COGNITIVE IMPAIRMENT IN MAJOR DEPRESSIVE DISORDER

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Abstract:
Cognitive impairment was considered for a long time to be part of depression and it was expected to disappear as other mood symptoms improved with treatment. Because of this assumption, cognitive complaints were rarely assessed or did not seem important enough in determining the best treatment strategy for major depressive disorder (MDD). The majority of studies revealed that cognitive deficits are present in all cognitive domains, mostly in executive functions, attention, verbal fluency and memory. Recognizing cognitive dysfunctions, even when the patients' evaluation is within a so called normal range, is an important aspect because in reality they perform significantly below their premorbid level. Currently there is plenty of evidence to support that cognitive impairment is a core symptom for MDD.

Key words: Cognitive impairment, Major depressive disorder, Executive functions.

INTRODUCTION
During the last decade, depression and other related mood disorders have become of large interest. (1) Major depressive disorder is a common mental illness, widely distributed in the population and according to Kessler et al, (2003) with a lifetime prevalence of 16.2%. (2) World Health Organization data indicate that by 2030 depression will be the leading cause of disability in the world. (3)

The Diagnostic and Statistical Manual 5 (DSM-5) characterizes MDD by persistent and severe low mood and/or loss of enjoyment, interest and significant functional impairment. (4) It is associated with a high rate of morbidity and mortality, especially with suicidal risk which increases 20 times in patients with a history of Major Depressive Disorder. (5) An alarming fact is that suicidal attempts have become the third leading cause of death, between the ages of 15-24. (6)

The economic cost of disease is becoming a constant concern for the health care system. Olesen et al, (2011) conducted a study that showed that the total cost of brain disorders, including mental and neurologic illnesses in Europe in 2010 was 798 billion Euros. From this, over 180 billion Euros represent the total cost for MDD. (7) Another sum of 83 billion Dollars represents the estimated annual costs attributable to MDD in the United States of America. (8) Overall, mood disorders are on top of the list of the most burdensome disorders in the world. Life expectancy is growing, which will be reflected in an increase in prevalence and cost of brain disorders. (7)

Impaired cognitive functioning is starting to be acknowledged as one of the nine core symptoms of MDD. Evans et al, in a systematic review, concluded that cognitive impairment significantly affects quality of life in depressed patients. (9)

Cognition can be divided into two separate functions, hot and cold functions that have different roles and meanings. (10) Hot cognition (emotion-laden) involves emotional stimuli and negative biases that represent an altered way of information processing with an excessive focus towards negative stimuli and away from positive ones. In contrast, cold cognition is emotion independent and includes abnormalities in several cognitive domains. Thus, hot cognitions can be considered as a state marker since they are mood associated and cold cognitions more of a trait marker that underlines the vulnerability. (11, 12, 13).

The review of Murrough et al (2011), indicates that patients diagnosed with MDD have deficits in all the cognitive domains, including attention, memory, verbal fluency, executive functioning and psychomotor speed. (14) McIntyre el al, (2013) showed that the most frequent complaints reported by depressed patients are problems with memory, concentration loss, difficulty in finding words, slow thinking and difficulties in problem solving. (8)

Initially, cognitive dysfunctions were described in the acute phase of a depressive episode- Burt et al, (1995); after that, Chamberlain and Sahakian, (2004) considered deficits as a residual effect because they persisted despite clinical recovery and, in present, it is considered that cognitive impairment may precede the clinical onset. (15, 16) In a recent review a question has been raised: whether cognitive deficits represent a state effect because they are symptom related, a scar effect since they appear as a result of a lesion done by a depressive episode or a trait effect because they are reported before the depression onset. (17)

Understanding that a significant portion of patients with MDD will continue having cognitive deficits even after depressive symptoms remit, should determine clinicians to monitor the cognitive status more often. (18) In present, many subjective and objective evaluation tools can be used in clinical practice. Some studies show that patients have worse results in self-reported tests than their objective evaluation on neuropsychological tests. (19) The explanation for this difference can be the negative interpretation of perceptions that is typical for depressed patients or that objective scales measure cognitive status.

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at a single point in time. On the other hand, self-reported tests assess cognitive difficulties over an extended period of time in different situations. (20)

Cognitive symptoms have an important impact on the clinical diagnosis and management of depression so there is a need to properly understand these functions. In a 3 year prospective study Conradi et al, (2010) reported that cognitive deficits could be identified for 94% of the time during depressive episodes, and in 44% of the remission period. (21)

ATTENTION

Attention is a complex cognitive function with different roles. One of these represents the capacity to maintain focus over time; this is called sustained attention. Selective attention involves the ability to focus in the presence of distracting stimuli and divided attention gives the ability to perform two tasks at the same time. (22)

A systematic review conducted by Hasselbalch et al, (2011) showed that 9 out of 11 studies included, reported significant alterations in sustained attention and selective attention. (23) Rock et al, (2013) found significant moderate deficits in attention functioning that were still present in remitted patients. (24) A small study conducted on bipolar and unipolar depressed patients reported that difficulties in divided attention at discharge could indicate a higher risk for future relapse. (25)

In a brief report Erickson et al, (2005) showed using the Affective Go/No-Go Task that naïve depressed patients had deficits in their ability to shift attention from one negative stimulus to a positive one (more omission errors were made when responding to happy than to sad words) suggesting an attentional bias towards negative affective valence in MDD. This fact explains an existing vulnerability for the impact of negative life events causing a higher recurrence of depressive episodes. (26,27)

MEMORY

Memory is the basal processes in which information is encoded, stored and retrieved, but these abilities are attention dependent and literature suggests different models of memory. Verbal learning and memory are considered to be associated with memorization and a retention of a list of words in order to be able to describe elements of associative learning. (22)

Working memory is an important cognitive function that allows us to manipulate concepts and material when we need it and then remove them from our mind when they are no longer relevant, in order to successfully solve problems. (28) Alloway's (2010) conclusions suggest that working memory at the beginning of formal education is a more powerful predictor of subsequent academic achievements than IQ. (29) It depends on the individual’s capacity to organize the new material during learning. (30)

Working memory impairment is not so often reported such as attention, processing speed or executive functioning problems, but studies show that there is evidence of working memory deficits. Memory impairment have been usually reported in more severe forms of depression, older, hospitalized patients, with psychotic symptoms. (31) In a longitudinal study, Biringer et al (2007) concluded that remission of depressive symptoms was followed by improvement in verbal memory but not in other cognitive domains compared to healthy individuals. (32) The same evidence is reported by Roca's et al, (2015) study which shows that improvement in verbal memory is associated with a remission of depressive symptom. (27) On the other hand, Reischies and Neu (2000) found that depressed inpatients retested at 3 to 6 months were still having verbal memory alterations in the remission phase. (33) Furthermore, Fennig's et al, (2002) findings suggest that verbal memory is correlated with general functioning for patients who are in remission for at least 9 months after their last episode. (34)

A meta-analysis concluded that individuals who were less educated than the control group had worse difficulties in verbal learning and memory and attentional switching. (35) This data suggests that subjects with higher levels of education have the ability to compensate for their cognitive dysfunction. (36)

The new information has to pass through the working memory before it is encoded into the episodic memory. There is data supporting that memory deficits have been identified in subjects who are at risk for developing depression. (37) In a follow-up study, Airaksinen et al, (2006) indicated that low results in episodic memory evaluation can be a reliable predictor for depression 3 years later. (38) In another study Wang et al, (2006) didn't find any verbal memory dysfunctions in a young group of nonpsychotic outpatients. (39) This data and the results from another 9 year follow-up study sustain that deficits in verbal memory tests are present in a more severe form of illness. (40) In contrast, Preiss et al, (2009) found no verbal memory impairment but bad performance on attention and executive functions in a group with long hospitalization time. (36)

LANGUAGE

Verbal fluency is commonly known as the speed of speech and usually represents 90 words per minute for a normal person. It is the ability to form and express words for communication and proper function. (41) In order to assess verbal fluency, patients are given a limited period of time to express as many words as possible within a semantic group (called semantic fluency) or starting with a given letter (phonemic fluency). (42)

McLure (1997) evaluating a young age group, found no verbal fluency impairments in the depressed group compared to controls. (43) In contrast, Wagner et al (2012) found in patients diagnosed with MDD significant deficits on semantic verbal fluency when compared with healthy subjects. (44) Roca et al, (2015) found a significant correlation between improvement in mood symptoms and better results on verbal fluency measures. (45) Data suggests that performance on semantic fluency evaluation is worse in first episode remitted patients than in recurrent episodes remitted subjects. (27)

Meta analyses suggest that reliable neurocognitive deficits can be determined in tests for mental flexibility and verbal fluency, especially phonemic fluency. (35)

EXECUTIVE FUNCTIONS

Executive functions represent a term that includes a higher order of cognitive abilities. These are represented by more specific functions such as planning and strategy development, prioritizing, decision making, task shifting, cognitive flexibility, finding alternative solutions, dealing with novelty. (46)

Dysfunction of executive functioning is shown to persist despite the fact that results on other cognitive test were almost the same with healthy controls. (47) A few studies suggest that symptom severity is correlated with
poor executive functioning and processing speed. (48) In a comparative study, melancholic patients had worse results in attention, working memory and reasoning/problem solving than non-melancholic subjects. (49) A study which evaluated older individuals who were treated with tricyclic antidepressants demonstrated that poor executive functioning is associated with the risk to of relapse over 16 weeks or to recurrence over a 2 year time, when compared to normal subjects. (50) Cognitive impairment especially in executive functions may predict the therapeutic outcome with antidepressant treatment, or the risk of relapse. (51)

In a review, Hasselbalch et al, (2011) found that depression with early onset is characterized by impaired episodic memory and the one with late onset affects predominately executive functioning and processing speed. (23) In contrast, Castaneda et al, (2008) conducted a study on young adults which concluded that the early age onset for MDD is associated with a higher probability for executive dysfunctions. (52)

CONCLUSIONS

In a meta-analysis Lee et al, (2012) concluded that attentional and executive functioning deficits can be considered important trait markers because they are not associated with mood symptoms. On the contrary, working memory, verbal memory and psychomotor speed were associated with clinical indicators of depression severity and may function as state markers. (35)

In the past, cognition has not been taken into consideration by clinicians who were treating depression. However, now, there is sufficient evidence to support cognition as an important focus in the management of MDD. Therefore, a new treatment goal that includes remission of mood symptoms, the resumption of full functioning should be considered for MDD.

REFERENCES


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