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The effects of antidepressants on human brain as detected by imaging studies. Focus on major depression

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ABSTRACT

Recent brain imaging studies have shed light on understanding the pathogenesis of mood disorders. Evidence of structural, chemical, and functional brain changes, particularly in prefrontal cortex, cingulate, and amygdala, has been revealed in major depressive disorder (MDD). Furthermore, imaging techniques have been applied to monitor the effects of antidepressants (ADs) both in the brains of healthy volunteers and MDD patients. Although with some discrepancies due to the differences in study designs and patient samples, imaging findings have shown that ADs, particularly those having effects on the serotonergic system, modulate the volumes, functions and biochemistry of brain structures, i.e. dorsolateral prefrontal cortex, anterior cingulate and amygdala, which have been demonstrated abnormal in MDD by earlier imaging studies. This paper reviews imaging studies conducted in MDD patients and healthy controls treated with different ADs.

1. Introduction

Although antidepressant (AD) agents have been largely used for the treatment of major depressive disorder (MDD), the neurobiological mechanisms of their efficacy are not well understood (Manji et al., 2003; Brambilla et al., 2003, 2005a; Sala et al., 2006, 2009; Verdoux et al., 2009). Moreover, different clinical courses after treatment may be present: some patients have fewer depressive episodes and achieve a rapid remission and some others have a prolonged, remittent or refractory illness (Keller et al., 1992; Cipriani et al., 2005; Patten et al., 2005; Slade et al., 2008). A wide range of antidepressants is commonly prescribed in clinical practice. Most of them have pharmacologic effects on monoamine levels, such as serotonin, norepinephrine and dopamine in specific brain areas (Rapaport, 2009). Tricyclic agents (TCAs), such as amitriptyline and clomipramine, are known as first generation antidepressants. Newer agents, selective serotonergic reuptake inhibitors (SSRIs), such as citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline and paroxetine; serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, noradrenergic; and specific serotonergic antidepressants (NaSSAs), such as mirtazapine; norepinephrine reuptake inhibitors (NRIs), such as reboxetine; and norepinephrine–dopamine reuptake inhibitors (NDRIs) such as bupropion, have demonstrated a comparable efficacy to TCAs (Maurer and Colt, 2006). Moreover, they are claimed to be more tolerable and safer in the prescription dosage (Williams et al., 2000).

On this regard, evaluating the brain structural and functional antidepressant effects will allow a better understanding of the pathogenesis of MDD and its response to AD treatment. The neuroimaging findings may potentially be used for monitoring treatment response and predicting the clinical outcome of MDD patients after treatment. In particular, limbic structures, i.e. the hippocampus and the amygdala, and the prefrontal areas, i.e. the anterior cingulate and the dorsolateral prefrontal cortex (DLPFC), have been suggested to play a key role in the emotional and cognitive processing of MDD (Sala et al., 2004; Brambilla et al., 2005b). On the other hand, the hypothalamus and the brain stem have been suggested to be involved in the neurovegetative symptoms of MDD patients (Drevets, 2000a).

Because of high contrast sensitivity and spatial resolution, and no radiation exposure, MRI has become the gold standard for exploring the pathophysiology of psychiatric disorders (Caetano et al., 2004; Lacerda et al., 2005). In addition to conventional MRI, recent methods

Abbreviations: AD, antidepressant; BOLD, blood oxygenation level dependent; CNS, central nervous system; MDD, major depressive disorder; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NRI, norepinephrine reuptake inhibitor; PET, positron emission tomography; rCBF, relative cerebral blood flow; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex.

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have significantly increased the knowledge of the functional, biochemical and vascular organization of the human brain. fMRI examines the neural activation in response to specific experimental tasks or in resting state based on blood oxygenation level dependent (BOLD) methods (Ogawa et al., 1993). Magnetic resonance spectroscopy (MRS) allows *in vivo* measurement of brain metabolites, such as N-acetylaspartate, choline, myo-inositol and phosphomonoesters (Brambilla et al., 2002c, 2004b). Finally, positron emission tomography (PET) and single photon emission computed tomography (SPECT) measure brain hemodynamics using principles of indicator-dilution theory, and examine brain pharmacokinetic profiles using radiological binding assays (Alavi et al., 1986; Kumar and Mann, 2007).

In this review, we focus on structural, biochemical and functional effects of ADs in healthy subjects and in patients with MDD.

2. Structural magnetic resonance imaging (sMRI) studies (see Table 1)

Structural MRI (sMRI) have documented several brain structural changes in MDD, including amygdala, hippocampus, cingulate, orbitofrontal cortex (OFC), DLPFC and ventral prefrontal cortex (Campbell et al., 2004; Lacerda et al., 2004; Caetano et al., 2006; Monkul et al., 2007; Hamilton et al., 2008; Bearden et al., 2009; McKinnon et al., 2009). In particular, as reported in meta-analyses, MDD has been shown to be associated with the reduction of hippocampal volumes (Campbell et al., 2004; McKinnon et al., 2009). However, controversial findings have been found in other regions such as corpus callosum, thalamus and basal ganglia (Caetano et al., 2001; Brambilla et al., 2002a,b; Lacerda et al., 2003; Brambilla et al., 2004a; Lacerda et al., 2005).

Regarding ADs, treatment duration was found to be directly correlated with the change of hippocampal volume of MDD patients (Sheline et al., 2003; Frodl et al., 2008). Up to now, only few structural MRI studies have evaluated the brain volume changes by specific antidepressants. Reduced amygdalar volume in unmedicated patients, but increased amygdalar (Hamilton et al., 2008) and hippocampal sizes have been found in medicated MDD subjects after a 3-year follow up (Frodl et al., 2008), suggesting potential neuroprotective/neurostimulatory effects of antidepressant treatment (Malberg et al., 2000; Perera et al., 2007). However, a previous study on SSRIs did not find significant brain volumetric changes in MDD patients treated with either fluoxetine (N = 20), sertraline (N = 1) or venlafaxine (N = 1) after 10 months of follow-up (Vythilingam et al., 2004) (see Table 1).

3. Functional magnetic imaging (fMRI) studies (see Tables 2 and 3)

Several fMRI studies have assessed brain activation of healthy subjects in response to antidepressive drugs, administered as either a single dosage or a short time medication. However, the results of these studies are not fully comparable as the hemodynamic responses vary according to different compounds and dosage of AD, and the fMRI task paradigms. Interestingly, increased brain activations in amygdala, hippocampus, striatum and thalamus have been observed in resting healthy subjects with intravenous injection of citalopram (McKie et al., 2005), indicating a specific pharmacologic target site of citalopram in the brain areas, which have been shown involved in the pathogenesis of MDD, revealed by functional imaging studies (Drevets, 2000b).

3.1. Emotional processing tasks

3.1.1. Healthy controls

fMRI studies investigating emotional processing, such as face emotion recognition, have shown that emotionally salient stimuli tended to activate amygdala (Costafreda et al., 2008), anterior cingulate cortex, OFC, insula and striatum in unmedicated healthy controls, especially during unpleasant (facial expressions of fear and disgust) stimuli processing tasks (Phan et al., 2004).

In healthy subjects, SSRIs, such as citalopram, escitalopram, and fluvoxamine have been reported to reduce amygdalar, OFC, hippocampal, parahippocampal and insular activation compared to placebo during aversive stimuli in most (but not all) of the fMRI studies (Del-Ben et al., 2005; Takahashi et al., 2005; Harmer et al., 2006; Anderson et al., 2007; Bigos et al., 2008; Simmons et al., 2009; Murphy et al., 2009; Bruhl et al., 2010; Windischberger et al., 2010). In contrast, NRI reboxetine, which acts on the noradrenergic system rather than the serotonergic one as SSRIs do, has been shown to increase amygdalar, thalamic and prefrontal cortex activation in response to negative stimuli but decrease amygdalar activation to pleasant stimuli in healthy brain (Kukolja et al., 2008; Onur et al., 2009). The noradrenergic system, through a locus coereleus–amygdalar network, is considered to play a key role in the development of maladaptive stress response and anxiety disorder (Buffalari and Grace, 2007). Acute noradrenergic stimulation by reboxetine could elicit exaggerated amygdalar response to stress signals (Rauch et al., 2006).

3.1.2. MDD patients

In MDD patients, the increased amygdalar activation, and decreased insular and anterior cingulate reactivity in response to negative stimuli, particularly fearful stimuli, were reversed by fluoxetine, sertraline, venlafaxine or bupropion (Kalin et al., 1997; Sheline et al., 2001; Davidson et al., 2003; Fu et al., 2004, 2007; Robertson et al., 2007).

In regard to emotion regulation, it is important to keep in mind that amygdala plays a key role in humans (Posamentier and Abdi, 2003; Fitzgerald et al., 2006), particularly, during negative affective states, such as sadness and anxiety (Davidson and Irwin, 1999) and that MDD patients tend to perceive positive or ambiguous events as negative stimuli (Mayberg, 1997; Elliott et al., 2002) with the consequence of higher activation of amygdala. Since amygdala has a dense serotonergic innervation, these findings suggest that SSRIs could modulate the activity of the amygdala by reducing its responsiveness to unpleasant stimuli through the serotonergic pathway (Deakin, 1998). Indeed, the amygdalar activation induced by acute administration of NRIs, could be explained by the enhancing effect of norepinephrine on this area (Kukolja et al., 2008). Anterior cingulate, prefrontal, OFC, and insula are interconnected to amygdala (Kent et al., 1998; Phillips et al., 2003; Bellani et al., 2010); thus their activities are influenced by the serotonergic compounds through the pathways interconnected to amygdala (Vollm et al., 2006), such as the reward processing (O'Doherty et al., 2000).

Table 1
Structural MRI studies on the effect of antidepressants in patients with MDD.

Article	Participants	Antidepressants	Treatment duration	MRI	Results in patients with MDD
Vythilingam et al. (2004)	22 outpatients (8 males)	Fluoxetine, sertraline, venlafaxine	Open label, 7 ± 3 months	MRI 1.5 T baseline, 1 scan; follow-up, 7 ± 3 months	No difference in volume at follow-up compared to baseline
Frodl et al. (2008)	30 patients (21 males) 30 healthy controls (21 males)	Multiple antidepressants	Open label, 3 years	MRI 1.5 T baseline, 1 scan; follow-up, 3 years	↑ volume in hippocampus in patients at follow-up compared to baseline