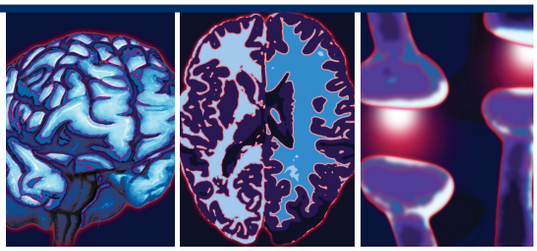
REVIEW



Systematic review of neurocognition and occupational functioning in major depressive disorder

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Practice points

- Major depressive disorder is a burdensome illness that disrupts occupational functioning, resulting in absenteeism and 'presenteeism', or reduced productivity at work.
- Cognitive problems, a common symptom of depression, probably contribute to the disruption in occupational functioning.
- Although the extent of cognitive impairments in depression remains to be clarified, measurable deficits have been found in processing speed, sustained and selective attention, learning and memory, and executive function.
- A systematic literature review found only two empirical research articles evaluating the relationship between objective cognitive impairments and occupational functioning.
- The two studies showed evidence for cognitive impairments that were associated with poorer work outcomes in currently and previously depressed individuals, although sample sizes and assessment of work outcomes were limited, and analyses only correlational.
- There is much opportunity for future research, which should examine specific cognitive domains, include validated assessments of occupational functioning and compare work-related outcomes in depressed individuals with and without cognitive impairment, in both acute and remitted states of depression. Furthermore, longitudinal studies of these populations will help determine the causal relationship between neurocognitive deficits and work outcomes.

SUMMARY Occupational impairment accounts for much of the burden and economic costs associated with major depressive disorder (MDD). Many studies have documented neurocognitive deficits in MDD, and depression-associated cognitive dysfunction would be expected to have significant effects on occupational functioning. We systematically reviewed the literature for studies on neurocognition and occupational functioning in MDD. Electronic databases (e.g., MEDLINE, PsychInfo and Cochrane Clinical Trials) were searched using appropriate terms and bibliographies of relevant publications were scanned for additional citations. Two reviewers independently reviewed papers for inclusion and data extraction,

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with conflicts resolved by consensus. Inclusion criteria were diagnosis of MDD using validated criteria (e.g., DSM-IV or ICD-10), use of objective neuropsychological tests and use of a specific measure of occupational functioning. Of 630 citations identified in the initial search, only two studies met inclusion criteria and were included in a qualitative review. Both had significant methodological limitations. Nonetheless, the depressed samples had significant neurocognitive deficits that were associated with employment status and work impairment. Neurocognitive dysfunction is probably associated with impairment in occupational functioning in individuals with MDD, but the evidence is limited. Further research should examine specific cognitive domains, and use validated measures of work functioning and productivity.

Major depressive disorder (MDD) is a leading cause of disability for young and middle-aged adults [1]. Depression in the work force has enormous implications, not only in terms of human suffering, but also for society in terms of the economic costs of absenteeism and lost productivity. Absenteeism refers to missed work days due to health problems; people with depression miss more days of work than people without depression [2,3]. Moreover, there is concern about 'presenteeism' [4,5] or diminished productivity while people impaired by health problems are still at work. People with depression report significantly more lost productive time than people who are not depressed [6,7]. Presenteeism might be overestimated in some studies that rely on self-reported productivity due to reporting biases in depressed individuals, who commonly show negative biases when evaluating their performance [8]. Nevertheless, given the high estimated costs of depression-related presenteeism [9], it is probably a significant contributor to the total economic cost of MDD.

The specific symptoms and problems associated with depression that underlies absenteeism and presenteeism are not well understood. Cognitive dysfunction, a cardinal feature of depression, may be particularly disruptive to occupational functioning [10,11]. Lam *et al.* surveyed employed adults with MDD using a questionnaire examining how symptoms interfere with work functioning. The symptoms perceived by patients to interfere most with work functioning were fatigue and low energy, insomnia, concentration and memory problems, anxiety and irritability. Problems with concentration and memory that interfered with work functioning in a major way were reported by 45 and 39% of the sample, respectively [12].

Cognitive impairment in people with depression can be subjectively experienced, objectively measured or both. Most patients with depression have the subjective sense that they have cognitive deficits, but there is some evidence that only a minority have objectively measurable cognitive impairment [13]. The nature and extent to which depression causes objectively measurable cognitive impairment, however, is not fully understood. Moreover, subjective cognitive complaints are not well correlated to objective cognitive deficits, as measured by neuropsychological testing, in some studies [14,15].

It is reasonable to assume that even mild cognitive impairment would have an adverse effect on work productivity, and specific types of cognitive deficits might be more or less relevant for certain occupations. The specific cognitive deficits associated with depression have not been determined definitively, but researchers have reported problems with information processing speed [16], sustained and selective attention [17,18], different aspects of learning and memory [18,19], and executive functioning [20–23]. We conducted a systematic literature review for studies that explored the relationship between objectively measured neurocognitive deficits and occupational functioning in people with MDD.

Methods

The extant English-language literature up to 15 June 2012 was searched through the following databases: MEDLINE, EMBASE, Science Direct, PsycInfo, Academic Search Complete, Biomed Central, the Cumulated Index to Nursing and Allied Health Literature, Cochrane Clinical Trials, Clinical Trials, and ProQuest Dissertations and Theses **(Figure 1)**. Multiple databases were also searched simultaneously using Web of Science. To ensure studies with both objective measures of cognitive deficits and measures of occupational functioning in specifically depressed populations were targeted, three main sets of search terms (combined within each set using an OR operator) were combined using an AND operator:

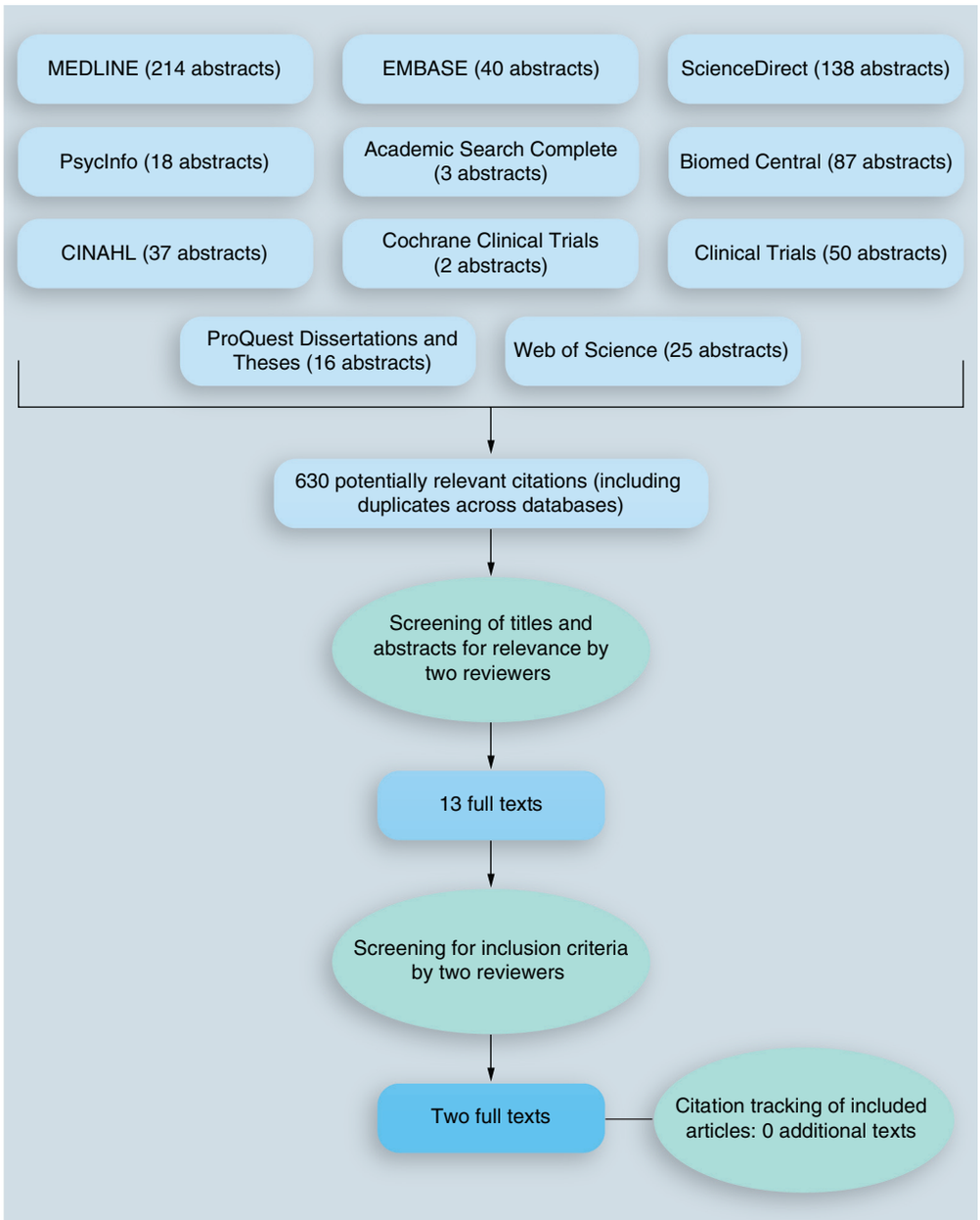

Figure 1. The study selection process.
CINAHL: Cumulated Index to Nursing and Allied Health Literature.

- Major depression, major depressive disorder and depress*;
- Permutations of cognitive, neurocognitive and neuropsych* with impairment, deficit, performance and test;
- Occupation, work, vocation*, employment, productiv*, job*, functioning, success, performance, absenteeism, presenteeism, burnout, socioeconomic status and sick leave.

When appropriate, Medical Subject Headings were used, otherwise the terms were searched as free text; results were limited to human adult populations and excluded nontarget populations (e.g., those with Alzheimer's disease, dementia or schizophrenia). After collecting all relevant publications, bibliographies were searched for additional relevant articles.

Studies were selected for the review if they included the following:

- Subjects meeting validated diagnostic criteria for unipolar MDD (e.g., defined according to the DSM-IV or ICD-10);
- An objective measure of neurocognitive functioning (i.e., neuropsychological tests);
- A specific assessment of occupational functioning (e.g., employment status or work functioning scale).

Two reviewers independently examined the studies to determine eligibility. Conflicts were resolved by consensus with a third reviewer.

Results

Figure 1 shows the study selection process and results. The initial database search yielded 630 citations, 13 of which had titles and/or abstracts that indicated they may be eligible for inclusion. The most common reasons for excluding citations were: study populations with diagnoses other than unipolar MDD (e.g., bipolar disorder, schizophrenia or neurological disorders) and lack of specific assessments of neurocognitive or occupational functioning. Of the 13 papers selected for detailed review, only two met the strict inclusion criteria (Table 1). The excluded papers lacked either objective measures of cognitive functioning or specific data on occupational outcomes. Due to the limited number of included publications, we present a qualitative review.

Baune *et al.* studied patients recruited from the community and from outpatient practices: 26 patients diagnosed with a current major depressive episode (moderately depressed, with mean Hamilton Depression Rating Scale score: 18.0; standard deviation [SD]: 5.9), 44 patients with a history of MDD but not in a current episode and 206 healthy subjects without a history of depression [24]. Most patients with previous and current depression (84.6 and 84.1%, respectively) were being treated with a variety of antidepressants at the time of the study. All participants underwent neuropsychological testing with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [25]. The RBANS includes tests measuring immediate memory, visuospatial/constructional abilities, language, attention and delayed memory, but notably not executive function. Specific tests for each domain are listed in Table 1.

Patients with current depression performed significantly worse in all cognitive domains compared with the healthy subjects. They also performed worse than the group with a prior history of MDD; they had significantly lower scores on the visuospatial/constructional index, attention index and the RBANS total score. Patients with a previous MDD also performed worse compared with the healthy subjects, having significantly lower immediate memory and attention index scores.

The only measure of occupational functioning was employment status, assessed as either present (full- or part-time) or absent. For the total MDD sample (n = 70), patients who were unemployed performed much more poorly on neuropsychological testing than those who were employed. Their scores were significantly lower on four out of the five RBANS index scores and the total score (i.e., immediate memory, visuospatial/constructional ability, language and delayed memory). Subgroup analysis of patients who were currently depressed (n = 26) demonstrated that there were no significant differences on cognitive testing between those who were employed versus unemployed. However, numerical differences suggested that the unemployed patients had greater difficulty than the employed patients in the immediate memory and visuospatial/constructional domains. Given the small size of the currently depressed subsample, there is the possibility that these analyses were underpowered to detect meaningful differences in cognition. By contrast, in the subgroup of patients with prior depression (n = 44), those who were currently unemployed performed worse on testing than patients with prior depression who were employed. They had significantly lower visuospatial, language, delayed memory and total index scores [24].

Godard *et al.* recruited 30 patients from an outpatient clinic, 16 with MDD and 14 with bipolar disorder (while they were experiencing a depressive episode) and 30 healthy subjects [26]. Patients with MDD were chronically (mean duration of current episode: 22.7 months; SD: 22.1) and moderately (mean Montgomery–Asberg Depression Rating Scale score: 28.5; SD: 8.6) depressed and were on a variety of medications, including antidepressants (25%), lamotrigine (25%), benzodiazepines (44%) and antipsychotics (19%). All participants underwent neuropsychological testing with an assortment of tests, including those from the Delis–Kaplan Executive Function System (D-KEFS) [27] and CogitEx II batteries [28] assessing the following cognitive domains:

Table 1. Summary of the included studies.

Study (year)	Samples	Neurocognitive measures and tests	Occupational functioning measures	Main findings	Ref.
Baune *et al.* (2010)	26 patients with MDD, currently depressed; 44 patients with MDD, not currently depressed; and 206 healthy subjects	RBANS, including [25]: Attention: ▪ Digit Span ▪ Coding Tests Immediate memory: ▪ List Learning ▪ Story Memory Tests Delayed memory: ▪ List Learning Free Recall ▪ List Learning Recognition ▪ Story Memory Free Recall ▪ Figure Free Recall Tests Visuospatial/constructional: ▪ Figure Copy ▪ Line Orientation Tests Language: ▪ Picture Naming ▪ Semantic Fluency Tests	Employment status: employed (full- and part-time) vs unemployed	The combined MDD group was impaired in all cognitive domains compared with healthy subjects. Unemployment was strongly related to poor cognitive performance across all cognitive domains. Individuals with current depression showed a similar degree of cognitive deficits across all domains, regardless of employment status. Individuals with previous depression showed differential cognitive dysfunction depending on employment status: unemployed individuals had lower scores overall, and in visuospatial, language and delayed memory domains	[24]
Godard *et al.* (2011)	16 patients with MDD, currently depressed; 14 patients with bipolar disorder, currently depressed; and 30 healthy subjects	Attention: ▪ CogitEx II tests: Simple Reaction Time Test, Divided Attention Test, Conditional Reaction Time Test and Choice Reaction Time Test ▪ Continuous Performance Test [57] ▪ D-KEFS tests: Color–Word Interference Test [27] Executive function: ▪ CogitEx II tests: Sequential Memorization Test ▪ D-KEFS tests: Verbal Fluency Test, Design Fluency Test, Tower Test and Twenty Questions Test [27] Verbal learning and memory: ▪ California Verbal Learning Test [58] Visual functions: ▪ Block Design Test [59]	LIFE-RIFT [29], Work subscale	The majority of patients with MDD had deficits in attention, executive function, verbal learning and memory. All of the depressed sample experienced significant work impairment. The maximally impaired domain of the Work subscale of the LIFE-RIFT was correlated to attention (specifically alertness; r = -0.50), executive function (spontaneous flexibility; r = -0.49) and verbal memory (retrieval; r = -0.49) in the depressed groups	[26]

D-KEFS: Delis–Kaplan Executive Function System; LIFE-RIFT: Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MDD: Major depressive disorder; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

attention; executive function; verbal learning and memory; and visual functions **(Table 1)**.

The group of patients with MDD (n = 16) had significantly impaired attention and information processing speed when compared with healthy subjects. This manifested itself as patients being less able to mobilize attentional resources, deal with multiple streams of information and carry out simultaneous tasks. These patients also had difficulty with problem solving. The most frequently impaired cognitive functions were alertness, information processing speed, sustained and divided attention, and spontaneous flexibility. Of the 16 patients with MDD, four (25%) had impaired attention, two (14%) had impaired executive function and seven (44%) had deficits in more than one cognitive domain.

The measure of occupational outcome used was the Work subscale of the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) [29]; other subscales of the LIFE-RIFT include Interpersonal Relations, Life Satisfaction and Recreation. The Work subscale yields a score from one (very good functioning) to five (very poor functioning). All of the patients with MDD had impairments in the employment category of the Work subscale (mean: 4.6; SD: 0.8). Work impairment was significantly correlated with the following cognitive domain scores: attention (alertness; r = 0.50), executive functioning (spontaneous flexibility; r = -0.49) and verbal memory (retrieval; r = -0.49) [26].

Discussion

Occupational impairment has been identified as an important topic both for individuals with depression and for society. There is extensive literature on neuropsychological deficits in unipolar MDD and it is widely believed that these deficits adversely affect work functioning. Hence, it is surprising that, after an extensive systematic literature search, only two studies were identified that examined the relationship between neurocognitive deficits and occupational functioning, and neither had this as a primary study objective. Both studies included only small numbers of depressed participants, did not control for premorbid intelligence or medication use, and had other significant methodological limitations that limit conclusions about specific cognitive deficits and occupational functioning in MDD. For example, in the Baune study, only employment status was used as an occupational measure; in the Godard study, there was very little information reported on the work functioning measure (the Work subscale of the LIFE-RIFT) and it was unclear whether patients were employed or not. Furthermore, both studies were cross-sectional and their analyses correlational, preventing any conclusions about the causal relationship(s) between the observed neurocognitive deficits and occupational outcomes.

Despite these limitations, both studies found significant cognitive deficits in patients with MDD that were associated with occupational dysfunction. In the Godard study, depressed patients were most impaired in attentional variables and information processing, with the majority of patients showing impairment in executive function, followed by verbal learning and memory deficits. All of the depressed patients experienced negative effects on work functioning. In the Baune study, all cognitive domains were significantly impaired in currently depressed patients compared with healthy subjects, but employment status was not associated with specific deficits [24]. By contrast, cognitive deficits were more pronounced in unemployed patients with a past history of MDD (but who were not currently depressed) compared with those who were employed. Although neurocognitive functioning often improves with treatment of depression [30–33], some studies have suggested that cognitive deficits, especially in attention and executive function, may persist in some patients following remission of depressive symptoms [34–39]. Therefore, it is possible that persisting cognitive deficits would adversely affect ability to work even in the absence of other depressive symptoms [39].

Although both studies found significant cognitive deficits in their respective depressed cohorts, other studies suggest that cognitive impairment associated with depression may be quite limited and difficult to detect [40,41], with deficits more likely to be present in those who are older or more seriously ill [42–46]. Moreover, there is some evidence to suggest that cognitive impairment associated with depression might be limited to a minority of patients, with the majority being broadly cognitively normal. In part, this may be related to the different definitions used to define cognitive impairment. For example, in a study using various criteria to define impairment in each cognitive domain, the percentage

of depressed patients with an impaired domain score ranged from 62% with less strict definitions (i.e., 1 SD or ≤16th percentile, below a normative control sample) to 35% using a more strict definition (i.e., 2 SDs or ≤2nd percentile, below the control sample) [12]. The criterion that best differentiated patients with depression from a normative healthy subject sample was having two domain scores at or below the 5th percentile. This criterion identified 31% of the patients as having cognitive deficits versus 8% of the comparison sample. Further research should examine this cognitively impaired subgroup to determine whether they are differentially impaired in work functioning.

There are additional measurement challenges in the assessment of work functioning and productivity in individuals. Employment status and days off for sick leave are seen as 'objective' measures but may be highly variable and dependent on external factors such as corporate sick leave policies, the availability of other staff to cover for absences, and the availability of disability or unemployment insurance. Productivity may be a more important metric than work absence, but it is difficult to objectively measure work performance in most jobs; hence, self-report measures are typically used in studies of productivity. A number of self-report instruments to evaluate work functioning have been used in depressed populations [47,48], but the quality of the evidence to validate measurement properties of these scales remains limited [49–51]. Some studies have shown reasonable correlations of self-report scales with objective evaluations of work productivity [52,53].

Another confounding factor is that cognitive deficits may differentially interfere with occupational functioning depending on the individual and their occupation. For example, small deficits in cognitive functioning in a physician or lawyer may result in notable occupational impairment, while the same deficits may not cause impairment for a sales clerk. Conversely, in the Godard study, 19% of the participants with MDD had no cognitive deficits and still reported poor occupational functioning. These observations are consistent with the complex and multifactorial relationships between symptoms and functioning in individuals with depression [9,10,54]. They also illustrate that functioning and depressive symptoms, such as cognition, should be independently assessed during assessment and treatment of depression.

Conclusion & future perspective

In summary, this systematic review identified only two studies that examined the impact of neurocognitive deficits on occupational functioning in MDD or the effects of deficits in specific cognitive domains such as executive function. Neurocognitive dysfunction appears to be associated with poorer occupational outcomes, but any conclusions are tempered by methodological limitations of the studies. However, these research questions are likely to have great relevance for the clinical management of depression. Although treatment for MDD is generally associated with improved work outcomes, including gains in productivity [55,56], there may be specific treatments for depression-related cognitive dysfunction that can optimize occupational functioning. These may be especially relevant if neurocognitive impairment in MDD persists during clinical remission. Clearly, it will be important to further elucidate, in both cross-sectional and longitudinal studies, how neurocognitive deficits in depression can affect work functioning and impairment. Future studies should examine specific cognitive domains, especially executive function, use validated instruments to assess work functioning and productivity, and compare cognitive dysfunction and occupational outcomes during acute and remitted states of depression.

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