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Review

Cognitive dysfunction in unipolar depression: Implications for treatment

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ABSTRACT

Objective: The primary objective of this review is to examine the literature assessing abnormalities in neural circuitry and cognition early in the course of major depressive disorder (MDD) and the impact of these features on treatment selection and long-term outcomes.
Data Sources: English language and peer-reviewed publications were obtained by *PubMed*/*Medline* (www.pubmed.org) searches using combinations of major depressive disorder, major depression, or unipolar depression and "first episode", early, cognition, cognitive, executive function and memory. The terms bipolar and psychosis were excluded from the searches. These searches yielded 409 records.
Study selection: A total of 12 studies, systematic reviews and meta-analyses were selected that evaluated learning, memory and executive function in individuals with major depressive disorder. Additional publications meeting these criteria were identified from the bibliographies of the 12 selected articles and from the "related citations" section of PubMed.
Results: Difficulty in concentrating and indecisiveness are reported as among the most troubling symptoms by patients with MDD and may limit functional recovery. Cognitive deficits in memory and decision-making are present early in the course of MDD and may be accompanied by structural abnormalities in the hippocampus and prefrontal cortex involved in cognitive functions. Although resolution of cognitive symptoms of depression lags behind recovery from mood symptoms in many patients, preliminary evidence suggests they may improve with antidepressant therapy, but can also persist residually.
Conclusions: New strategies that target cognitive symptoms of depression in addition to mood symptoms are needed to improve long-term outcomes, particularly functional recovery.

Contents

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1. Introduction

Cognitive symptoms are common among patients with major depressive disorder (MDD) (Fava et al., 2006; Lee et al., 2012; Wagner et al., 2012a; Murrough et al., 2011; Millan et al., 2012), although the true prevalence is not known. We do know cognitive difficulties associated with depression, such as memory impairment, difficulty making decisions, and loss of cognitive flexibility are associated with considerable disability and limited functional recovery (Jaeger et al., 2006; McCall and Dunn, 2003; Naismith et al., 2007). This is particularly troubling because these symptoms frequently persist after remission of a depressive episode (Hasselbalch et al., 2011; Herrera-Guzman et al., 2010; Weiland-Fiedler et al., 2004; Neu et al., 2005; Paelecke-Habermann et al., 2005; Clark et al., 2005; Marcos et al., 1994; Hammar et al., 2010; Airaksinen et al., 2006; Ardal and Hammar, 2011). Nonetheless, there is evidence that cognitive symptoms improve with antidepressant therapy (Wagner et al., 2012a; Herrera-Guzman et al., 2009), and preliminary results show that some classes of antidepressants may be more effective in improving specific cognitive symptoms than others (Herrera-Guzman et al., 2009). These findings suggest that functional outcomes should be monitored during treatment and raise the possibility that interventions which improve cognition may speed functional recovery in patients with MDD (Greer et al., 2010).

Many questions remain regarding the differential expression of cognitive impairment in patients with MDD, such as the timing and duration of their presence, the implications of their presence for long-term outcomes, and the role of treatment to mitigate these symptoms (Wagner et al., 2012a; Millan et al., 2012). This review will focus on: (1) cognitive deficits associated with depression, with an emphasis on those found early in the course of the disease, (2) the neural circuitry associated with cognition and its disruption in depression, (3) the impact of early cognitive dysfunction on recovery, and (4) the impact of antidepressant treatment on cognition. Additionally, the challenges in studying neurocognitive symptoms in patients with MDD will be discussed.

2. Methods

English language and peer-reviewed publications were obtained by *PubMed*/*Medline* (www.pubmed.org) searches. The search terms: major depressive disorder, major depression, and unipolar depression were combined with “first episode”, early, cognition, cognitive, executive function and memory; searches excluded bipolar and psychosis and were limited to papers published in English. A total of 409 records were retrieved and manually screened to eliminate articles primarily discussing stroke, Parkinson's disease, Alzheimer's disease, or post-partum depression. The remaining 37 abstracts were reviewed to identify studies, systematic reviews, and meta-analyses evaluating learning, memory, and decision-making in patients with major depressive disorder. Twelve studies met those criteria (Hasselbalch et al., 2011; Herrera-Guzman et al., 2009; Lee et al., 2012; McDermott and Ebmeier, 2009; Wagner et al., 2012b; Maalouf et al., 2011; Castaneda et al., 2008; Hermens et al., 2011; Majer et al., 2004; Alexopoulos et al., 2000; Herrera-Guzman et al., 2008; McLennan and Mathias, 2010). Additional references meeting those criteria were identified from bibliographies of selected papers and review of related citations via PubMed.

2.1. Cognitive neurocircuitry

Cognition in healthy adults is mediated by neural circuits involving multiple neurotransmitter systems and connecting regions of the basal ganglia, thalamus and cortex (Fig. 1) (Millan et al., 2012). For example, circuits connecting the dorsolateral prefrontal cortex to the dorsolateral caudate nucleus are involved in programming and planning, while those connecting the anterior cingulate cortex to the nucleus accumbens are used in decision making. Response inhibition is attributed to circuits connecting the orbito-prefrontal cortex with the ventromedial caudate. The hippocampus is central to declarative learning and memory, but it is also an area that is connected to many cortical regions, and may be particularly important for the integration of cognitive and emotional processes (Millan et al., 2012; Small et al., 2011; Femenia et al., 2012). Several of the neurocircuits involved in cognitive processes overlap to some degree with those involved in mood and emotion, and are influenced by reciprocal connectivity to the hypothalamic-pituitary-adrenal (HPA) axis and amygdala, both of which are associated with emotional processes (Femenia et al., 2012). It is the integrated functioning of these circuits that may be most influential in the relationship between cognition and mood disorders (Femenia et al., 2012).

The neuronal circuits bridging cognition and depression are created by reciprocal actions among serotonin (5-HT), norepinephrine (NE), and dopaminergic (DA) neurons. (Fig. 2) (Trivedi et al., 2008) Serotonergic neurons appear to modulate neuronal activity in the prefrontal cortex via opposing actions of 5-HT1a and 5-HT2a receptors on pyramidal cells and interneurons. These actions in turn modulate activities of other neuronal cell types. The availability of 5-HT at the synapse is well established as a therapeutic target for treatment of depression. In addition, serotonin has been implicated in the regulation of cognitive flexibility, attention, and impulsivity in both humans and preclinical models (Puig and Gulledge, 2011). As will be discussed, preliminary evidence suggests antidepressants, such as duloxetine, that acts as receptors for targets other than the 5-HT transporter, appear to be more effective in improving cognitive symptoms of depression (Herrera-Guzman et al., 2010). It is also becoming clear that other neuromodulators, such as neurotrophic factors and cytokines, play an important role in intact cognition and disruptions of these neuromodulators may contribute to cognitive impairments associated with depression (Millan et al., 2012). In particular, brain-derived neurotrophic factor (BDNF) and its receptor, neurotophic tyrosine kinase receptor B (TRKB), have come under scrutiny as potential therapeutic targets for treating cognitive symptoms. Both BDNF and TRKB are involved in learning and memory requiring neuronal plasticity in the hippocampus and prefrontal cortex. Preclinical studies have shown that activation of TRKB protects against stress-induced disruption of long-term memory (Millan et al., 2012). In humans, carriers of a common single-nucleotide polymorphism in the BDNF gene (Val66Met) have impaired episodic memory (Egan et al., 2003) that is associated with decreased hippocampal activity on fMRI (Hariri et al., 2003). However, efforts to establish a relationship between BDNF (Val66Met) and MDD have yielded inconsistent findings (Verhagen et al., 2010).

Evidence suggests that neurobiological abnormalities in brain regions involved in cognition are present early in the course of the disease. However, studies in early MDD have been mixed. Structural abnormalities in hippocampus and amygdala have been observed in the first diagnosed episode of MDD (Frodl et al., 2002a, b). Evidence from a meta-analysis of data from 32 MRI studies found significant decreases in hippocampal volumes in patients with multiple illness episodes or whose MDD was of more than 2 years duration (McKinnon et al., 2009). The small population size of patients with first episode MDD may have precluded detection of a significant difference in hippocampal volume in this analysis. In two other studies, one using functional MRI and the other using diffusion tensor imaging, morphometric differences in corticolimbic regions were observed in treatment naïve patients