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Neuroimaging Approaches in Mood Disorders: Technique and Clinical Implications

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Background. *Clinical research in mood disorders increasingly involves advanced neuroimaging techniques. The encompassing aim of this review is to provide the mental health care practitioner with a pragmatic understanding of neuroimaging approaches and their possible clinical application.*
Methods. *We conducted a literature search of English-language articles using the search terms, major depressive disorder and bipolar disorder, cross-referenced with available neuroimaging technologies and analytical approaches, The search was supplemented with a manual review of relevant references. We organize the review by reviewing frequently asked questions on the topic of neuroimaging by mental health-care providers.*
Results. *Magnetic resonance (MR) approaches provide information on white and gray matter pathology (segmentation), cellular metabolism (MRS), oxygen consumption (BOLD), and neurocircuitry (DTI). Radionuclide-based neuroimaging methodologies provide quantitative estimates of brain glucose metabolism, regional blood flow, and ligand-receptor/transporter binding. Clinical implications of neuroimaging methodologies are reviewed.*
Conclusions. *Advances in neuroimaging technology have refined models of disease pathophysiology in mood disorders and the mechanistic basis of antidepressant action. Multivariate analysis of functional and structural neuroimaging data, longitudinal analysis in the depressed and remitted states, and inclusion of representative patients with medical and psychiatric comorbidities will enhance the clinical translation of future research findings.*

Keywords Neuroimaging, MRI, PET, SPECT, DTI, VBM, MRS, Antidepressant, Antipsychotic, Major depressive disorder, Bipolar disorder

INTRODUCTION

Mood disorders are highly prevalent, chronic medical disorders largely diagnosed and treated in primary-care settings (1). Currently, mood disorders are a leading cause of disability globally and an important risk factor for the development of major medical disorders such as coronary artery disease (CAD) (2,3). The development of more effective therapeutic regimens for major depressive disorder has been identified as a national health priority in the United States and elsewhere (4).

Mood disorders are complex conditions of multifactorial etiology. Regional alterations in regional brain structure and function, as indexed by neuroimaging abnormalities, are hypothesized to subserve the symptomatic expression of mood

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disorders (5–10). Refining the pathophysiological model of mood disorders may provide novel (preferably disease modifying), treatment approaches. For example, deep brain stimulation (DBS) arises from a hypothesis that anterior limbic networks are awry in mood disorders (11).

The role of neuroimaging in the diagnosis and treatment selection in mood disorders is currently limited to secondary mood disorders (e.g., mood disorders secondary to organic brain syndrome) (12). Nevertheless, it remains uncertain how neuroimaging approaches may inform the diagnostic process or treatment decisions in individuals with primary mood disorders (i.e., major depressive disorder, bipolar disorder).

The encompassing aim of this review is to provide the mental health care practitioner with a pragmatic understanding of neuroimaging approaches and their possible clinical application. Toward this aim, we review frequently asked questions on the topic of neuroimaging by mental health-care providers.

METHODS

We conducted a literature search of English-language articles published between January 1964 and September 2006. The search terms were major depressive disorder, and bipolar disorder cross-referenced with functional magnetic resonance imaging (fMRI), single-photon-emission computed tomography (SPECT), computerized tomography (CT), positron emission tomography (PET), voxel-based morphometry (VBM), region of interest (ROI), blood-oxygen-level-dependent (BOLD), glucose metabolism, statistical parametric mapping (SPM), magnetic resonance spectroscopy (MRS), and diffusion-tensor imaging (DTI). The search was supplemented with a manual review of relevant references. Articles selected for inclusion were determined by author consensus. The authors organize the review by reviewing frequently asked questions on the topic of neuroimaging by mental health-care providers.

Evaluating the Hypothesis: Are Mood Disorders Associated with Quantifiable Changes in Global or Regional Neuroanatomy?

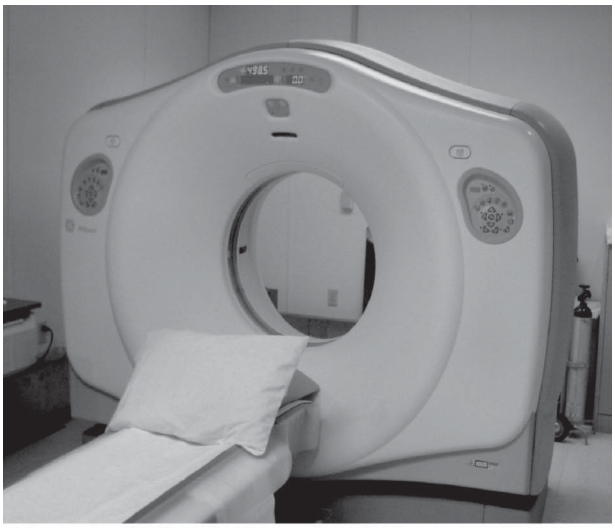
Volumetric investigations evaluating patients with mood disorders have consistently identified several anatomical abnormalities in brain neurocircuits that putatively subserve affect regulation and emotional expression (13). The advent of computed tomography (CT) allowed researchers to quantitatively document volumetric and morphological (i.e., variations in shape) changes in brain structures. Increased ventricular size, ventricular-brain ratios, and smaller cerebellar volumes (14,15) were reported in bipolar subjects with CT imaging.

The advance offered by computed tomography (CT) versus conventional radiological techniques was largely due to improved spatial resolution (2-dimensional x-rays) and accessibility to deep brain structures (e.g., basal ganglia). Methodologically, the CT scanner contains a rotating gantry equipped with an x-ray tube and arc-shaped detector encircling the patient (Figure 1a). For each complete rotation, a thin section (slice) of brain structure is acquired. Successive sections are later reconstructed by a dedicated computer into two-dimensional representations of the scanned region with a resolution approaching 2 × 2 mm (15,16).

The major limitations of CT technology included exposure to ionizing radiation, spatial resolution, and a reduced sensitivity to distinguish white and gray matter (17). For example, a human subject is capable of receiving 3 röntgen equivalents in men (rem) per single administration and 5 rem per year (2–4 CT scans) (18). Over the past decade, computed tomography (CT) approaches have been largely supplanted by magnetic resonance imaging (MRI) as the structural neuroimaging modality of choice on the grounds of improved operating characteristics and safety indices (19).

Magnetic resonance imaging (MRI) is based on the principle that differential magnetic properties exist amongst hydrogen

a)



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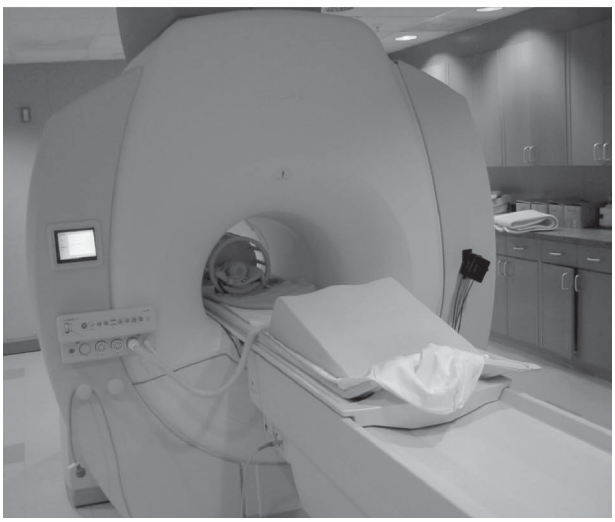

Figure 1 Structural Imaging Apparatus (a) CT Scanner (b) MRI Scanner.

atoms across different biological tissues (20) (Figure 1b). Current MRI techniques offer a spatial resolution exceeding 1 mm^3 affording the possibility of visualizing and quantifying smaller brain structures. Additional advantages over CT include the absence of ionizing radiation, and with three-dimensional MRI acquisition technology, the opportunity for more refined perspective of brain regions of interest (21). A limitation however, of MRI is the elucidation of anatomical boundaries of brain regions that are not well circumscribed (e.g., lateral thalamus) (13).

Disparate abnormalities have been reported in subjects with mood disorders evaluated with volumetric neuroimaging technique (13,15,22). Preliminarily volumetric differences in subcortical regions have been reported between MDD and BD (13,15). For example, relative reduction (versus healthy controls) in basal ganglia volume are reported in MDD subgroups (23–29), while increased striatal volumes have been reported in BD populations (30–33). Decreased prefrontal cortex volumes, on the other hand, have been reported in both BD and MDD cohorts (34,35).

The majority of investigators have report decreased hippocampal volume in MDD populations (36–48). Two independent meta-analyses provide further corroborative evidence, concluding that the pooled effect size of hippocampal volume loss is significant in both hemispheres for subjects with MDD (49,50).

By contrast, there is less support altered hippocampal volume in BD. Only four investigations in the last two decades (51–54) while others have failed to find a smaller hippocampus in BD (31,32,52,55–66).

Using a meta-regression analysis, it was further determined that the total number of depressive episodes significantly correlated with decreases in right hippocampal volume in subjects with MDD (36). Other analyses have also revealed a significant logarithmic association between illness duration and hippocampal volume (49,50). These results suggest that repeated glucocorticoid-mediated stress during recurrent depressive episodes may result in cumulative hippocampal injury as reflected in volume loss (67).

On the other hand, the thalamus has been a region of particular interest in BD as it is an integral component of the dysfunctional limbic-cortical-striatal-pallidal-thalamic circuit. Investigations evaluating thalamic volumes in BD have reported larger (31,68), smaller (69–72), and unchanged (53,57,63,73–75) thalami compared to healthy control groups. This heterogeneity in observations may be partially accounted for by the technical limitations of MRI in the delineation of the lateral edge of this structure (13).

Limitations of MRI include the incompatibility of the procedure with intra-cranial or intra-abdominal metallic implants, devices, clips, and other monitoring equipment (e.g., pacemaker) (76,77). Moreover, the single unit of MRI resolution (1 mm^3) encompasses a large cell number (>10,000 neurons) rendering the detection of a smaller, yet clinically significant, cellular loss difficult.

Evaluating the Hypothesis: Are Mood Disorders Associated with Changes in Brain Function?

In contradistinctions to structural neuroimaging techniques, functional neuroimaging offers a dynamic composite of brain activity in contrast to the static snapshot of neuroanatomy afforded by volumetric investigations. Broadly speaking, brain function can be evaluated at the regional level through blood perfusion analyses, at the cellular level through indices of metabolism, and at the intracellular level through ligand-occupancy studies. A constellation of perfusion, metabolic, and cell-surface abnormalities have been documented in limbic and prefrontal structures in mood disorders with radionuclide-based (PET, SPECT) and magnet-based (fMRI) neuroimaging techniques.

In a recent meta-analysis of 55 investigations of emotional processing in healthy subjects, Phan et al. divided the brain into 20 non-overlapping regions, and characterized each region by its responsiveness across individual emotions and to different stimuli presentation techniques. According to the mood induction paradigm employed, different brain regions were activated; occipital cortex and the amygdala for visual stimuli and anterior cingulate and insula for emotional recall (78). The investigators concluded that while the medial prefrontal cortex had a general role in emotional processing fear activated the amygdala, while sadness was associated activation of the subcallosal cingulate. The subcallosal cingulate corresponds to Brodmann area 25 (BA 25), the anatomical target of deep brain stimulation for treatment resistant depression (11).

It has been proposed that affective processing, a core dysfunction in mood disorders, is modulated by the intersection of two neural systems: a ventral and a dorsal system (79). The amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate and prefrontal cortex comprise the ventral system which identifies the emotional significance of environmental stimuli, prepares subsequent affective states, and regulates appropriate autonomic responses (80). The effortful, or conscious, regulation of affective states is accomplished by the dorsal system (hippocampus and dorsal regions of the anterior cingulate and prefrontal cortex). Affective processing is further influenced by other brain circuits that are responsible for executive function, selective attention, and future planning (79).

Hyperactivity in the amygdala, subgenual cingulate, ventral striatum, and prefrontal cortex in BD may subserve an oversensitive but dysfunctional system in the identification of emotional significance and the production of affective states. Alteration in the aforementioned dorsal system may also impair the effortful regulation of emotional behavior. In contrast to the lowered threshold in the attachment of emotional salience and production of affective states in BD, subjects with MDD may experience an increased tendency to identify stimuli as emotional and experience affective states, but within a predominantly negative context. Decreased activity in the dorsal components may be

responsible for the associated impairments in executive function and effortful regulation of affective processing (79,81).

Radionuclide Neuroimaging Techniques: Metabolism and Blood Flow

The localization of an injected radioactive neurotransmitter-derivative serves as the mechanisms by which PET and SPECT produce three-dimensional images of the brain. With PET, these synthetic ligands are labeled with a rapidly decaying radioactive atom, usually Carbon-11, Fluorine-18, Oxygen-15, or Nitrogen-13. Single-photon emission computerized tomography (SPECT) is a technique similar to PET, with radioactive nuclei that have a longer half-life than those used in PET, and emit *single*, instead of double, gamma rays (Xenon-133, Technetium-99, Iodine-123) (82).

A subject, in the supine position, is injected with a radioactive tracer that incrementally progresses through the PET or SPECT camera. A gamma ray detector array captures the gamma rays that are produced at the collision site between a positron emitted from the radioactive substance and an electron in the tissue (in PET), or directly from the radionuclide (in the case of SPECT). As in CT scanning, the process is repeated, producing a series of two-dimensional thin slices of the brain that are later converted to a three-dimensional representation.

Although, SPECT is relatively less expensive than PET, its sensitivity and spatial resolution are inferior. A pragmatic advantage of SPECT scanners is that they do not require juxtaposition to a particle accelerator center. Analysis of regional blood flow with SPECT has generally been replaced by ^{15}O-H_2O-PET or functional MRI (see below). Early investigations employing SPECT technology analyses reported correlations between depression severity and frontal hypoactivity in depressed subjects (83).

Positron emission tomography can provide data on blood flow (i.e., hypo/hyperperfusions) or other biochemical functions, depending on the identity of the radioactively tagged molecule. Group differences in neuronal glucose metabolism can be evaluated via injection of a fluorine-tagged, non-hydrolyzable form of glucose, ^{18}F-2-fluoro-2-deoxyglucose (FDG) to depressed and non-depressed cohorts. Early FDG investigations in mood disorder subjects examined brain activity with a basic neuropsychological attention task (84–86). Although challenge studies utilizing blood flow as an outcome measure have greater temporal sensitivity, FDG has the advantage of being decoupled from the direct effects of pharmacological agents on cerebral circulation (87).

Decreased regional cerebral metabolic glucose rates in the prefrontal cortex (PFC) of depressed subjects have been a consistent finding in mood disorders, although relative hypermetabolism in distinct regions of the PFC has also been reported (88–93). Preclinical animal models and case reports also implicate PFC dysfunction with impairments in emotional perception and experience (94,95).

The subgenual region of the anterior cingulate cortex has been associated with hypoactivity relative to healthy controls (34,96), although if this is corrected for reduction in grey matter volume (97), the actual metabolic activity may be elevated, as opposed to reduced (5). This interpretation is also consistent with a coupling between metabolic activity in the subgenual ACC and depression severity (93,98). Available evidence suggests that metabolic hyperactivity in the amygdala may be also be a state-dependent phenomenon (99,100). Differential metabolism in the pregenual, or rostral, anterior cingulate may predict response to various modalities of antidepressant treatment (7,101).

Radioactively labeled water (^{15}O-H_2O) provides an elegant technique for evaluating regional brain differences in cerebral blood flow (CBF). The relatively short half-life of ^{15}O (~2 min) provides an opportunity to administer a new bolus every 12–15 minutes and to acquire a new snapshot of blood flow within the same scanning session. Soon after the tracer enters the smaller vessels in the brain, data acquisition can begin and usually lasts 60–90 seconds. The acquisition of multiple data points during a single scanning session allows the possibility of provocation paradigms, and the exposition of aberrant neurocircuitry underlying dysfunctional attitudes that may not be apparent under resting baseline conditions.

Changes in glucose metabolism and blood flow comprise an aggregate of chemical and hemodynamic processes involved in neural activity putatively representing the neurobiological signature of terminal field synaptic transmission. In a representative provocation paradigm, changes in CBF or glucose metabolism data acquired during the execution of a neuropsychological task are compared with images obtained within the subject during a control condition. Regional increases in CBF or glucose metabolism are conceptualized as a proxy of increased synaptic transmission (5).

Test-retest investigations suggest that relative hypometabolism normalizes with effective antidepressant treatment in a patient's self-reported mood. Major depressive disorder has also been associated with abnormal activation of key limbic and paralimbic structures, including regionally distinct frontal and temporal lobes, the amygdala-hippocampus complex, and the cingulate gyrus.

Radionuclide Neuroimaging Techniques: Ligand Studies

A ligand is a molecule with an affinity for a unique biological target, most often a protein receptor or transporter. Developments in PET and SPECT methodologies incorporating ligands provide an opportunity to carefully scrutinize the cellular pharmacodynamics of psychotropic medications (104–106). Ligands provide a surrogate of drug activity by measuring the ratio of ligand-receptor occupancy, versus drug occupancy. Several radiotracers have been developed for human imaging studies, targeting disparate neurotransmitters (e.g., acetylcholine (107–109), glutamate (110), dopamine (111,112) and serotonin (113–118)).

Both pre-synaptic and post-synaptic neuronal sites can be labeled with a radiotracer. Pre-synaptic sites can be involved in the regulation of neurotransmitter release from nerve terminals, while post-synaptic sites are at the beginning of the cascade of molecular events that will lead to the biological response (119). Therefore, the binding of different radiotracers pre- or post-synaptically may reveal different stages in diseases involving these systems.

Magnet Based Neuroimaging of Brain Function: Functional Magnetic Resonance Imaging

Through a modification of conventional MRI scanning characteristics, it is possible to study the dynamics of brain function. Functional Magnetic Resonance Imaging (fMRI) subsumes several related techniques. For example, the Blood-Oxygen-Level-Dependent (BOLD) technique relies on the ratio of deoxygenated to oxygenated blood. An area with less oxygenated blood will have more of the ferromagnetic deoxyhemoglobin and hence, a higher magnetic susceptibility. When a particular brain region is activated, arterial oxygenated blood will redistribute in this area. The activated area subsequently exhibits a decrease in oxygenated blood as oxygen is extracted by the active regional neurons (source of the fMRI signal). Afterward, the amount of blood flowing to the area far outweighs the amount of oxygen that is extracted, so that oxygenated blood is now higher (120).

Changes in blood oxygenation with impressive spatial (3–4 mm) and temporal resolution (<1s) allow the imaging of transient cognitive events and their impact on relatively smaller brain structures (e.g., amygdala). Moreover, unlike PET and SPECT, most fMRI techniques are noninvasive and radiation-free, enabling repeat scans through different disease states (e.g., imaging a bipolar patient in manic, depressive, and euthymic states) (121).

Sequential BOLD fMRI evaluations may be used to compare regional brain activity between symptomatic and asymptomatic states (122–124). BOLD-fMRI paradigms generally have several periods of rest alternating with several periods of activation. The images collected during the active phase are then compared with the periods at rest (Figure 2). With current technology, fMRI-BOLD is most applicable for processes that can be subjectively modulated (e.g., language, vision, movement, hearing, and memory) (125).

Limitations of the BOLD-fMRI technique include its sensitivity to movement, partially limiting the available tasks to those without head movement (e.g., speaking). Moreover, artifacts in neighboring air (i.e., sinuses) may distort the results, potentially complicating the examination of regions at the base of the brain such as the orbitofrontal and medial temporal cortices.

Magnet Based Neuroimaging of Brain Function: MRS

While the MRI technique provides cross-sectional anatomic images based on the tissue water content, magnetic resonance spectroscopy (MRS) is a technique that measures the concentration of in-vivo brain biochemical metabolites. MRS employs a magnetic field and a resonant radio-frequency (RF) pulse to observe the signal from a specific nucleus (e.g., proton [^{1}H] or phosphorus [^{31}P]) in the sample of interest) (126).

The MRS technique can be optimized to evaluate disparate intracellular hypotheses through the selection of a particular nucleus of interest, specific MR field strength, and select data-acquisition parameters. The MR signal sensitivity of the more frequently employed ^{1}H spectroscopy is about 15 times greater than that of ^{31}P spectroscopy (Figure 3).

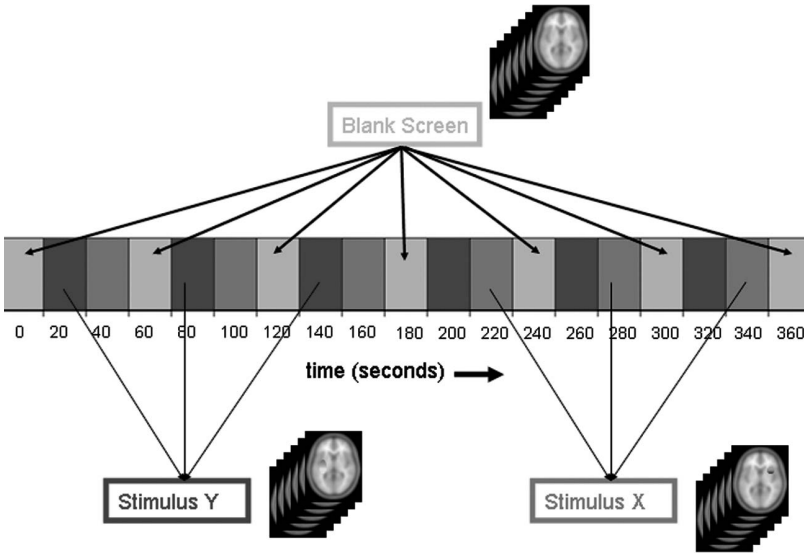

Figure 2 Block Design.

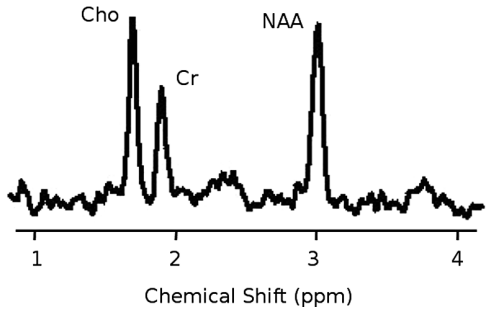

Figure 3 Magnetic Resonance Spectroscopy.

With ^{1}H spectroscopy, one can assess the viability of neurons, glutamate-glutamine-γ-aminobutyric acid (GABA) neurotransmitter cycling, and the second messenger system by evaluating metabolite levels of N-acetylaspartate (NAA), glutamate, glutamine, GABA, and myo-inositol respectively. Spectroscopy employing ^{31}P nuclei yields metabolite levels of adenosine triphosphate (ATP), phosphocreatinine (PCr), and inorganic orthophosphate (Pi), molecules associated with high-energy phosphate metabolism. Membrane phospholipid (MPL) synthesis and membrane degradation can also be assessed by measuring the freely mobile, water-soluble phosphomonoesters (free-PME, PC, PE) and phosphodiesters (free-PDE, GPC, GPE).

A survey of MRS studies in bipolar disorder supports frontotemporal abnormalities, with additional abnormalities noted in the basal ganglia and thalamus (127). MRS technology can be used to evaluate the pharmacokinetics of psychotropic agents. For example, brain lithium levels have been determined to be approximately half of peripheral plasma levels and may be a superior correlate of lithium efficacy (128).

Magnet Based Neuroimaging of Brain Function: Diffusion Tensor Imaging

Aberrant neurocircuitry has been postulated to underlie the pathophysiology of MDD (10) and BD (129). The breakdown, or loss of myelin (demyelination), such as seen in several neurodegenerative diseases (e.g., multiple sclerosis), results in impaired nerve impulse transmission. Higher rates of white matter hyperintensities (WMHs) in patients with mood disorders, particularly late-life or treatment-resistant disorders, also implicate white matter abnormalities in mood disorder etiology (130).

Diffusion tensor imaging (DTI) measures the microscopic diffusion of water. White matter exhibits remarkable differences in diffusion, depending on which direction the diffusion sensitizing gradients are applied allowing for the detection of white matter tracts (131). Diffusion tensor imaging measures are thought to be representative of brain tissue microstructure and are particularly useful for examining organized brain regions, such as white matter tract bundles.

Preliminary DTI investigations have confirmed impairment in neural connectivity in schizophrenia. Regions specifically identified as having diffusion abnormalities include the corpus callosum and distinct regions of the frontal cortex supporting theories of frontotemporal and frontoparietal disconnectivity in schizophrenia. Investigators are also beginning to examine DTI alterations in late-life depression, a diagnostic entity complicated by its association with cerebrovascular disease and other neurodegenerative processes (132). With advances in magnet strength and pulse sequences, DTI holds promise for connectivity analyses of neurocircuitry in mood disorders.

Analysis of Neuroimaging Data: Regional Differences

The choice of image analysis technique employed is influenced by the investigators' specific questions and preferences; sensitivity to detect small differences in a specific locus, or the ability to survey the entire brain volume for statistically significant differences. The smallest unit of neuroimaging resolution is called a voxel, or volume element, and represent a distinct location on a three-dimensional (-x -y -z) coordinate system (Figure 4).

When an affected brain region can be unambiguously delimited, region of interest (ROI) analyses offer the greatest sensitivity for detecting abnormalities. Most, ROI approaches involve overlaying the PET/SPECT/fMRI functional data on an anatomic MRI image, and manually demarcating the region. The inherent variability in ROI criteria between studies, however, and the absence of ROI validation, provide the impetus for an approach that avoids the problems of unvalidated ROIs through an unbiased survey of the entire brain at the voxel level.

Statistical parametric mapping (SPM) is a technique that evaluates the whole brain volume independent of distinct neuroanatomical regions and produces a parametric map containing an average value for each voxel. The statistical value, usually a derivative of the t-test, evaluates the hypothesis that a particular voxel is differentially activated between the two groups or conditions (133). Before analysis, all brains are "transformed" to fit into a standardized template and smoothed to minimize the impact of misalignment error and anatomical differences This loss of spatial resolution, however, offers relatively decreased sensitivity for detecting abnormalities in small structures (e.g.,, amygdala) or areas characterized by high anatomic variability (e.g.,, orbital cortex). This decrease in sensitivity, however, is offset by the confidence that activations in brain regions outside an ROI are not ignored.

Voxel-based morphometry (VBM) is an adaptation of the SPM technique that permits an evaluation of segmented grey and white matter voxel concentrations or volumes (134,135). As in SPM, macroscopic *within-group* differences are minimized, allowing *between-group* differences in local tissue composition to be explored without employing invalidated regions of interest (136). Abnormalities in gray matter distribution have been reported with VBM in subjects with MDD (37,40,76,137,138) and in other mood disorders, particularly BD (69,70,136,139–141).

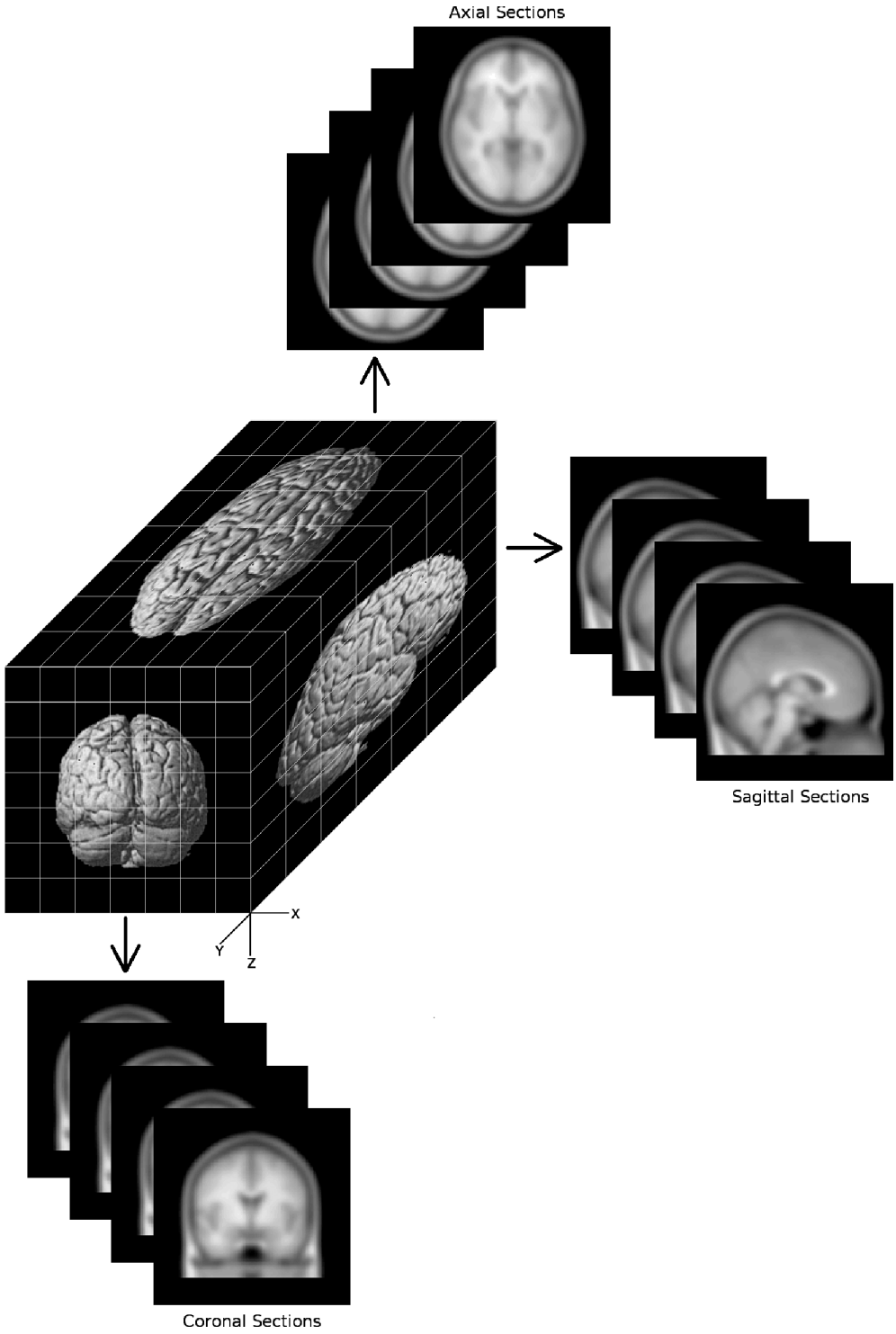

Figure 4 Neuroimaging Analyses: Coordinate System.

Effects of Treatment

Several longitudinal investigations have sought to characterize the effect of sychotropic administration on volumetric changes. For example, paroxetine treatment of OCD has been associated with a normalization (reduction) of amygdala (142) and thalamic volumes (143). Cross sectional investigation evaluating unmedicated BD patients and their chronically medicated counterparts revealed a larger SGPFC volume (144) and an increase in prefrontal grey matter volume (145) associated with mood stabilizer use.

Investigations of volumetric changes following non-pharmacological interventions, including repetitive transcranial magnetic stimulation (146) and cognitive behavioral therapy (147) have not confirmed statistically significant changes following the intervention.

Decreases in glucose metabolism in ventral regions of the prefrontal cortex (103,148) and increases in the temporal cortex (96,149) have been previously associated with response to SSRIs. Additional pre-post changes in the subgenual cingulate (BA25), ventrolateral prefrontal and temporal cortex, posterior cingulate (BA29) and putamen have also been reported with non-SSRI antidepressant pharmacotherapy (150–153). Response to cognitive behavioral therapy (CBT) has been associated with metabolic increases in hippocampus and dorsal cingulate (BA24) and decreases in dorsal (BA 9/46), ventral (BA 47/11), and medial (BA 9/10/11) frontal cortex (151).

The co-localization of common regional brain metabolic changes associated with response to either psychotherapy or pharmacotherapy may represent treatment-independent effects of clinical response. In a randomized controlled trial of venlafaxine versus CBT, response to either treatment modality was associated with decreased glucose metabolism bilaterally in the orbitofrontal cortex and left medial prefrontal cortex, along with increased metabolism in the right occipital-temporal cortex (154).

CONCLUSIONS

Currently, there are no clinical indications for functional neuroimaging methodologies in clinical psychiatry, although this technique holds considerable promise for unraveling the neuroanatomical basis of psychiatric disease. Structural imaging techniques are indicated to rule out organic pathologies associated with mental status disturbances.

Neuroscientists use fMRI clinically to noninvasively map language, motor, and memory function in patients undergoing neurosurgery. Researchers in mood disorders are currently combining neuroimaging approaches with clinically relevant cognitive measures (41), genotyping (155), neuroendocrinology (156), and surgical interventions (11).

If receptor occupancy is integral to the pharmacotherapy of mood disorders, then PET ligand studies could possibly guide medication dosing (157). Over the past decade there has been an accumulation of PET and SPECT radiotracers, which are currently being used to investigate numerous neurological targets in psychiatric disorders. As PET technology becomes more widely available, there is potential for growth in the field, with more radiotracers becoming available, targeting a variety of biological sites.

In parallel, future neuroimaging investigations will also benefit from methodological advances in MR magnet strength, and tissue segmentation techniques (69) and diffusion tensor imaging (158). Moreover, simultaneous analyses of functional and structural neuroimaging findings, longitudinal analysis in the depressed and remitted states, and inclusion of representative patients with medical and psychiatric comorbidities, represent other promising research vistas.

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