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Attention deficits in adults with Major depressive disorder: A systematic review and meta-analysis

Xiang Wang [a,b,c], Huan Zhou [a,b,c], Xiongzhao Zhu [a,b,c,*]

[a] Medical Psychological Center, the Second Xiangya Hospital, Central South University, Changsha, Hunan, China
[b] Medical Psychological Institute of Central South University, Changsha, Hunan, China
[c] National Clinical Research Center for Mental Disorders, Changsha, Hunan, China

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ABSTRACT

Attention deficits have been proven in patients with major depressive disorder (MDD). However, a detailed characterization of attention deficits in MDD was unclear. The aim of current study was to explore the specific deficits of attention in different sub-domains of attention so as to produce an overall picture of contemporary research on this field. We performed a systematic review and meta-analysis of published researches. PubMed, EMBASE, Cochrane Library and review of references were searched up to October 2019. Studies using at least one objective measurement to assess attention performances of MDD patients were included. Effect sizes were calculated using random-effects models for attention outcomes. Publication bias was evaluated using Egger's test. Twenty-three eligible studies including 1371 MDD patients were enrolled in this meta-analysis. Significant deficit of global attention was observed. For the specific outcomes, MDD patients showed significant deficits in psychomotor speed/attention, auditory attention, visuo-spatial attention, sustained visual attention, ranging from small to moderate, but not in selective attention. Larger sample sizes and more detailed subgroup analyses based on features of patients should be conducted to produce a more accurate conclusion.

1. Introduction

Major depressive disorder (MDD) is one of the most well-known psychiatric disorders characterized by a profound state of sadness, anhedonia for at least 2-week, accompanied by a minimum of five symptoms affecting behavior (disturbed sleep, changes in appetite or weight, fatigue, slowed movement) and/or cognition (feelings of guilt, worthlessness, thoughts of death, difficulty in concentration or indecisiveness) (American Psychiatric Association, 2013). Compared with other mental health problems, MDD is quite highly prevalent. According to the World Health Organization, there are approximately 350 million people suffering from depression worldwide (Smith, 2014). MDD is a highly disabling multidimensional psychiatric illness, which has significant adverse personal and public health consequences. MDD often damage people's cognitive, emotional and social function in multiple aspects (Kessler et al., 2015). A recent worldwide survey containing 195 countries indicated that approximately 34.1 million people lived with disability (YLDs) due to MDD each year, accounting for 4.2 % of the total YLDs (Disease et al., 2017). Thus, MDD is thought to be a leading contributor to the global burden of diseases and human sufferings (Disease et al., 2017; Ferrari et al., 2013).

Although MDD is traditionally recognized as a disturbance of mood, another core feature of MDD is impaired cognitive function. Increasingly evidences support that cognitive deficits occur in MDD patients (Afridi et al., 2011; Butters et al., 2004; Snyder, 2013), including executive function (Hammar and Ardal, 2009; Snyder, 2013; Wagner et al., 2011), memory (Maeshima et al., 2012; McClintock et al., 2010; Zhou et al., 2017), attention and psychomotor speed (Keller et al., 2019; Koetsier et al., 2002; McClintock et al., 2010; Porter et al., 2003). As a typical symptom of MDD, "difficulty in attention" has received a lot of attention. "Attention" plays a critical role in both cognitive and emotional functioning. There is no doubt that attention is inextricably linked to human's intellectual function and the major components of human cognition including perception, learning and memory, and executive function (Kantak and Wettstein, 2015). Many aspects of cognitive functioning require supports from attention or concentration, such as short-term memory and higher-level cognitive functions involved in goal-directed behavior (Hagerty et al., 1997; Lezak, 1982). Previous

* Corresponding author at: Medical Psychological Center, the Second Xiangya Hospital, Central South University, Renmin Middle Road 139#, Furong District, Changsha, 410011, Hunan, China.
E-mail addresses: xiangwangpsy@csu.edu.cn (X. Wang), zhuan0l@163.com (H. Zhou), xiongzhaozhu@csu.edu.cn (X. Zhu).

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studies also found that one of the most frequent and earliest prodromal signs of depression as reported by people with current episodes was difficulty in concentration or attention (Ferrari et al., 2013). This is consistent with MDD's diagnosis criteria of American Psychiatric Association (APA), which included "difficulties with concentration or attention" as one of the diagnostic criteria for MDD (American Psychiatric Association, 2013). Therefore, these findings suggest that attention is an important participant in many cognitive functions, so that impaired attention may affect other attention-related domains of cognitive functions, such as memory, executive function. In sum, it is meaningful to understanding the features of attention of MDD patients.

Numerous studies have demonstrated that patients with MDD performed significantly worse than healthy control in attention function (Brown et al., 1994; Keller et al., 2019; Koetsier et al., 2002; Lee et al., 2012; Majer et al., 2004; Rock et al., 2014). In recent years, some systematic reviews have also been conducted with or without a meta-analysis of the cognitive deficit of MDD, including attention performance. For example, a meta-analysis including 784 MDD patients found that compared to healthy individuals, MDD patients showed moderate deficits across executive function, memory and attention (Mesulam, 1985). Another meta-analysis from a systematic review including 5 studies enrolling 157 patients also reported small attention deficit in MDD patients (Rock et al., 2014). These studies showed that relative to healthy individuals, MDD patients exhibited small to moderate attention deficits. However, we also found inconsistent conclusions by reviewing specific studies. Schock et al. (Schock et al., 2011) found that depressive patients did not show significant spatial attention deficits compared with controls in their study. Gallagher's (Gallagher et al., 2015) case-control study also showed no differences between healthy and depressed adults in their reaction time (RT) of sustained attention task. It seems that attention features differ in different sub-domains of attention among MDD patients. Therefore, it is necessary to explore the features of sub-domains of attention of depressed individuals. Previous reviews with or without meta-analysis just conducted a simple test to examine whether global attention was impaired. There have been no systematic studies to discuss the specific characteristics of attention changes in depressed individuals. To address this gap, the overall purpose of current study was to initially examine the changes in attention function of patients with MDD, and then to produce an overall picture of contemporary research on this field by exploring the specific characteristics of attention performances in different sub-domains of attention. We conduct this systematic review and meta-analysis of several case-control studies, which were published before October 2019.

2. Methods

2.1. Data sources and study selection

Literature retrievals were conducted in PubMed, EMBASE and the Cochrane Library until October 2019 using the following combination of keywords: ("major depressive disorder"[MeSH Terms] OR "major depression"[MeSH Terms] OR "depression"[MeSH Terms]) AND ("attention"[All Fields] OR "sustained attention"[All Fields] OR "continuous attention"[All Fields] OR "selective attention"[All Fields] OR "go-nogo"[All Fields]). Meanwhile, additional studies were manually searched from reference lists of identified and relevant review article.

The titles and abstracts of all publications obtained by the search strategies were screened by two reviewers. The inclusion criteria for study were: 1) adult MDD patients (mean age≥18 years) according to Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) or International Classification of Diseases (ICD) (World Health Organization, 1993) criteria; 2) including a healthy control group; 3) use at least one objective neuropsychological test to assess attention performance; 4) sufficient data were reported to estimate effect sizes (eg. mean and standard deviation or standard error data) for both patients and controls; 5) Only case-control studies were included. Studies including subjects with bipolar disorder, MDD patients with psychotic features or with comorbid ADHD or substance abuse were excluded.

2.2. Data extraction, study quality assessment and publication bias

Titles and abstracts were screened by two reviewers independently to test whether those studies qualified for this review before full-text were obtained and assessed according to pre-specified eligibility criteria. Disagreements were resolved by discussion with the third reviewer. Data were extracted by using data extraction forms, which was upfront designed. One reviewer (XW) extracted the data into the structured forms, and then, another reviewer (HZ) verified its completeness and accuracy. Extracted data included author, publication year, age, gender of participants and outcomes of tests for attention.

The quality of included studies was assessed by the Newcastle-Ottawa Scale (NOS) (Wells et al., 2008), which is a method for assessing the quality of non-randomized studies in meta-analyses. The NOS uses "star system" to evaluate the quality of studies from three dimensions covering eight items: SELECTION, COMPARABILITY, EXPOSURE or OUTCOME for case-control or cohort studies. The scales allocate stars for each item of three dimensions. A maximum of nine 'stars' could be given to each study; herein, a total star of 7–9 indicates a high methodological quality, 4–6 indicates a moderate quality and ≤3 points a low quality. The quality of included studies was also independently assessed by two reviewers (XW and HZ). Any disagreements were resolved by consensus discussion with all authors.

As our meta-analysis only included published studies, it could be at risk of publication bias. Egger's test was typically recommended to assess publication bias only when more than 10 samples were included in the pooled effect size (Egger et al., 1997; Sterne et al., 2000). Therefore, egger's test was conducted in our meta-analysis.

2.3. Statistical analysis

Stata version MP/14.2 was used for data analysis. We calculated standardized mean differences (SMDs) and 95 % confidence intervals (CIs) indicating the difference between adults with MDD and healthy participants. When neuropsychological test was repeated as the outcome measure (i.e. baseline and posttreatment), only baseline scores were considered for the meta-analysis to prevent practice effects. Meanwhile, the sample size was generally greater and the population more representative at baseline because of attrition. In the event that more than one neuropsychological index was used to measure a sub-domain of attention performance, effect sizes were averaged within that domain and study (Douglas and Porter, 2009; Lee et al., 2012). The neuropsychological tests included in our study and the sub-domains of attention they traditionally measured were displayed in Table 1. Only neuropsychological tests used by at least two studies were included in the quantitative analysis, otherwise they were reviewed separately. The magnitude of SMDs indicates: (0−0.2) = negligible effect, (0.2−0.5) = small effect, (0.5−0.8) = moderate effect, (0.8+) = large effect (Cohen, 1988). Heterogeneity was estimated with the I^2 statistic. I^2 statistic of 25 %, 50 % and 75 % were generally interpreted as small, moderate and high heterogeneity, respectively (Higgins et al., 2003). In order to address heterogeneity, the random effect model was used.

3. Results

3.1. Included studies and quality assessment

Two hundred and sixteen full-text articles were assessed for eligibility after excluding irrelevant records based on title and abstract. Eighteen studies have been retained. An additional 5 articles were

Table 1
Neuropsychological tests and domains included in current study.

Domain	Neuropsychological Tests (Subtests)/Variables
Psychomotor speed/ attention	Trail Making Test-Part A (TMT-A); Brief Assessment of Cognition in Affective Disorder (BAC-A) subtest-Symbol-Coding; Digit Symbol Test; Symbol Digit Modalities Test; Test Battery for Perception and Attention Functions (WAF) Alertness subtest
Auditory attention	Digit span forward
Visuo-spatial attention	Spatial span forward; Test Battery for Perception and Attention Functions (WAF) subtest Extinction-Neglect
Sustained visual attention	Continuous Performance Test (CPT); Reaction Time (RT) pooled from sustained attention tests
Selective visual attention	d2-Letter Cancellation Test; Go-Nogo task
Divided attention	Test Battery for Attention Performance (TAP) subtest-divided attention

included, collected from reference lists. Ultimately, 23 studies enrolling 1371 MDD patients were included in our study. The detail process of selection was summarized in Fig. 1.

All of included studies were case-control study which were published between 2000 and 2018. Sample size ranged from 15 to 123 patients. Participants types included healthy individuals and MDD patients. There were a total of 1371 patients among the 23 studies, with the mean age ranging from 28.5 ± 3.82 to 72.95 ± 6.8 years. There were 1196 healthy controls among 22 studies, with the mean age ranging from 28.2 ± 3.6 to 74.6 ± 6.3 years. Of the 23 studies, 15 studies reported data for psychomotor speed/attention (N = 1057), 3 for visuo-spatial attention (N = 115), 8 for auditory attention (N = 428), 6 for sustained visual attention (N = 236), 3 for selective visual attention (N = 104) and 1 for divided attention (N = 53). The detail characteristics of included studies were summarized in Table 2.

3.2. Quality assessment of included studies

Table 3showed the quality assessment of included studies. The average of the total NOS score was 7.04. In all included studies, only three studies showed moderate methodological quality, the judgement of remaining 20 studies revealed high methodological quality.

For the SELECTION dimension, all MDD patients were diagnosed according to DSM or ICD criteria; both MDD patients and healthy individuals have its representativeness; all healthy controls were derived from community and excluded mental disorders history. For the COMPARABILITY dimension, case and control group in all studies matched age and/or other controlled factors (eg. gender, education) to ensure the comparability of the groups. For the EXPOSURE dimension, only four studies used independent blind rater to conduct neuropsychological test procedures; response rates were of no interest for the current study.

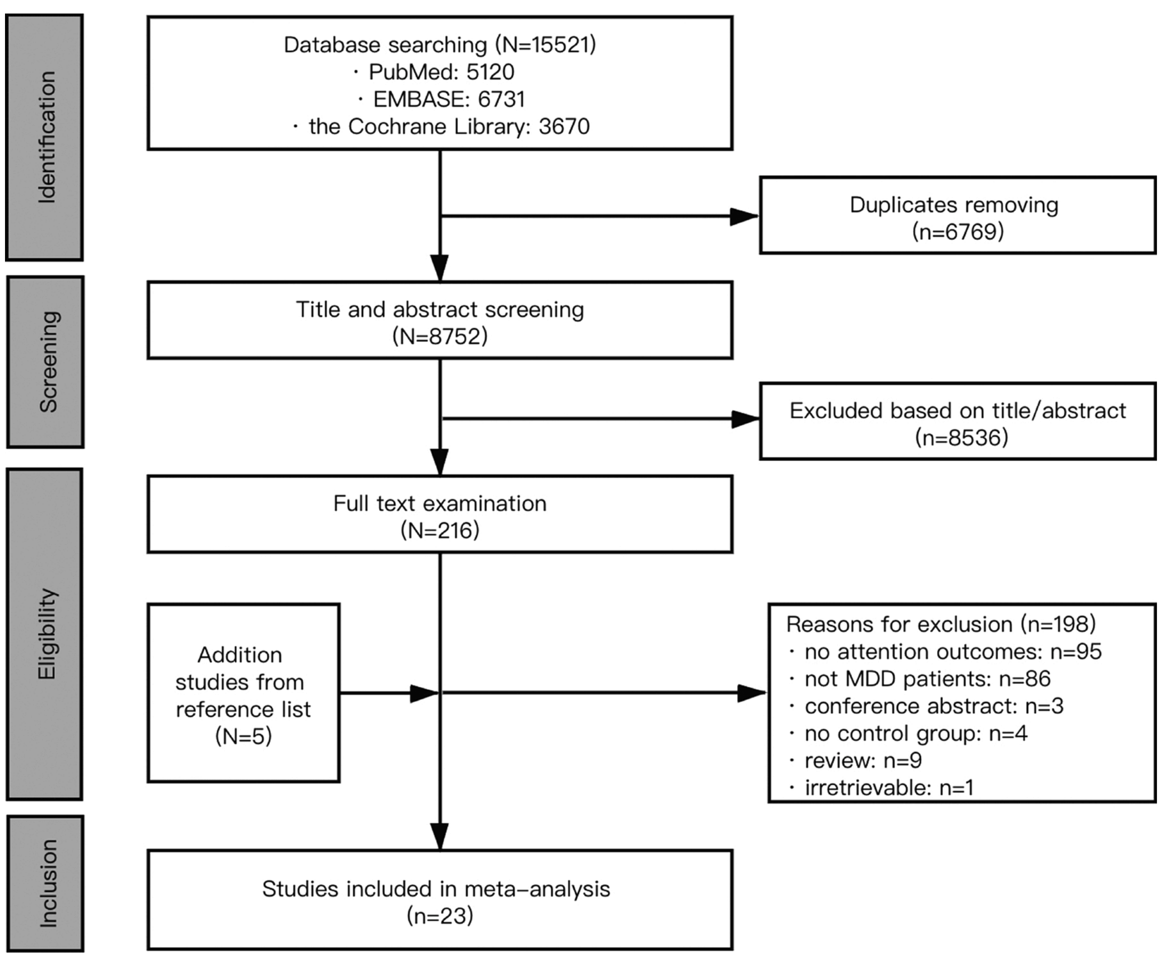

Fig. 1. Flowchart of trial selection process.

Table 2
Characteristics of included studies.

Study	Year	Patient N (female)	Patient Age (years)	Patient Diagnostic criteria	Patient Depression severity	Control N (female)	Control Age (years)	Neuropsychological tests
Ilonen	2000	20 (13)	36.5 ± 10.8	DSM-IV	Severe	30 (10)	34.2 ± 10.7	Digit Symbol
Reischies	2000	57 (42)	53.7 ± 11.4	DSM-IV	BRMS: 18.56 ± 4.37	82 (58)	52.3 ± 10.74	TMT-A
Grant	2001	123 (NR)	39 ± 10.4	DSM-IV	HAMD-17: 16.7 ± 5.4 BDI: 17.3 ± 9.1	36 (NR)	40.2 ± 9.7	TMT-A; CPT; Digit Span Test; Digit Symbol
Koetsier	2002	52 (32)	52.5 ± 8.7	DSM-IV	HAMD-17: 27.3 ± 5.2	73 (37)	39.7 ± 11.4	Digit Symbol; CPT
Ravnkilde	2002	40 (28)	41.6 ± 12.3	DSM-III-R	HAMD-17: 23.7 ± 4.4	49 (31)	41.2 ± 11.6	TMT-A; Digit Span Forward; Digit Symbol
Porter	2003	44 (29)	32.9 ± 10.6	DSM-IV	HAMD-17: 21.1 ± 4.4 MADRS: 28.9 ± 5.5 BDI: 27.9 ± 10.2	44 (29)	32.3 (11.4)	CPT
Fossati	2004	51 (40)	41.75 ± 14.73	DSM-IV	MADRS: 26.3 ± 4.7	88 (50)	43.7 ± 14.76	Digit Span Forward
Neu	2005	27 (19)	53.43 ± 10.84	DSM-IV	HAMD-x: 24.95 ± 6.22	30 (18)	52.69 ± 8.97	TMT-A
Mahurin	2006	30 (6)	36.7 ± 7.1	DSM-IV	HAMD-17: 30.9 ± 4.9	30 (12)	31.0 ± 8.6	TMT-A
Sárosi	2007	71 (52)	51.3 ± 10.6	DSM-IV	MADRS: 30.3 ± 11.0 BDI: 17.9 ± 7.8	30 (21)	50.7 ± 10.0	TMT-A
Westheide	2007	15 (0)	45.1 ± 11.4	DSM-IV	HAMD-21: 6.3 ± 3.5 BDI: 9.1 ± 6.1	15 (0)	42.1 ± 9.8	Digit Span Forward; d2-Letter Cancellation Test
Castaneda	2008	46 (34)	28.5 ± 3.8	DSM-IV	Mild to severe	70 (35)	28.2 ± 3.6	TMT-A; Digit Span Forward; Spatial Span Forward; Digit Symbol
Preiss	2009	97 (51)	46.3 ± 12.2	ICD-10	MADRS: 4.4 ± 3.0 BDI-II: 11.8 ± 7.0	97 (51)	46.1 ± 12.8	TMT-A
Reppermund	2009	53 (28)	43.5 ± 8.0	DSM-IV	HAMD-x: 25.1 ± 5.1	13 (7)	46.4 ± 9.5	TMT-A; Digit Span Forward; Spatial Span Forward; d2-Letter Cancellation Test; TAP subtests
Kaymak	2010	20 (20)	32.0 ± 8.52	DSM-IV	HAMD-17: 23.1 ± 4.2	15 (15)	29.3 ± 5.8	TMT-A; Digit Span Forward
van Wingen	2010	35 (24)	33.6 ± 11.4	DSM-IV	$HAMD\text{-}17_{Depressedt}$: 21.8 ± 4.2 $HAMD\text{-}17_{Recovered}$: 3.2 ± 2.0 $BDI_{Depressedt}$: 27.4 ± 8.9 $BDI_{Recovered}$: 9.2 ± 4.5	28 (15)	35.8 ± 12.0	TMT-A; Symbol Digit Modalities Test
Schock	2011	16 (10)	44.7 ± 9.1	DSM-IV-TR ICD-10	HAMD-x: 25.4 ± 9.3 BDI: 17.1 ± 9.5	16 (10)	45.3 ± 9.6	WAF subtests
Schnabel	2012	80 (48)	44.7 ± 9.3	DSM-IV-TR	NR	80 (40)	41.5 ± 13.9	Digit Span Forward
Vasudev	2012	41 (31)	70.4 ± 5.9	DSM-IV	MADRS: 13.4 ± 10.8 GDS: 12.9 ± 8.6	32 (20)	74.6 ± 6.3	Power of Attention & Continuity of Attention derived from Cognitive Drug Research (CDR) battery
Gallagher	2015	39 (24)	32.3 ± 10.11	DSM-IV	HAMD-21: 22.4 ± 5.29	39 (NR)	32.5 ± 10.37	Vigil CPT
Koch	2015	36 (25)	47.05 ± 10.85	DSM-IV	NR	36 (21)	32.81 ± 9.96	d2-Letter Cancellation Test
Koenig	2015	310 (235)	72.95 ± 6.8	DSM-IV	$HAMD\text{-}17_{Depressed}$: 18.28 ± 4.5 $HAMD\text{-}17_{Euthymic}$: 5.83 ± 2.7	128 (78)	71.43 ± 7.1	TMT-A; Digit Symbol Substitution Test
Lee	2018	68 (44)	45.2 ± 12.5	DSM-IV-TR	HAMD-17: 7.0 ± 4.1	135 (77)	44.5 ± 12.9	BAC-A subtest-Symbol coding

Abbreviations: DSM-x, Diagnostic and Statistical Manual of Mental Disorder; ICD-x, International Classification of Diseases; TMT-A, Trail Making Test-Part A; BAC-A, Brief Assessment of Cognition in Affective Disorder; WAF, Test Battery for Perception and Attention Functions; CPT, Continuous Performance Test; TAP, Test Battery for Attention Performance; BRMS, Bech-Raffaelsen Melancholia Scale; HAMD-17/21/x, Hamilton Depression Rating Scale (17-/21-item/unstated version); BDI, Beck Depression Inventory; MADRS: Montgomery-Asberg Depression Rating Scale; GDS, Geriatric Depression Scale; NR, Not Report.

3.3. Meta-analysis results

In this meta-analysis, we first examined the global attention performance of MDD compared to healthy control. In order to explore the characteristics of attention performances in different sub-domains of attention, we also conducted corresponding specific meta-analysis of sub-domains of attention. The specific outcome variables of attention sub-domains included psychomotor speed/attention, auditory attention, visuo-spatial attention, sustained visual attention and selective visual attention, which were measured by Trail Making Test-Part A (TMT-A) or Digit Symbol Test, Digit Span Forward, Spatial Span Forward, RT pooled from neuropsychological test of sustained attention and other indices of Continuous Performance Test (CPT), Letter Cancellation Test, respectively. Because only one study assessed divided attention in our included studies, which cannot be conducted quantitative analysis, the outcome of its neuropsychological tests was discussed in systematic review.

Fig. 2 showed the overall effects of attention performance in MDD compared to healthy control, which was calculated by data of 25 samples from 23 studies (the samples of two studies were divided into "previously" and "currently" depressed patients, contributing 4 independent samples (Koenig et al., 2015; van Wingen et al., 2010)). The result demonstrated that compared to healthy individuals, MDD patients had moderate deficit in global attention performance (Effect Size: 0.59; 95 % CI: 0.45 to 0.74; $p < 0.001$), with the I^2 of 66.2 %. Meanwhile, the Egger's test revealed no evidence for a publication bias (Egger's intercept = 0.060, 95 % CI: -2.32 to 2.44; p = 0.959).

The results of sub-domains of attention were as follows:

3.3.1. Psychomotor speed/attention

Data assessing psychomotor/attention were derived from different neuropsychological tests reported by 17 samples from 15 studies (similar to global attention performance). MDD patients showed moderate deficit in overall psychomotor speed/attention (Effect Size: 0.64; 95 % CI: 0.45 to 0.84; $p < 0.001$),with the I^2 of 74.6 %. For the specific neuropsychological tests, depressed individuals also significantly performed worse than healthy controls in TMT-A and Digit Symbol (Effect Size: 0.59; 95 % CI: 0.36 to 0.81; $p < 0.001$ & Effect Size: 0.49; 95 % CI: 0.19 to 0.80; p = 0.001, respectively), although significant heterogeneity between studies was observed. ($I^2 = 76.4$ % for TMT-A, $I^2 = 84.4$ % for Digit Symbol).

Table 3
Quality assessment for the included studies.

Study	Selection				Comparability	Exposure		Total score[a]
	Case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same ascertainment for case/control	
Ilonen	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	8
Reischies	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Grant	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Koetsier	⋆	⋆	⋆	⋆	⋆		⋆	6
Ravnkilde	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Porter	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Fossati	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Neu	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Mahurin	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Sárosi	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Westheide	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Castaneda	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	8
Preiss	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Reppermund	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Kaymak	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
van Wingen	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Schock	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Schnabel	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Vasudev	⋆	⋆	⋆	⋆	⋆⋆		⋆	7
Gallagher	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	8
Koch	⋆	⋆	⋆	⋆	⋆		⋆	6
Koenig	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	8
Lee	⋆	⋆	⋆	⋆	⋆		⋆	6

A study can be awarded a maximum of 1 star for each item within the selection and exposure categories; a maximum of two stars can be given for comparability. ⋆=yes.
[a] a total score of 7–9 indicates a high methodological quality, 4–6 indicates a moderate quality and ≤3 points a low quality.

3.3.2. Auditory attention

Eight of included studies conducted Digit Span Forward test to assess auditory attention. The result of meta-analysis showed that compared with healthy controls, MDD patients showed a small deficit in auditory attention (Effect Size: 0.27; 95 % CI: 0.10 to 0.44; $p = 0.001$), with an I^2 of 13.0 %.

3.3.3. Visuo-spatial attention

Visuo-spatial attention was assessed by Spatial Span Forward test and Test Battery for Perception and Attention Functions (WAF) subtest Extinction-Neglect from three of included studies. Compared with healthy control, MDD patients showed small deficit in visuo-spatial attention (Effect Size: 0.40; 95 % CI: 0.02 to 0.78; $p = 0.037$), with an I^2 of 32.2 %.

3.3.4. Sustained visual attention

Data assessing sustained visual attention were derived from RT pooled from sustained attention tests reported by six studies, omission errors and commission errors reported by two studies. The result showed that MDD patients had significantly longer reaction time (Effect Size: 0.54; 95 % CI: 0.18 to 0.91; $p = 0.004$; $I^2 = 69.3$ %), more omission errors (Effect Size: 0.82; 95 % CI: 0.35 to 1.29; $p = 0.001$; $I^2 = 61.1$ %) and commission errors (Effect Size: 0.63; 95 % CI: 0.34 to 0.92; $p < 0.001$; $I^2 = 0.0$ %) compared to healthy control.

3.3.5. Selective visual attention

Selective visual attention was assessed by d2 Letter Cancellation Test and Go-Nogo task reported by three of included studies. MDD patients did not differ from healthy control in overall selective visual attention (Effect Size: 0.44; 95 % CI: 0.00 to 0.87; $p = 0.052$; $I^2 = 39.4$ %). However, for the specific neuropsychological test and index, depressed individuals significantly performed worse than healthy controls in concentration score of d2 test (Effect Size: 0.46; 95 % CI: 0.04 to 0.87; $p = 0.031$; $I^2 = 33.0$ %).

The details of attention performances in MDD compared to healthy control were shown in Table 4.

4. Discussion

The current meta-analysis investigated attention performances of adults with MDD as compared to healthy controls. Twenty-five samples of twenty-three studies were included in our quantity analysis. The results suggested that MDD patients had a moderate deficit in their global attention performance (Effect Size: 0.59; 95 % CI: 0.45 to 0.74; $p < 0.001$), although results between studies were largely heterogeneous ($I^2 = 66.2$ %, $p < 0.001$). Significant heterogeneity might be influenced by many factors. In included studies, the characteristics of MDD, the age of patients, the severity of depression and the features of neuropsychological tests were various. For example, the patients of Ravnkilde et al.'s study (Ravnkilde et al., 2002) were current depressed patients, but partly remitted male MDD patients were included in Westheide et al.'s study (Westheide et al., 2007). Meanwhile, in van Wingen et al.'s study (van Wingen et al., 2010), both current and recovered depressed individuals were included. The mean age of patients among included studies were also different, ranging from 28.5 ± 3.82 to 71.23 ± 7.0 years. Furthermore, in our meta-analysis, the effect sizes within study and attention sub-domain were averaged if more than one neuropsychological index was used to measure attention performance or a sub-domain of attention. It might also have influence on heterogeneity. This meta-analysis confirmed the results of previous studies demonstrating significant differences in attention between adults with and without MDD (Koetsier et al., 2002; Lee et al., 2012; Porter et al., 2003; Rock et al., 2014), demonstrating the global attention performance of MDD patients were significantly worse than healthy controls. Consistent conclusions could also be found in previous reviews and meta-analyses (Lee et al., 2012; Rock et al., 2014). Overall, our results support that impaired attention is prominent symptom of adult depression.

In order to explore the changes of MDD patients in specific sub-domains of attention, we also conducted sub-analyses for each attention sub-domains. For the attention sub-domains, depressed individuals showed deficits in their psychomotor speed/attention (Effect Size: 0.64; 95 % CI: 0.45 to 0.84; $p < 0.001$; $I^2 = 74.6$ %), auditory attention (Effect Size: 0.27; 95 % CI: 0.10 to 0.44; $p = 0.001$; $I^2 = 13.0$ %), visuo-spatial

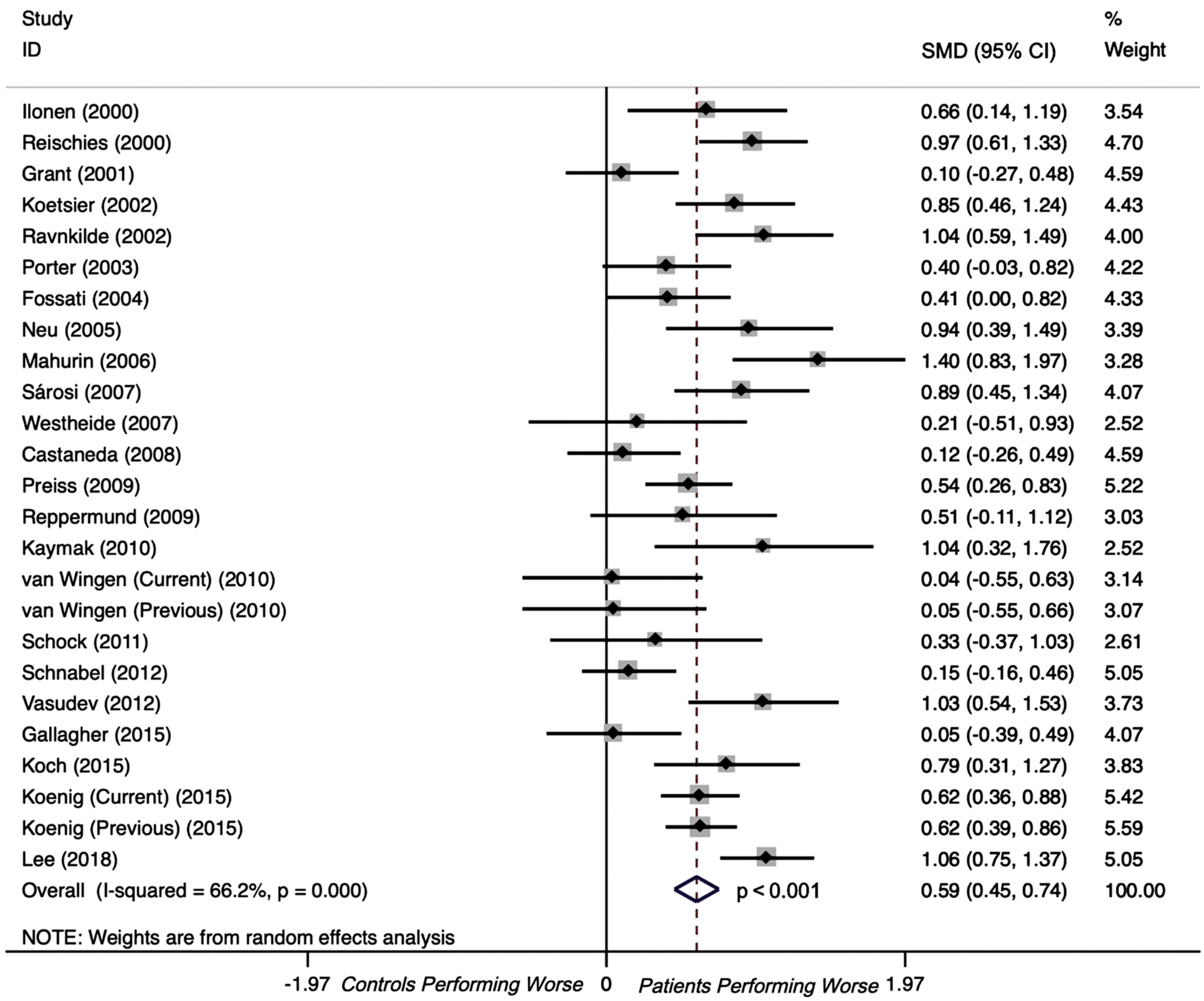

Fig. 2. Forest plots of effect estimates of global attention performance in MDD compared to healthy control.

Table 4
Comparison of attention performances between MDD patients and healthy controls.

Variable	*k*	*n*	N	SMDs (95 % CI)	*p* value (overall effect)	I^2 value (%)	*p* value (heterogeneity)
Global attention	23	25	1371	0.59 (0.45, 0.74)	**< 0.001**	66.2 %	< 0.001
Psychomotor speed/attention	15	17	1057	0.64 (0.45, 0.84)	**< 0.001**	74.6 %	< 0.001
TMT-A	12	14	877	0.59 (0.36, 0.81)	**< 0.001**	76.4 %	< 0.001
Digit symbol	8	10	677	0.49 (0.19, 0.80)	**0.001**	84.4 %	< 0.001
Auditory attention	8	8	423	0.27 (0.10, 0.44)	**0.001**	13.0 %	0.008
Visuo-spatial attention	3	3	115	0.40 (0.02, 0.78)	**0.037**	32.2 %	0.229
Sustained visual attention							
Reaction Time	6	6	236	0.54 (0.18, 0.91)	**0.004**	69.3 %	0.006
Omission errors	2	2	87	0.82 (0.35, 1.29)	**0.001**	61.1 %	0.109
Commission errors	2	2	87	0.63 (0.34, 0.92)	**< 0.001**	0.0 %	< 0.001
Selective visual attention	3	3	104	0.44 (0.00, 0.87)	0.052	39.4 %	0.192
Concentration score of d2	3	3	104	0.46 (0.04, 0.87)	**0.031**	33.0 %	0.225

Notes: Bold data indicate significant effect size.
Abbreviations: TMT-A, Trail Making Test-Part A; *k*, number of studies; *n*, number of patient samples; N, number of patients; SMDs, Standardized Mean Differences; CI, Confidence Interval.

attention (Effect Size: 0.40; 95 % CI: 0.02 to 0.78; p = 0.037; $I^2 = 32.2$ %), sustained visual attention (0.54 for RT, 0.82 for omission errors, 0.63 for commission errors), but not in selective visual attention.

4.1. *Psychomotor speed/attention*

Although psychomotor speed and attention belong to different cognitive functions, they are closely related. Attention is an important participant in psychomotor speed. Researchers often measured attention using the same neuropsychological test as psychomotor speed (eg. TMT-A and Digit Symbol test) (Preiss et al., 2009; Ravnkilde et al., 2002; Sárosi et al., 2007). Some studies also combined psychomotor speed and attention as the same variable (Koenig et al., 2015; van Wingen et al., 2010; Wu et al., 2018). Although we cannot equate psychomotor speed with attention, there is no doubt that psychomotor speed includes simple attention function. For these reasons, we included "psychomotor speed/attention" as a sub-domain of attention. Our results demonstrated that MDD patients showed moderate deficit in psychomotor speed/attention compared to healthy controls, with the effect size of 0.64 (95 % CI, 0.45 to 0.84; $p < 0.001$). This result is consistent with conclusions from previous studies. In previous studies, psychomotor speed/attention had been proven impaired in MDD patients relative to healthy control (Kaymak et al., 2010; Sárosi et al., 2007). Similar outcomes could also be found in euthymic phase of MDD patients (Koenig et al., 2015; Preiss et al., 2009). In sum, all these studies had demonstrated that deficit of psychomotor speed/attention could be found in MDD patients compared to healthy individuals. The results of our meta-analysis also support this conclusion. As a result, relative to healthy individuals, MDD patients showed significant deficits in psychomotor speed/attention.

4.2. Auditory attention

Auditory attention, which was generally assessed by Digit Span forward test, was defined in terms of sensory channels. Digit span forward was also considered to assess attention span (Ravnkilde et al., 2002), attention efficiency (Williams et al., 2000), and immediate verbal recall (Ravnkilde et al., 2002; Reppermund et al., 2009). Numerous studies have proven that depressed patients evince deficit in auditory attention compared to healthy controls (Kaymak et al., 2010; Ravnkilde et al., 2002; Reppermund et al., 2009). Some studies also showed no significant differences in digit span forward between MDD patients and healthy individuals. Castaneda et al. (Castaneda et al., 2008) included 46 young adults with lifetime history of MDD and showed that no significant differences between patients and healthy control in digit span forward test, although the scores in the patient group were slightly lower than in the healthy control group. Similar results could also be found in Westheide's (Westheide et al., 2007) study. Partly remitted MDD patients were included in his study and also showed slightly lower score than healthy controls in digit span forward test, although the difference was not significant. The results of our meta-analysis indicated that MDD patients displayed small deficit on auditory attention compared to healthy controls, with the effect size of 0.27 (95 % CI, 0.10 to 0.44; $p = 0.001$). This result supports most of the conclusions of previous researches, which showed the existence of auditory attention deficits in MDD patients. Nevertheless, looking back to aforementioned studies, we found that auditory attention might also influenced by the phase of depression. Future research should further explore the differences in auditory attention in different phases of depression.

4.3. Visuo-spatial attention

Visuo-spatial attention was assessed by Spatial span forward test (Castaneda et al., 2008; Reppermund et al., 2009) as well as the Extinction-Neglect subtests of the Test Battery for Perception and Attention Functions (WAF) (Schock et al., 2011). Meanwhile, in Castaneda's study (Castaneda et al., 2008), TMT-A was also considered to assess visuo-spatial attention and performance speed. Our meta-analysis showed that MDD patients had small deficits in visuo-spatial attention compared to healthy control, with the effect size of 0.40 (95 % CI, 0.02 to 0.78; $p = 0.037$; $I^2 = 32.2$ %). However, previous studies have shown inconsistent results in studies of visuo-spatial attention performance in MDD patients. A study enrolling 46 participants with a lifetime history of MDD (severity of depression ranged from mild to severe) showed no significant difference relative to healthy control in spatial span forward test (Castaneda et al., 2008). Another study from Reppermund et al. (Reppermund et al., 2009) used the same test and reported that patients with current MDD (depression ranged from moderate to severe, mean score of Hamilton Rating Scale for Depression was 25.1 ± 5.1) significantly performed worse in spatial span forward test than healthy controls. It seems that visuospatial attention performance may be influenced by phases of depression and/or depression severity. Other behavioral studies also reported left visual filed impairments in depressive patients (Lee et al., 2012; Liotti et al., 1991), as well as in healthy subjects during conditions of induced sadness (Banich et al., 1992; Cavézian et al., 2007; Ladavas et al., 1984). These results might indicate a hypothesis that sad mood is an influencing factor of visuo-spatial attention deficit. Schock et al. (Schock et al., 2011) tested this hypothesis and reported that relative to healthy individuals, although no significant spatial attention deficits in depressive patients were found, linear regression analysis showed that sadness could predict impaired visuospatial in the left hemifield of an individual, showing a rightward bias of spatial attention. This result also supports the hypothesis that sad mood can suppress the visuospatial attention processing of the right hemisphere and therefore favour impairment of left visual field (Liotti and Mayberg, 2001). In fact, imaging study also showed that sad mood could result in deactivation of cortical regions which have been known to support attention to the environment (Liotti and Mayberg, 2001). Thus, it seems that sad mood or depression severity were closely related to attention performances. Nevertheless, our results are consistent with most of previous studies and demonstrate that MDD patients attest visuo-spatial attention deficits. Future studies should also explore the effect of depression severity on visuospatial attention in MDD patients, as well as other sub-domains of attention.

4.4. Sustained visual attention

Sustained attention was defined as ability to direct and focus cognitive activity on specific stimuli over a significant period of time (Wagner et al., 2015). Sustained attention was one of the most frequently examined aspects of attention in mood disorders including MDD, which were generally assessed by Continuous performance tests (CPT) (Beck et al., 1956). Absolute errors, signal detection indices or mean reaction time (RT) over subcomponents or the overall task were typically used in most CPTs (Gallagher et al., 2015). Numerous studies have demonstrated that MDD patients in symptomatic states showed deficits in CPT's performance (Koetsier et al., 2002; Porter et al., 2003). However, some studies found no significant differences in RT for sustained attention between MDD patients and healthy controls (Gallagher et al., 2015; Schock et al., 2011). Actually, because of the existence of differences in responses within subjects, RT was not considered as the most appropriate indicator of sustained attention. In recent years, researchers increasingly recognized that it is necessary to go beyond such measures and take into account inconsistency of responses or intra-individual variability (IIV) (Gallagher et al., 2015). IIV can be simply obtained by calculating individual standard deviation (*iSD*) and the coefficient of variation (*CoV*). An increasingly application of these measures was found in the cognitive ageing literature (Nilsson et al., 2014) and reported that IIV indices were better than mean RT in differentiating early neurodegeneration from healthy ageing (Hultsch et al., 2002), and were strongly related to broader cognitive function (Bielak et al., 2010). In MDD patients, Gallagher's study (Gallagher et al., 2015) might also support this opinion. The results of his study indicated that patients with MDD showed significantly greater *iSD* of CPT than healthy controls, and it was also a statistical trend for greater *CoV* for depressed MDD, although no significant differences were found in average RT. In our meta-analysis, the results indicated that relative to healthy individuals, MDD patients had moderate deficit in sustained visual attention. MDD patients had significantly longer reaction time, more omission errors and commission errors compared to healthy control. Nevertheless, because of reasons mentioned above, further studies should also calculate IIV indices to assess the changes of sustained attention in MDD patients.

4.5. Selective visual attention

Selective attention is the ability to selectively attend to important stimuli in lieu of unhelpful or irrelevant distraction (Serences and Kastner, 2014). Selective attention was considered to be an important sub-domain of attention, which was particularly relevant to mood and therefore MDD (Keller et al., 2019). d2-letter cancellation test was used to assess selective visual attention and concentration index (KL) was calculated (Brickenkamp, 1994). The go-nogo paradigm measured response selection and inhibition, and the index of misses (MIS) was also used to assess selective attention in several studies (Gunther et al., 2004, 2011; Wilkinson and Goodyer, 2006). For the selective attention, previous studies (Gunther et al., 2004, 2011; Wilkinson and Goodyer, 2006) and reviews (Wagner et al., 2015) showed no significant deficits in children and adolescent MDD patients compared to healthy controls. In adult MDD patients, we found inconsistent results. In our included studies, Westheide et al. (Westheide et al., 2007) used letter cancellation test and go-nogo task and found that there were no differences in KL of letter cancellation test and omission errors of go-nogo task between MDD patients and healthy individuals. However, Reppermund's (Reppermund et al., 2009) study reported that MDD patients performed worse than healthy controls in letter cancellation test. Differences in severity of depression might contribute to the inconsistent results. In Westheide's study, patients with MDD were partly or fully remitted. Whereas, depression severity of patients from Reppermund's study ranged from moderate to severe. These results support the opinion we mentioned above that attention performances were sensitive to sad mood or depression severity. In addition to the possible impact of depression severity in these studies, other studies have also reached inconsistent conclusions (Koch and Exner, 2015; Lautenbacher et al., 2002). Differences in neuropsychological tests and indices might affect the results. In Koch's study, concentration score was calculated with the number of correctly processed items minus errors of commissions, but Lautenbacher's study used mean reaction time. Due to these reasons mentioned above, the result of our meta-analysis showed that there was no significant difference in selective visual attention between MDD patients and healthy controls. However, the interpretation of this result requires caution due to the limited sample sizes (only three studies covering 104 patients) and different indices. In addition, because of the good reliability of d2 test of attention, we also conducted a subgroup analysis of d2 test performance and showed that MDD patients performed worse than healthy control in concentration scores of d2 test. It suggests that the performances of selective attention in depression should be further clarified with more standardized and consistent methods. Furthermore, the effect of depression severity should also be considered in future studies.

4.6. Divided attention

Divided attention is ability of simultaneously attending to two or more different stimulus or performing multiple tasks (Kantak and Wettstein, 2015). Majer et al.(Majer et al., 2004) thought that divided attention was a more specific deficit within the domain of attention and this deficit might represent a marker for predicting the further course of depression. Impaired divided attention predicts delayed response and risk to relapse in patients with depression. Only one study from Reppermund et al. (Reppermund et al., 2009) which was included in our study, assessed divided attention using divided attention subtest of Test Battery for Attention Performance (TAP). Reppermund et al. found that MDD patients performed worse than healthy controls in mean reaction time for target present of divided attention test. Another study from Lautenbacher et al. (Lautenbacher et al., 2002) also found that depressed patients significantly performed slower than the healthy controls in mean reaction times of divided attention test of TAP. Lautenbacher et al. pointed that this dual-task paradigm for divided attention requires subjects to monitor two visual stimuli simultaneously, which produced a higher attentional load than other single-task paradigms. Thus, depressed individuals were more likely to produced attentional problems in these complex tasks at their limits of attentional capacity (Lautenbacher et al., 2002). However, because of limited studies, more studies are needed to further verify the stability of this result.

Overall, this systematic review and meta-analysis provide evidence that patients with major depressive disorder show deficits in attention functions. Meanwhile, we also examined performances of MDD patients in sub-domains of attention and produced more detailed results of this field. For the sub-domains of attention, results indicated MDD patients showed small to moderate deficits in psychomotor speed/attention, auditory attention, visuo-spatial attention and sustained visual attention, but not in selective visual attention. However, patients with MDD performed worse than healthy controls in concentration scores of d2 test for selective attention. It suggests that more standardized and consistent methods should be used in future studies to further clarify the performances of selective attention in MDD patients. For the divided attention, although meta-analysis was not conducted, previous studies also showed MDD patients showed deficits in divided attention compared to healthy controls.

As we mentioned above, attention is inextricably linked to human's intellectual function and the major components of human cognition. Moreover, attention is often impaired in patients with MDD. Accordingly, attention is considered as a valuable therapeutic target in MDD (Kantak and Wettstein, 2015). It is also recommended that early detection of attention deficits in depressed patients should be given more attention. Effective interventions should also be considered to alleviate the negative outcomes related to attention deficits.

5. Limitations and future directions

The findings of our study provide evidence of attention deficits in patients with major depressive disorder. We also conducted meta-analyses for various sub-domains of attention performance and produced a more concrete understanding for attention changes in MDD patients. However, the results of our meta-analysis should be interpreted with caution due to several limitations. Firstly, the heterogeneity of included studies was great. The heterogeneity observed in this study may be attributed to different characteristics of patients, multiple neuropsychological tests and outcome measures across studies. Therefore, a random effects model was used throughout to provide a conservative estimate. Secondly, the number of studies and sample sizes in some attention sub-domains were inadequate. For example, only three studies ($n = 115$) reported data of visuo-spatial attention and three studies ($n = 104$) for selective attention, which might influence the accuracy and reliability of our results. Finally, we did not examine the attention performances of patients with different depressive characteristics, such as first-episode, recurrent, euthymic phase and remitted. Therefore, to produce a more accurate conclusion, further studies should include more studies with large sample sizes and conduct more detailed subgroup analyses to explore the attention performances in different phases of depressed patients.

6. Conclusions

In conclusion, this systematic review and meta-analysis provide evidence that patients with major depressive disorder show deficits in attention functions. For the sub-domains of attention, results indicated MDD patients exhibit small to moderate deficits in psychomotor speed/attention, auditory attention, visuo-spatial attention and sustained visual attention, but not in selective visual attention. It thus suggests that attention deficits in MDD should be understood in more detail according to different sub-domains of attention. Larger sample sizes and more detailed subgroup analyses should be conducted to produce a more accurate conclusion.

Author contributions

XW conceived the study. The literature search and screening data were done by XW. Data extraction and quality assessment were carried out independently by XW and HZ. XW analyzed and interpreted data and wrote the manuscript. XZ revised the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declared no potential conflicts of interests with respect.

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