Cognitive dysfunction in depression: an unmet clinical need

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Abstract

Cognitive dysfunction is an important yet overlooked aspect of depression. Cognitive problems in depression tend to be persistent and are associated with poorer psychosocial functioning. Most available treatments for depression do not specifically address cognition. A comprehensive approach is required to investigate the underlying mechanisms and examine the potential treatment options to match the unmet clinical need.

Cognitive dysfunction is an overlooked aspect of depression, despite the repercussions on clinical outcomes, occupational and social functioning. The World Health Organisation listed depression as one of the largest contributors to disease burden (1). Functional impairments in depression are linked to cognitive symptoms (2). Patients often report problems in cognition both during episodes and as residual symptoms when in remission (3). On average, patients show poorer performance in tests of memory, attention and executive function compared to healthy volunteers (4). Patients with cognitive dysfunction have poorer psychosocial functioning (5), and higher rates of relapse (6). Memory and concentration problems in depression are linked to unemployment and work impairment (7, 8). Depression is one of the main causes of both absenteeism and presenteeism (9). Cognitive problems may contribute to both absenteeism (i.e. the direct impact of depression on the ability of people to attend work) and presenteeism (i.e. decreased performance at work or the inability of people to return to previous performance levels after an episode).

A meta-analysis of studies using CANTAB (Cambridge Neuropsychological Test Automated Battery) showed that the magnitude of cognitive deficits during an episode and in remission were comparable (10). Persistence of cognitive deficits after mood symptoms recover may lead to a longer-term detrimental effect on functioning (11). On the other hand, the recurrent nature of depressive disorders and accompanying cognitive dysfunction could contribute to the additional disability associated with depression. The accumulated impact of repeated episodes (12) on cognition, also known as "scarring" (13), was proposed to explain the persistent nature of cognitive dysfunction. According to this view, each episode leads to more vulnerability, hence leading to further decline in cognitive functioning over the years. In later life, memory deficits seen in depression could be vulnerability factors for dementia (14). In a longitudinal epidemiological study (the Baltimore Longitudinal Study of Aging), depressive symptoms over the life course were associated with an increased risk of dementia (15).

Despite its clear impact on the course of depression, cognition is yet to be accepted as a treatment target for depression. In a recent survey, more than 90% of the patients with a history of depression reported an impact of cognitive problems in their day-to-day lives. However, only 50% of patients with depression have ever been asked about cognitive dysfunction by a healthcare professional (16). Most currently-available treatments are beneficial for mood symptoms, whereas their effects on cognitive functions have rarely been tested in double-blind placebo-controlled trials. In those studies that have included cognitive outcomes, the assessment methods and clinical features of study populations varied markedly. Most of the studies were not placebo-controlled, and focus was heavily on depression in older adults. Overall, conventional antidepressants have very limited, if any, effect on cognition in depression (17). In

one randomised longitudinal study, 8-week treatment with escitalopram, sertraline, or venlafaxine did not have significant effects on cognitive functions as measured by a comprehensive neuropsychological battery. This also applied to patients who had achieved clinical remission with treatment (18).

More recently, the antidepressant vortioxetine was licensed by the European Medicines Agency for the treatment of cognitive symptoms in depression. The first study to report pro-cognitive effects of vortioxetine showed improvement in digit symbol test performance in elderly depressed patients (19). Consistent with the initial findings, further randomised-controlled trials showed that vortioxetine also improved cognitive functions in non-elderly patients with depression (20, 21). Multiple regression analyses revealed that there was a direct effect on cognition independent from the effects on mood. It should be noted that effect sizes in these studies were small for most tests, except the digit symbol substitution test, and replication is needed. Vortioxetine is a multi-modal pharmacological agent acting on a number of neurotransmitters including dopamine and noradrenaline, and with diverse actions on different serotonin receptors. It was suggested that the pro-cognitive effect of vortioxetine might be associated with its stimulatory effects on 5-HT_{1A} receptors and its inhibitory effects on 5-HT_3. Both mechanisms enhance cortical glutamatergic transmission (22).

Another medication that could potentially be used to address cognitive dysfunction in depression is modafinil. A previous open-label study reported that adjunctive modafinil led to improvements in cognition in patients with depression (23). In a recent study using CANTAB, we showed that modafinil improved working memory and episodic memory in patients with remitted depression (24). The results from this proof-of-concept study were promising, suggesting that the potential of modafinil should be investigated further. One of the proposed mechanisms for the pro-cognitive effect of modafinil is through augmenting glutamatergic transmission in the hippocampus (25). Modafinil has other beneficial effects on mood, fatigue, and motivation that may help patients with depression. In a meta-analysis of randomised-controlled trials in unipolar and bipolar depression, we showed that modafinil augmentation therapy was associated with improvements in mood and fatigue (26). Modafinil has also been shown to increase task-related motivation while participants perform cognitive tests (27). Those effects may have implications for restoring work-related dysfunction associated with depression.

The majority of studies have investigated the cognitive dysfunction in so-called cognitive domains (i.e. planning, attention, and short-term memory). The impact on emotion-laden cognition, i.e. hot cognition, was researched to a lesser extent. One line of studies has shown favourable effects of monoaminergic antidepressants on hot cognition, however. Antidepressants were linked to altered response biases to emotional stimuli very early in the course of treatment (28).The mechanism linking this effect to the clinical effects is yet to be elucidated.

The interplay between negative emotional biases and cognitive functions in depression has been formulated in the cognitive neuropsychological model. According to this model, proposed by Roiser, Elliott and Sahakian, bottom-up affective biases and top-down attentional biases (due to dysfunctional cognitive control) help to maintain the depressive state (29). Pharmacological interventions (i.e. antidepressant medication) alter the affective processing of emotional stimuli, thus helping to reverse negative biases and eventually leading to remission of mood symptoms. Within this model, it is suggested that psychological treatments work towards gaining cognitive control over negative biases. The cognitive neuropsychological model could help to guide research to identify treatments specifically addressing cognition.

Growing evidence for the link between inflammation and depression may have implications for a better understanding of the underlying mechanisms of cognitive dysfunction in depression (30). In preclinical models, the pro-inflammatory state was associated with depressive-like behaviour and infiltration of cytokines into critical brain structures for memory such as the hippocampus (31). At the population level, an association between IL-6 levels and impaired cognitive function has been demonstrated (32). Patients with high baseline inflammatory markers show persistent cognitive dysfunction (33). Inflammation may be a potential target for treatment as a mediator of cognitive dysfunction in depression. Intervention studies should shed light into the potential of anti-inflammatory agents in the treatment of cognitive dysfunction in depression. The Insight study, for example, is underway to examine the effects of tocilizumab, an IL-6 receptor antagonist, on somatic symptoms and cognition in depression (34).

The challenges and potential research areas in cognitive dysfunction in depression were discussed in a report by the National Academy of Sciences (35). It was highlighted that one of the main points regarding research into new interventions is the need for changes in trial design to include cognitive outcomes. Regulators such as the Food and Drug Administration in the USA hold the expectations that interventions should help people to function better in work and daily living activities, therefore psychosocial functioning measures are equally important. With the developing mobile technologies, and more accessible neurocognitive testing methods, future studies should be capable of providing much-needed information on cognitive functioning in depression. New trial designs could be utilised to test promising interventions for improving cognition in depression. Repeated testing in large samples may provide better understanding of the link between cognitive dysfunction and depression. It might also allow researchers to identify the appropriate functional outcome measures. A preliminary study in a selective cohort (the UK Biobank study) has shown an association between a history of severe depression and poorer cognitive performance (36). Future studies investigating the temporal stability of cognitive functions and their relationship with depression are warranted. The use of online cognitive testing holds potential for large-scale studies. Self-reported depression that is widely used in large-scale studies is subjective and may not correspond to clinically diagnosed depression. Cohorts with clinician-confirmed diagnostic assessments should provide more reliable information on the link between depression and cognitive functions (37). Prospective cohort studies that incorporate neurocognitive testing can also be valuable (38).

In summary, cognitive dysfunction is an overlooked, but clinically important, aspect of depression. The cognitive outcomes should be more commonly included in intervention studies, as well as in clinical practice. New research into the underlying mechanisms of cognitive dysfunction should give rise to potential treatment options. The increasing availability of large-scale data, along with technological advances allowing more frequent online testing, will play a major role in a better definition and treatment of cognitive problems. In our opinion cognition is a key target for treatment in depression.

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