Neuroimaging findings in depression

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Abstract

Neuroimaging techniques are important clinically to exclude organic disorders as origins of depression. For research, they provide insight into brain structure, function and network organization, indicating the relevance of different brain circuits for certain brain functions and how these are altered in major depressive disorder (MDD). Here, the findings from cross-sectional and longitudinal neuroimaging studies on major depression will be reviewed, focusing on structural, functional and diffusion imaging, as well as MR spectroscopy. Overall, structural, functional and diffusion imaging studies show alterations in networks consisting of the cingulate cortices, prefrontal cortices, amygdala and subcortical regions like the hippocampus and basal ganglia which may play key roles in MDD. Excitatory and inhibitory neurotransmitters as well as glutathione measured using MR spectroscopy were found to be decreased in MDD compared to controls, while membrane turnover is thought to be increased in some regions. Assessing distinct functional deficits associated with different underlying pathophysiological mechanisms, which in turn might inform about different promising therapies, is currently a research direction.

Major depressive disorder

Currently, the diagnosis of major depressive disorder (MDD) is based on clinical observations and reports by patients, caregivers, parents and teachers. This approach has improved diagnostic reliability in clinical practice and research. Unfortunately, there are currently still no objective markers that might help to facilitate diagnosis or guide therapy. Neuroimaging has great potential in this regard, both for MDD and other psychiatric disorders.

Structural imaging in MDD

Currently, structural MRI is important in clinical practice to exclude structural brain abnormalities, such as tumours, infections or neurodegeneration, but it is not being used to predict the outcome of MDD. However, MRI investigation in humans has shown strong evidence that the disorder is associated with brain structural changes. Many studies have reported, for example, that patients have reduced hippocampal volumes compared to healthy controls and this finding has been confirmed by recent meta-analyses (1-3). Other brain regions affected in MDD are the basal ganglia and orbitofrontal cortex, in particular the gyrus rectus (4). Interestingly, a longitudinal study of 30 patients with MDD and 30 healthy controls demonstrated that a negative clinical outcome with more relapses and a chronic course during a three-year follow-up was associated with a decline in hippocampal, amygdalar, anterior cingulate cortex and dorsomedial prefrontal cortex volumes. In patients who achieved remission, however, these structural changes did not occur (5). Therefore, a predisposition to depression might be associated with smaller hippocampal volumes, which might further decline during the course of chronic illness, but normalize during remission. However, this hypothesis is speculative at present and needs to be investigated in studies with longitudinal designs. Using new high-field MRI techniques it is now also possible to investigate smaller structures or even subregions of brain areas, like the hippocampal subfields or amygdalar nuclei.

Functional neuroimaging

fMRI studies examining neural responses to emotional stimuli in patients with major depression have indicated increased responses in the amygdala, anterior cingulate cortex (ACC), fusiform gyrus, putamen and prefrontal cortical regions (6-8). Many researchers have suggested that the depressive syndrome might arise from abnormal interactions between brain regions; therefore, several neuroimaging stud-

ies have examined the functional connectivity of neural networks in MDD patients. Overall, a network consisting of the cingulate, prefrontal cortex, amygdala and subcortical regions may play key roles in MDD. Compared to healthy controls, patients showed increased functional connectivity between the amygdala, hippocampus, and caudate-putamen regions during emotion processing (9) but significantly reduced amygdala–prefrontal connectivity (10). At present, fMRI is an ever-growing research method and neuropsychological tasks that can disentangle functional network abnormalities are constantly being developed.

Interest is also growing in the use of resting-state fMRI, which does not require the completion of a task and which has become a popular means of complementing the results of task-based fMRI studies. Resting-state fMRI allows the examination of large-scale neural systems that exhibit spontaneous synchronous fluctuations during goal-directed and non-goal-directed behaviour (11). Several resting-state studies of MDD have found increased resting-state functional connectivity in the cognitive control network (12, 13), increased connectivity in the default-mode network (DMN) (14, 15), as well as increased functional connectivity in the affective network (14).

Diffusion imaging in MDD

Structural neuroimaging studies in MDD show volume reductions in limbic and frontal brain regions; functional imaging studies indicate functional disconnectivity between them. Alterations in white matter fibre bundles extending between these areas can be investigated with diffusion tensor imaging (DTI).

DTI is a novel neuroimaging technique that can evaluate both the orientation and the diffusion characteristics of white matter tracts *in vivo* (16) and represents the forefront of neuroimaging techniques in the characterization of microstructural alterations (17). Findings concerning MDD are heterogeneous, but a meta-analysis of DTI studies identified changes of white matter integrity in the fascicles connecting the prefrontal cortex with the frontal, temporal and occipital lobes, and amygdala and hippocampus (18), consistent with structural and functional findings. We conducted a meta-analysis of available studies, including 188 patients with MDD and 221 healthy controls. The analysis showed white matter alterations in the superior longitudinal fasciculus (SLF) and fronto-occipital fasciculus (FOF) of patients. Our findings suggest that white matter organization in these structures might also play an important role in the pathogenesis of depression. However, more research in larger samples is still needed, especially to track changes during the course of the disease (19).

MR spectroscopy

Throughout the years, the investigation of the biochemical alterations associated with MDD has highlighted changes in neurotransmitter systems of depressed patients (20). In particular, proton magnetic resonance spectroscopy (MRS) is a non-invasive technique that has often been used to detect differences in tissue concentration of various chemical compounds *in vivo* (21). Even on routinely available 1.5 T scanners, this technique can identify N-acetylaspartate compounds (NAA), choline (Cho) and creatine (Cre). At higher field strengths (3-7 T), glutamate (Glu), glutamine (Gln) and myo-inositol (Ins), can also be individually resolved. Finally, γ-aminobutyric acid (GABA) as well as glutathione (GSH) are optimally quantified at the highest field strengths with special editing and acquisition techniques (22, 23), although GSH has been shown to be reliably measured at lower field strengths using fitting routines such as LCModel after acquisition (24).

MRS studies have often reported a reduction of glutamate, the most common excitatory neurotransmitter, in the prefrontal cortex of MDD subjects compared to controls (25, 26). Glutamine (Gln), an amino acid synthesised from glutamate in the glia (27), and GABA have also been found to be decreased in MDD in this region (28, 29). Glutathione, which is involved in synthesis and degradation of proteins and DNA, has recently been found to be reduced in the occipital cortex of depressed patients, suggesting the presence of oxidative stress in this cohort (30). Choline, which is related to membrane metabolism and turnover, has been found to correlate with mood in healthy subjects (31) and to be increased in MDD patients compared to healthy controls in the basal ganglia (32). Most studies have found negative results for NAA involvement in MDD (32) and mixed results for Cre levels (33).

Thus, excitatory and inhibitory neurotransmitters as well as glutathione were found to be decreased in MDD compared to controls, while membrane turnover is thought to be increased in some regions.

Longitudinal trials using imaging

A few longitudinal antidepressant trials have previously investigated BOLD responses induced by emotional stimuli processing using fMRI in depressed patients. Findings include a significant decrease of BOLD responses in the hippocampus, basal ganglia, thalamus and cerebellum of patients treated with venlafaxine (a serotonin and noradrenaline reuptake inhibitor) and a significant increase of BOLD responses in the middle cingulate cortex and supplementary motor area of patients treated with mirtazapine (a selective serotonin and noradrenaline reuptake inhibitor) (34). These findings suggest different locations for the action of different treatment strategies. A meta-analysis summarized results of nine fMRI studies and showed that antidepressant treatment resulted in an increase of BOLD responses of dorsolateral, dorsomedial and ventrolateral prefrontal cortices. On the other hand, subcortical regions and those related to emotion processing, such as the amygdala, hippocampus, parahippocampus, cingulate cortex, orbitofrontal cortex, insula and precuneus, showed decreased BOLD responses (35).

Overall, fMRI is a tool that can be used to show normalization of brain response following drug action. Therefore, this technique can be used to understand the mechanisms of action of antidepressant medication, providing potential support for new drug efficacy evaluation.

Conclusion

Structural, functional and diffusion imaging studies show alterations in networks involved in affect recognition, emotion regulation and reward, consisting of the cingulate cortices, prefrontal cortices, amygdala and subcortical regions which may play key roles in MDD. Altered functional and structural connectivity can be detected in these networks, which is also associated with reduced volumes of the regions involved. Moreover, excitatory and inhibitory neurotransmitters as well as glutathione measured using MR spectroscopy were found to be decreased in MDD subjects compared to controls. A breakthrough would be when it becomes possible to assess distinct functional deficits associated with different underlying pathophysiological mechanisms using functional and diffusion imaging, which might need distinct special therapies. Thus, these imaging alterations might offer opportunities to inform individual therapy plans.

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