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REVIEW ARTICLE

Cognitive impairment in major depressive disorder

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Cognitive dysfunction is a symptomatic domain identified across many mental disorders. Cognitive deficits in individuals with major depressive disorder (MDD) contribute significantly to occupational and functional disability. Notably, cognitive subdomains such as learning and memory, executive functioning, processing speed, and attention and concentration are significantly impaired during, and between, episodes in individuals with MDD. Most antidepressants have not been developed and/or evaluated for their ability to directly and independently ameliorate cognitive deficits. Multiple interacting neurobiological mechanisms (eg, neuroinflammation) are implicated as subserving cognitive deficits in MDD. A testable hypothesis, with preliminary support, posits that improving performance across cognitive domains in individuals with MDD may improve psychosocial function, workplace function, quality of life, and other patient-reported outcomes, independent of effects on core mood symptoms. Herein we aim to (1) provide a rationale for prioritizing cognitive deficits as a therapeutic target, (2) briefly discuss the neurobiological substrates subserving cognitive dysfunction, and (3) provide an update on current and future treatment avenues.

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Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling mental disorder associated with significant morbidity and mortality.[1] MDD affects approximately 350 million individuals worldwide and is projected to be a top contributor to global functional disability in the following decades. Lifetime prevalence of individuals with MDD comprises up to 15% of the general North American population.[2] By 2030, MDD is projected to become a leading cause of global disease burden according to the World Health Organization (WHO).[3] In addition, the economic costs associated with MDD are immense. For example, in 2016 alone, decreased workplace productivity and impaired occupational functioning associated with MDD resulted in losses of $32.3 billion and $201.5 billion in Canada and the United States, respectively.[4]

MDD is a syndrome of disturbances in mood, energy, metabolism, motivation, and cognition. Many studies have shown that cognitive dysfunction, in particular, is a powerful predictor of occupational and social functional impairment in adults with MDD.[5–7] Indeed, cognitive dysfunction is well established as a core diagnostic criterion of MDD according to the Research Domain Criteria (RDoC). The RDoC approach dissects MDD into domains of analyses with the aim of more easily identifying biological underpinnings of MDD (ie, understanding cognitive impairment) and predicting treatment outcomes.

A significant subpopulation of individuals with MDD does not achieve functional remission after treatment with multiple FDA-approved pharmacological agents. It is important to note that improvements in mood do not necessarily translate into improvements in function.

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Hitherto, only 2 antidepressants (ie, duloxetine and vortioxetine) have demonstrated direct, independent, and clinically relevant effects on cognitive dysfunction in MDD.[8] The persistence of cognitive deficits after remission of depressive symptoms has been shown to contribute to the failure in achieving full functional recovery in MDD.[5] Vice versa, functional impairments can also contribute to the persistence of cognitive symptoms in MDD.[9]

Domain-specific cognitive deficits in learning and memory, executive function, processing speed, and attention and concentration are highly replicated findings in individuals with MDD presenting with a major depressive episode (MDE). Moreover, cognitive dysfunction in MDD has been proposed to be an endophenotype that worsens as a function of episode frequency.[9,10] Other well-characterized symptoms in patients with MDD include anhedonia (the lack of interest) and depressed mood. The trifecta of cognitive dysfunction, anhedonia, and depressed mood is thought to be a critical mediator of MDD-related functional disability.[6,11] These interconnected domains of depression contribute to self-perpetuating cycles of illness and impairment.

Multiple neurobiological mechanisms have been proposed to contribute to cognitive dysfunction observed in individuals with MDD. These mechanisms have been extensively reviewed elsewhere.[12] Neuroinflammatory pathways are postulated to play a key role in the pathoetiology of MDD. Indeed, individuals with inflammatory and metabolic comorbidities are at greater risks of mood disorders and cognitive dysfunction.[13,14] A derivative of the foregoing observation is that disturbances in cognitive function in individuals with MDD and/or persons with metabolic/inflammatory morbidity may exhibit improvement with multimodal treatment targeting inflammatory-metabolic systems. This article provides an overview of the determinants, substrates, and treatment approaches related to cognitive impairments in MDD.

Cognition: Glossary

A domain-based approach provides an opportunity to disambiguate the complex phenomenological features of cognition. Disturbances in concentration, executive function, decision-making, and learning and memory are part of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) items that determine whether an individual meets criteria for cognitive dysfunction in MDD.[6] Cognitive constructs have been further classified into typologies that are useful in different settings (eg, clinical versus research settings). For example, the 4 subdomains of executive function, learning and memory, attention and concentration, and processing speed are differentially operationalized in clinical and research practice.[15] These interconnected and dissociable cognitive phenomena often share overlapping, yet discrete, neurobiological substrates. Disparate neurobiological systems, including, but not limited to, arousal, mood, impulsivity, reward, anhedonia, energy, fatigue, and suicidality, all contribute to cognitive changes in MDD.[16,17]

The current discourse on cognition is limited by the absence of consistent language delineating observable cognitive domains. In this regard, the concepts of "hot" and "cold" cognition are relevant. "Hot" cognition refers to cognitive functions that are emotionally valenced. In other words, "hot" cognitive processes are influenced by an individual's emotional state.[18] Examples of "hot" cognition include, but are not limited to, rumination, anticipatory anhedonia, negative attentional bias, and emotionally linked recall. Conversely, "cold" cognition refers to cognitive processes that are uncoupled from emotional valence.[18] Prominent examples of "cold" cognition include the aforementioned subdomains of executive function, learning and memory, attention and concentration, and processing speed, which are uncoupled from emotional processing. Despite the foregoing typologies separating "hot" and "cold" cognition into distinct entities, a discrete separation between "hot" and "cold" cognition in neurobiological terms cannot be parsed.[17]

Cognition: Neurobiology

Specific neurobiological mechanisms subserving cognitive function in MDD have not been fully elucidated. Notwithstanding, multiple levels of analysis (eg, genetic, molecular, cellular, circuit) have been implicated. Herein, the working hypothesis postulates that there is a disturbance in the structure, function, and interconnectivity of brain circuits and networks related to cognitive control and function.

The well-established monoamine abnormalities in MDD likely contribute to impaired cellular signaling and neurocircuit deficits.[19] Peripheral inflammation and systemic activation of proinflammatory cytokines may also play a role in the pathogenesis of cognitive symptoms. For instance, the degree and severity of cognitive dysfunction has been shown to be mediated by the location of inflammation, neurotoxicity, and apoptosis.[20] Consequently, the amplification of inflammatory signals provides a compelling explanation for the emergence of cognitive symptoms in depressed individuals. The role of inflammation in the pathoetiology of MDD has been extensively reviewed elsewhere.[9,21,22]

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The structure, function, and chemical composition of fronto-temporal and fronto-subcortical circuitry have also been implicated in the emergence of cognitive symptoms in MDD.[23,24] Nodal structures such as the hippocampus, amygdala, and the anterior cingulate cortex (ACC) have demonstrated susceptibility to volumetric and functional changes as a consequence of greater illness severity, episode frequency, and duration.[25] Neurochemical changes (eg, catecholaminergic disturbances) have also been implicated as a mediator of cognitive dysfunction in MDD.[26]

Circuits of the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), and the ACC are particularly relevant in the pathogenesis of MDD. Dorsal cognitive networks, formed by the dorsal ACC working in concert with the hippocampus and the DLPFC, have been implicated in deficits of executive function.[27] Ventral affective networks, formed by the perigenual ACC, the amygdala, and the OFC, working in concert with the hippocampus, have also been shown to be important for a variety of cognitive processes such as establishing salience, mediating contextually appropriate responses, planning, working memory, and executive function.[27]

It is recognized that individuals with MDD exhibit a bilateral reduction in hippocampal volume. The foregoing reduction in hippocampal volume may be a consequence of decreased neuronal and dendritic density, and/or reduced size of neuronal soma.[28] The reduction in hippocampal volume has also been shown to be proportional with the frequency of illness episodes. For example, the findings of one study demonstrated that performance in verbal memory decreases as a function of episode frequency in MDD.[29] In addition, individuals with MDD exhibit hypoactivity of the prefrontal cortex, which is associated with increase in activity of the ACC. Abnormalities in the connections between cortical and subcortical structures (ie, prefrontal cortical regions and the ACC) have been hypothesized to lead to poor functional outcomes in MDD.[24,30] These observations may be mediated by domain-specific deficits in executive function, attention, learning, memory, and processing speed.

The cognitive impairments in individuals with MDD may also be explained by an increase in neural effort. The n-Back test is a validated measure of working memory in which subjects were asked to recall the previous stimuli that was observed. In one study, although performance on the n-Back test did not differ significantly between MDD subjects and healthy controls, differences were observed in the activation and deactivation of nodal substrates.[31] Specifically, MDD subjects exhibited greater activation of working memory networks relative to healthy controls.[31] These findings suggest that individuals with MDD require greater neural effort to achieve the same level of cognitive performance as healthy controls. One theory posits that abnormal activity in the medial prefrontal cortex may contribute to the requirement of increased neural effort in individuals with MDD.[31]

The neurobiological substrates underlying cognition are both integrated and segregated and rely on a system of reciprocity between integrated and segregated cognitive structures. For example, anti-correlation, which refers to the selective reciprocal activation and deactivation of various brain regions, is critical for proper cognitive functioning.[32] Dysregulation of the normal reciprocity between nodal structures within default mode networks, therefore, may be involved in substrate disturbances and suboptimal functional outcomes resulting from cognitive impairments and reduced cognitive efficiency observed in individuals with MDD.[33]

Mediators of aberrant neural circuitry, structure, and function are hypothesized to involve imbalances in hormonal regulation (ie, insulin resistance, glucocorticoid abnormalities), neurotrophin dysregulation (ie, brain-derived neurotrophic factor), immunoinflammatory activation, and oxidative stress.[34–37] There is wide recognition of reciprocal relationships between mood, cognition, and metabolic disorders.[38] For example, evidence linking diabetes mellitus type 2 and insulin resistance with cognitive deficits in mood disorders is well-documented.[39] Moreover, an imbalance in insulin and counterregulatory neurohormonal systems (ie, glucocorticoids) has been suggested to alter proapoptotic intracellular signaling cascades, resulting in loss of neuronal and glial cells as well as accelerated neurocognitive decline. In addition, metabolic syndrome and obesity have been consistently shown to negatively impact cognitive functions.[40]

In summary, the pathoetiology of cognitive dysfunction in MDD involves both structural and functional disturbances in neural circuits as well as disturbances in the connectivity of cognitive networks. Substrates that subserve cognition in MDD are discrete but may overlap functionally with other substrates that contribute to affective, metabolic, and inflammatory processes. Interventional strategies should, therefore, take into consideration these underlying pathophysiological changes subserving cognitive deficits in MDD.

Cognition: Implications of Function

In individuals with MDD, symptomatic remission does not always translate into functional recovery. The foregoing disconnect indicates that determinants of functional outcome are mediated by other factors, which are not adequately measured using standard clinical indicators of illness severity. For example, most of the

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questionnaires that are used clinically to measure the severity of depressive symptoms (eg, Hamilton Depression Rating Scale, Montgomery–Åsberg Depression Rating Scale) tend to underemphasize cognitive symptoms.[41] In addition, it may be surmised that cognitive function is more indicative of self-reported health outcomes than measures of total depressive symptom severity.[7] Therefore, a holistic, domain-based approach that incorporates a dimensional measure of cognition may be superior in predicting functional outcomes. In this regard, cognition should be appropriately dimensionalized and integrated into larger composite measures of depressive symptom severity.

Cognition has been previously established as a principal mediator of health outcomes in MDD.[42] Cognitive disturbances are more commonly observed in individuals with MDD compared to the general population. Individuals who are unemployed are more likely to exhibit decreases in cognitive performance and those who are employed will experience a greater loss of workplace productivity.[7] In addition, cognitive impairment predicted overall psychosocial function in individuals with MDD.[6] Results from the International Mood Disorders Collaborative Project (IMDCP), a collaborative effort between the University of Toronto and Cleveland Clinic, indicated that cognitive function is a greater determinant of overall workplace function than measures of depression severity among working adults with MDD. Moreover, evidence from a recent meta-analysis showed that reductions in cognitive function are predictive of poorer functional and metabolic outcomes.[14] Despite the foregoing evidence, current antidepressant regimens do not primarily target psychosocial impairments and workplace disability in MDD. Therefore, there is a need to target cognitive dysfunction in individuals with MDD to prospectively improve overall performance in occupational and functional domains.

Cognition: Treatment

One approach to treating cognitive symptoms observed in individuals with MDD involves modifying factors that contribute to and/or exacerbate these symptoms. For example, the management of underlying medical conditions, psychiatric comorbidities, and iatrogenic confounds may help reduce cognitive symptoms in MDD.

Nonpharmacological interventions

Psychosocial approaches such as cognitive remediation therapy (CRT) appear promising in treating cognitive dysfunction in MDD. CRT improves learning and enhances cognitive activation via strategy development, monitoring, and pruning. During CRT, individuals are instructed to complete a computerized task that stimulates neuroplastic processes in the brain. Regardless of changes in performance over time, the task ensures that users have relatively high success rates to elicit sustained motivation.[43] The ultimate goal of CRT is to develop useful strategies for overcoming cognitively challenging tasks with the support of social networks (eg, therapists and peers). "Far-transfer" is the final step in CRT where improvements in cognition and problem-solving are applied to challenges faced in daily life.[44] To date, only the first step of CRT (ie, cognitive activation) has been applied to the treatment of cognitive dysfunction in MDD. Preliminary results suggest that adjunctive CRT may improve cognitive outcomes in individuals with MDD, when combined with pharmacotherapy.[45–47]

Computerized working memory tasks have also shown efficacy to improve cognitive function. For example, Siegle et al[48] reported that use of the Paced Auditory Serial Addition Test (ie, which requires patients to add sequentially presented digits) increased cognitive skills, decreased maladaptive thoughts (ie, rumination), and improved depressive symptom severity in individuals with MDD.[48] Furthermore, computer programs focused on sequencing mental arithmetic problems have been reported to improve full-scale intelligence quotient (IQ) in individuals with MDD.[49] Computerized working memory tasks have been shown to improve psychosocial and occupational functioning, as well as hippocampal and frontotemporal activation.[50] Notwithstanding the foregoing evidence, the specific efficacy of computerized measures of cognitive function in clinical populations remains elusive. Moreover, the implementation of such computational measures is a challenge. Nevertheless, the emergence of big data approaches and blockchain technologies may aid in the development of such computational tasks.[51]

Manualized psychotherapy approaches (eg, cognitive behavioral therapy [CBT] and mindfulness therapies) are effective in the acute treatment of cognitive symptoms in MDD.[52,53] For example, CBT has shown to be effective in treating cognitive symptoms in ADHD, a disorder characterized by significant disturbances in executive function and attention.[54] However, current psychotherapies primarily target "hot" cognitive deficits, and therefore effective strategies targeting "cold" cognition still require further investigation.

Studies have shown that brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have procognitive effects in subpopulations with depression.[55] For example, brain stimulation therapies have been associated with greater tolerability, reduced likelihood of cognitive impairment, and higher rates of remission in treatment-resistant individuals. As a result, brain stimulation therapies may be useful in targeting cognitive symptoms associated with treatment-resistant MDD.[56] Indeed, brain imaging studies in individuals

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with MDD have shown that rTMS may be a viable precognitive neuromodulatory strategy.[57]

Aerobic exercise in combination with resistance training is another potential treatment avenue that is cost-effective and accessible. Aerobic exercise improves cognition, has negligible side effects, and is scalable (ie, has the potential to be a population-wide health intervention).[58] For example, a recent review by Stanton and Reaburn[59] found that performing aerobic exercise 3–4 times a week for 9 weeks at moderate intensity is effective in alleviating depressive symptoms.[59] Likewise, a recent study showed lower depression relapse rates in individuals partaking in an aerobic exercise regimen compared to individuals treated with sertraline, a selective-serotonin reuptake inhibitor (SSRI).[50] Both acute and regular aerobic exercise have been shown to improve cognitive functions such as memory. Acute physical activity (ie, single bout of exercise lasting between 10–30 minutes in duration) has been shown to have a positive impact on short- and long-term memory.[60] However, greater improvements in memory have also been observed with regular sustained exercise in individuals with mild cognitive impairments compared to individuals without cognitive impairments, suggesting that individuals with cognitive difficulties due to depressive disorders may be more sensitive to the procognitive effects of exercise.[58,59,61]

Pharmacological interventions

Available evidence indicates that improvements in measures of cognitive function with the use of conventional antidepressants are associated with improvements in depressive symptom severity. However, it remains to be seen whether most conventional antidepressants exert direct and clinically significant effects on cognitive functions in individuals with MDD. There is currently a paucity of FDA-approved pharmacological agents and/or interventions that are efficacious, tolerable, and specifically target cognitive dysfunction associated with MDD. Several studies have examined the efficacy of various antidepressant agents in improving cognitive function in individuals with MDD. For example, bupropion and escitalopram have been reported to improve some aspects of verbal memory and delayed free recall.[49,62] Similarly, sertraline has been shown to improve psychomotor performance.[63,64]

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has been demonstrated to have procognitive effects compared to placebo.[65] In addition to improving general symptoms of depression, duloxetine improved verbal learning and memory. Both duloxetine and the multimodal antidepressant, vortioxetine, have been shown to improve learning, memory, and verbal recall as measured by scores on the Rey Auditory Verbal Learning Test (RAVLT). In addition, individuals on vortioxetine also showed significant improvements in acquisition time and delayed recall. While both duloxetine and vortioxetine improved measures of depressive symptom severity, vortioxetine demonstrated a larger direct effect on RAVLT recall and acquisition scores compared to duloxetine.[66] Duloxetine was evaluated from the point of view of multiple domains of cognitive function identical to those evaluated in studies with vortioxetine. Duloxetine did not exhibit a statistically significant improvement when compared to placebo on composite measures of cognitive function in contradistinction to vortioxetine.[67] In addition, vortioxetine appears to improve a broader range of cognitive functions (ie, executive function, learning, memory, processing speed, concentration) than duloxetine, which has only been shown to improve measures of learning and memory.[66] Currently, vortioxetine is the only FDA-approved antidepressant agent that has demonstrated direct and independent procognitive effects in individuals with MDD. Specifically, as of May 2018, the FDA has updated the product monograph for vortioxetine based on data from the FOCUS and CONNECT trials to mention that vortioxetine is capable of improving performance on the Digit Symbol Substitution Test (DSST), indicating improvement in processing speed in individuals with MDD.[67,68]

Psychostimulants have also been used to treat depressive symptoms in individuals with MDD; however, available evidence is mixed. Notwithstanding the inconsistent evidence, lisdexamfetamine has been shown to specifically target and improve deficits in executive function in individuals with MDD, particularly among individuals with milder cognitive symptoms comorbid with executive function deficits.[69]

Ketamine, a dissociative anesthetic that antagonizes NMDA glutamatergic receptors, has been demonstrated to have rapid-onset antidepressant effects in individuals with treatment-resistant MDD.[70] Available evidence indicates that baseline cognitive function may serve as a predictor of response to ketamine treatment.[71] Moreover, it seems the antisuicidal effects of ketamine are mediated by improvements in executive function.[71] A review written by Lee et al[71] discusses procognitive effects of ketamine treatment in greater detail.

Preliminary data suggest that incretins may also improve cognitive function. Incretins are a group of metabolic hormones involved in the regulation of blood glucose levels. Incretins are involved in gastric motility, and act as insulin secretion analogues. Exogenously administered glucagon-like peptide (GLP-1) agonists (eg, liraglutide) are FDA-approved for the treatment of adults with type II diabetes mellitus. Glucagon-like peptide is synthesized in the nucleus tractus solitarius and has receptors distributed throughout the brain, with

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a topographical organization of receptors in cognitive controls regions. Preliminary evidence indicates that liraglutide administered at a dose of 1.8 mg is able to improve depressive and cognitive measures in adults with a depressive mood disorder.[72] The foregoing results validate previous findings suggesting neuroprotective and neurotrophic properties for liraglutide.

Metabolic regulators present unique opportunities as treatment targets in depressed subpopulations with elevated metabolic and inflammatory status. For example, intranasal insulin has been shown to be procognitive in individuals with MDD. In particular, the procognitive effects of intranasal insulin are stronger in individuals with a history of diabetes and insulin dysregulation comorbid with MDD. In the brain, insulin inhibits proapoptotic pathways and plays critical roles in neuroplasticity, neurogenesis, and neuronal growth and survival. Insulin receptors are found throughout the brain, particularly in regions involved in cognitive and emotional processing.[49] Therefore, treatment strategies targeting brain insulin may prove efficacious in treating cognitive symptoms in MDD.

Elevated levels of circulating proinflammatory cytokines have been consistently reported in individuals with MDD.[73] Cognitive impairment has been observed in individuals with elevated inflammation.[21] Among the most consistently identified proinflammatory cytokine disturbances in MDD is tumor necrosis factor alpha (TNF-α).[17,74] Treatment with TNF-α antagonists is postulated to be an efficacious adjunctive approach to target cognitive symptoms in individuals with MDD. Infliximab is a promising TNF antagonist that binds to soluble and transmembrane domains of TNF-α, thus preventing the binding of TNF-α to its receptors.[74,75] Treatment with TNF antagonists has been associated with lower depressive symptoms subscores in subpopulations with MDD comorbid with elevated peripheral inflammation[73] and in individuals with rheumatoid arthritis.[75] Evidence also demonstrates efficacy of TNF antagonists in subgroups with treatment-resistant depression.[76,77] Whether adjunctive infliximab is an efficacious approach to treating cognitive symptoms in depressive mood disorders has yet to be determined but is currently being investigated by our group in Toronto (NCT02363738).

Conclusion

Cognitive deficit is a core domain of depressive psychopathology and a principal mediator of psychosocial and workplace functioning. Obtaining cognitive recovery in individuals with MDD is necessary to achieve optimal functional outcomes. This objective is limited by the current clinical paradigm, which insufficiently addresses the deficits in cognitive function experienced by individuals with MDD, and the lack of mechanism-oriented drug development. However, further research is necessary to elucidate the neural substrates and metabolites involved in the development of cognitive symptoms in MDD. A domain-based approach to the assessment and treatment of psychiatric conditions, including MDD, may be more pragmatic and may lead to better therapeutic outcomes for patients. Finally, creating a standard discourse related to cognitive dysfunction in psychiatric disorders and understanding the neurobiological mechanisms underlying cognitive dysfunction will be critical steps toward optimally treating cognitive symptoms across psychiatric conditions.

Disclosures

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