

Neuroimaging in mood disorders

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Summary

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The neural basis of mood disorders is still incompletely understood. Syndromes classified as mood disorders are composed of broad and quite inhomogeneous combinations of a multitude of psychological and physical signs and symptoms, which typically vary across time, are modified by comorbid conditions, personality traits, socio-cultural background and genetic factors. While many effective therapy options exist, still a large proportion of patients with depression and related disorders do not sufficiently respond to treatment. In addition, there is a lack of information that could help to clearly identify patient-related factors optimising individual treatments. The emergence of brain imaging technologies during the past decades is leading to a rapidly growing data-base providing sophisticated information about the neuroanatomy of mood disorders. The currently available information from neuroimaging studies in mood disorders starts to converge into some generalisable patterns of structural and functional brain changes. Although some inconsistencies exist between cross-sectional neuroimaging studies, an increased prevalence of white matter and periventricular hyperintensities appears to be associated with mood disorders. In addition, neuroimaging studies suggest structural and functional alterations in prefrontal cortex and cingulate cortex, the amygdala, hippocampus and other portions within the limbic system, and in the basal ganglia. These areas receive rich serotonergic, noradrenergic and dopaminergic projections and play a central role in the regulation of the hypothalamic-pituitary adrenocortical system. Both are fundamental to current concep-

tions of antidepressant drug action. Some of these cross-sectional changes appear to be associated with severity and/or duration of the illness, and with outcome during treatment. For example, antidepressants appear to have a protective effect on hippocampal volume loss in major depression, a finding that relates to the capacity of antidepressants to normalise the hypothalamic-pituitary adrenocortical system and to reduce the level of corticosteroids, which in turn can be toxic to hippocampal neurons. It is unquestioned that neuroimaging approaches represent a promising lead in understanding the neural basis of mood disorders. Future directions of brain imaging research in such complex diseases, however, should attempt to more directly associate structural, resting state metabolic and task-dependent functional changes, both in cross-sectional and longitudinal investigations. Nevertheless, the increasing understanding of brain circuits that are specifically associated with certain aspects of the disease provides particularly useful information for translational research, which will foster novel hypotheses that are mutually testable in clinical and preclinical settings. Notably, the available evidence summarised in this article is based on group studies, which do not allow to draw inferences for individual patients. One of the long-term perspectives is that patterns of specific dysfunctional brain activity may be used to select and optimise individually tailor-made treatments. The non-invasiveness and increasing technical sophistication of brain imaging techniques and the synergistic combination of them, keeping in mind the many caveats also briefly outlined in this article, and securing a careful control of clinical and other possible confounds, hold great promise for this challenge.

Keywords: *depression; functional neuroanatomy; PET; MRI; structural; functional; cross-sectional; longitudinal; treatment monitoring; disease progression; trait-marker; state-marker*

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Introduction

Major depression consists of a detrimental cluster of psychological and physical signs and symptoms persistently sustained over a period of weeks or months and which differ from the individual's habitual state. Of these, the most prominent symptoms include depressed mood, diminished interest or pleasure in activities, altered appetite and weight loss, sleep disturbances such as insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, indecisiveness, thoughts of death and suicidal ideation or behaviour. These symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning [1] and are complicated by a high comorbidity rate [2]. Of those individuals affected with recurrent major depression, only 70–75% experience full inter-episode recovery. That is, about 25–30% of these patients do not fully remit between depressive episodes. The long-term prognosis regarding functional recovery, as opposed to syndromal recovery, is even worse in some diagnostic subgroups [3]. Although the superiority of antidepressant drugs over placebo has occasionally been questioned, comprehensive evidence-based meta-analyses clearly demonstrate that the efficacy of antidepressants is unfeigned [4]. In the past decades, a plethora of pharmacological, psychotherapeutic and other non-pharmacological therapy options have become available for the treatment of depression. Although novel antidepressant drugs with heightened receptor-binding specificity and more advantageous adverse effect profiles have been introduced in the past years, the overall efficacy measures do not appear to have improved significantly. This is true in the case of selective serotonin reuptake inhibitors, the comparative efficacy of which has most extensively been evaluated [5]. The latency from the initiation of antidepressant drug treatment to the clinical response is still a matter of several weeks and has not greatly diminished with the new generation of antidepressants. Towards this end, a more comprehensive understanding of the neurobiological and psychological bases of the pathophysiology of depression is required, one which may lay the foundation for more rational treatment strategies of depression and other mood disorders in the future.

Since the introduction of computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and other less extensively used techniques some decades ago,

brain imaging has increasingly been employed to study the neural underpinnings of mental disorder in the living brain. This article is intended to give a broad overview of how brain imaging can help us understanding depressive and related illness.

Brain imaging approaches to mood disorders

Among the many psychological and neurobiological approaches to an understanding of depression and its resolution are various forms of brain imaging techniques, including the most extensively used PET and MRI. PET can provide information about blood flow and glucose metabolism, as well as about binding properties of specific neurotransmitters and other ligands in the brain, both during resting state and in relation to specific cognitive and emotional tasks. MRI can provide information about brain structures with unsurpassed spatial resolution, utilisable for example to identify changes in volumetric conformations of and small lesions within specific brain regions. In addition, MR-spectroscopy can quantify specific endogenous and exogenous metabolites in the brain, for example N-acetylaspartate as a marker of cellular viability or drug metabolites. Diffusion-based MRI allows, to a certain extent, to quantify microstructural pathologies and, as a more recent lead, to track fibres within the white matter. Functional MRI (fMRI) provides functional information by quantifying local changes in blood oxygenation (the so-called blood oxygenation level-dependent contrast, BOLD), which are strongly related to neural activity.

Neuroimaging techniques allow us to address specific questions regarding structural, metabolic and functional alterations associated with a brain disease. Thereby, the neuroanatomy of mood disorders can be studied from different viewpoints, including the analysis of cross-sectional differences between depressive and healthy subjects, and subjects with other illness or subtypes of mood disorder. The cross-sectional nature of studies is now being increasingly enriched by longitudinal studies, fostered by the non-invasiveness of neuroimaging techniques, allowing to follow brain changes over time and associate them with different aspects of illness. This provides useful information for disease monitoring, the separation between traits and states or between subtypes of a given mood disorder. In addition, longitudinal information that non-invasive neuroimaging can provide is favourable for studies aiming at a better understanding of treatment effects or the prediction of outcome related to treatment.

Challenges to brain imaging in mood disorders

All scientific approaches to mood disorder including neuroimaging face the fundamental challenge imposed by the complexity of the syndromal conformation of symptoms. For instance, the pattern of affective dysregulation is very heterogeneous, varies across different types of a particular mood disorder, changes with the patients' age and the number of disease recurrences and is affected by the patients' personality trait, genetic background and by comorbid psychiatric and physical conditions. In addition, the longitudinal course of mood disorders is typically associated with time-related changes, the most impressing example of which is bipolar illness that is often characterised by dramatic and rapid swings or switches in symptomatology. Furthermore, the course of cognitive and emotional alterations during depression and related disorders is often not even stable across a single day and can greatly vary from the morning to the evening hours. Such co-factors can bias not only identifiable functional mechanisms within specific brain circuits but also structural parameters.

In the functional domain, one should consider that resting state functional neuroimaging studies must be viewed with the perspective of what the definition of a "resting brain" is. The living brain never rests, and differences between patients and healthy controls, for example, in non-task-dependent experimental paradigms may be related to different cognitive and emotional processes, such as rumination, anxieties, sorrow and other activities that a subject may carry out spontaneously and silently during scanning. In addition, task-dependent fMRI and functional PET paradigms typically compare some sort of "activated state" with some more or less well-defined sort of "resting state". Given that the resting-state baseline, to which activated levels are typically related to, will have a great impact upon the measurable task-related amplitude both in haemodynamic and metabolic measures, altered resting-state levels can lead to false-negative and/or -positive inferences of neural phenomena. Furthermore, because the fMRI and perfusion PET signals do not derive from neurons themselves but from their vascular system, any drug that influences the haemodynamics and the neurovascular coupling cascade will change the measured signal. For example, vasodilators such as acetazolamide or carbon dioxide produce a dose-related increase in baseline signal levels and thus a reduction in the BOLD and perfusion signal amplitudes without changing neural activity. In case of psychoactive drugs, an interaction between

neural and haemodynamic influences needs to be assumed. Furthermore, given that mood disorders are often associated with volumetric changes within particular brain circuits, the magnitude of functional task-related responses, including BOLD, blood flow and glucose metabolism, can be affected due to different volumes of the source structures, the so-called partial volume effect.

Brain alterations associated with mood disorders

Probably the most influential functional neuroimaging studies opening the field to a systematic brain imaging approach to mood disorders have originally been reported by Drevets and his colleagues. Using PET, they found increased resting-state blood flow in the medial prefrontal cortex extending to the lateral orbital and ventrolateral prefrontal cortex, as well as in the amygdala [6] and the medial thalamus [7]. In an independent sample of depressed patients they found in addition to their previous results a decreased level of glucose metabolism within the subgenual portion of the anterior cingulate cortex [8]. These functional changes largely overlap in space with brain regions showing altered blood flow in response to self-induced sadness in healthy subjects [9, 10]. However, the majority of neuroimaging studies in mood disorders are based on structural MRI and CT. A large number of studies suggest quite consistently the presence of white matter and periventricular hyperintensities [11–14]. Although some inconsistency exists, there appears to be a tendency of enlargement of the lateral and/or the third ventricles associated with unipolar and bipolar depression [13], which is partly reminiscent of findings in schizophrenia. A comprehensive literature review covering all controlled cross-sectional studies between 1966 and 2002 reveals that the majority of studies found volumetric brain abnormalities in mood disorders, with quite consistent changes in hippocampus and basal ganglia in unipolar depression, and with changes in amygdala and cerebellum in bipolar patients [14]. To some extent, these findings are paralleled by MR-spectroscopic evidence suggesting reduced cell viability in some of these regions [15]. Volumetric changes in prefrontal cortex associated with mood disorders have been found in some [16, 17] but not all studies.

However, although a majority of studies suggests volumetric differences for example in anterior cingulate between patients with unipolar or

bipolar depression, results inconsistent with this evidence need to be carefully considered. A recent study comparing a relatively large sample of patients with familial and non-familial mild unipolar and bipolar depression and healthy control subjects found no volumetric differences in the subgenual prefrontal cortex, neither between the patient groups nor between patients and controls [18]. Whether this apparent inconsistency with previous studies suggesting volume loss in this brain area in familial mood disorder [8, 19] is related to the fact that this study examined patients with only mild degrees of mood disorder remains to be elucidated. Notably, however, most studies compared patients with various forms of depression with healthy age-matched control subjects, rather than with age-matched subjects suffering from other diseases or subtypes of mood disorders. While white matter and periventricular hyperintensities were identified as state- and trait-markers, they were also found to be associated with poor responsiveness to antidepressant treatment [20], however, little is known about the significance of these findings for disease progression or for the identification of subjects at risk. In addition, the exact boundaries to other conditions such as dementia remain to be further elucidated. Although the findings from cross-sectional studies are interesting and promising in generating testable hypotheses, it appears that mainly longitudinal studies are required to better understand morphological changes associated with the various forms of depressive and associated illness [14].

Recent evidence demonstrates that the volume loss in the hippocampus found in cross-sectional studies with untreated patients with depression [21] is progressively associated with the duration of untreated depressive illness [22] and that antidepressant treatment may have a protective effect [22]. Similarly, volumetric studies in depression also suggest an association between the clinical severity of depression and the decrease in prefrontal lobe volumes [23]. For instance, this association is not globally found in the brain and is, for example, not present in the temporal lobe. On the other hand, recent evidence also suggests an association between global gray matter volume and duration of illness in female patients with recurrent depression [24]. Regarding the amygdala, evidence clearly suggests that dysfunction results in signs and symptoms reminiscent of the mood disorder syndrome [25]. For example, electrical stimulation of the amygdala leads to emotional changes often seen in depression such as anxiety, dysphoria and alterations in emotional memory recollection, which are accompanied by increased

secretion of cortisol [26, 27], one of the neuro-endocrine core findings in depression [28].

Trait versus state

A recent fMRI study examined trait- versus state-dependent patterns of brain activity in patients with bipolar disorder [29]. Using a cognitive probe to stimulate the cingulate and ventral prefrontal cortex, the authors found that patients with depressed mood showed exaggerated BOLD responses in the left hemisphere, while patients with elevated mood had blunted responses in the right hemisphere as compared to patients in euthymic state. In addition, all bipolar patients together, compared to healthy control subjects, showed blunted activation in a spatially distinct rostral region in the left ventral prefrontal cortex which was independent of their current mood state. As such, this study suggests the existence of state- and trait-dependent modulation of brain activity in response to a cognitive challenge. Imaging of genetic variation is a field that is just about to emerge and, as outlined below, is yielding results that are highly promising for the future in terms of endophenotyping mood and other complex human disorders [30].

Brain imaging related to treatment

Enlargement of cerebrospinal fluid space, e.g. in the sylvian fissure region, has been reported to predict poor outcome and treatment response in depression [31]. Regional cerebral blood flow and metabolism have been found decreased in the subgenual portion of the anterior cingulate cortex both in bipolar and unipolar depression [8], and hypometabolism in this brain area has been associated with poor response to antidepressant medication [32]. Some evidence also suggests that resting state glucose metabolic rate in major depression after successful antidepressant treatment decreases to normal levels in the subgenual portion of the anterior cingulate cortex and in the left amygdala [33], and that increased emotionally stimulated amygdala responsiveness in depression normalises with successful treatment [34]. However, other studies did not find differences in the response to positive and negative emotional stimuli in the amygdala of patients with major depression and healthy controls, but report reduced task-dependent response in the patients' left lateral prefrontal cortex [35]. Most notable is that the response magnitude to such stimuli before

treatment in the anterior cingulate cortex was positively correlated with clinical outcome after an eight-week treatment with antidepressants. A similar relationship between prefrontal cortex activity and treatment response has been found using sleep deprivation as antidepressant measure. Thereby, pretreatment hypermetabolism in the anterior portion of the anterior cingulate was predictive of the antidepressant response to one night of wakefulness [36]. Furthermore, changes in metabolic rate in the anterior cingulate cortex were associated not only with response to sleep deprivation but also with outcome during antidepressant medication [37]. An interesting new lead offered by MRI is the quantification of fractional anisotropy of diffusion-weighted image sets [38]. This approach allows to a certain degree to delineate the structure of white matter fibres and thus to obtain some measure of connectivity between different brain areas. A recent preliminary study has examined the fractional anisotropy of frontal white matter contributing to frontostriatal connections in depressed patients. Interestingly, treatment response to antidepressants was positively associated with the degree of fractional anisotropy and thus with the integrity of frontal lobe white matter [39].

Neuroimaging of neurochemical systems alterations in mood disorders

The pertinent question whether the specific neurochemical changes in serotonergic, norepinephrinergic and dopaminergic neurotransmission, which are well known to be associated with mood disorders, converge within common or different brain circuitries is a fundamental question that has recently been addressed. In a first glucose metabolism PET study [40] tryptophan depletion, which leads to an overall decrease in the availability of serotonin in the brain and which precipitates depressive relapse in patients successfully treated with serotonin reuptake inhibitors for depression [41], has been shown to produce metabolic decrease in those areas where the most consistent alterations have been described in other imaging studies of depression, including the dorsolateral prefrontal cortex, thalamus and orbitofrontal cortex [40, 42–44]. The metabolic decrease after the serotonin depletion challenge correlated with the change in clinical depressive symptoms. To address the question whether this finding was restricted to dysfunctional serotonergic transmission or generalisable to other neurotransmitter systems, the same authors employed a noradrenaline and dopamine depletion challenge using alpha-

methylparatyrosine in remitted patients treated with norepinephrine reuptake inhibitors [45]. This probe, which had previously been shown to provoke depressive symptoms in patients treated with noradrenergic antidepressants [46], produced metabolic decreases in virtually the same frontal and thalamic brain areas as the serotonin depletion probe did. Together, these studies demonstrate that, independent of the neurochemical system challenged, metabolism within common brain circuitries is affected during symptom provocation in patients successfully treated with antidepressant drugs. An additional finding of these studies was that increased metabolic rates in orbitofrontal cortex, middle frontal gyrus, hippocampus, parahippocampus and amygdala prior to both tryptophan depletion and alpha-methylparatyrosine administration predicted the magnitude of depressive relapse provoked by the challenge [40, 45].

Within the serotonin system in the brain the serotonin 1A receptor subtype has been implicated in the pathophysiology and drug treatment of depression [47]. Recent PET studies show a strong reduction in serotonin 1A receptor subtype binding potential in the midbrain raphe nuclei and in limbic and neocortical areas in the mesiotemporal, occipital and parietal cortex of patients with major depression [48, 49].

Association of neuroimaging with other neurobiological approaches to mood disorders

Depression is often associated with disturbances in sleep regulation, which represents to some degree a functional window to the depressed brain [50]. An interesting and promising lead is to associate brain metabolic alterations and electrophysiological changes of sleep in depression. For example, it was found that that whole-brain absolute metabolic rate during non-rapid-eye-movement sleep is increased in patients with major depression as compared to normal controls [51]. As outlined above, sleep deprivation, a non-pharmacological antidepressant measure, is associated with a normalisation of pretreatment hypermetabolism in prefrontal cortex of depressed patients [36, 37]. This is paralleled by fMRI studies which have shown that sleep deprivation also alters task-dependent functional activity in prefrontal cortex of healthy subjects [52]. Recently, an fMRI study using emotionally valenced visual stimuli, which typically produce an activation within the amygdala, has demonstrated that healthy subjects with a genetic polymorphism in the promoter region of the serotonin transporter gene known to be related with

anxiety traits [53] exhibit an increased amygdala response to such stimuli [54]. Most interestingly, the genetic variations between the studied subjects were not associated with clinical or normal psychological differences, thus suggesting that functional brain imaging can identify genotypes that do not necessarily penetrate and translate into psychological phenotypes. This finding suggests that neuroimaging starts to be useful to study the genetic contribution to complex behaviours as well as to the vulnerability to neuropsychiatric illness [30].

Possible model generalising emotional system alterations in mood disorders

A fundamental question if brain circuits altered in mood disorders are addressed is, which are the emotional disturbances typical of mood disorders that can be associated with specific target structures in the brain. The changes of emotions in mood disorders are complex and can vary strongly across different types and phases of the disease. To delineate generalisable core elements of emotional disturbances in mood disorders, a physiological framework of emotions has recently been proposed, which may help conceptualising testable hypotheses [55]. According to this model, emotion perception can be grouped into three aspects: identification of emotional significance of a stimulus, production of an affective state and emotional behaviour, and regulation of affective states and emotional behaviour. Converging evidence from animal, human lesion and neuroimaging studies suggests that the three aspects of emotion perception can be related to two different mutually interacting neural circuitries, a ventral and a dorsal system. The ventral system includes the amygdala, insula, striatum, prefrontal cortex and the anterior portions of the anterior cingulate cortex. It plays an important role in the identification of the significance of a stimulus and the consequent production of affective states and emotional behaviours. On the other hand, the dorsal system including the hippocampus, more dorsal regions of the cingulate cortex and prefrontal cortex plays a role in the regulation of affective states and emotional behaviour.

This framework may be useful to generate testable hypotheses about the neuroanatomy of mood disorders [56]. Accordingly, the cognitive and emotional disturbances in major depression can broadly be characterised as impairment in executive functioning, including selective attention, planning and effortful regulation of affective states,

and a bias towards negative interpretations associated with the identification of emotional stimuli. On the other hand, in contrast to the restricted emotional range in major depression, the cognitive and emotional disturbances seen in bipolar disorder can broadly be characterised by an inability to regulate mood states, including irritability, distractibility and emotional lability. Structural changes paralleling the psychological disturbances in major depression, according to a series of studies, include volume reduction in the amygdala and the ventral striatum, the anterior cingulate cortex, prefrontal cortex regions and hippocampus. Functionally, these changes are associated with an increase in resting blood flow and metabolism in the amygdala, insula, striatum and thalamus and an increased responsiveness to emotional stimuli in these regions, as well as with increased metabolism in anterior cingulate and ventrolateral prefrontal cortex, and with decreased metabolism in dorsomedial and dorsolateral prefrontal cortex. In bipolar depression, a differential pattern of changes emerges, including increased volumes in amygdala and caudate nucleus, and decreased cortical volumes in anterior cingulate and prefrontal cortex, which are paralleled by neuropathological post-mortem findings [57–59]. In addition, resting [60] and stimulated (with aversive stimuli [61]) metabolic rates in different prefrontal cortex regions are reduced in bipolar depression.

However, although this model [56] offers a framework to formulate experimental predictions, which is clearly needed to design more broadly comparable studies, some of the assumed underlying evidence is not unequivocal. For example, the direction of reported volume change in the amygdala of unipolar depression is inconsistent, with some studies reporting smaller [62] and other studies reporting enlarged [63, 64] or unchanged [65, 66] amygdala volumes. However, within the population of patients with depression volume decrease in amygdala and hippocampus appears to be associated with the severity of clinical symptomatology [66] and magnitude in dysregulation of the hypothalamic-pituitary adrenocortical system [67], which in turn is central for the pathophysiology of mood disorders and drug action [28].

Concluding remarks

Neuroimaging in mood and other psychiatric disorders is an exciting area of research with a bright future. The accumulating database on the functional and structural neuroanatomy of mood disorders provided by existing and emerging neuro-

imaging techniques, in combination with other neurobiological and psychological approaches, will ultimately lead to a better understanding of the pathophysiology, which is a precondition of the development of more efficient and individually tailor-made treatment options.

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