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Review article

The prefrontal cortex influence over subcortical and limbic regions governs antidepressant response by $N=H/(M+R)$

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ABSTRACT

We review the evidence for relationships between metabolic activity of cortical, subcortical and limbic brain regions in depression and the efficacy of antidepressant agents. The influence of these regions can be described by an algebraic equation, $N=H/(M+R)$, where N represents a homeostatic level of executive function, H represents prefrontal (Brodmann areas 9, 10, 11, 12; 46) and cingulate cortex activity (24, 25; 32), M represents subcortical (hippocampus, parahippocampal gyrus) influences, and R represents limbic (amygdala) influences. This hypothesis is based on depressed prefrontal cortex and enhanced amygdala and hippocampal metabolism in major depressive disorder, and the remission of these changes by most antidepressant interventions. The therapeutic efficacy of antidepressant strategies may depend less on their presumptive molecular mechanisms of action and more on their ability to restore the predominant metabolic and executive functions of the prefrontal cortex, and dampen excessive subcortical and limbic influences.

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1. Introduction

The mechanism of action for an increasing variety of antidepressant strategies, and reasons for their varying therapeutic latencies, have been subjects of intense speculation. A number of molecular mechanisms have been advanced, yet discrepant results over time have weakened their basic foundations. It may

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be that brain region-specific metabolic effects may better predict antidepressant efficacy than the diverse mechanisms used to differentiate these approaches, or at least their many classes.

It is noteworthy that the core depression symptoms of diminished joy, energy, self-confidence, problem-solving ability or ability to make strategic plans are also manifestations of diminished prefrontal cortex function. Conversely, the enhanced anxiety and fear that also characterize depression appear to reflect heightened limbic function. If so, major depressive disorder (MDD) may result from these functional changes, and the remission of MDD core symptoms may occur through an activation of prefrontal cortex function, a deactivation of limbic function, or both. As reviewed here, either mechanism is consistent with symptom remission, and together, they suggest that antidepressant efficacy may be predicted by increases in the ratio of prefrontal to hippocampal/limbic activity. The present review analyzed published reports of statistically significant changes in brain metabolism to see which brain areas, and directions of change, characterize depression, and if reciprocal changes in metabolic activity characterize remission in ways consistent with this hypothesis.

2. Methods

2.1. Literature search

Literature searches conducted from October 2010–December 2011 used the National Institutes of Health PubMed database to identify peer-reviewed studies of adolescents and adults with major depressive disorder, for any year covered by the database. The following terms were used to define brain areas: *frontal*, *cortex*, *cortical*, *amygdala* OR *limbic*. These were searched for association with *antidepressant*, *depression*, *anxiety*, *treatment*, *efficacy*, *remission* OR *response*, or for specific drugs and drug classes used to treat depression, such as *desipramine*, desmethylimipramine OR a selective norepinephrine uptake inhibitor. Most of the searches required associations in human subjects, and results were included if they were published in English, involved males and females with no requirement for equal numbers of each, included depressed individuals who had recent onset or chronic illness, and for whom group statistics revealed significance of experimental effect of at least $p < 0.05$. References within reviewed articles were frequently scrutinized to discover other relevant studies. With few exceptions, the studies used functional magnetic imaging (fMRI), including blood oxygenation level-dependent (BOLD) fMRI, and positron emission tomography (PET) imaging methodologies.

2.2. Summary of literature results

The goal of the search was to identify those brain areas most commonly implicated in depression and related conditions such anxiety, and in which a statistically significant direction of metabolic or other functional change in brain function was reported following therapeutic response or remission. The results of these studies were tabulated for each brain region to determine the frequencies with which areas were involved in disease or treatment effect, which direction of metabolic change characterized disease or therapeutic response, and if these changes were reciprocal or parallel for each brain area. To quantify this, the number of studies reporting these changes were summed for each brain area (Table 1). Conflicting changes were subtracted from the predominant form of change, and the sums were represented graphically (Fig. 1) to demonstrate regionally contiguous brain areas implicated in depression and its treatment by diverse approaches.

3. Results and discussion

3.1. Diminished executive function in depression

Executive function, a domain of the prefrontal cortex, is compromised in unipolar depression (Clark et al., 2005; Channon and Green, 1999), late-life depression (Alexopoulos, 2003; Morimoto et al., 2010), obsessive-compulsive disorder (Basso et al., 2001), and treatment-resistant depressed patients (Li et al., 2010). Importantly, executive function improves when unipolar depression remits, and does so to such a degree that complete recovery from depression can restore normal executive function (Biringer et al., 2005). Conversely, depressed patients with the greatest decrements in executive function are less likely to remit (Morimoto et al., 2010). While executive function is commonly compromised in depressed patients, neither verbal learning, visuospatial memory, delayed recall, recognition memory, nor other memory domains of the temporal cortex and hippocampus appear to be so at risk (Clark et al., 2005; Tsaltas et al., 2010).

The syndrome of depression with diminished executive function also has a basis in dysfunction of limbic–frontal cortical pathways (Mayberg, 1997; Mayberg et al., 1999; Alexopoulos, 2003) and frontostriatal pathways (Mayberg et al., 2000; Morimoto et al., 2010). These dysfunctions may extend to obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and post-traumatic stress disorder (PTSD) due to greater amygdala and anterior cingulate activation, and, as observed in bipolar disease, decreased prefrontal cortex activation (Ketter et al., 2001). Augmented amygdala activity adversely influences decision-making and other cognitive functions of the prefrontal cortex, including a lessening of frontal cortex activation during tasks that require heightened attention (Mayberg, 1997; Mayberg et al., 1999).

3.2. Stress and depression decrease frontal cortex dominance of subcortical and limbic areas

Childhood stress reduces prefrontal cortex function and volume when measured in adolescence and adulthood, and even when adjusted for total brain volume (Arnsten, 1999; van Harmelen et al., 2010; Carrion et al., 2010). Stresses in early life and beyond greatly increase the vulnerability for depression and anxiety in adulthood if stress re-emerges (Gibb et al., 2007; Spinhoven et al., 2010). Brain atrophy and decreased metabolism in the orbitofrontal and dorsolateral prefrontal cortex contribute to this vulnerability (Lavretsky et al., 2005; New et al., 2004). Like adult depression (Weniger et al., 2006), pediatric depression (MacMillan et al., 2003) is associated with increases in amygdala size, and patients with the largest amygdalae show the greatest levels of anxiety and impairments in learning emotional facial expressions (MacMillan et al., 2003; Weniger et al., 2006).

A reciprocal relationship between metabolic activities of the prefrontal cortex and the limbic brain is well established in human depression and in response to one of its key antecedents, stress (see Seminowicz et al. (2004) for review). As summarized in Table 1, major depressive disorder is most commonly associated with decreased metabolism in the dorsolateral prefrontal, anterior prefrontal, orbitofrontal, and ventral anterior and subgenual cingulate cortex, as highlighted in bold or bold italics (Goldapple et al., 2004; Mayberg et al., 2000, 1997; Takano et al., 2006; Kohn et al., 2007; Aizenstein et al., 2009; Aihara et al., 2007; Kimbrell et al., 2002; Milo et al., 2001). Brain areas implicated in depression or their treatment by only one or no publication are excluded from the Table. Decreases in frontal cortical metabolism during depressed mood have also been identified with ^{11}C-glucose PET imaging (Hasler et al., 2008). As shown in italics, limbic regions including the amygdala, hippocampus, and parahippocampal gyrus are hyperactive in depression (Aihara et al., 2007; Kennedy et al., 2001; for reviews, see Fitzgerald et al., 2008a, b; Drevets, 1999; Drevets, 2000; Savitz and Drevets, 2009) and in depression associated with bipolar disease (Ketter et al., 2001; Savitz and Drevets, 2009). fMRI investigations reveal heightened amygdala activity at baseline (Drevets et al., 2002a, b), and elevated response to negative (Sheline et al., 2001) and positive (Davey et al., 2011) emotional stimuli. Even positive social feedback in depressed individuals elicits an increase in amygdala fMRI signal which is not seen in normal controls (Davey et al., 2011). Limbic hyperactivity has not been found in all studies of major