Psychiatry Research 248 (2017) 127–133

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Neuropsychological profiles of major depressive disorder and bipolar disorder during euthymia. A systematic literature review of comparative studies

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A B S T R A C T

Bipolar disorder and major depressive disorder have been shown to be associated with neurocognitive abnormalities during periods of clinical remission. However, at present, there is no consensus on whether these disorders have distinctive cognitive profiles. The aim of this study was to provide an updated systematic review of studies comparing neuropsychological functioning between bipolar disorder and major depressive disorder during remission. Main findings included the following: 1) no differences regarding performances in measures of attention and processing speed, executive functions and theory of mind were found between both patient groups and 2) regarding verbal memory, preliminary evidence points towards a more defective performance in patients with bipolar disorder than those with major depressive disorder. However, several variables with negative impact on cognition (medication status, age at onset, premorbid IQ, bipolar subtype, among others) were not adequately controlled in most studies. In conclusion, evidence from studies exploring neuropsychological profiles in bipolar disorder and major depressive disorder could not provide clues to differentiate these mood disorders. Larger studies with adequate control of confounding variables would be necessary to elucidate if the finding of more defective verbal memory performance in bipolar disorder is truly explained by distinct underlying mechanisms.

1. Introduction

Major Depressive Disorder (MDD) and Bipolar Disorder (BD) are complex chronic illnesses that affect mood and other biological rhythms, causing distortions of normal behavior that carry varying levels of burden and even disability in many cases (Ustün et al., 2004; Whiteford et al., 2013). Recent data suggest that the prevalence of these disorders is higher than previously reported, reaching 17–30% for MDD (Kessler et al., 2005; Angst et al., 2016) and 2–4% for BD when broad diagnostic criteria are applied (Kessler et al., 2005; Merikangas et al., 2011). Thus, mood disorders represent a major public health concern (WHO, 2012). Several studies (Fennig et al., 2002; Martino et al., 2008; Yen et al., 2011; Gilbert and Marwaha, 2013; Mackala et al., 2014; Baune and Malhi, 2015) have linked poor functional outcomes in subjects suffering from both mood disorders to neuropsychological abnormalities, which involve a broad array of domains and persist even during periods of clinical remission (Torres et al., 2007; Arts et al., 2008; Mann-Wrobel et al., 2011; Bora et al., 2013; Rock et al., 2014; Porter et al., 2015; Bora et al., 2016). Cognitive disturbances in these patients appear to be, at least partly, independent of medication status and other illness-related variables, as similar abnormalities, though of smaller magnitude, have been found in healthy relatives of affected subjects (Christensen et al., 2006; Arts et al., 2008; Balanzá-Martinez et al., 2008; Bora et al., 2009).

In recent years, great emphasis has been placed on characterizing cognitive aspects of mood disorders. In this scenario, a number of studies comparing cognitive performance between MDD and BD have been published. However, their results were contradictory and incon-

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http://dx.doi.org/10.1016/j.psychres.2016.12.031
Received 4 May 2016; Received in revised form 9 November 2016; Accepted 23 December 2016
Available online 24 December 2016
0165-1781/

Table 1
Summary of studies comparing neuropsychological performance between MDD and BD during euthymia.

Primary Study	Sample	Criteria of euthymia	Matched	Neuropsychological Domain	Main Results
Albus et al. (1996)[a]	Adult first-episode inpatients: MDD (*n*= 10), BD I (*n*=17) and HC (*n*=27).	NA	Age Sex Education Socio-economic status	Executive function Episodic memory (verbal and visual) Attention and processing speed Attention (sustained attention)	BD and MDD underperformed HC on processing speed and memory. Only subgroups of MDD and BD with psychotic features underperformed HC on executive functions and attention. BD and MDD performed equally on all measures.
Paradiso et al. (1997)	Adult recurrent MDD (*n*=20), BD (*n*=11) and HC (*n*=19).	HDRS < 15 MBRS < 17	Age Sex Education Severity of depressive symptoms* Duration of illness* General cognitive status (MMSE)* Remission time*	Attention and Processing speed Executive function Episodic memory (verbal)	Only MDD presented with more defective performance than HC in all measures. MDD underperformed BD in executive function.
Robertson et al. (2003)	Young, adolescent-onset MDD (*n*=30), BD I (*n*=44), and HC (*n*=45)	BDI < 13	Sex	Attention (sustained) and processing speed	There were no differences between patient groups and HC. Performance of BD was not significantly different from MDD.
Clark et al. (2005b)	Adult BD (*n*=13), MDD (*n*=15) and HC (*n*=46)	HDRS < 9 YMRS < 9	Age Crystallized IQ	Attention (sustained) and processing speed	No differences were found between patient groups in sustained attention, but BD underperformed HC on this measure, while MDD did not. There were no differences in processing speed between MDD and BD performance, while both underperformed HC.
Smith et al. (2006)	Young adult patients with recurrent depressive episodes: MDD (*n*=42), BD-NOS (*n*=21), and HC (*n*=33).	HDRS < 9	Age Sex Premorbid IQ Severity of depressive symptoms Age at onset* Number of depressive episodes* History of deliberate self-harm*	Episodic memory (verbal) Executive function Attention and Processing speed	BD were significantly more impaired than MDD and HC on tests of executive function and verbal memory. MDD did not differ significantly from HC on verbal memory function but performed less well on a test of executive function. BD underperformed HC in all measures.
Canuto et al. (2010)	Elderly with early-onset mood disorders: MDD (*n*=36), BD (*n*=22: 11 BD I and 11 BD II), and HC (*n*=62).	GDS < 5 YMRS < 5	Education General physical status	Episodic memory (verbal) Attention and Processing speed Executive function	BD underperformed MDD and HC on processing speed, working and episodic memory. No differences were found between MDD and HC performances.
Gildengers et al. (2012)	Elderly MDD (n=122), BD (n=43: 33 BD I and 10 BD II), and HC (n=92).	HDRS < 11 YMRS < 11	Age	Episodic memory (verbal) Processing speed Executive function	BD and MDD underperformed HC across all measures. BD had worse cognitive performance than MDD across all measures.
Xu et al. (2012)[b]	Adult MDD (*n*=100), BD (*n*=94, 42 BD I and 52 BD II), and HC (*n*=202)	HDRS < 8 YMRS < 6	NA	Attention and processing speed Episodic memory (visual)	Both BD and MDD underperformed HC on processing speed and visual memory. MDD underperformed BD and HC groups on executive functions.

(continued on next page)

Table 1 *(continued)*

Primary Study	Sample	Criteria of euthymia	Matched	Neuropsychological Domain	Main Results
Daniel et al. (2013)	Adult MDD (*n*=25), BD I (*n*=25) and HC (*n*=29)	HDRS < 8	Age	Executive function	No significant differences in performance were found in other domains
				Episodic memory (logical)	Significant differences in executive functioning were found between both patient groups and HC.
				Executive function	
		YMRS < 5	Sex	Attention and Processing speed	Performance on neurocognitive tasks did not differentiate MDD from BD-I.
			Education		
			Severity of depressive symptoms*		
Purcell et al. (2013)	Adult MDD (*n*=29), BD (*n*=26) and HC (*n*=28).	IDS-C < 12	Age	Social cognition (theory of mind – mental state decoding)	BD, MDD and HC performed equally in this test.
		YMRS < 8	Gender		
			Education		
			Severity of manic symptoms		

BD= bipolar disorder patients; MDD=major depressive disorder patients; BD-NOS=bipolar disorder not otherwise specified patients; HC=healthy control subjects; MMSE=Mini Mental State Examination; GDS= Geriatric Depression Scale; HDRS= Hamilton Depression Rating Scale; YMRS= Young Mania Rating Scale; MBRS= Manic Behavior Rating Scale; BDI= Beck Depression Inventory; IDS-C=Inventory of Depressive Symptomatology-Clinician Rating; NA= not available.

* Only patient groups are matched on these variables

[a] In Albus et al. (1996) euthymia was assessed with standardized scales (Brief Psychiatric Rating Scale and Hamilton Rating Scale for Depression), but cutoff scores are not informed.

[b] Clinical and demographic data for the sample of mood disorder subjects at baseline are available from Xu et al. (2012) No data on these variables are available for the subgroup of subjects achieving remission after follow-up.

clusive (Albus et al., 1996; Borkowska et al., 2001; Reichenberg et al., 2009; Daniel et al., 2013; Cotrena et al., 2016; Gallagher et al., 2015; Maalouf et al., 2010), as they were conducted in different phases of illness or included mixed samples of patients in different states. Then, at present, it is not clear whether the cognitive profiles of BD and MDD differ during euthymia, and, if so, whether they do it qualitatively, quantitatively, or both.

Characterizing cognitive profiles of MDD and BD during euthymia may have multiple assets. First, cognitive performance may be used as an objective marker that may aid, in combination with other tools, in the differential diagnosis of these disorders when symptomatic remission has been achieved. Second, identifying more specific cognitive profiles would contribute to better understanding the neurobiology of these illnesses. Finally, it would promote the development of specific interventions, such as cognitive remediation therapy, aimed at preventing or arresting cognitive impairment linked to poor functional and clinical outcomes.

The aim of this study was to provide an updated review of research reports comparing neuropsychological functioning between MDD and BD in order to gain a better insight into the cognitive features of mood disorders.

2. Materials and methods

2.1. Search strategy and study selection criteria

MOOSE guidelines (Stroup et al., 2000) were followed to conduct this study. PubMed/PsycINFO databases were extensively searched, covering the period from January 1980 to January 2016, using combinations of the following keywords: *mood disorders, affective disorders, major depressive disorder, bipolar disorder, mania, depression, affective psychosis, cognition, neuropsychology, memory, executive, social cognition, theory of mind* and *attention*. Moreover, the reference lists of retrieved reports and systematic reviews on cognitive aspects of affective disorders were cross-checked for further relevant investigations.

Our search strategy was aimed at identifying all the available reports exploring neuropsychological domains in both euthymic subjects with MDD and BD. Articles were included in this review if they met the following criteria: i) were available in English; ii) ascertained euthymia on the basis of standardized measures; iii) reported separate behavioral results for each mood disorder group; iv) used standardized criteria to determine the diagnosis; v) included at least ten subjects in each group. Studies employing general cognitive measures were excluded from the present review. Titles, abstracts and articles were reviewed by three independent reviewers (AGS, JMS and MPV). Further, two groups of independent reviewers (AGS, MPV, JMS and CS) extracted data on each study and a third investigator (DJM) resolved any discrepancies. Data on sample characteristics, definition of euthymia, matching criteria and main neuropsychological domains assessed were extracted. Authors were contacted in case of any missing information.

3. Results

Across all databases, our search strategy generated 2349 journal articles using the search terms in their title and abstracts. After thorough analysis, 50 studies were considered as potentially relevant and full text was assessed manually. Of these, 37 were excluded because the study sample was not entirely composed of euthymic patients or information about mood status was not completely available. One study was excluded because it lacked domain-specific cognitive assessment of participants as they were evaluated through general cognitive status measures (Kessing, 1998). Other two studies were excluded due to the lack of a direct comparison between MDD and BD patients (Inoue et al., 2004; Clark et al., 2005a). Finally, ten studies

were included in the present review. Of these, nine assessed neurocognitive variables (Albus et al., 1996; Paradiso et al., 1997; Robertson et al., 2003; Clark et al., 2005b; Smith et al., 2006; Canuto et al., 2010; Gildengers et al., 2012; Xu et al., 2012; Daniel et al., 2013) and one study evaluated a social cognitive domain (Purcell et al., 2013). MDD and BD samples were recruited from an outpatients clinic sample with the exception of Albus et al. (1996) -exclusively MDD and BD inpatients- and Xu et al. (2012) -mixed sample from outpatients and inpatients-. In most studies, groups were well matched by age and years of education (Table 1).

3.1. Attention and processing speed

3.1.1. MDD and BD vs. HC

Four studies revealed that both MDD and BD groups had worse performance on this domain than HC (Clark et al., 2005b; Smith et al., 2006; Gildengers et al., 2012; Xu et al., 2012). However, Paradiso et al. (1997) found that only MDD subjects displayed poorer performance than control subjects with large effect size (Cohen's d=0.88), whereas Canuto et al. (2010) reported that only BD patients underperformed HC with small effect size (Cohen's d=0.36). Albus et al. (1996) reported that solely those affective patients with psychotic features underperformed HC. Finally, two studies with small sample sizes observed no differences between mood disorder patients and HC (Robertson et al., 2003; Daniel et al., 2013). Regarding sustained attention, Clark et al. (2005b) showed that only BD patients (and not MDD) underperformed the HC group with intermediate effect size (Cohen's d=0.67).

3.1.2. MDD vs. BD

Nine studies assessed attention and processing speed in MDD and BD patients. Six studies with small sample sizes found no between-group differences (Albus et al., 1996; Paradiso et al., 1997; Robertson et al., 2003; Clark et al., 2005b; Smith et al., 2006; Daniel et al., 2013). A larger study also found no differences between these groups (Xu et al., 2012). Two studies informed that BD patients had worse overall performance than MDD subjects (Canuto et al., 2010; Gildengers et al., 2012) with small and moderate effect sizes (Cohen's d=0.35 and d=0.62 respectively).

Three small studies (Albus et al., 1996; Robertson et al., 2003; Clark et al., 2005b) addressed the comparison between MDD and BD patients regarding sustained attention and found no significant differences between them.

3.2. Episodic memory

Seven studies explored episodic memory. Of these, five assessed verbal memory (Albus et al., 1996; Paradiso et al., 1997; Smith et al., 2006; Canuto et al., 2010; Gildengers et al., 2012), one assessed logical memory (Daniel et al., 2013) and two explored visual memory (Albus et al., 1996; Xu et al., 2012). Gildengers et al. (2012) informed a composite score of delayed memory, which included logical, visual and verbal memory tasks.

3.2.1. MDD and BD vs. HC

Two of the seven studies included found that both patient groups performed worse than HC on this domain (Albus et al., 1996; Gildengers et al., 2012). On the other hand, two studies reported that only BD patients underperformed HC with large effect sizes (d=0.92 and 0.90, respectively) (Smith et al., 2006; Canuto et al., 2010) and one study found that only MDD patients performed poorer than control subjects with large effect size (Cohen ‘s d=0.93) (Paradiso et al., 1997).

One study (Daniel et al., 2013) compared logical memory between these groups. No differences were found between mood disorder groups and HC.

Finally, both Albus et al. (1996) and Xu et al. (2012) found that MDD and BD patients underperformed HC on a measure of visual memory.

3.2.2. MDD vs. BD

Three studies found a poorer performance in the BD group with large (Smith et al., 2006; Canuto et al., 2010) and small effect sizes (Gildengers et al., 2012). Both Canuto et al. (2010) and Smith et al. (2006) found that BD patients underperformed MDD patients on immediate and delayed recall, while Smith et al. (2006) reported that BD patients also underperformed MDD patients on recognition. Two small studies found comparable performance between the two patient groups (Albus et al., 1996; Paradiso et al., 1997).

Regarding visual memory, Albus et al. (1996) and Xu et al. (2012) did not find significant differences between patient groups.

3.3. Executive functions

Seven studies assessing executive functions in MDD and BD patients were included. Of these, six assessed cognitive flexibility (Albus et al., 1996; Paradiso et al., 1997; Smith et al., 2006; Canuto et al., 2010; Xu et al., 2012; Daniel et al., 2013), four response inhibition (Paradiso et al., 1997; Smith et al., 2006; Canuto et al., 2010; Daniel et al., 2013), four working memory (Albus et al., 1996; Canuto et al., 2010; Xu et al., 2012; Daniel et al., 2013), two verbal fluency (Canuto et al., 2010; Xu et al., 2012) and one planning (Xu et al., 2012). Gildengers et al. (2012) reported a composite factor score reflecting the domain of Information Processing Speed/Executive Function.

3.3.1. MDD and BD vs. HC

Most studies showed impaired performance in both patient groups on at least one measure of executive function with large effect sizes (Cohen's d from 0.8 to 1.5) (Albus et al., 1996; Smith et al., 2006; Gildengers et al., 2012; Daniel et al., 2013), except for two studies that showed preserved cognitive performance in the BD patient groups (Paradiso et al., 1997; Xu et al., 2012), and one study (Canuto et al., 2010) that did not report significant differences between MDD and HC.

3.3.2. MDD vs. BD

Studies found no significant between-group differences in most measures, except for cognitive flexibility and working memory. Regarding cognitive flexibility, contradictory results arose. Smith et al. (2006) found that MDD outperformed BD patients with moderate effect size (Cohen's d=0.62), whereas Paradiso et al. (1997) reported that BD performed better than MDD patients with large effect sizes (d=1.0). As for working memory, Canuto et al. (2010) reported that MDD outperformed BD patients with moderate effect size (Cohen's d=0.6). Finally, Gildengers et al. (2012) reported worse performance in the BD group in comparison to MDD on a composite measure of executive functioning with small effect size (Cohen's d=0.5).

3.4. Theory of mind

3.4.1. MDD and BD vs. HC

A small study by Purcell et al. (2013) found no significant between-group differences.

3.4.2. MDD vs. BD

No significant differences were found in the only study assessing this neuropsychological construct (Purcell et al., 2013).

3.5. Moderating variables

Two studies evaluated the influence of medication status on their results. Xu et al. (2012) found that, in BD type I patients, results of the Trail Making Test part A (Reitan, 1958) were predicted by antipsycho-

tic usage, being patients with later age at onset and treated with antipsychotics those with worse performance on processing speed measures. Moreover, patients with BD type II receiving valproic acid underperformed those medicated with lithium or lamotrigine on the Wisconsin Card Sorting Test (Nelson, 1976). Daniel et al. (2013) found that verbal memory performance was positively correlated with mood stabilizers usage (r=0.4, $p < 0.001$) and negatively correlated with antidepressants usage. Three studies assessed the potential impact of psychotic symptoms on their results. Albus et al. (1996) and Xu et al. (2012) found that those patients presenting with psychotic features underperformed those without. Gildengers et al. (2012) reported that, excluding those BD patients presenting with psychotic features, the BD group still underperformed the MDD group on all cognitive measures.

Regarding age at onset, Canuto et al. (2010) reported that group differences between MDD and BD patients persisted after adjustment for this variable. In keeping, Daniel et al. (2013) did not find significant correlation between cognitive performance and the age at onset considering all patients as a single group. In addition, Xu et al. (2012) reported worse cognitive performance associated with later age at onset in BD patients type I and II and in unipolar depressive patients.

Concerning subsyndromal symptoms, one study (Daniel et al., 2013) found that residual manic symptoms in BD patients were associated with poorer performance on tasks assessing executive functions but better performance on verbal memory tasks.

Finally, only one study matched MDD and BD patients on the number of previous depressive episodes (Smith et al., 2006) and found more defective verbal memory performance in BD patients. Three studies reported significant differences in the number of previous episodes between MDD and BD groups (Xu et al., 2012; Daniel et al., 2013; Purcell et al., 2013) with BD patients presenting with more episodes than MDD patients. One study was performed on a sample of first-episode patients (Albus et al., 1996) while the remainder did not inform the number of episodes of their samples (Paradiso et al., 1997; Robertson et al., 2003; Clark et al., 2005a; Canuto et al., 2010; Gildengers et al., 2012).

4. Discussion

This study was aimed at reviewing research reports comparing neuropsychological functioning between MDD and BD during euthymia. According to the results of this review, both mood disorder groups present with cognitive impairment during euthymia, in keeping with numerous meta-analyses and systematic reviews on this subject (Mann-Wrobel et al., 2011; Bourne et al., 2013; Rock et al., 2014; Porter et al., 2015).

Regarding group differences between MDD and BD patients, controversial results arose. Overall, most of the primary studies included found no differences concerning the domains of attention and processing speed, executive functions and theory of mind. Finally, when examining the episodic memory domain, findings seemed more homogeneous, with three studies showing a poorer performance in the BD group when compared with MDD (Smith et al., 2006; Canuto et al., 2010; Gildengers et al., 2012). Furthermore, two out of these three studies point towards a qualitative difference in performance since only BD patients underperformed the HC group (Smith et al., 2006; Canuto et al., 2010). This finding could provide new insight into neurobiological differences between these mood disorders during euthymia.

Several points must be taken into consideration when interpreting the results of the present review. As stated above, a number of confounders arise when analyzing cognitive performance in patient groups and most of the studies included did not completely address these variables.

First, quality of the studies included varied. Most primary studies had low statistical power as they were based on small samples. Consequently, they could have failed to detect true differences between mood disorders. Further, no sample size calculation was performed in any of the studies included. Additionally, no systematic appraisal of study quality and risk of bias has been conducted. Moreover, as only studies published in English were included, publication bias cannot be ruled out.

Second, it was not possible to assess the impact of pharmacological treatment on the results obtained. For example, when analyzing studies informing poorer performance of BD patients on episodic memory, a proper consideration of this confounder was not found. In the study by Canuto et al. (2010), more patients with BD were receiving antipsychotics than patients in the MDD group; Gildengers et al. (2012) reported that more patients in the BD group were receiving mood stabilizers (lithium and valproic acid), being these drugs frequently associated with poorer cognitive performance (Wingo et al., 2009; Dias et al., 2012). In keeping, as stated above, a study assessing the impact of pharmacological treatment on their results found that mood stabilizers usage was associated with poorer cognitive outcomes (Xu et al., 2012). However, the study by Smith et al. (2006) revealed that BD patients displayed more defective cognitive performance despite comparable rates of antipsychotics and mood stabilizers usage between groups.

Third, the presence of subsyndromal symptoms was not always correctly addressed. This is relevant, since neurocognitive deficits are known to worsen during acute mood episodes (Kurtz and Gerraty, 2009). In this sense, using less conservative criteria of euthymia may not allow to infer whether the cognitive deficits reported are part of a trait or a state marker, thus blurring the implications of the findings. In this regard, it might be said that the three studies reporting worse episodic memory performance in BD used stringent remission criteria (Smith et al., 2006; Canuto et al., 2010; Gildengers et al., 2012), although Smith et al. (2006) did not assess manic symptoms. On the other hand, the two studies reporting no differences in performance between the two disorders used broader criteria to define remission (Paradiso et al., 1997) or did not inform the cut-off scores used (Albus et al., 1996). It may be possible, thus, that this result reflects that differences in performances become evident during euthymia and may disappear during acute episodes, suggesting that this deficit might be a state rather than a trait marker in MDD (Rock et al., 2014).

Fourth, some key variables frequently used to match groups in studies of cognitive performance were not correctly controlled in the primary reports reviewed. Between-group differences regarding premorbid IQ were hardly available. The lack of this information is important, since attributing cognitive deficits to one or the other disorder in this context is more speculative. In this regard, most of the studies reporting worse memory performance in the BD group when compared with MDD did not address correctly this variable (Canuto et al., 2010; Gildengers et al., 2012). However, in the study by Smith et al. (2006), group differences persisted even after controlling for premorbid IQ.

Fifth, there are numerous reports supporting the idea of different subgroups of affective patients in terms of cognitive performance (Martino et al., 2008; Iverson et al., 2011; Reinares et al., 2013). Patients with higher number of recurrences (especially manic ones), poorer response to treatment or presenting with psychotic symptoms may correspond to the subgroup of affective patients with poorer cognitive performance, even with worse cognitive functioning than usually reported in literature (Martino et al., 2016). Accordingly, controlling for these variables might be useful to determine whether the proportion of these ‘severe patients’ were similar between the patient groups. Regarding psychotic features, this information was hardly available across studies. Albus et al. (1996) reported that, although MDD and BD patients performed equally on neurocognitive variables, those presenting with psychotic symptoms performed worse than those without. However, there is no report of the proportion of MDD and BD patients presenting these features, nor is there an analysis of performance in the subgroup of MDD and BD without

these features. Gildengers et al. (2012) reported that the subgroup of BD without psychotic features still underperformed MDD patients and Xu et al. (2012) found no differences between patient groups regarding psychotic symptoms, and also no differences regarding cognitive performances.

In addition, the subtype of BD was not always informed and could be relevant to cognitive outcomes. For instance, a meta-analysis by Bora et al. (2011) reported that type II BD patients outperformed type I BD subjects on some measures, mainly verbal memory.

Lastly, we are still far from being able to accurately distinguish between these two diseases, so it is possible that undiagnosed BD patients were included in the MDD group, given the controversies surrounding diagnosis boundaries in mood disorders. This fact may have masked any other possible difference in cognitive outcomes between patient groups.

In summary, there is no evidence to conclude that specific neuropsychological profiles are able to differentiate MDD from BD patients. Evidence for more defective verbal memory performance in BD patients is mainly preliminary, as most confounders were not properly assessed in the primary studies included in the present review. In addition, there is a dearth of studies on non-traditional cognitive measures such as decision-making or social cognition (i.e., emotional processing tasks), which cannot exclude that differences may be present in these domains. Further research in this area is warranted given the potential clinical and theoretical implications of this matter.

Conflict of interest

None.

Acknowledgements

No acknowledgements.

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