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Review

Differences between effects of psychological versus pharmacological treatments on functional and morphological brain alterations in anxiety disorders and major depressive disorder: A systematic review

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ABSTRACT

The most prevalent mental disorders, anxiety and mood disorders, are associated with both functional and morphological brain changes that commonly involve the 'fear network' including the (medial) prefrontal cortex, hippocampus and amygdala. Patients suffering from anxiety disorders and major depressive disorder often show excessive amygdala and reduced prefrontal cortex functioning. It is, however, still unclear whether these brain abnormalities disappear or diminish following effective treatment. This review aims to compare the effects of psychotherapy and pharmacotherapy on functional and morphological brain measures in these disorders. Sixty-three studies were included, 30 investigating psychotherapy effects and 33 investigating pharmacotherapy effects. Despite methodological differences, results suggest a functional normalization of the 'fear network'. Pharmacotherapy particularly decreases over-activity of limbic structures (bottom-up effect) while psychotherapy tends to increase activity and recruitment of frontal areas (top-down effect), especially the anterior cingulate cortex. Additionally, pharmacotherapy, but not psychotherapy, has been associated with morphological changes, depending on the disorder. These findings suggest that both types of treatments normalize (functional) brain abnormalities each in specific ways.

Contents

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1. Introduction

Anxiety and mood disorders are estimated to be the most prevalent mental disorders in the United States and internationally (Kessler et al., 2005). Although several distinct subtypes of these disorders are described in the DSM-IV, anxiety and mood disorders share similar symptoms and treatments, are highly comorbid and alike in etiology and pathophysiology. More specifically, anxiety and mood disorders have consistently been associated with morphological and functional brain changes (van Tol et al., 2010; see also Fitzgerald et al., 2008; Koolschijn et al., 2009 for recent reviews). It is still insufficiently clear, however, whether these brain abnormalities are pre-existing (trait) or a consequence of these disorders (state), and whether these abnormalities thus disappear or diminish following effective treatment with psychotherapy and/or pharmacotherapy. This review aims to elucidate the effects of psychotherapy versus pharmacotherapy on functional and morphological measures in anxiety disorders (post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), phobias and panic disorder (PD)) and in major depressive disorder (MDD), the most common mood disorder. Neuroimaging techniques and functional and morphological abnormalities commonly found in anxiety disorders and in MDD will briefly be reviewed before findings on the effects of treatment on brain function and morphology are presented.

1.1. Neuroimaging methodology

Briefly, three different kinds of neuroimaging techniques are used in neuropsychiatric research. First, for morphometric studies, structural magnetic resonance imaging (sMRI) is the method of choice due to its high resolution (below 1 mm) and excellent contrast between white matter, grey matter and cerebrospinal fluid. For volumetric studies, researchers previously used manual delineation of regions of interest (ROIs) while nowadays these methods have mostly become automated, such as in voxel-based morphometry (VBM). Second, neuroimaging techniques such as single proton emission computed tomography (SPECT) and positron emission tomography (PET) allow researchers to directly assess regional perfusion differences (e.g., regional cerebral blood flow [rCBF] and glucose metabolism), while functional MRI (fMRI) indirectly assesses neural activity. Compared to PET and SPECT that use radioactive tracers, functional MRI is non-invasive and has superseded PET and SPECT. In fMRI, regional neural activity is measured through changes in MR-signal resulting from variations in oxyhemoglobin, the so-called blood oxygen level dependent (BOLD) contrast. Although fMRI has some drawbacks, such as sensitivity to artifacts and scanner noise, it has become the most widely used tool for functional brain imaging studies due to its excellent spatial as well as temporal resolution. A third application of PET/SPECT and MRI techniques is molecular imaging. For MRI, molecular imaging can be performed as magnetic resonance spectroscopy (MRS or ^{1}HMRSI), which is used to measure relative concentrations of molecules like choline, creatine, lactate or N-acetyl aspartate (NAA, a marker of neuronal integrity). With PET/SPECT, tracers can be synthesized which bind to specific (neuro)receptors, such as for dopaminergic, serotoninergic or GABA-ergic neurons, and allow research on molecular communication between structures implied in cognitive processes or specific to a psychiatric disorder.

1.2. Functional and morphological abnormalities in anxiety disorders and major depressive disorder

Anxiety and mood disorders are by far the most prevalent psychiatric disorders, with an estimated combined lifetime prevalence of 28.8% (Kessler et al., 2005). Within the overall categories of DSM-IV-TR anxiety and mood disorders (APA, 2000), several disorders are included such as PTSD, MDD, besides being the most common mood disorder, is also highly comorbid with anxiety disorders, OCD, GAD, phobias (general, social, simple and specific) and PD. These disorders share common features, for example involving feelings of fear and worry that lead to avoidant or compulsive behavior. These behaviors are associated with recruitment of at least a part of the 'fear network', which involves the thalamus, the hippocampus, the amygdala and the prefrontal cortex (LeDoux, 1998). Over the past two decades, neuroimaging research has contributed greatly to our knowledge regarding the neuronal basis of each disorder. A brief overview of brain regions reportedly involved in these disorders is presented below.

Post traumatic stress disorder – Neuroimaging studies in PTSD – which is characterized by intrusions of the traumatic event, avoidance, emotional numbing and hyperarousal (DSM-IV-TR; APA, 2000)—have consistently shown that three major structures, i.e., the hippocampus, amygdala and medial prefrontal cortex (mPFC) including the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC) and the medial frontal gyrus, are involved in the pathophysiology of PTSD (Metcalfe and Jacobs, 1998; Rauch et al., 2006). Functional neuroimaging studies of PTSD patients revealed that amygdala hyper-responsiveness in particular (Protopopescu et al., 2005; Rauch et al., 1996; Shin et al., 2004a) is coupled with decreased responsiveness of the hippocampus (Bremner et al., 2003a,b; Shin et al., 2004b) and the mPFC (Bremner et al., 1999; Lanius et al., 2001; Shin et al., 2004a). Additionally, volumetric studies have reported decreased hippocampal (e.g., for reviews and meta-analyses Smith, 2005; Woon and Hedges, 2008) and ACC grey matter volumes (Corbo et al., 2005; Kasai et al., 2008; Woodward et al., 2006). Molecular neuroimaging showed decreased levels of NAA in the hippocampus, particularly in veterans and in childhood abuse victims (Freeman et al., 1998; Mohanakrishnan Menon et al., 2003; Schuff et al., 2001).

Major depressive disorder – In MDD, a limbic-cortical-striatal-pallidal-thalamic circuit is thought to play an important role in the pathogenesis and maintenance of the disorder (Drevets, 2000). This circuit has connections to the mPFC and a region including the dorsomedial/dorsal anterolateral PFC, the mid- and posterior cingulate cortex, a region in the anterior superior temporal gyrus and sulcus and the entorhinal and posterior parahippocampal cortex (Kondo et al., 2005; Saleem et al., 2008). This circuit also has connections with sensory areas and visceral control structures such as the hypothalamus and the periaqueductal grey (Ongur et al., 2003). Research investigating neurophysiological correlates of MDD generally showed decreased rCBF and glucose uptake in the dorsolateral PFC implicated in executive functions such as working-memory. In contrast, rCBF and metabolism was increased in ventral