Neuroimaging and the Pathophysiology and Treatment of Depression: Recent Advances and Future Needs

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Abstract

Imaging the human brain still cannot be considered a clinical tool in the field of psychiatry and currently (early 2010) does not contribute directly to the alleviation of patient suffering. However, recent years have witnessed a rapid increase in the number of studies moving us closer to this goal through incorporating neuroimaging techniques into studies of treatment mechanism and prediction of treatment response and those studies taking genotype into account. In addition, the range of neuroimaging modalities and outcome parameters in use, to index abnormalities of the brain, continues to expand and technical developments in the quality of derived parameters and images confer ever increasing levels of sensitivity. Disease models of depression currently include early- and later-life stress including immigration, genetic loading or liability, neurotransmitter system abnormalities, and structural and physiological perturbations that interfere with brain function. It is now indisputable that imaging of the brain has contributed profoundly to the development of the latter 3 models. However, despite these advances in our understanding of depression, imaging has not yet affected clinical monitoring or treatment practices, presaged treatment response, or ultimately affected outcome for patients today. This chapter endeavours to highlight the latest imaging findings that demonstrate the potential to achieve such goals in the near future.

The Pathophysiology of Depression: Imaging Studies

The Molecular and Neurochemical Pathophysiology of Depression

Molecular and neurochemical studies have used single photon emission tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS) techniques in depressed populations to examine receptors, transporters,
enzymes, neurotransmitter concentrations and storage capacities, markers of neuronal membrane turnover and integrity, metabolic turnover, pharmacokinetic characteristics of drugs such as lithium and drug occupancy rates. To date these studies have revealed the dysfunctional involvement of several neurotransmitter systems in depression. In addition to assessing target binding, studies in depression have assessed the rate of uptake of serotonin (5-HT, L-[11C]5-HTP) and dopamine ([11C]L-dopa), and 5-HT synthesis (α-[11C]MTrp), estimated dopamine storage capacity ([11C]raclopride), and have assessed 5-HT and dopamine involvement using depletion studies. Norepinephrine lacks such radioligand availability but has been investigated using less direct methods including pharmacological challenge during assessment of cerebral blood flow. Based on evidence for disruption in each of these 3 monoamine neurotransmitter systems, it will be important to assess the involvement of vesicular monoamine transporters in depression ([11C]dihydrotetrabenazine). We are currently unable to assess numerous further targets of interest such as the norepinephrine transporter as efforts are still underway to develop suitable radioligands. The latter step is a significant challenge to the field and the quality of the PET images and data produced for a given target molecule are vitally dependent on the selectivity and specificity of the radioligand developed among other factors [1].

In major depressive disorder (MDD), brain 5-HT uptake and synthesis in frontal, temporal and cingulate cortices are reduced, while its metabolism by monoamine oxidase A is elevated. In addition, the levels of the 5-HT transporter, which removes 5-HT from the intrasynaptic space, reducing signalling, has also been reported to be elevated [2–5], though not consistently [6, 7]. Reduced somatodendritic and postsynaptic 5-HT_{1A} and 5-HT_{2} receptors have been reported in orbitofrontal and anterior insular cortices, and in the hippocampus in older depressed subjects. However, elevated levels of 5-HT_{2} receptors have been associated with MDD involving severely pessimistic or dysfunctional attitudes [8] and were positively related to measures of these characteristics among patients. On the whole, these data support the depressed mood state being associated either with (1) abnormalities that are compensatory in nature and in response to acutely elevated 5-HT concentrations, perhaps as a result of stressful events, or (2) abnormalities that are etiological in nature, that result in reduced 5-HT neurotransmission thereby causing depressive signs and symptoms. However, discerning which or what combination of these abnormalities of the 5-HT system is playing a causative role is probably the greatest challenge currently to progressing our understanding of the pathophysiology of the serotonergic system in depression.

The dopamine system has been explored using PET to examine its synthesis ([18F]fluoro-L-dopa), release ([11C]raclopride, [18F]fallypride), the effects of dopamine depletion (α-methyl-p-tyrosine), D\textsubscript{1} receptor ([11C]SCH-23390, [11C]NNC) and D\textsubscript{2} receptor ([11C]FLB-457, [18F]fallypride) binding, and clearance capacity ([11C]RTI-32, [123I]βCIT). Dopamine synthesis or [18F]dopa uptake rate (K\textsubscript{s}) was reduced across the blood-brain barrier as well as in the striatum in depression with affective
flattening and psychomotor retardation and in the anterior cingulum and hypothal-
amus in those who were impulsive. These data implicate distinct dopaminergic sig-
nalling systems underlying different depressive phenotypes. $[^{11}C]hRaclopride$ binds
to striatal D$_{2/3}$ receptors and is sensitive to competition from the release of endog-
enous dopamine. $[^{11}C]hRaclopride$ binding was higher in the putamen during depre-
sion associated with psychomotor retardation in medication-free subjects relative
to healthy controls suggesting lower dopamine concentrations but not in a study
involving MDD in which just 36% of subjects presented with psychomotor retarda-
tion. Extrastriatal D$_{2/3}$ receptor binding ($[^{11}C]hFLB-457$), on the other hand, did not
differ in a small sample of individuals with MDD (n = 7) and 7 healthy controls.
Consistent with the possibility of reduced dopamine levels during depression, dop-
amine depletion studies using a-methyl-$p$-tyrosine induce depressive symptoms and
several antidepressants raise dopamine concentrations. Dopamine transporter levels
assessed using PET and $[^{11}C]hRTI-32$ in the striatum were reduced during depres-
sion potentially indicating a reduced capacity for dopamine clearance in select brain
regions. Finally, D$_1$ and D$_2$ receptors are reduced in the striatum in MDD subjects
exhibiting motor retardation, while no difference was detected in D$_2$ receptor levels
in extrastriatal regions. Clearly, perturbation of striatal dopaminergic neurotransmis-
sion is more pronounced in those depressed subjects also experiencing psychomotor
symptoms than other subpopulations.

Other neurotransmitter systems have been less extensively investigated in MDD
using imaging techniques. Widespread reduction in cholinergic muscarinic 2 autore-
ceptor levels, most pronounced in the cingulate cortices in depression, is associated
with bipolar disorder but not MDD [9]. Decreased levels of histamine 1 receptor have
additionally been detected and related negatively to the severity of depressive symptoms
[10]. Finally, in individuals who did not meet criteria for a depressive or anxiety disor-
der or mild cognitive impairment, subsyndromal depression and anxiety scores were
related to amyloid senile plaques and tau neurofibrillary tangle binding in the medial
temporal cortex, and in the medial temporal and frontal cortices, respectively [11].

Several recent advances in molecular imaging in particular should help progress
our understanding of the pathophysiology of depression. The resolution available
to PET studies has been superseded by the development of high-resolution research
tomography (HRRT) [12]. The HRRT can achieve a resolution of 2.5–3 mm com-
pared to a PET scanner which gives 6–7 mm. This will permit more accurate quanti-
fication of molecular target binding in smaller brain regions than previously possible.
The increased resolution also confers more sensitivity in the form of greater statisti-
cal quality of PET data and the detection of smaller biological signals, and increased
power when comparing a control and patient population thus reducing the number
of participants necessary.

Perhaps most frequently investigated in MDD using $[^{1}H]hMRS$ (for reviews,
see Ende et al. [13] and Dager et al. [14]) are the concentrations of glutamate and
$\gamma$-aminobutyric acid (GABA) or the Glx peak comprising glutamate, glutamine and
GABA. In depression, the concentration of glutamate assessed using MRS has been reported to be reduced in the cingulate and prefrontal cortices and temporal lobe. However, this signal is contributed to by the total pool of glutamate in the human brain (approx. 9 mm) and only a small proportion of that signal will represent intra-synaptic glutamate. Interpretation of the impact of such a deficit in depression is therefore multifaceted and non-specific. Lower GABA concentrations have been detected in the occipital cortex in both depressed and unmedicated remitted MDD subjects, and more recently with the advent of technical advances in MRS in dorsomedial/dorsoanterolateral areas of the prefrontal cortex in depressed subjects with MDD. The latter is consistent with glial cell abnormalities detected in these prefrontal regions using post-mortem based techniques. GABA\(_A\) receptors have additionally been reported to be reduced in bilateral parahippocampal and lateral temporal regions in depressed MDD outpatients using PET and \([^{11}C]\)flumazenil with an inverse relationship to the hypothalamic-pituitary-adrenal axis activity (dexamethasone suppression corticotrophin-releasing hormone test) suggesting that a contribution of reduced GABAergic signalling in hypothalamic-pituitary-adrenal axis hyperactivity is associated with MDD. Early studies detected no difference in GABA\(_A\) receptor binding between MDD and healthy groups; however, these were performed at a reduced resolution using SPECT and \([^{123}I]\)iomezenil.

Reduced neuronal integrity (N-acetyl aspartate, \([^{1}H]\)MRS) has been detected in some but not all studies examining depressed subjects. No change in N-acetyl aspartate/creatine ratio, inositol/creatine ratio or choline/creatine ratio was observed, for instance, in the dorsolateral prefrontal cortex in drug-naïve females during their first episode of depression. Reports on choline levels are mixed with elevations, reductions and no differences reported. \([^{31}P]\)MRS studies in depression have identified reduced brain energy metabolism and pH in depressed, manic and euthymic states in bipolar disorder potentially implicating mitochondrial dysfunction, and state-specific abnormalities in phospholipid membranes including reduced phosphocreatine levels during depression.

MRS, first used clinically in the early 1980s, in general has a trade-off between spatial and temporal resolution that has been rapidly advancing through the increased field strengths, coil sensitivity and spectral analysis methods including proton editing methods to decipher peaks such as the Glx peak into its glutamate, glutamine and GABA components. Hyperpolarizing carbon-13 confers a 10,000-fold increase in the signal over conventional nuclear magnetic resonance and is currently used to label pyruvate to study metabolism. Efforts are currently focusing on extending this to other suitable agents such as bicarbonate, which permits measurement of pH distribution, and hyperpolarized carbon-13 may in the future permit measurement of metabolic flux rates relevant to psychiatric disorders. Ultimately, these advances should permit further enhancement of the signal/noise ratio and permit more spatially refined voxels to be investigated and should provide more anatomically localized information regarding the metabolic abnormalities associated with depression to date.
Structural anatomical abnormalities associated with depression have been examined in vivo for several more decades than molecular aspects, using computerized tomography (CT) and magnetic resonance imaging (MRI) with a continuing linear trend in the improvement in resolution capabilities. Grey and white matter concentrations are examined most commonly and using structural MR images such as the \( T_1 \)-weighted image. Computational neuroanatomy techniques employed for these purposes include the region-of-interest approach and voxel-based morphometry. While region-of-interest-based studies are confined to regions that can be reliably delineated visually, voxel-based approaches have enabled whole-brain analyses albeit with some limitations such as the sensitivity to registration accuracy. Less widely used techniques include cortical or surface mapping to examine curvature and thickness, and deformation-based and tensor-based morphometry. In the case of depression, the structural pathology has proved subtle in magnitude relative to neurological disorders, and in the case of several structures has proved elusive to consistent replication.

Of the many studies comparing grey and white matter concentration between depressive disorder and healthy control groups, the most consistent findings are those reporting enlarged ventricle size mostly of the third and lateral ventricles. However, the latter has largely been derived from studies in elderly and chronically depressed late-onset populations and has not been replicated unanimously. The aetiology of ventriculomegaly is poorly understood but has been suggested to be related to tissue loss in adjacent structures, cerebrovascular disease, and other structural anomalies that may lead to accumulation of cerebrospinal fluid. White matter hyperintensities additionally have commonly been associated with MDD [15] and bipolar disorder [16]. A variety of types of evidence have since emerged that suggest that depression is associated with white matter pathology, including post-mortem, genetic association, structural magnetic resonance, and most recently diffusion-weighted imaging (DWI) studies. However, white matter hyperintensities are a particularly non-specific phenomenon, and are present in almost all individuals by the age of 85 [17]. The incidence of deep frontal and basal ganglia white matter hyperintensities is increased in MDD and bipolar disorder with a late age of onset of depression. On an MR image, a white matter hyperintensity represents an encapsulated area of water, which can result from demyelination, astrogliosis, neuropil atrophy, or ischaemia due to local vesicular pathology among other cerebrovascular risk factors. The clinical implications of white matter hyperintensities are currently unclear, but will vary with the spatial extent of the lesion and the functional specialization of the affected fibres. Functionally, poorer performance on the Stroop test has been linked to an increased frequency of white matter lesions [18]. White matter hyperintensities have regularly been reported in the medial temporal [19] and deep frontal white matter, areas that connect the hippocampus and amygdala to the frontal cortex. White matter abnormalities are now more widely examined in depression using DWI. Sulcal widening
has also been associated with depression and total cerebral volume appears to be conserved, unlike in schizophrenia. On the other hand, numerous reports of local grey matter concentration abnormalities have been associated with depressive disorders with varying degrees of consistency.

In MDD, morphometric studies examining the hippocampus have generally converged to support the degenerative model of depression showing reduced volume in adults. However, these studies include mostly elderly, middle-aged or chronically ill populations and several studies failed to replicate this finding (for a review, see Savitz and Drevets [20]). Overall, the literature suggests that the volume of the basal ganglia structures (caudate, putamen, globus pallidus, subthalamic nuclei and substantia nigra) may not be altered in MDD or bipolar disorder, although a reduced volume has been associated with late-onset MDD and chronic or severe illness. Subgenual anterior cingulate cortex involvement in depression has recently been reviewed [21]. Recent reviews [20, 22] and meta-analyses [23] are available in the extensive body of literature studying morphometric changes associated with depression. Most recently, Savitz and Drevets [20] provided an up-to-date and comprehensive review of grey and white matter morphometric studies in MDD and bipolar disorder. Across this large body of literature, there is an indication of a divide between the abnormalities observed in the elderly, adults and children with depression, and between early- and late-onset subgroups. Further factors that currently inhibit comparison across these studies include medication status, mood state, disease heterogeneity, methodology employed and genotype (rarely explicitly examined; see section ‘Combining neuroimaging and genotyping in the study of depression’). Evidence is mounting for the role of each of these factors in complicating the interpretation of structural MR studies.

While grey matter structural abnormalities are most commonly studied using T1- or T2-weighted MR acquisition sequences that produce greyscale images with good grey-white matter contrast, the contrast within the white matter in these images is poor. In order to study the microstructural organization of white matter, MR images weighted to be sensitive to diffusion (Brownian motion, DWI) of water molecules have proven highly informative [24]. In particular, DWI data obtained across multiple gradient directions capture the rate of diffusion (eigenvalues, $\lambda_1$, $\lambda_2$ and $\lambda_3$) along 3 principal directions (eigenvectors, $v_1$, $v_2$ and $v_3$) in the case of diffusion tensor imaging (DTI). Images of the apparent diffusivity coefficient (or mean diffusivity) represent the average of the values of 3 eigenvalues $(\lambda_1 + \lambda_2 + \lambda_3)/3$ per voxel. Fractional anisotropy maps, on the other hand, are weighted towards $\lambda_1$, the principal diffusion direction, therefore providing more information about the organization or coherence in the direction in which diffusion is greatest. Diffusion in white matter fibres is greatest parallel to the fibre $(\lambda_1)$ and impeded by the axonal wall and myelin sheath in the directions perpendicular to the fibre $(\lambda_2$ and $\lambda_3$). As a result, fractional anisotropy is expected to be impaired in regions where the microstructural organization of bundles of white matter fibres is altered either through increased radial diffusivity or reduced axial or longitudinal diffusivity. Increased radial diffusivity has been suggested to...
result from a loss of myelin sheath integrity along the axon, consistent with evidence of macromolecule loss (thought to primarily reflect loss of myelin) detected in depression using magnetization transfer imaging. Fractional anisotropy maps have been analysed using a voxel-based approach, region-of-interest analyses, tract-based spatial statistics and most recently by comparing fractional anisotropy for tracts derived following a range of tractography procedures under rapid development.

In MDD during depression, reduced fractional anisotropy has been detected in the sagittal stratum, cingulate cortex and the posterior body of the corpus callosum, the anterior limb of the internal capsule, and the superior longitudinal fasciculus, and no difference has been reported in the brainstem relative to non-depressed controls. Reduced fractional anisotropy was additionally associated with depression in an older population (mean age 70) relative to remitted age-matched MDD subjects, in the anterior and posterior cingulate cortices, genu of the corpus callosum, parahippocampal gyrus, insula, neostriatum, temporal and parietal regions, dorsolateral prefrontal cortex and midbrain. During depression associated with bipolar disorder, the white matter tract that mediates signalling between the subgenual cingulate and amygdala-hippocampal complex has been implicated as have the frontal cortex, the internal capsule, cingulum, longitudinal fasciculi, uncinate fasciculi and optic and anterior-thalamic radiations and the genu of the corpus callosum. The latter is consistent with the increase in white matter hyperintensities detected in the corpus callosum in bipolar disorder. Some of the inconsistencies observed in this literature to date are likely to be due to the widely varying analysis methods employed and to variation in the medications involved at the time of scanning across studies. For instance, fractional anisotropy in the genu of the corpus callosum has been reported to be 6–7% greater in two studies [25, 26] but reduced in a separate study [27]. Deciphering which abnormalities are specific to the pathophysiology of disease versus medication effects will significantly advance our understanding of the white matter abnormalities that underlie the neurobiological basis of affective illnesses.

White matter fibre bundles contain myelinated neuronal axons and glial cells. The myelinated axons connect grey matter regions and are integral to neuronal communication between grey matter regions. Post-mortem studies in mood disorders may inform these in vivo findings, which may be associated with reductions in markers of astrocytes reported in the frontal cortex, for example, or the observed reductions in the density of oligodendroglia in BA9 and apoptotic and necrotic changes in satellite oligodendroglia in BA10 in the caudate nucleus. Glial cells and neurons have a well-established reciprocal relationship that underlies their mutual development, proliferation and functioning. This is achieved via neurotrophic factors and cytokines synthesized and released by astrocytes and microglia which include brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor, and nerve growth factor. Glial-derived neurotrophic factor functions to promote synaptic plasticity and BDNF plays a role in differentiation and growth of new neurons and synapses. This role of glial cells in providing energy and trophic factors to neurons suggests that
altered white matter could feasibly contribute to the consistently reported changes in activation in response to emotional stimuli and abnormal volume of grey matter structures detected in depression. With the advent of in vivo neuroimaging-based evidence for glial dysfunction in depression using DWI, such PET radiotracers as those developed to measure glial metabolism may become more relevant for application in depressive disorders [28].

It is clear that MDD-associated morphometric abnormalities alone are not and may never be diagnostically useful. Rather their potential may more readily be realized in prediction of treatment response and monitoring of illness course (see section ‘Neuroimaging and the treatment of depression’) and/or upon re-examination taking sample genetic homogeneity into account (see section ‘Combining neuroimaging and genotyping in the study of depression’).

The Functional Pathophysiology of Depression

Functional imaging has provided a myriad of information on the pathophysiology and regional localization of functional disturbances both at rest and in emotion-related tasks during various mood states. Imaging outcome measures contributing to these data range from cerebral blood flow ([15O]H2O) and glucose metabolism ([18F]FDG), to MRI to assess blood flow (perfusion or arterial spin labelling MRI), and activation and deactivation [blood oxygen level-dependent (BOLD) signal]. Additionally, MRI has been combined with pharmacological challenge to probe the role of neurotransmitter systems in cognition and/or drug actions. Less commonly used methods employed to study the functional pathophysiology of depression that are spatially restricted to the surface but provide excellent temporal resolution include assessing electrical activity directly (electroencephalography, EEG), the magnetic fields produced by electrical brain activity (magnetoencephalography, MEG), and surface haemoglobin levels as an indicator of activation (near-infrared spectroscopy).

By far, the most commonly applied of these to date is BOLD functional MRI (for reviews, see Sava and Yurgelun-Todd [29] and Bandettini [30]). In general, elevated activity in the amygdala has been associated with depression in response to negatively valenced stimuli [20] and is most likely to relate to altered mood or affect regulation, in particular in response to aversive stimuli or stressors during depression associated with MDD. Considerably fewer studies exist and they disagree on a functional role for the hippocampus in depression with recovery being associated with increased and reduced metabolism. Thus, it is currently difficult to understand exactly how hippocampal pathophysiology relates to the signs and symptoms in MDD; however, they are likely to play a role in the deficits identified in MDD in emotion-related memory and executive function [31]. Reduced blood flow and metabolism in the caudate nuclei and putamen during depression associated with MDD is well replicated