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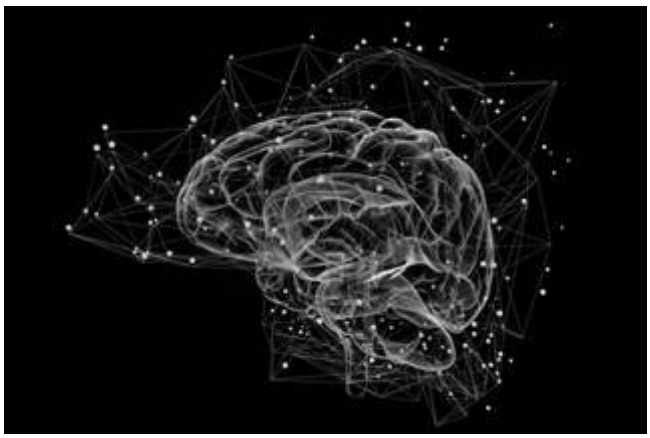
September 20, 2016

Cognition in Depression: A Critical Domain for Health Outcomes, Measurement, and Treatment

Dr. Roger McIntyre suggests that the clinical relevance of cognitive dysfunction for any individual patient can only be adjudicated on a case-by-case basis.

Cognitive Dysfunction as a Critical Mediator of Health Outcomes

During the past decade, it has emerged that cognitive dysfunction is a common and persistent disturbance in many adults affected by major depressive disorder (MDD).[1] Indeed, aspects of cognitive functions have been a criterion item within the polythetical list of a major depressive episode (MDE) for several Diagnostic and Statistical Manual (DSM) iterations. Difficulties in concentration, thinking, and decision making have been the specific item(s) within the MDE criteria. Notwithstanding the common occurrence of cognitive dysfunction in MDD, the emphasis has historically been on "emotional" (eg, depressed mood) and "physical" (eg, disturbance in energy) symptoms.[2]



Cognitive dysfunction in major depressive disorder is a primary therapeutic target that should be screened for and measured.

The availability of a disparate assortment of psychotropic medications, manual-based psychotherapies, and neuromodulatory approaches, as well as a variety of innovative/investigational approaches (eg, ketamine, cognitive remediation), have provided clinicians and patients with a surfeit of opportunities to mitigate symptoms, and therefore improve patient function and integration. Available evidence, however, indicates that the vast majority of individuals receiving the forgoing treatments as part of an integrated care model still do not achieve patient-reported outcomes (PROs) that are prioritized as therapeutic objectives (eg, full functional recovery).[3] For example, most individuals achieving symptomatic remission continue to evince psychosocial impairment and workplace disability. The failure to achieve both symptomatic and functional objectives has provided the impetus for identifying determinants of health outcomes in adults with MDD. This pursuit has resulted in the identification of cognitive dysfunction as a critical mediator of health outcomes for many adults with MDD.

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Results from epidemiological and clinical studies indicate that disturbances in cognitive functions in adults with MDD are the most robust predictor of functional recovery amongst individuals in the community and post-discharge from hospitalization.[4,5] Results from the International Mood Disorders Collaborative Project indicate that amongst adults (ages 18-65) who are gainfully employed (ie, greater than/equal to 20 hours of employment, schooling, volunteering per week), self-reported measures of cognitive dysfunctions are a more powerful determinant of workplace attendance and participation than is total depression

symptom severity.[6] The forgoing finding provides rationale for asserting that cognitive dysfunction in depression is a primary therapeutic target which should be screened for and measured.

"Hot" and "Cold" Cognitive Functions

Cognitive function can be atomized into four interrelated hierarchical functions. The highest order of cognitive function is executive function, with other cognitive domains including learning/memory, processing speed, as well as attention/concentration. A useful typology that has been proposed to describe cognitive function is “hot” and “cold” cognitive functions.[7] The moniker “hot cognitive functions” refers to those cognitive functions that are emotionally valenced; examples include rumination and negative attentional biases. “Cold cognitive functions,” conversely, refers to those that are not emotionally valenced.

Individuals with MDD exhibit deficits across all four atoms of cognitive function. It is important to emphasize that deficits in cognitive functions persist between episodes despite the amelioration of mood and physical symptoms. More specifically, over 90% of adults with MDD report and/or exhibit cognitive dysfunction during a MDE, and approximately 50% continue to manifest cognitive deficits between episodes (ie, in “euthymic” states).[8] The clinical relevance of the cognitive deficits can be benchmarked by using Cohen's effect sizes (ES). A Cohen's ES is expressed as small (ie, 0.2), medium (ie, 0.4-0.6), or large (ie, 0.8 or greater). A Cohen's ES of equal to or greater than 0.2 is accepted as clinically significant. Results from meta-analyses indicate that the Cohen's ES of cognitive deficit in MDD ranges from 0.2 to 0.7.[9]

Clinical Relevance of Cognitive Dysfunction

Indeed, it should be kept in mind that the clinical relevance of cognitive dysfunction for any individual patient can only be adjudicated on a case-by-case basis. For example, an individual who is employed in a sector that demands high-level cognitive functions (eg, air-traffic control) would be expected to be negatively affected by a relatively minor reduction in cognitive function.

The magnitude of cognitive deficits observed in MDD is affected by sociodemographic (eg, age, education), clinical, anamnestic, and treatment-related factors. Individuals with multiple-episode depression are more likely to exhibit cognitive deficits than individuals with a single episode (although single-episode depression also exhibits cognitive dysfunction). In addition, longer illness duration and a host of comorbid conditions [eg, hypothyroidism, obesity, type II diabetes, and substance use disorder (SUD)] are also associated with poor cognitive performance.[1] Available evidence suggests that past history of trauma may also moderate cognitive outcomes in adults with MDD. Moreover, iatrogenic cognitive dysfunction is not uncommon with treatments including, but not limited to, benzodiazepines and select antipsychotic agents.

In light of the ubiquity, progressivity, and pertinence of cognitive dysfunction in MDD to health outcomes, there is tremendous interest in determining whether specifically targeting cognitive dysfunction in MDD can directly improve functional outcomes. The current state of the art does not permit a definitive conclusion on this critical question, but available evidence suggests improving cognitive functions is associated with improvements in several domains of psychosocial functions.[10]

Treatment Modalities

A related question is the extent to which available antidepressants independently and specifically improve cognitive functions in adults with MDD. Indeed, it would be expected that improvement in MDD symptoms would be accompanied by an improvement in overall cognitive performance. However, that would not establish direct and independent effects on cognitive measures. Emerging evidence indicates that some antidepressants have direct and independent effects on domains of cognitive function. Unfortunately, most antidepressants have not been subjected to sufficient scrutiny in this regard and, as a consequence, it is unknown whether most antidepressants are directly pro-cognitive. In addition to antidepressants, there is an interest in a variety of treatments as to whether they may improve cognitive functions (eg, psychostimulants, Modafinil, R-Modafinil), with insufficient evidence, again, for any conclusions.[11] In addition, there is tremendous interest in whether cognitive-behavioural strategies, cognitive remediation, and/or neuromodulatory approaches (eg, r-transcranial magnetic stimulation) positively affect cognitive functions.

Cognitive Function Assessment

The gold-standard approach to assessing cognitive functions is a comprehensive neuropsychological evaluation. Such an approach, however, does not comport with busy office practice. In addition, timely access, as well as affordable price, may also

be barriers for many individuals. Consequently, there is a need for a freely accessible, patient-administered, brief, computerized cognitive assessment that can provide actionable information. The recently validated THINC-it tool is the first such tool that satisfies psychometric properties required (eg, sensitivity, temporal reliability, specificity) that is also freely available for download. The THINC-it tool provides information as to whether the patient with MDD has cognitive dysfunction and, if so, to what extent is the cognitive dysfunction expressed as a standard deviation reduction. An advantage of the THINC-it tool is that includes both subjective and objective measures of cognitive function, which is critical, as these measures are not correlated, with the former being closely associated with depression symptom severity.

The recently completed Florida Medicaid Guidelines for the treatment of adults with MDD recommend assessing cognitive functions in MDD.[12] Pragmatic approaches to the prevention/treatment of cognitive dysfunction in MDD are to treat MDE symptoms to remission, prevent recurrence of illness, target comorbidities, discontinue anti-cognitive medications, restore normal sleep rhythms, and the encouragement of healthy lifestyle and exercise. Over the next decade, it is expected that several treatments will become available that may be able to target cognitive functions directly, which would be a welcome addition.

It is tempting to speculate that treatments that are pro-cognitive may also have anti-suicide properties insofar as the pro-cognitive profile may have salutary effects on hot cognitive functions and/or may reduce impulsivity, which is subserved by executive function.

Taken together, a Copernican revolution is occurring, wherein not only feeling but also thinking is the centre of the depressive disorder universe. For practicing clinicians, they are reminded that treating-to-target includes targeting cognitive dysfunction in depression, as cognitive performance is "too big to fail."[13,14]

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