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Is major depression a cognitive disorder?

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ABSTRACT

This is a review of cognitive abilities in major depression, which is associated with attention problems, memory deficit and wide impairment in executive functions. Depressed patients show two major cognitive biases: excessive processing of negatively valenced emotional stimuli; and increased self-focus. Both of these biases help to facilitate the integration of negative self-related information in depressed patients and to maintain their negative mood. Brain imaging studies suggest that this cognitive impairment is characterized by abnormal cooperation between the cognitive and limbic networks involved in cognitive control and self-referential processing. In general, depression is a disorder of multiple networks with emotional, cognitive and emotional symptoms. Among these symptoms, cognition is a major determinant of functional and social outcomes.

1. Introduction

Major depression is one of the most costly brain disorders in Europe as it constitutes a tremendous burden for patients, families and the healthcare system [1]. Diagnosis of a major depressive episode is based on a clinical interview and a collection of symptoms related to the emotional, motivational, cognitive and behavioral domains. Physicians usually pay more attention to the emotional changes (such as persistent sadness, mood lability, anhedonia) associated with depression. However, the present review takes a very different perspective, suggesting that cognitive problems are the core features of major depression and, thus, good predictors of functional and social outcomes in depressed patients.

2. "Hot" and "cold" cognition

"Cognition" is an umbrella term that refers to several processes and domains including, among others, attention, memory, language, executive functions and socio-emotional processes. To better describe the cognitive domains affected by major depressive episodes, it has been proposed to separate "hot" from "cold" cognition [2].

"Hot" cognition refers to cognitive processes related to emotional and social stimuli, and takes into account the reciprocal interaction between emotion and cognition. For instance, the mood congruency effect in memory – that is, better memory in depressed patients for negative emotional material – is a typical example of a "hot" cognitive problem in major depression [3]. On the other hand, the impairment of

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depressed patients in working memory tasks involving neutral emotional material is a ''cold'' cognitive problem (see below).

At first sight, neurodegenerative disorders (such as Alzheimer's disease) should mainly affect cold cognitive domains, whereas affective disorders like major depression should induce hot cognitive deficits. However, it is now well accepted than major depression can be associated with attentional, working memory and executive deficits for neutral emotional material as well. Although the effect size of these deficits is moderate and lower than those observed in neurological diseases, these deficits are nevertheless major determinants of functional impairment in depressed patients [4,5]. One meta-analysis [6] has shown that cognitive problems are linked to depression severity, as assessed by the classic depression-related scales, while the severity of depression is related to attentional problems, episodic memory and executive functioning. Likewise, depressed hospitalized inpatients present with more objective cognitive problems than those who remain ambulatory.

3. Executive functions and major depression

The term ''executive functions'' encompasses a set of processes – inhibition, flexibility, updating – involved in the cognitive control of behavior and emotional regulation [7]. Major depression is consistently associated with the impaired performance of neuropsychological measures of executive functions, with effect sizes ranging from 0.30 to 0.97 [8]. Executive deficits in major depression are found in inhibition, updating and flexibility processes, which is consistent with the idea that major depression involves the impairment of multiple aspects of executive functioning [9]. However, several clinical characteristics can moderate the association between executive dysfunction and depression, including the number of depressive episodes, mean duration of depressive episodes, actual severity of depression and treatments [8,10].

One specific executive test, the N-Back task, has been extensively studied in unipolar major depression. During this test, subjects are required to match a stimulus – a letter or number – to stimuli presented either one (1-Back), two (2-Back) or three (3-Back) tasks previously. Thus, subjects need to constantly monitor and update the content of their working memory and, usually, the performance monotonically decreases from 1-Back to 3-Back. The present author was part of the very first group to demonstrate that acutely depressed patients, compared with healthy controls, showed a decreased level of performance (accuracy of response) in all conditions of the task (from 1-Back to 3-Back) [10]. However, this working memory deficit was not related to rumination, a clinical marker of difficulties with monitoring and updating the content of working memory [11].

On the other hand, it was possible, using functional magnetic resonance imaging (fMRI), to assess the neural correlates of N-Back impairment in another sample of acutely depressed patients. These depressed patients unexpectedly showed increased activity in their working memory network [particularly the dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (DLPFC)] compared with healthy controls [12]. While the latter performed at a normal level, the depressed patients had to activate more of their dACC and DLPFC compared with the non-depressed controls. These results suggest reduced efficiency of the working memory network in depression. As this was seminal research, several studies attempted to replicate these findings, but found contradictory results instead [13,14].

Impairment in a working memory task is a cognitive marker of acute depression and may persist in remitted depressed patients. Indeed, recent data have shown that an impaired neural signature during a working memory task may arise in subjects at risk of depression even before a depressive episode happens [15]. Moreover, vortioxetine, a new antidepressant drug with pro-cognitive effects, can reduce the persistent abnormal blood-oxygen-level-dependent (BOLD) signal during the N-Back task in remitted depressed patients, an effect dissociated from the mood effects of the drug [16].

How to explain the increased activity of the working memory network in major depression? According to previous findings [17], subjects deactivate the limbic region (especially the medial part of the prefrontal cortex) to perform the N-Back task. However, unlike controls, depressed patients have difficulty deactivating the medial prefrontal cortex (MPFC) [12], and a recent study extended these findings using network analyses of functional brain data [18]. Two groups of remitted depressed patients respectively with and without residual emotional symptoms were tested with an emotionally neutral N-Back task. The dynamics of cooperation between the control executive network (CEN), including the dACC and DLPFC, and default mode network (DMN), including the MPFC, differed between the two groups. Consistent with our hypothesis, patients with vs. those without residual depressive symptoms showed a significantly decreased inverse correlation between the DMN and CEN during the N-Back test.

As with the findings of Kelly et al. [19], the strength of the inverse correlation was significantly and positively related to less variability of behavioral performance in the non-symptomatic patients while performing the 3-Back task. Conversely, the DMN–CEN inverse correlation and 3-Back reaction-time variability were negatively correlated in patients with residual symptoms. Moreover, in these latter patients, the less the inverse correlation between the DMN and CEN, the more the patients tended to have higher scores on the ruminative rating scale, in contrast to patients in the other test groups. These results suggest that the brain dynamics between the DMN and CEN may be more involved with coping with ruminative thinking and self-referential processing (see below) than maintaining the allocation of attentional resources towards the external environment in remitted patients with emotional blunting.

4. Hot cognition and major depression

Regarding the relationship between cognition and emotion, two major biases are observed in depressed patients. The first is related to increased attention and memory towards negative emotional stimuli (see, for example, the report by Harmer and Cowen [20]). The second cognitive bias is increased self-focus: depressed patients tend to personalize and refer neutral and emotional stimuli back to themselves.

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