such as Digit Span, n-back, Wechsler Memory Scale and Spatial Working Memory (SWM). While two studies found no evidence for working memory deficits (Korhonen et al., 2002; Baune et al., 2012), two studies reported medium to large effect sizes. Of these, one study reported a large effect size for working memory differences between MDD and controls using a Spatial Working Memory task (Matthews et al., 2008), whereas the other study found significant impairment for both the minor depression group (large effect size) and medium effect sizes for the MDD group using the measure of digit span (Klimkeit et al., 2011).

3.1.2.2. Verbal learning and memory. Verbal learning (VL) is typically associated with the memorisation and retention of lists of words, in order to describe basic elements of associative learning. Verbal learning tends to involve more than just the memorisation of words since many stimuli such as pictures, odours, locations, etc. can be studied. During verbal learning and memory tasks, the types of mental events that occur in verbal learning studies go beyond passive memorisation, as learners can play a very active role in manipulating experimental stimuli.

The domain of verbal learning and memory was investigated in three (McClure et al., 1997; Smith et al., 2006; Baune et al., 2012) out of the seven studies, none of which showed significant differences between depressed and control groups. Two of these negative studies employed the *California Verbal Learning Test* (*CVLT*) (McClure et al., 1997; Smith et al., 2006), which allows a direct comparison of study results, whereas the third other study used the *Rey Auditory Verbal Learning Test* (*RVLT*) (Baune et al., 2012).

3.1.2.3. Visual (-spatial) memory. Visual memory (VM) describes the relationship between perceptual processing and the storage and retrieval of the resulting neural representations. Those memories of visual images (e.g., dinner plates) are stored in what is called visual memory.

This domain was investigated in a small number of two studies, one of which found numerous differences of large effect sizes between depressed and control groups related to tests results of *pattern and spatial recognition*, *delayed matching to sample* (*DMtS*) and *paired associated learning* (*PAL*) (Matthews et al., 2008). The other study reported a negative finding on visual-spatial memory using the *Rey Osterreith Complex Figure-Recall* and *Non-Verbal Selective Reminding Tests* (McClure et al., 1997). Interestingly, MDD patients showed poorer performance with a large effect size for a measure of visual spatial perception (*Judgement of line orientation test – JOL*), which is regarded as a cognitive ability that may influence visual memory performance (McClure et al., 1997).

3.1.3. Attention

Attention (A) is a cognitive process of selectively concentrating on one aspect while ignoring other aspects of the environment and belongs to a commonly studied cognitive domain in depression research. In the domain of attention, impairments of selective attention, divided attention, and vigilance have been reported in depression (Beblo et al., 2011). However, it is still a matter of debate whether depressed patients show cognitive slowing. Christensen et al. (1997) conclude from their meta-analysis that depressed adult patients show impaired performance on timed tasks, but it remains unclear whether this impairment is due to a slowing of cognitive processing or, alternatively, has to be regarded as a consequence of the increased rumination that is regularly reported among patients with depression.

Our review shows that the domain of attention has rarely been examined in this cohort applying a widely accepted measure of attention such as a behavioural inhibition test (affective Go, No-Go task). In the 12–25 years age group, a single study showed no differences in attention using this measure between cases and controls (Kyte et al., 2005).

3.1.4. Psychomotor and processing speed

Psychomotor processing speed (PPS) is based on the measure of reaction time to a task that measures time elapsed between the presentation of a sensory stimulus and the subsequent behavioural response. Typical measures of processing speed are *simple reaction time*, *recognition*, *choice reaction time* (*CRT*), *Digit Symbol Substitution Test*, *discrimination reaction time*, *Trail Making Test A*. In the studies included in this review, the domain of psychomotor and processing speed was measured by using a variety of tests including individual tests in the areas of both cognitive speed and

motor speed (see Table 1). In total, four out of seven studies employed individual tests measuring this domain including one study measuring processing speed as part of the executive functioning construct (Korhonen et al., 2002) that showed negative results for PPS. In a single study, euthymic MDD patients performed worse on the Trail Making Test A compared to controls with a medium effect size (Smith et al., 2006) suggesting processing speed deficits even during remission. In addition, two studies reported impaired psychomotor processing speed in depressed participants compared to controls with differing effect sizes depending on subdomains: large effect sizes were found for tests of psychomotor skills (slower movement times) (Matthews et al., 2008) and motor speed (slower movement preparation and execution times) (Klimkeit et al., 2011), and additionally, in the study by Klimkeit et al. (2011), medium effect sizes were found for differences between depressed and control groups on a task of cognitive speed (inspection and reaction times). This study (Klimkeit et al., 2011) has used separate measures for cognitive speed and motor speed, whereas the study by Matthews et al. (2008) employed a combined measure of psychomotor speed.

4. Discussion

This review of neuropsychological performance in depressed adolescents and young adults (12–25 years) shows that a limited number of case-control studies have been performed and no prospective studies are published in this age group. The main findings suggest that depression in this younger age group is related to neuropsychological impairment in a variety of cognitive domains. Most convincingly, three out of four studies investigating WM and three out of four studies investigating PPS found statistically significant effect sizes in MDD. EF deficits were reported only in three out of seven studies with small, medium and large effect sizes indicating less consistent evidence for EF deficits in MDD in adolescents and young adults. While some evidence was found for impaired VM and VF, no evidence was observed for attention and verbal learning and memory; however, these domains have been less extensively studied.

A limited number of studies have been performed to test performance in verbal fluency, verbal learning and memory, visual (-spatial) memory and attention, although the limited studies show high effect sizes for deficits in VF and VM. Importantly, these domains are clearly understudied. A little more consistently, negative findings have been reported for the domain of verbal learning and memory, however, this domain has a small study base of three original investigations only.

Although neuropsychological impairments have often been regarded as a feature of older adults and the elderly with depression, our review suggests that the younger adults and adolescents with depression already exhibit neuropsychological deficits primarily in the domains of executive function, working memory and psychomotor speed. The importance of the early age of depression onset for the presence of neuropsychological deficits has been underscored by a study on cognitive functioning in a population-based sample of young adults (aged 21–35 years) with a lifetime history of non-psychotic unipolar depressive disorder. While no cognitive deficits were reported for the whole sample (21–35 years of age), younger age at depression onset was associated with impaired executive functioning (Castaneda et al., 2008) as compared to the whole sample with early and later onset of depression, which is suggesting that onset of depression at a younger age might be more relevant to neuropsychological dysfunction (EF in this case) than higher age at onset of depression.

The results of our review show large similarities with studies on neuropsychological performance in adults with depression on several of the affected cognitive domains in both age groups. A recent meta-analysis revealed significant moderate cognitive deficits in executive function, memory and attention in adult patients with current or remitted depression relative to controls (Cohen's *d* effect sizes ranging from -0.34 to -0.65) based on studies employing the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Rock et al., 2013). Interestingly, the effect sizes of deficits in these domains reported in our review tended be somewhat higher (range ≥ 0.8) than in the meta-analysis by Rock et al. (2013) (ranging from -0.34 to -0.65). Even across different large neuropsychological test batteries, the domains of attention, executive function, and memory have been reported to be primarily affected in adult depression (Beblo and Lautenbacher, 2006). Overall, the moderate to large effect sizes as reported in our review, indirectly corroborate previous postulates suggesting that the severity and the profile of cognitive deficiencies in depression is clinically relevant and comparable to those seen in moderately severe traumatic brain injury (Veiel, 1997).

The finding in our review about impaired psychomotor and processing speed is worth discussing further. Two out of four studies found slower psychomotor processing speed and reaction time in adolescents and young adults with depression compared to controls (Matthews et al., 2008; Klimkeit et al., 2011). The study by Klimkeit et al. (2011) reported both statistically significant cognitive speed (inspection time, reaction time) and motor speed (movement preparation time) deficits, whereas the study by Matthews et al. (2008) employed a measure that combined both reaction time and movement times, suggesting that the underlying constructs for motor and cognitive speed are similar across both studies. Moreover, two other studies reported different results in the PPS domain. The cross-sectional study by Korhonen et al. found no impairment on motor speed in 16 treatment seeking adolescents (aged 16 to 20 years) measured by using Stroop Colour-Word test and Trail Making Tests B (Korhonen et al., 2002); unfortunately, the authors did not specify in their report how motor speed was measured specifically using those tests. In contrast, Kyte et al. reported that recently depressed adolescents (first episode) were faster (rather than slower) to make their decision on a decision-making task ($p < 0.02$) (Kyte et al., 2005). According to the authors, this latter finding was probably associated with increased impulsivity, and less specific to psychomotor speed. However, when evaluating psychomotor speed, a clear distinction between tasks measuring motor speed and cognitive processing speed is important since motor speed appears to be a function that may reach maturity by early adolescence (Huttenlocher and Dabholkar, 1997), whereas cognitive processing speed and reaction time are measures that continue to progress through adolescence (Anderson et al., 2001; Leon-Carrion et al., 2004; Luna et al., 2004; Luciana et al., 2005). These findings might also be related to elevated glucocorticoid levels associated with chronic stress in depression, as correlations have been found between improvement of information processing speed and a reduction in cortisol levels (Zobel et al., 2004; Reppermund et al., 2007), however, none of the studies included in this review have published cortisol levels.

In this review we decided to include a response inhibition (using an affective Go, No-Go task) as a measure of attention that showed no deficits in this domain. Although this single study result is preliminary, this may suggest that the domain of attention is less typically affected in adolescents and young adults as compared to adults and elderly studies (Beblo and Lautenbacher, 2006; Klimkeit et al., 2011).

It has previously been suggested that higher severity (see meta-analysis by McDermott and Ebmeier, 2009), recurrent episodes (Andersson et al., 2010) and remission status (Baune et al., 2010; Bhardwaj et al., 2010; Rock et al., 2013) in depression in adults are related to more severe impairment of neuropsychological function

as compared to healthy controls. Although the study base in adolescents and young adults as reported in our review is small, first observations have been made to suggest that a first episode of depression is associated with poorer function in executive function, motor speed, cognitive speed and working memory (Klimkeit et al., 2011). In contrast, a study in first episode depression reported no differences between cases and healthy controls in executive functioning, attentional flexibility and behavioural inhibition tasks (Kyte et al., 2005). However, the differences between the Klimkeit et al. (2011) and Kyte et al. (2005) studies might be due to measuring depressive symptoms related to the first depressive episode at different time-points: while the study with positive results tested depressive symptoms at the time of the first episode of depression (Klimkeit et al., 2011), the negative study included participants with a first episode in the past year; hence, several of the participants most likely were not severely depressed at the time of testing as indicated by data from the depression measure at study commencement (Kyte et al., 2005). However, when strict criteria for euthymic mood states of MDD at study commencement were applied, our review reported from a single study that 42 euthymic MDD patients showed poorer performance on Trail Making Test A and Trail Making Test B of large to moderate effect sizes ($d=1.01$ and $d=0.76$, respectively). Since no other studies with young (12–25 years of age) MDD participants of euthymic mood states have been published so far, further research into the important question whether neuropsychological impairment is a state, trait or both in depression is required.

Moreover, the diagnostic classification of mood disorder is of particular importance for evaluating neuropsychological deficits in mood disorders of young adults and adolescents. The literature in older adults suggests that Bipolar Disorder (BD) is associated with larger neuropsychological deficits as compared to MDD (Burt et al., 2000), although other studies suggest at least similar levels of impairments for both MDD and BD disorder patients (Taylor Tavares et al., 2007). In our review, we identified a single study that compared neuropsychological deficits in MDD to bipolar spectrum disorder (BSD) and reported that BSD patients performed worse on tasks for verbal memory (short delay recall, $p=0.009$ and recognition hits, $p=0.02$) and on Trail Making Test B ($p=0.03$) (Smith et al., 2006). Further research is needed in the adolescent and young adult groups to explore the characteristics and possible differences between MDD and BD in this age group.

Additional clinical factors such as comorbidity may influence the reported results, although this area is still controversial (Castaneda et al., 2010). For example, the comorbidity status (e.g., ADHD) in depressed adolescents and young adults may have significant impact on cognitive function potentially causing a substantial bias in the results of the neuropsychological evaluation in this age group (Favre et al., 2009; Klimkeit et al., 2011). Although several of the primary studies assessed such comorbidity, their consideration in the analyses is limited in the reviewed studies and need consistent consideration in future studies. Similarly, this requirement applies to medical comorbidities as it has been shown that chronic medical conditions such as diabetes type I with comorbid depression, are associated with neuropsychological impairment (Sinnamon et al., 2013). In general, since clinical factors such as comorbidities have previously been shown to impact on cognitive function in adult depression (Beblo et al., 2011), careful consideration of these factors is warranted in future studies on cognitive function in depression in younger age groups.

5. Limitations and strengths

The presented review has strengths and limitations. Due to the age inclusion criteria of 12–25 years of age, a number of studies in adults and in children were excluded. This approach left the review with a small study base of seven original studies in adolescents and young adults (12–25 years of age). The interpretation of the presented results needs to consider this small study base and caution is warranted. However, since numerous reviews and meta-analyses have already been undertaken on neuropsychological function in depression in adults, we aimed at the adolescent and young adult age group for this review. Accordingly, we excluded studies that spanned across both adult and adolescence age groups in the same study in order to be able to make an age-specific comparison of studies in the chosen age bracket of 12–25 years. This focus, albeit limited, may also be seen as advantageous in the context of the international clinical focus on understanding and tracing the early development of mental illness, its early detection and intervention as well as prevention in adolescents and early adulthood in recent years. To identify early signs of functional deficits such as cognitive deficits in young people with depression may aid this clinical direction. Another limitation of the literature that challenged this review is the heterogeneous methodology of neuropsychological assessments and definitions of cognitive domains. We tried to address this limitation by pre-defining cognitive domains and by aligning the individual neuropsychological tests used in the original studies to the pre-defined cognitive domains uniformly across the included studies. Hence, we feel that the comparison of study results based on this approach has gained validity and it reduced somewhat the heterogeneity of how cognitive domains were defined. Although the calculation and comparison of effect sizes in our review is an advantage over a purely narrative review, a meta-analysis would be the preferred option; however the study base in the field of neuropsychological function in adolescents and young adults is still limited and the heterogeneous methodology of how cognitive domains were measured limits a meta-analytic approach at this point in time, especially with the current small study base.

6. Recommendations for future studies and conclusions

This review supports the view that a broader range and clinically meaningful neuropsychological deficits are present in adolescents and young adults with depression, which have clinical implications for detection and treatment of mood disorders and depression in particular in this age group. However, the clinical base of case-control and prospective studies needs to be broadened generally, but specifically for understudied domains such as verbal learning and memory, visual (-spatial) memory and verbal fluency.

Some of the differences in study results could possibly be attributed to the heterogeneity of applied methodology. Several recommendations can be made to improve study design and comparability between studies for future analyses. Specifically, future studies on neuropsychological function should investigate diagnostic subgroups (e.g., melancholic, atypical) of depression, explore more specifically the impact of clinical characteristics of depression (e.g., symptom severity, comorbidity, disease status such as current and recurrent course, euthymic) as well as the onset, duration and number of depressive episodes. Importantly, future research could attempt to relate neuropsychological functioning to the staging model of depression in this age group (Hetrick et al., 2008). In addition, quality of life, daily functioning, education and IQ need evaluation to specify the understanding of neuropsychological impairments (Beblo et al., 2011) in adolescence and young adults. Moreover, future study results would be better comparable across studies by using a more uniform approach to neuropsychological testing and evaluation as well as homogeneous descriptions of the considered neuropsychological

domains. The consideration of mental and physical comorbidities as confounders when evaluating neuropsychological function appears to be a neglected area and requires more attention in future studies.

Furthermore, prospective studies in this research area are largely lacking apart from a few exceptions. A six-year follow-up study on predictors of long-term outcome after first hospital admission of adolescent inpatients suggested that depression at follow-up was predicted by admission symptomatology, but not by cognitive deficits (Pogge et al., 2008). Further research investigating the bi-directional longitudinal relationship between depression and neuropsychological functioning would greatly enhance our clinical knowledge in this field by (a) exploring the longitudinal nature and clinical relevance of neuropsychological impairments associated with depression; (b) determining the direction of effects between depression and neuropsychological impairments and (c) investigating how these impairments may affect psychosocial and emotional developments over time. Additionally, it appears relevant to interpret neuropsychological function and dysfunction in the context of physiological structural and functional maturation processes of the brain since some of the neuropsychological deficits such as in attentional processes might be temporary. Since neuropsychological measures appear to be fine markers of psychosocial, emotional and brain maturation processes during adolescence and early adulthood, research findings could turn into clinically useful measures of early signs of depression in adolescents and young adults. Finally, an improved understanding of the complex relationship between depression and neuropsychological functioning during development offers opportunities for early detection, early intervention and improved treatment outcomes of adolescents and young adults with mood disorders.

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