Cognitive Deficits as a Mediator of Poor Occupational Function in Remitted Major Depressive Disorder Patients

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Cognitive deficits in major depressive disorder (MDD) patients have been described in numerous studies. However, few reports have aimed to describe cognitive deficits in the remitted state of MDD and the mediational effect of cognitive deficits on occupational outcome. The aim of the current review is to synthesize the literature on the mediating and moderating effects of specific domains of cognition on occupational impairment among people with remitted MDD. In addition, predictors of cognitive deficits found to be vocationally important will be examined. Upon examination of the extant literature, attention, executive function and verbal memory are areas of consistent impairment in remitted MDD patients. Cognitive domains shown to have considerable impact on vocational functioning include deficits in memory, attention, learning and executive function. Factors that adversely affect cognitive function related to occupational accommodation include higher age, late age at onset, residual depressive symptoms, history of melancholic/psychotic depression, and physical/psychiatric comorbidity, whereas higher levels of education showed a protective effect against cognitive deficit. Cognitive deficits are a principal mediator of occupational impairment in remitted MDD patients. Therapeutic interventions specifically targeting cognitive deficits in MDD are needed, even in the remitted state, to improve functional recovery, especially in patients who have a higher risk of cognitive deficit.

KEY WORDS: Depression; Remission; Cognition; Occupational outcome.

INTRODUCTION

Major depressive disorder (MDD) is a chronic mental disorder with a lifetime prevalence of 5-20%.1,2 MDD is associated with functional impairment both at home and in the workplace, significantly and chronically reducing quality of life.3-5 Further, MDD has been found to be the fourth leading contributor to disease burden worldwide5 and is predicted to be the second leading cause of disability adjusted life-years in 2020 and the leading cause of disability adjusted life-years in 2030 according to the Global Burden of Disease Study.5,6

Functional impairment in MDD patients is attributable to several factors including but not limited to mood disturbances, cognitive dysfunction, lack of energy and motivation, psychomotor retardation, fatigue, and insomnia. The severity of functional impairment in MDD patients was significantly correlated to the severity of depressive symptoms. Judd et al.9 reported that with each increasing level of depressive symptom severity, impairments in global function, as well as function at work and at home, was significantly increased.

Of note, even milder forms of the disorder, such as minor depression, dysthymia, or subthreshold depressive symptomatology can significantly affect function. 9-12 Further, functional impairment is not restricted to mood episodes; similar levels of impairment have been noted during periods of remission.13 Indeed, symptom improvement is a poor predictor of functional improvement and work loss.13,14

Of the functional domains affected by MDD (work, household duties or schoolwork), the most disrupted was work impairment; severe impairment was observed during a considerable portion of the follow-up period (20-30% of months).15 Also in a study with US workers, a significant component of the overall disability and cost associated with depression relates to impaired workplace performance.16

Received: May 13, 2015 / Revised: July 21, 2015
Accepted: August 26, 2015
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Cognitive deficits associated with MDD may be a key factor affecting patients’ ability to function in the workplace. Cognitive impairment has been widely reported in patients during episodes of major depression. Further, cognitive deficits can still be detected in periods of remission and significantly affect the individual's social and occupational function. Indeed, meta-analyses have shown that cognitive deficits are still present in remitted patients. Moreover, persistent cognitive dysfunction has been shown to be a key mediating factor of impaired occupational function. In a large, cross-sectional study with data from the European Study of the Epidemiology of Mental Disorders (ESEMeD) including 21,425 adults from six European countries, only two factors, including cognitive dysfunction and embarrassment, mediated the association between depression and role functioning. In this study, role functioning was evaluated with ESEMeD and World Health Organization Disability Assessment Scale (ESEMeD-WHODAS) which assessed work functioning at home and in paid employment. Taken together, cognitive dysfunction may be a significant mediating factor of the functional impairment in the workplace observed in MDD patients during mood episodes as well as during periods of remission.

Impairment in the workplace is often of great concern for patients, clinicians and employers alike. However, in MDD, treatment and prognostication of workplace disability is often complex and uncertain. Therefore, the aim of the current review is to describe the role of cognitive impairment in functional outcome after remission from MDD, especially targeted at work functioning. Toward this aim, we review (1) cognitive deficits in remitted MDD patients, (2) the effect of cognitive deficits on occupational functional outcome, and (3) predictors of cognitive deficits which related to poor occupational functional outcome after remission.

**MAIN SUBJECTS**

**Search Methods and Selection Criteria**

To identify studies on relationship between occupational outcome and cognitive function, we performed a comprehensive literature search using Medline and EMBASE. The search term were as follows; (employ* or occupation* or vocation* or function* or job or cognitive function or cognition) and (depression or depressive) and (remission or remitted or euthymic). We did not filter papers by age/gender or other demographic characteristics. The abstracts and titles of articles retrieved were reviewed to identify relevant papers. Selected articles were then reviewed and only articles written in English and investigated the relationships between more than two among depression, cognitive function or occupational function were included. Studies with only patients with bipolar depression or symptomatic depression were excluded. In addition, reference lists of selected articles were searched to identify additional references.

Cognitive Function in Depressed Patients during Periods of Remission

Several cognitive domains, including memory, attention, processing speed, and executive function, have been investigated during periods of remission (Table 1). In 2000, Reischies and Neu studied the degree of reversibility of cognitive dysfunction in depression. In their depressed state, the patients performed poorly in most neuropsychological tests, and about one third of MDD patients performed at an impaired level in tests of verbal memory and verbal fluency. In their remitted state, there was no normalization of cognitive test performance including verbal/visual memory and visual-motor sequencing, in spite of complete recovery of the affective symptoms. These results were in keeping with previous results, which reported impaired visual-motor sequencing and memory in euthymic patients with a history of chronic MDD. Neu et al. included 27 MDD patients and assessed them with neuropsychological tests at the beginning of the depressive episode and during a period of euthymia. At the onset of a depressive episode, patients performed significantly worse than the healthy controls in all tests including Rey Auditory Learning Test, Reitan Trail Making Test A, verbal fluency test and Wechsler Memory Scale (visual memory index). After sustained remission, the patient group still performed significantly worse in verbal memory and verbal fluency compared to healthy controls. A longitudinal study also reported impaired visual memory. In a recent study with 97 remitted patients and 97 healthy controls, patients with remitted MDD were impaired on verbal memory when compared to control. However, in a longitudinal analysis of neurocognitive function in MDD patients, remission of depression was followed by improvement in verbal memory function up to the level of healthy controls. Verbal learning, delayed recall, and recognition were unimpaired in another study with euthymic MDD patients. In young, euthymic pa-
Cognitive test performed performance and spatial working memory relative to tasks of rapid visual information processing, psychomotor 23 healthy control subjects, patients were impaired on aged, unmedicated, fully remitted patients with MDD to MDD. When compared between 28 young to middle-

patients with MDD, verbal memory was not significantly impaired from controls. A recent study investigated differences in neurocognitive performance between groups of euthymic patients with a history of MDD or bipolar I disorder and a healthy control group. It was noted that verbal memory was not significantly different between control and MDD or bipolar I disorder patients.

Some authors reported impairment in remitted depressed patients on attention as well. Weiland-Fiedler et al. described the neuropsychological functioning of fully remitted, unmedicated patients with a history of MDD. When compared between 28 young to middle-aged, unmedicated, fully remitted patients with MDD to 23 healthy control subjects, patients were impaired on tasks of rapid visual information processing, psychomotor performance and spatial working memory relative to controls. After correction for residual depressive symptoms, deficits in sustained attention remained significant and more subtle deficits were found in the mnemonic and strategic aspects of working memory. The authors suggested ongoing deficits in sustained attention as vulnerability marker for MDD. In another study including 40 euthymic MDD patients and 20 healthy controls, euthymic patients with MDD showed deficits in attentional set shifting, as well. They were more likely to fail the intra-dimensional/extra-dimensional shift task than the healthy comparison subjects and attention assessed with Trail

### Table 1. Impaired cognitive domains in remitted major depressive disorder patients

| Study | Cognitive test performed | Cognitive domains Impaired |
|-------|-------------------------|---------------------------|
| Beats et al. | CANTAB | No significant difference between patients and healthy controls |
| Kessing | Cambridge Cognitive Examination, Mattis Dementia Rating Scale, Gottfries-Bråne-Steen Dementia Rating Scale, Mini-Mental State Examination, Global Deterioration Scale | Patients significantly impaired on all tests |
| Weiland-Fiedler et al. | CANTAB | Patients significantly impaired on attention and working memory |
| Clark et al. | Rapid visual information processing task, CVLT, and the intra-dimensional/extra-dimensional shift task of the CANTAB | No significant difference between patients and healthy controls |
| Neu et al. | RAVLT, Trail-Making Test (part A), verbal fluency test (animal naming), Wechsler memory subscale (visual memory) | Patients impaired on executive function |
| Paeckel-Habermann et al. | Visual orienting task (computerized test), sustained attention task (card sorting task), executive attention, behavioral assessment of the dysexecutive syndrome test | Patients significantly impaired on attention and executive functions |
| Smith et al. | CVLT, Brixton spatial anticipation Test, Trail Making Test (part A and B), Stroop Color Word | Patients significantly impaired on trials verbal learning, attention, and executive function |
| Biringer et al. | Stroop Color, Stroop Word, Stroop Color Word, WCST perseverative responses, and California Computerized Assessment Package simple reaction time | No significant difference between patients and healthy controls |
| Yuan et al. | RAVLT, Trail Making Test (part A and B); Clock drawing test, Digit Span test | Patients significantly impaired on verbal learning, attention and executive function |
| Nakano et al. | WCST, Stroop test and verbal fluency test | Patients significantly impaired on executive function |
| Preiss et al. | Auditory Verbal Learning Test, Trail Making Test (part A and B) | Patients significantly impaired on verbal learning and attention |
| Hasselbalch et al. | Trail Making Test (part A and B), Symbol Digit Modalities Test, RAVLT, modified version of Category Cued Recall, Rey-Osterrieth Complex Figure Test, Familiar Faces, Boston Naming Test, verbal fluency test (phono logical and semantic), Stroop test, WCST, Letter-Number Sequencing | Patients significantly impaired on executive function |
| Daniel et al. | Babcock Story Recall Test, WCST, Trail Making Test (part B), Stroop Color Word Test, Symbol-Number Association Test from WAS-R, Digit Span from WAS-R | Patients significantly impaired on executive function and attention |

CANTAB, Cambridge Automated Neuropsychological Test Battery; WCST, Wisconsin Card Sorting Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; WAS-R, Wechsler Adult Intelligence Scale-Revised.
Making Test A.\textsuperscript{30} However, the impairment in sustained attention in remitted MDD patients was not replicated on an independent sample of 15 remitted MDD patients.\textsuperscript{37} Sustained attention deficit was confirmed only in the euthymic bipolar patients. These results are also inconsistent when compared to a recent study, which investigated differences in neurocognitive performance between groups of patients with MDD or bipolar I disorder in a euthymic state and a healthy control group. In this study, patients demonstrated reduced performance on attention/working memory\textsuperscript{33} compared with healthy controls. Performance on neurocognitive tasks did not differ between patients with MDD versus bipolar I disorder.

Executive function was another cognitive domain reported as impaired in remitted MDD patients. Paelecke-Habermann \textit{et al.}\textsuperscript{35} showed that euthymic patients with MDD exhibited deficits in executive functions (behavioural assessment of the dysexecutive syndrome, word fluency, memory span) compared to healthy controls. In another study which included 79 remitted MDD patients and 85 healthy controls,\textsuperscript{30} the remitted MDD group showed significantly poorer performance on Stroop test. The elderly MDD group showed significantly lower scores for verbal fluency test than the control group and the young MDD group. Impaired executive function in remitted MDD was further supported by Yuan \textit{et al.},\textsuperscript{39} who examined the relationship between neuropsychological deficits and brain regional activity in elderly remitted MDD patients. They reported significantly worse performance on the delayed recall of Rey Auditory Verbal Learning Test and executive function (Trail Making Test A and B) in the MDD group when compared with the control group. Impairment in executive function was reported in several studies.\textsuperscript{26,27,30,32} Daniel \textit{et al.}\textsuperscript{35} recently reported deficits in executive function in patients with remitted MDD or bipolar I disorder when compared to healthy controls. Lin \textit{et al.}\textsuperscript{30} compared remitted MDD patients with melancholic, atypical, or undifferentiated type with healthy controls. Attention and executive function were impaired in melancholic and undifferentiated types of MDD compared to healthy controls. Verbal fluency was impaired in melancholic MDD. Conversely, Biringer \textit{et al.}\textsuperscript{41} reported returning of executive function to normal levels accompanied with remission. They found an improvement in executive functions in young depressive patients in remission (both medicated and non-medicated) in accordance with the improvement of depressive symptoms; there was a significant positive association between improvement on the Hamilton Depression Rating Scale (HDRS) score and improvement of executive function. During remission, overall executive function and the measures used to test, it were no longer different from the baseline performance of healthy controls. However, in a recent study with strictly defined inclusion criteria, only including patients that had been remitted for a substantial period of time,\textsuperscript{42} multiple linear regression analyses with simultaneous adjustment for age, gender, education level, premorbid intelligence quotient (IQ), and residual depressive symptoms showed a diagnosis of MDD predicted lower performance on attention and processing speed (the Trail Making Test, the Symbol Digit Modalities Test) and on executive function (the Stroop test). The authors also reported that there was a trend toward the patient group performing worse than the healthy control group in all the tested cognitive domains including verbal/nonverbal memory, verbal function.

Recently, Bora \textit{et al.}\textsuperscript{43} conducted a systematic review and meta-analysis of cognitive deficits in studies of euthymic MDD patients compared with healthy controls. In global cognition, euthymic MDD patients showed significantly lower score compared with healthy controls (d=0.47). Moreover, healthy controls significantly outperformed euthymic MDD patients in all cognitive domains. Task-specific analyses indicated that healthy controls performed significantly better than MDD patients in Stroop interference (d=0.74), Trail Making Test A (d=0.39), Trail Making Test B (d=0.48), digit span backwards (d=0.41), list learning (d=0.42), list recall (d=0.39), and animal naming (d=0.57), but not in phonetic fluency, Wisconsin Card Sorting Test perseveration, digit span forwards and list recognition.

Taken together, that majority of studies support the hypothesis that cognitive deficits exist in patients with MDD during periods of remission. Pooling of results in the previously described meta-analysis further supports this hypothesis. Measures of attention, executive function, and verbal memory were the most reproducibly reported cognitive domains affected, despite a few contradictory results. Although studies by Beats \textit{et al.},\textsuperscript{44} Clark \textit{et al.}\textsuperscript{37}, and Biringer \textit{et al.}\textsuperscript{29} reported no significant difference in cognitive performance between remitted MDD patients and healthy controls, this discrepant findings may have resulted from the prevalent methodological drawbacks; studies used various diagnostic criteria (International Classification of Diseases-10; Diagnostic and Statistical Manual of Mental Disorders [DSM] third edition, revised; or DSM 4th edition), inconsistent cut-off values on depressive symptom scale score (cut-off scores were 6-8 on
There has been considerable evidence that some ‘cold’ cognitive abnormalities (as described above) do not disappear completely upon remission, some investigators emphasize the role of ‘hot’ cognition, particularly on tasks that utilize feedback, on which depressed patients have been reported to exhibit a “catastrophic response to perceived failure”.45) ‘Cold’ cognition refers to information processing in the absence of any emotional influence. Theoretically, cold cognition is engaged on tests where the stimuli are emotionally neutral and the outcome of the test is not motivationally relevant; commonly used standardized neurocognitive test such as the California Verbal Learning Test, the Trail-Making Test, and the Wisconsin Card Sort Test are considered as ‘cold’.45) ‘Hot’ cognition denotes emotion-laden cognitive processes, i.e., cognitive processes which are colored by feeling or emotion.45 In MDD, ‘hot’ cognition is biased in attention, perception and memory for negative cues and/or perception and memory for positive cues are reduced.46,47) There has been considerable evidence that abnormalities in ‘hot’ cognition are observed in individuals with a history of depression and can be triggered by external stimuli although it appears to be resolved or absent in these patients following clinical remission.47,48) For example, patients with remitted MDD also exhibit a persistent susceptibility to distraction by negative emotional information, which impedes their performance in ‘cold’ cognitive tasks.49) In 1996, Beets et al.44) reported a pattern of behavior; when depressed patients made an error on a test, they were proportionately more likely than controls to make an error on the subsequent trial. The “catastrophic response to perceived failure” raises the possibility that at least some of the poor performance on neurocognitive tests in depression might be due to altered ‘hot’ cognition, which is trait related.50,51) In summary, it is hypothesized that depression is associated with abnormalities in ‘hot’ cognition qualitatively (i.e., changes in the nature of the cognitive processes), as well as in ‘cold’ cognition quantitatively (i.e., neuropsychological performance deficits). These two aspects of cognition may exert mutual influences on each other.47)

### Cognitive Deficits Underlying Poor Occupational Functioning in Remitted MDD Patients

As reviewed in the previous section, remitted MDD patients are impaired in their verbal/visual memory, visual-motor sequencing, attention, working memory and executive function. In several studies to explore the relationship between cognitive and functional outcome in MDD patients, performance in at least one cognitive domain (most commonly executive function, attention, psychomotor speed, and certain aspects of memory) was associated with functional outcome.52) Moreover, there have been reports that cognitive impairment could be a contributing factor that determines levels of social and occupational impairment in different phases of MDD.53,54) Here, we discuss the cognitive deficits underlying poor occupational functioning in remitted MDD patients.

### Relation between cognitive deficit and occupational disability in other conditions

Although there have been studies for the effect of neurocognitive deficits as a mediator of occupational disability in schizophrenia and bipolar disorder, there has only been minimal investigation with MDD. Therefore, studies assessing cognition as a mediator of occupational disability in bipolar disorder and schizophrenia will be briefly reviewed. While these results may not be completely generalizable to the MDD population, they may provide some insight into occupational effects of impairment of the specific domains of cognition assessed.

In studies with schizophrenic patients, impaired attention was associated with poor occupational performance. Patient with difficulties in selective and sustained attention may be distracted easily by extraneous stimuli or internal thought causing difficulties in encoding relevant task information for processing and recall.55) Poor sustained attention also means that they are unable to monitor engagement of a task for extended periods of time, resulting in concentration lapses that will delay completion of a work task.56-58)

Reduced ability in working memory and verbal learning may also impair work function. Problems in declarative working memory may induce the inability to retain and retrieve information during learning of new work tasks, therefore reducing acquisition of work skills.59,60) Poor verbal learning is found to be associated with poorer work habits, poorer work quality and fewer number of hours worked in competitive jobs in patients with schizophrenia.61,62) Impairment in executive function could also be a limiting factor in occupational function for these patients.
patients. The same study reported that improved executive functioning was associated with higher wages earned and more hours worked.

The neurocognitive factors including verbal learning and memory, and executive functioning were predictors of workplace performance in bipolar patients as well. Gilbert et al. found that self-reported cognitive impairment at baseline, especially concentration problem, increased the chances of not working at both baseline and follow-up of 15-43 months. A study using neurocognitive tests reported that high scores on the measure of executive function, digits backwards test, was a predictor of lower occupational functioning. Verbal learning deficit assessed with the Strauss Carpenter performance scale, used to measure work disability. 

The relationship between cognitive deficit and occupational functioning. Verbal learning deficit assessed with the California Verbal Learning Test were independently associated with higher scores on the Strauss Carpenter work outcome scale, used to measure work disability.  

The executive/reasoning scale independently predicted low versus high occupational adaptation in this study. Motor speed domain was predictive of occupational adaptation in schizophrenic patients. In bipolar patients, a composite neurocognitive score at baseline was the strongest independent predictor of good versus poor occupational adaptation and executive/reasoning domain predicted occupational adaptation level at one-year follow-up. In another study with schizophrenic and bipolar I patients, a composite neurocognitive score at baseline was the strongest independent predictor of good versus poor occupational adaptation in schizophrenic and bipolar patients. Among the neurocognitive domains, independent predictors of occupational adaptation were the motor speed domain in schizophrenic patients and the executive/reasoning domain in bipolar patients. These cognitive abilities impaired in bipolar patients are related to learning new tasks, acting purposefully and making decisions. 

Lee et al. investigated cognitive markers that predict later socio-occupational functioning in outpatients with major psychiatric disorders among 93 young (mean 21.6 years old) patients (MDD=34, bipolar=34, psychosis=29). At the point of follow-up after 21.6 months of baseline evaluation, the best independent predictors of good socio-occupational functioning were verbal and visual memory, working memory and executive functioning.

Relation between cognitive deficit and occupational disability in symptomatic MDD

There have been a few studies to support cognitive deficits in MDD specifically as a mediator of functional/occupational impairment. In a study aimed to characterize psychosocial and cognitive profiles among MDD and bipolar patients during a major depressive episode and to compare the profiles of the patient groups for 12 months, MDD and bipolar patients during a depressive episode in the case of severe mood disorders. All MDD and bipolar patients had global psychosocial dysfunction, characterized by occupational and relational impairments. At the time point of follow-up, occupational and relational impairments, as well as neurocognitive dysfunction, persisted sufficiently to alter daily functioning of the patients. 

Naismith et al. examined the relationship between subjective disability and subjective/objective measures of cognitive performance in MDD patients. A small sample (n=21) of adults patients exhibited a moderate relationship between objectively measured psychomotor speed and self-rating cognitive deficits with physical disability. Functional disability was moderately correlated with objective measures of memory retention too. McIntyre et al. also evaluated the deleterious effect of cognitive deficits on functional outcomes in MDD including workplace performance. The authors noted that abnormalities in many cognitive domains of executive function, working memory, attention, and psychomotor processing speed may account for the largest percentage of variance with respect to the link between workforce performance and MDD.

Relation between cognitive deficit and occupational disability in remitted MDD

Baune et al. evaluated the association between cognitive dysfunction and MDD as compared with age- and gender-matched healthy controls in participants with current MDD (n=26) and those with previous MDD only (n=44). The mean HDRS-17 score in past MDD group was 6.8. The results showed that participants with previous MDD but who were currently employed performed significantly better in the visuospatial, language and delayed memory domains (except immediate memory and attention) as well as on the total score than their counterparts without employment. In another study which investigated the relationship between quality of life and neurocognitive dysfunction in patients with remitted MDD, remitted MDD patients had poorer neurocognitive performances than healthy controls for psychomotor speed, attention, and verbal memory than age and education matched healthy subjects. Delayed verbal recall was associated with poor general health perceptions. Of note, the functional outcome was not evaluated in this study. In the results from Jaeger et al. which examined the degree to
which neurocognitive deficits explain functional outcome 6 months following hospitalization for a major depressive episode, five out of seven cognitive domains showed significant findings in models of concurrent associations at the 6-month time point. Most measures at 6 months follow-up within attention, ideational fluency, non-verbal (visuospatial) and learning domains were highly associated with life function disability at the 6-month time point, which means the degree to which neurocognitive deficits present at the 6-month time point are associated with level of functional recovery at that point. Cognitive impairment at acute phase of depression could predict poor occupational outcome after remission. Memory and executive function at admission was predictive of poor occupational function at approximately 4 months after discharge.\textsuperscript{74} The significant cognitive predictors for Social and Occupational Function Assessment Scale at follow-up were shortened Wisconsin Card Sorting Test perseverative errors and prospective memory categories.

Taken together, cognitive deficits in memory, attention, learning and executive function appear to be mediators of impairment in vocational function. In addition, specific cognitive domains may exert more influence at certain phases of occupational adjustment after remission. Bryson and Bell\textsuperscript{61} discovered that attention is more important for earlier phase of work performance, and verbal memory and psychomotor speed becomes more important for sustained improvement in work performance. It was postulated that learning new tasks with attention was more crucial in the initial phase of work, and cognitive demands shifted towards remembering instructions and keeping up with the speed of work at a later stage.\textsuperscript{61} However, cognitive demands may be dependent on the type of jobs; a job requiring repetitive actions may have a higher demand on sustained attention, whereas a job requiring taking down orders will require verbal memory.\textsuperscript{55} These suggestions from schizophrenia and bipolar disorder may potentially also be applied to remitted MDD patients. Further studies are still required to specifically assess the effects of cognitive dysfunction in MDD on workplace performance.

**Predictors of Neurocognitive Deficit Related to Occupational Function in Remitted MDD Patients**

There have been several demographic and clinical factors shown to be predictive of cognitive deficits in MDD. These factors include age, age at onset, duration of illness, episode frequency, baseline symptom severity, subtype of MDD, psychiatric/medical comorbidity and educational level (Table 2).

**Table 2. Predictors of cognitive deficits related to poor occupational function in remitted major depressive disorder patients**

| Cognitive domains adversely impact on occupational function | Predictors of cognitive deficit |
|-------------------------------------------------------------|--------------------------------|
| Global cognition\textsuperscript{69,71}                      | Older age\textsuperscript{77} |
|                                                           | Lower education\textsuperscript{76,77,86} |
|                                                           | Residual depressive symptom\textsuperscript{77} |
|                                                           | Psychotic depression\textsuperscript{42,104,107} |
|                                                           | Psychiatric comorbidity\textsuperscript{86} |
|                                                           | Higher number of illness episode\textsuperscript{71,122} |
| Attention\textsuperscript{22,25,63}                        | Longe r total duration of illness\textsuperscript{107} |
|                                                           | Lower education\textsuperscript{78} |
|                                                           | Melancholic type\textsuperscript{78} |
| Working memory\textsuperscript{22,124}                    | Lower school attainment\textsuperscript{113} |
|                                                           | Older age\textsuperscript{78} |
|                                                           | Later age at onset\textsuperscript{63,82} |
|                                                           | Lower education\textsuperscript{78} |
|                                                           | Melancholic depression\textsuperscript{102} |
|                                                           | Psychotic depression\textsuperscript{10,106} |
| Executive function\textsuperscript{22,45,68,73}           | Older age\textsuperscript{70} |
|                                                           | Early age at onset\textsuperscript{63} |
|                                                           | Late age at onset\textsuperscript{116} |
|                                                           | Melancholic depression\textsuperscript{80,102} |
|                                                           | Psychotic depression\textsuperscript{78} |
|                                                           | Comorbid anxiety\textsuperscript{116} |
|                                                           | Higher number of illness episode\textsuperscript{106} |
| Visuo-spatial processing\textsuperscript{22,77}           | Lower education\textsuperscript{79} |
| Language\textsuperscript{71}                               | Melancholic depression\textsuperscript{83} |
| Psychomotor function\textsuperscript{70}                  | Older age\textsuperscript{70} |
|                                                           | Psychotic depression\textsuperscript{78} |
|                                                           | Comorbid anxiety\textsuperscript{116} |
| Visual learning/memory\textsuperscript{70}                | Older age\textsuperscript{70} |
|                                                           | Psychotic depression\textsuperscript{10,106} |
|                                                           | Comorbid anxiety\textsuperscript{117} |
| Memory\textsuperscript{68,71,73}                           | Higher number of illness episode\textsuperscript{70} |
|                                                           | Longer total duration of illness\textsuperscript{76} |
|                                                           | Residual depressive symptom\textsuperscript{95} |
|                                                           | Melancholic depression\textsuperscript{96} |

**Age**

Thomas \textit{et al.}\textsuperscript{75} compared neuropsychological performance of younger (< 60 years) and older (≥ 60 years) adults with MDD and healthy controls. The late-life depression group had greater impairment in verbal learning, memory and motor speed but not in executive function. The authors suggested that late-life depression is associated with more severe impairment in verbal learning, memory and motor speed than depression in earlier adult life and this is not due to aging alone, while this study reported normal executive function in older patients. In a meta-regression analysis of studies in adults with a first-episode MDD,\textsuperscript{76} age significantly contributed to heterogeneity in effect sizes in some cognitive domain. Studies with patients who were, on average, older than controls reported significantly worse performance for...
psychomotor speed, visual learning and memory, and all aspects of executive functioning examined.

In a recent study, age was positively associated with impaired executive functioning in euthymic MDD and bipolar I disorder patients. Moreover, Gorwood et al. reported higher age as an independent predictor for poor memory function. These results support previous studies suggesting that higher age was associated with overall cognitive deficits in euthymic mood disorder patients. However, In a recent meta-analysis with remitted MDD subjects of various clinical stage by Bora et al., age had no statistically significant influence on the nature of cognitive deficits observed in euthymic MDD patients. Taken together, age appears to be an important factor for impairment in memory and learning function in MDD patients; however, results have been variable.

**Age at onset**

Herrmann et al. compared early onset and late onset depression patients for white matter hyperintensities in manetic resonance imaging scans which have been known to be related to cognitive decline in various domains, particularly executive skills, attention and mental speed. They reported that late onset depression was characterized by more frequent and intense white matter abnormalities. However, another study reported an association of impaired executive functioning with younger age at onset, and no significant correlation between age at onset and cognitive performance. In a relatively large study with remitted MDD patients, Wekking et al. reported a correlation with later age of onset and a slower speed of information processing and lower verbal memory performance. Moreover, in a recent meta-analysis with remitted MDD subjects by Bora et al., cognitive deficits in late onset patients (onset after 50-65 years, depending on the study) were significantly more severe than those in early onset patients in terms of processing speed and verbal memory. There were also trend level differences for global cognition and executive function. In meta-regression analyses, older age of onset was associated with more severe verbal memory deficits.

However, in another recent study by Daniel et al., age at onset was not correlated with executive functioning, working memory or verbal memory in euthymic MDD or bipolar I disorder patients. But the authors noted that the association between performance on neurocognitive tasks and age at onset could be overshadowed by associations between performance on neurocognitive tasks and education.

Age at onset could therefore be a mediating factor of cognitive impairment in MDD. Patients with early onset may suffer predominantly from impaired episodic memory, and those with late-onset mainly from reductions of executive function and processing speed. Presence of structural abnormalities such as vascular lesions in late onset subjects may account for the severe cognitive deficits seen in late onset depression. Although this is a subject of ongoing discussion, age of onset may be associated with different risk factors including genetic predisposition to developing recurrent depression, somatic disease and vascular pathology.

**Education**

Educational attainment in patients may be predicted to correlate with higher neuropsychological performance. In a recent meta-regression analysis of studies in adults with a first-episode MDD, patients with lower levels of education showed more severe deficits in cognitive functioning in first-episode MDD. In this study, patient groups that were, on average, less educated than controls demonstrated worse verbal learning and memory, visual learning and memory, and attentional switching; yet, higher levels of education in patients relative to controls appeared to mitigate learning and memory and attentional switching deficits in first-episode MDD. In euthymic state, Gildengers et al. reported that patients with MDD and bipolar disorder were impaired across all cognitive domains compared with controls. The impairment was most prominently in information processing speed and executive function. In this study, worse overall cognitive function was associated with lower education. This is in line with the results from a previous study; Gorwood et al. reported education level as an independent factor for overall cognitive performance, and education level was significantly related to immediate memory, language, delayed memory, and the total score, even though these studies did not restrict inclusion to remitted patients. Considering overall results, education seems to provide some protection against deficits on cognitive function, especially on executive function and memory in patients with MDD as noted by Kurtz and Gerraty.

**Severity of depressive symptom**

Increased severity of depression may be related to greater impairment on cognitive performance and the relationship between symptom severity and cognitive impairment could differ across cognitive domains. Several authors have suggested that increased severity of depression was related to greater impairment on overall cognitive
function,88) executive function,89,90) processing speed,89) and semantic memory.89) However, there have been contradictory findings on overall cognition,91) executive function,92,93) episodic memory,94) semantic memory,89,90) visuo-spatial memory,95) and processing speed.88,89) In 2009, McDermott and Ebmeier96) conducted a meta-analysis to examine the relationship between severity of depression and cognitive function. The results showed significant correlations between depression severity and cognitive performance in some domains of cognitive function (e.g., episodic memory, executive function, and processing speed), yet there were limitations to this analysis, namely, a small number of included studies and heterogeneity in methodological designs and outcome measures.

Since the majority of previous studies which investigated relationship between depressive symptom severity and cognitive functions have concentrated on the acute phase of illness and were not specifically concerned with euthymic patients, the evidence of cognitive dysfunctions in remitted depression remain insufficient and unclear. Some authors have suggested that the patients with higher residual symptom severity more likely to have significant neurocognitive deficits.97) Weiland-Fiedler et al.34) compared cognitive performance in remitted MDD patients with controls. They suggested that residual depressive symptoms influence cognitive function in remitted MDD patients because deficits in some cognitive domain lost statistical significance after correction for residual depressive symptoms. In a study comparing 20 inpatients recently remitted from severe MDD with 20 healthy matched control participants on learning tasks, high scores on Beck’s Depression Inventory was correlated with poorer explicit learning.98)

However, relatively recent studies did not agree with this association in remitted MDD patients. Preiss et al.99) reported that the individual level of depressive symptoms was not related to the cognitive performance in euthymic MDD patients. Wekking et al.83) performed standardized neuropsychological tests of mental speed, memory and executive functioning in 137 recurrent, remitted patients as part of a larger randomized controlled clinical trial and compared with clinically used published normative data. There was non-significant correlation between neuropsychological test scores and residual depressive symptoms. A meta-analysis published recently43) supported these results by showing that current (i.e., residual) depressive symptoms had no statistically significant influence on the nature of cognitive deficits observed in euthymic MDD patients. Taken together, there appears to be no clear association between cognitive function and residual symptom severity; however, there is still debate in this area and further studies are needed.

Subtype of depressive episode

The inconsistent findings from researches concerning cognition in depression could be caused by the effects of heterogeneity between patients with mixed melancholic and non-melancholic subtype of MDD. Several works have reported qualitative cognitive changes associated with acute melancholic depression across a number of domains, namely, psychomotor speed,90) memory functions of learning100) and delayed recall,101) and executive functions.

In a longitudinal study comparing the cognitive performance of patients with melancholic and non-melancholic MDD102) at acute admission and 3 months after recovery, melancholic patients performed more poorly on tests requiring memory acquisition, mental flexibility, set-shifting, selective attention, concept-formation and multi-tasking compared to those with non-melancholic depression after correcting for depression severity. The authors reported no group-by time differences for any of the memory or executive function measures showing that these groups had a comparable rate of improvement in task performance over time. These results suggested that the melancholic group was more impaired at follow-up but this was consistent with the group initially presenting with more severe cognitive dysfunction. Pedersen et al.99) studied patients who recently remitted from severe MDD and reported that although not statistically significant, patients remitted from melancholic MDD revealed poorer implicit learning performance compared with patients remitted from non-melancholic MDD.

Psychotic features during the course of MDD could also be predictive of poorer cognitive performance. In a meta-analytic study on psychotic depression, the authors reported that patients with psychotic symptoms are more cognitively impaired than non-psychotic depressed subjects.103) Bora et al.104) have reported that patients with affective psychoses in general are significantly impaired in many cognitive tasks, with large effect sizes for most measures. The domains of cognitive function affected by the presence of psychotic depression include executive function, verbal and visual memory, and psychomotor skills.105) In a recent meta-analysis which compared neurocognitive performance between non-psychotic MDD versus psychotic MDD, psychotic MDD was impaired in verbal learning/memory, visual learning/memory, and
processing speed. Hasselbalch et al. showed significant associations between global cognition and the cumulative duration/total number of psychotic depression and they implied that a history of psychotic depression may be the strongest predictor of future impairment in most domains of cognitive function.

Comorbidity

Large numbers of patients suffer from MDD comorbid with medical illness, such cardiovascular disease, stroke, diabetes and cancer, which can also independently negatively impact cognitive function. For example, diabetes and vascular illness have been associated with independent adverse effects on cognitive function. Moreover, psychiatric comorbidities such as substance abuse and anxiety are important to consider in depressed patients because of their independent potential effects on cognition. Lots of studies reported association of cognitive impairment with substance use disorders and anxiety disorders. Kizilbash et al. reported that there was an adverse effect on memory (specifically, immediate recall and amount of acquisition, and the retrieval of newly learned information) when depression was compounded by anxiety. This result was replicated in elderly MDD subjects who had responded to treatment; DeLuca et al. followed up to four years at yearly intervals with assessment of their symptoms, cognitive status, and functional disability. The anxious group showed a greater decline in memory than non-anxious, but not in other cognitive measures or measures of functional status. Comorbid anxiety disorder may impair executive function and psychomotor speed. Basso et al. compared nonpsychotic depressed inpatients with and without comorbid anxiety disorders. Both groups of depressed patients showed worse memory function than normal control group. The comorbid anxiety group had more impaired in executive function and psychomotor function than non-anxious depressed group.

For general psychiatric comorbidities, Baune et al. investigated the association between cognitive performance and psychiatric and medical comorbidity in depression. They evaluated the cognitive performance of patients diagnosed as bipolar disorder with a major depressive episode or MDD in relation to the presence of medical and/or psychiatric comorbidity. The subjects divided into four groups of comorbidity; no comorbidity, medical comorbidity, psychiatric comorbidity, and both medical and psychiatric comorbidity. The result showed that psychiatric comorbidity significantly decreased cognitive performance in the visuospatial/constructional and the language domains and the total score. In addition, increasing numbers of psychiatric comorbidities were related to worse cognitive performance. In contrast, medical comorbidity alone had no impact on any of the domains of cognitive performance. There was an additive effect of medical and psychiatric comorbidities in depression on visuospatial/constructional cognitive abilities. The authors suggested that the strongest predictor of poor cognitive performance in depression was psychiatric comorbidity.

Number of episodes / Duration of illness

It has been found from brain imaging studies that repeated and prolonged duration of depressive episodes is associated with structural changes in brain regions which mediate some of the cognitive aspects of depression. Number of mood episodes and lifetime duration of illness seem to contribute to cognitive impairment in asymptomatic states, and number of episodes may be more closely linked to the degree of global cognitive impairment than the total duration of illness. However, prior studies are sparse and report divergent results.

Kessing found cognitive impairment to be associated with the number of mood episodes experienced, but the duration of the illness had no significant effect on cognitive function. In another study, it was found that patients who suffered more than two episodes were more impaired than patients with one or two episodes on executive function. Bharadwaj et al. proposed two possible explanations for these results. The first one is that cognitive impairments could be a trait marker for more recurrent depression rather than being a consequence of the depressive state. The second explanation is the concept of ‘kindling’, in which the early multiple episodes cause permanent change to the neural substrates of neurocognitive performance that makes subsequent episodes more likely. Moreover, such a residue might also explain the existence of cognitive deficits in remission.

In a study with a large sample (n=8,229) of MDD outpatients, among those 1,895 patients whose Hospital Anxiety and Depression Scale depression score decreased by 50% at the second visit (on average 42 days later), the number of past episodes and total length of MDD constituted a cluster that was significantly correlated with memory performance. The authors suggested there could be a toxic link between the burden of depression and cognition. Recently, Hasselbalch et al. investigated the relationship of cognition and duration of illness with the Danish registry, and the results showed an association be-
between the cumulative duration of depressive episodes and a decreased cognitive performance adjusted for age, gender, education, premorbid IQ and residual depressive symptoms.

On the contrary, no association between number of episodes and cognitive impairment was found in several studies. Reischies and Neu also reported that no correlation between the duration of the disease or number of episodes and cognitive deficits could be found. Lifetime duration of illness was not related to any cognitive domain or global cognition among bipolar and MDD subjects in another study. Non-significant correlation of neuropsychological test scores with number of previous episodes was supported by a relatively large study (n=137) by Wekking et al. In a recent study by Daniel et al., there was no correlation with number of episodes and deficits in cognitive performance including executive functioning, working memory or verbal memory in euthymic MDD or bipolar I disorder patients. However, the authors noted that the association between performance on neurocognitive tasks and number of episodes of illness might be overshadowed by associations between performance on neurocognitive tasks and education. Furthermore, in a recent meta-regression analyses, the number of episodes and duration of illness had no statistically significant influence on the nature of cognitive deficits observed in euthymic MDD patients. In summary, the data indicate that subjects and measurements are not consistent and homogeneous enough to reliably detect subtle effects of illness duration/number of episodes on cognitive performance.

Interventions on Occupational Function in Remitted Depression Patients

For depressed workers, a few modalities of intervention that can improve occupational functioning have been suggested and some of those are considered as effective. In a recent Cochrane review, work-directed intervention, and cognitive behavioural therapy that was provided online or by telephone were effective in improving occupational function. Although small and inconclusive, a small number of studies which examined cognitive remediation in MDD suggested that cognitive remediation could be an effective approach. For pharmacotherapy, in studies compared effectiveness on improving occupational function between selective serotonin reuptake inhibitor (SSRI) to serotonin-norepinephrine reuptake inhibitor (SNRI), the result from one study favored SSRI. On the other hand, there was no difference in sickness absence in two studies, and the meta-analysis showed a heterogeneous effect.

However, the above reports did not address occupational function in remitted depression patients although recent studies have indicated that residual cognitive deficits including attention, executive function, and verbal memory are repeatedly reported in remitted MDD patients. Because we were unable to find any studies which evaluated the effectiveness of interventions on occupational function in remitted subjects, it is hard to say whether the interventions effectively improving occupational functioning in depressed subjects is also effective in remitted depression patients or not. In that residual cognitive deficits appear to be mediators of occupational impairment in remitted state of MDD, interventions ameliorate cognitive deficit could improve occupational function as well. In 2010, Naismith et al. studied sixteen patients with a lifetime diagnosis of MDD but who had not clinical depressive symptom at recruitment. The subjects were randomly allocated to treatment or waitlist control conditions. The treatment consisted of 1 hour twice a week for 10 weeks cognitive training using the Neuropsychological Educational Approach to Remediation (NEAR). After 10 weeks, participants in the treatment condition demonstrated greater improvements on tests of memory encoding and memory retention than the control group. Naismith et al. also studied the effect of NEAR in geriatric depression patients. The subjects had a lifetime history of MDD but were ‘stabilized on medication’ and had depressive symptoms in the normal to mild range. The treatment consisted of weekly 1-hour sessions of computerized cognitive training. In addition, there was a weekly 1-hour group session of psychoeducation. Once again, cognitive training was associated with positive and significant effects on learning and memory. As the authors suggested, cognitive training may be an effective non-pharmacological treatment option for improving cognitive functions, which in turn, may improve psychosocial functioning and reduce disability.

CONCLUSION

Converging evidence is accumulating for cognitive impairment in various cognitive domains in remitted MDD. Recent studies have indicated that attention, executive function, and verbal memory are the most repeatedly reported cognitive domains as impaired in remitted MDD patients. These residual cognitive deficits in remitted patients appear to be mediators of impairment in occupational function in remitted state of MDD. However, due to the heterogeneity in the design of the included studies,
definitions of remission, clinical characteristics of the included samples, and lack of well-designed studies, suggesting definitive determinants for impairment in cognitive and occupational performance is difficult to assert at this time. Certain features may be predictive of vocational adjustment difficulties prospectively in remitted MDD patients; higher age, late age at onset, residual depressive symptom, history of melancholic/psychotic depression, and physical/psychiatric comorbidity may negatively affect cognitive function related to occupational accommodation and higher levels of education may have protective effect against cognitive deficit.

To date, there are very few published studies that have examined the relationship between cognitive function and social/occupational difficulty in remitted MDD patients, and these studies have some significant methodological limitations. Further studies include larger and more homogeneous samples, with more extensive and validated assessments of psychosocial and occupational function and multivariate statistical methods, are clearly necessary and warranted.

Acknowledgments

Young Sup Woo, Won-Myong Bahk, Joshua D. Rosenblat, and Ron Kakar have no conflicts of interest. Roger S. McIntyre has received research grant support from Lundbeck, Astra Zeneca, Pfizer, Shire, Otsuka, Bristol Myers Squibb, National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. Dr. McIntyre has also received speaker/consultant fees from Lundbeck, Pfizer, Astra Zeneca, Elli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol Myers Squibb and Shire.

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