Schizophrenia Bulletin vol. 39 no. 4 pp. 776–786, 2013
doi:10.1093/schbul/sbt054
Advance Access publication April 24, 2013

Structural and Functional Neuroimaging Studies in Major Depressive Disorder With Psychotic Features: A Critical Review

Geraldo F. Busatto*[,1,2]

[1]Department of Psychiatry, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [2]Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), Universidade de São Paulo, São Paulo, Brazil

*To whom correspondence should be addressed; Rua Ovidio Pires Campos s/n, CEP 05403-010, São Paulo–SP, Brasil; tel: -55-11-26618132, fax: -55-11-30821015, e-mail: geraldo.busatto@hc.fm.usp.br

The relationship between major depressive disorder with psychotic (MDDP) features and schizophrenia has long been recognized, and the neurobiological boundaries between these disorders can nowadays be investigated using neuroimaging techniques. This article provides a critical review of such studies, addressing how they support a dimensional approach to the nosology and pathophysiology of psychotic disorders. A proportion of neuroimaging studies carried out to date indicate that MDDP subjects display structural and functional abnormalities in some brain regions specifically implicated in the pathophysiology of mood disorders, such as the subgenual cingulate cortex. This reinforces the validity of the classification of MDDP in proximity to major depression without psychosis. There is some neuroimaging evidence that MDDP may be associated with additional brain abnormalities relative to nonpsychotic major depression although less prominently in comparison with findings from the neuroimaging literature on schizophrenia. Brain regions seen as critical both to emotional processing and to models of psychotic symptoms, such as the hippocampus, insula, and lateral prefrontal cortex, have been implicated in separate neuroimaging investigations of either schizophrenia or major depression, as well as in some studies that directly compared depressed patients with and without psychotic features. These brain regions are key targets for future studies designed to validate imaging phenotypes more firmly associated with MDDP, as well as to investigate the relationship between these phenotypes and possible etiological influences for MDDP.

Key words: depression/psychosis/magnetic resonance imaging/fMRI/PET

Introduction

Over almost 4 decades, studies using in vivo neuroimaging methods have provided highly relevant insights about the pathophysiological basis of psychotic disorders, particularly schizophrenia. These studies have documented global brain volume reductions in groups of subjects with schizophrenia relative to healthy control samples, as well as enlargement of the lateral ventricles and other portions of cerebrospinal fluid (CSF) space in the brain, from early stages of the disorder onward.[1] Moreover, neuroimaging studies of schizophrenia have also shown disproportionate volumetric and cortical thickness reductions in a network of gray matter structures including the superior temporal gyrus, hippocampus, amygdala, insula, prefrontal cortex, anterior cingulate gyrus, and thalamus[2–4]; white matter integrity changes affecting deep frontal and temporal regions, as well as the long tracts that interconnect these lobes and the anterior thalamic radiation, cingulum, and fornix[4–6]; and abnormal volume, shape, and white matter integrity of the corpus callosum.[4,7,8] Finally, using functional neuroimaging methods, several studies have demonstrated widespread patterns of brain activity deficits in prefrontal, temporolimbic, cingulate, parietal, and thalamic regions in schizophrenia patients relative to healthy controls.[9,10]

In recent years, the investigation of boundaries between schizophrenia and bipolar disorder has also attracted a great deal of interest in the neuroimaging literature based on clinical, epidemiological, and molecular genetic findings that suggest that these 2 diagnostic categories may share psychopathological characteristics and causative factors.[11] However, although some similarities in neuroimaging findings may be detected across studies of schizophrenia and bipolar disorder,[12–14] there are also clear distinctions in the patterns of brain anatomical,[13,15–17] white matter microstructural,[18] and functional abnormalities that characterize each of those conditions.[19,20] This indicates that, despite possibly overlapping etiological influences, there are underlying neurobiological specificities that clearly differentiate between those 2 diagnostic categories.

One other important but much less often explored field of research regards to the relationship between major depressive disorder (MDD) with psychotic features and nonaffective psychoses including schizophrenia. Classified as an MDD subcategory and characterized by the emergence of delusions and/or hallucinations on a background of major depressive symptoms, MDD with psychotic features is associated with greater illness severity compared with nonpsychotic MDD,[21–23] as well as with greater levels of cognitive impairment,[24] poorer prognosis, increased mortality,[22,23,25] and distinct patterns of response to standard treatments for depression.[21]

In the present article, neuroimaging studies of MDD with psychotic features are reviewed, and future directions in the field are outlined. The number of case-control imaging studies that assessed patients with psychotic MDD has been relatively limited to date, and both structural and functional imaging investigations are evaluated herein. By discussing findings in relation to the boundary between MDD with psychotic features and schizophrenia, the article aims to address how neuroimaging findings may be taken as supportive of a dimensional approach to the nosology and pathophysiology of psychotic disorders.

Overview of Structural and Resting-State Functional Neuroimaging Studies of MDD in General

Similar to schizophrenia, the in vivo neuroimaging approach that has provided the greatest deal of data informing the pathophysiology of MDD has consisted in the use of magnetic resonance imaging (MRI) to assess brain morphological patterns in groups of MDD patients vs control groups of healthy individuals matched for demographic variables.

In the majority of such morphometric MRI studies of MDD, volumetric measurements have been obtained by placing regions of interest (ROIs) around the whole cranium and CSF spaces, as well as over specific brain portions selected a priori. Recent meta-analyses of such structural MRI studies have shown, in MDD groups relative to controls, no differences in total-brain volumes or CSF spaces but significantly reduced volumes of selected brain structures including the frontal cortex, subgenual cingulate cortex, anterior cingulate cortex, hippocampus, caudate, and putamen.[26–30] In some of the more recent morphometric MRI studies of MDD, voxel-based methods have been incorporated to allow the detection of brain volume and cortical thickness changes across the entire cerebral volume in an automated fashion, with no need to circumscribe ROIs a priori. Although much less numerous than ROI-based studies, these voxel-based morphometry and cortical thickness studies have provided additional evidence of reduced volumes and thinning of prefrontal, hippocampal, and cingulate regions in association with the presence and severity of MDD symptoms,[28,31–34] as well as implicating other brain regions not previously assessed in ROI-based studies of MDD such as the insula.[35]

There is evidence that some of the above structural imaging findings reported in MDD samples may be influenced by illness chronicity and treatment effects.[30] However, there have been morphometric MRI investigations carried out with first-episode MDD patients (a proportion of which never exposed to treatment), and these studies have indicated that findings such as reduced hippocampal and frontal cortical volumes are detectable since early disease stages.[32,36] There are also suggestions that hippocampal volume reduction is present in drug-free major depressed patients but not in unmedicated, remitted MDD patients, thus possibly representing a biomarker of active symptoms in MDD.[37]

There have also been several functional imaging studies that used positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) to assess brain activity patterns at rest in untreated MDD samples relative to healthy controls, measuring either regional rates of glucose metabolism or regional cerebral blood flow (rCBF). In consistency with the above structural imaging findings, these resting-state functional imaging studies have detected brain activity deficits in frontal, hippocampal, basal ganglia, anterior, and subgenual cingulate regions in MDD patients relative to controls,[38] often with normalization of metabolic patterns after successful antidepressant treatment.[39–41] Thus volumetric reductions and functional deficits at rest in MDD samples relative to healthy control groups are consistently detectable in several brain regions known to be relevant to emotional processing.[42]

The literature above indicates that brain abnormalities in MDD samples are not as prominent and widespread as those seen in association with schizophrenia because the latter disorder is associated with global brain volume reductions and regional gray matter abnormalities involving a larger set of brain regions.[1,2,4] Nevertheless, it is notable that there is a considerable degree of overlap in the regional pattern of brain abnormalities across the 2 diagnostic categories because regions such as the hippocampus, prefrontal cortex, and insula are affected both in groups of subjects with MDD or schizophrenia compared with healthy controls, even at early stages of these disorders. Although seen as critical to emotional processing and to the emergence of mood disorders as highlighted above,[42] these brain regions have also been frequently implicated in neuropsychological and neurochemical models of psychotic symptoms.[43–46] Therefore, brain abnormalities located specifically in these regions may provide a substrate for the emergence of psychotic symptoms in MDD.

Finally, meta-analyses of morphometric MRI studies have shown an increased prevalence and severity of white matter hyperintensities (WMH) in association

with the diagnosis of MDD.[47] Nevertheless, there is little indication that WMH in MDD could render individuals vulnerable to the emergence of psychotic symptoms; structural MRI studies in mood disorders found no relationship between WMH and the presence of psychotic symptoms,[48] and there is no consistent evidence of an increased prevalence of WMH in patients with schizophrenia.[49] More recently, however, it has become possible to apply MRI methods to detect more subtle, microstructural white matter abnormalities in association with psychiatric disorders, using diffusion tensor imaging (DTI) methods. With some degree of convergence with the DTI findings reported in schizophrenia,[5,6] meta-analyses of DTI studies in affective disorders have shown that the diagnosis of MDD is associated with decreased white matter integrity within the frontal and temporal lobes and in tracts that interconnect such regions such as the uncinate fasciculus.[50]

Structural and Resting-State Functional Imaging Studies Evaluating Groups of MDD Subjects With Psychotic Symptoms

One other relevant but somehow neglected approach in neuroimaging research consists in assessing distinct groups of MDD patients currently presenting with (or with a previous history of) psychotic symptoms, directly in comparison against groups of nonpsychotic MDD patients, subjects with schizophrenia, or healthy controls. The detection of significant group differences in such studies may highlight patterns of brain abnormalities specifically associated with the emergence of psychotic symptoms in the context of MDD.

Early brain morphometric investigations using computed tomography (CT) reported findings of enlarged ventricles in groups of patients with MDD with psychotic features (predominantly chronic and treated with pharmacotherapy and/or electroconvulsive therapy [ECT]) compared with nonpsychotic MDD patients.[51–54] In one of these studies,[51] ventricle size in the group with MDD with psychotic features was directly related to findings of hypercortisolemia (assessed using the dexamethasone suppression test), a feature consistently associated with the presence of psychotic symptoms in MDD.[21] There have also been CT investigations reporting no CSF volume differences between psychotic and nonpsychotic depression,[55] and such inconsistency across studies has been attributed to the fact that some of these earlier samples combined unipolar and bipolar psychotic depressed patients.[21,48] In subsequent investigations using structural MRI and more sophisticated morphometric indices, increased volume of CSF spaces was reported in elderly patients with psychotic MDD compared with nonpsychotic MDD subjects[56]; however, these findings may have been confounded by illness chronicity and treatment effects because psychotic MDD patients in that study were twice more likely to be treated with ECT.[56] More recently, findings of increased CSF spaces in younger MDD subjects presenting with psychotic features relative to nonpsychotic MDD patients and healthy controls have been detected in a study that used structural MRI to investigate morphological brain abnormalities in separate groups of subjects with psychotic MDD, severe nonpsychotic depression, and first-episode schizophrenia.[57]

Differences in CSF volumes between psychotic and nonpsychotic MDD at early disease stages may provide a window of approximation between the neurobiological features underlying psychotic MDD and schizophrenia. In schizophrenia, larger CSF spaces detectable from early disease stages are seen as supportive of etiological models implicating early neurodevelopmental deficits.[2] If similar patterns of CSF enlargement can be confirmed specifically in association with psychotic MDD, this would support a view of etiological influences akin to schizophrenia in this MDD subtype. Clearly, however, further MRI investigations of CSF spaces in larger samples of subjects with recent-onset psychotic depression (with confirmed diagnosis of MDD) are needed. In our own recent MRI investigation of a modest sample of first-episode psychotic depressed patients ($n = 20$), most of whom with their diagnosis of MDD confirmed after 1 year,[58] no significant ventricle enlargement was detected relative to healthy controls to the same degree as seen in a larger sample of first-episode schizophrenia subjects ($n = 62$) recruited exactly in the same environmental setting.[59]

In regard to MRI investigations of regional volumes of gray matter brain structures, 3 studies to date have directly investigated groups of psychotic vs nonpsychotic MDD patients,[57,60,61] with additional studies having compared old-age depression patients with psychotic vs nonpsychotic depression.[56,62] In the 3 studies evaluating younger MDD samples, there has been a lack of differences between the 2 MDD groups in brain regions seen as critical to MDD in general or schizophrenia or both, including the frontal and temporal lobes,[57] hippocampus,[60,61] and subgenual anterior cingulate cortex.[61] One study reported smaller volume of the amygdala in depressed patients with psychosis relative to controls but not in depressed patients without psychosis.[60] The fact that only limited structural gray matter differences are detectable between nonpsychotic and psychotic MDD provides support to the classification of MDD with psychotic features as a subcategory of MDD.

One other morphometric MRI study evaluated a selected sample of MDD patients presenting with psychotic symptoms in comparison with similar sized groups of schizophrenia patients and healthy controls. Patients with psychotic MDD presented reduced volume of the posterior subgenual cingulate cortex relative to schizophrenia patients.[63] Such distinct involvement of the subgenual cingulate cortex in patients with psychotic MDD is interesting in light of the critical role of this

brain region in the processing of emotions and specifically in the pathogenesis of mood disorders in general.[28,42] This further reinforces the validity of the classification of MDD with psychotic features in proximity to major depression without psychosis.

Functional imaging studies evaluating groups of MDD patients with psychotic features using PET or SPECT have been extremely rare. Our own group conducted a resting rCBF study with SPECT in which unmedicated patients with MDD with psychotic features were compared with a group of nonpsychotic MDD subjects, as well as against a group of healthy volunteers.[64] MDD patients with psychotic features showed decreased rCBF in the left subgenual cingulate cortex relative to both nonpsychotic MDD patients and healthy controls, as well as decreased rCBF in the right inferior frontal region (with the voxel of maximal significance in the insula) vs the nonpsychotic MDD group. The same results were detectable when group analyses were repeated with covariance for the greater depression severity in the MDD group with psychotic features.[64] These findings support the view that the insula and prefrontal cortex may be specifically associated with the emergence of psychotic symptoms in MDD.

Neuroimaging Comparisons of Combined Groups of First-Episode Affective Psychoses (Major Depressive Disorder and Bipolar Disorder) vs Schizophrenia

One other recently explored neuroimaging research strategy consists in the investigation of samples of first-episode psychosis patients subdivided into 2 groups: nonaffective (schizophrenia-related) psychoses and affective psychoses (combining bipolar disorder and MDD), both of which compared separately with the same healthy control groups. Such studies may allow the delineation of brain abnormalities that could be commonly implicated in the emergence of psychotic symptoms across bipolar disorder and MDD, as well as distinguishing such features from the brain changes associated with schizophreniform psychosis.

Seven research groups across the globe have conducted such investigations to date using morphometric MRI methods.[7,65–70] In only one of those samples, there was a greater degree of brain abnormalities in affective psychosis patients than in first-episode nonaffective psychoses,[67] while in all others the degree and spread of anatomical brain changes were larger in schizophrenia subjects relative to patients with affective psychoses. Some brain regions, such as the superior temporal gyrus and corpus callosum, display a notable specificity for involvement in first-episode schizophrenia.[7,8,66,71] However, an important source of bias in these studies lies in the fact that the groups of schizophrenia subjects have been almost invariably larger than those of affective disorder subjects,[7,67,68,71,72] increasing the risk of type II errors in the comparisons involving the latter groups. Moreover, several of the cohorts of subjects with first-episode affective psychoses have included predominantly[7,67] or almost exclusively[65,68,70] patients with an established diagnosis of bipolar disorder. Such limitations also apply to the as yet diminute DTI literature using this research design; in one DTI study evaluating a small-sized sample of first-episode affective psychosis subjects (predominantly with bipolar disorder),[6] white matter integrity reductions in the uncinate fasciculus were present, but not as prominently as seen in first-episode schizophrenia patients and with no statistical differentiation from the quantitative indices obtained in the healthy control group.

Despite their limitations, the above MRI studies have often reported regional brain volume abnormalities in first-episode affective psychosis patients relative to healthy controls, variably implicating the prefrontal cortex, insula, and cingulate cortex, as well as other brain regions.[67,70,73–76] Volume reductions in brain regions seen as critical to mood disorders, such as the subgenual cingulate cortex, have shown diagnostic specificity for first-episode affective psychosis groups, with no similar findings in association with first-episode schizophrenia.[73] Thus, although the majority of the morphometric MRI studies of first-episode psychosis reveal that brain changes are most prominent in schizophrenia compared with affective psychoses, there is evidence that brain structural abnormalities are also detectable in first-episode affective psychoses subjects relative to healthy controls. The wide variability in the location of findings may be related to the pooling together of patients with MDD with psychotic features and psychotic bipolar episodes within the same group of first-episode affective psychoses.

From the above cohorts of subjects with first-episode psychoses evaluated with structural MRI, separate comparisons of brain morphometric abnormalities between patients with an established diagnosis of MDD vs bipolar disorder subjects were conducted only in our own MRI investigation carried out in Sao Paulo, Brazil.[66] In such study, similar sized groups of psychotic bipolar disorder and psychotic MDD, who had their diagnoses confirmed after 1 year, displayed distinct patterns of regional brain volume abnormalities against each other and in comparison with the same group of healthy controls. Such brain volume differences involved the dorsolateral prefrontal cortex (reduced in psychotic MDD patients) and the dorsal anterior cingulate cortex (increased in psychotic bipolar disorder subjects).[58] Rather than suggesting a common neurobiological substrate underlying psychotic symptoms in both bipolar disorder and MDD, such differences are instead consistent with previous suggestions that there are neuroimaging distinctions between bipolar disorder and MDD in general.[28,77] This highlights the importance of investigating

separately those 2 forms of affective disorders in studies of mood disorders with psychotic features.

Which Brain Regions Are Critically Involved in the Emergence of Psychotic Symptoms in MDD?

Recently identified genes responsible for the expression of proteins that regulate critical functions in the central nervous system, such as neuronal growth, synapse formation, myelination, glial cell migration, development of neural connectivity, and neurotransmission, among others, have been implicated in the risk of developing schizophrenia, affective disorders, or both.[78–81] Using *postmortem* brain tissue from individuals with schizophrenia and/or affective disorders, sophisticated proteomic methods now allow investigations of the expression of proteins related to the function of the above genes,[82–84] as well as large number of other proteins involved in biochemical pathways of potential interest to psychotic disorders, in the search for proteomic signatures associated to these clinical conditions.[85] Importantly, proteomic studies using *postmortem* methods have indicated that abnormal protein expression in schizophrenia and mood disorders may be detected in some brain regions and specific neuronal cortical layers, but not in others.[82–84] Such region-specific effects highlight how important contemporary in vivo neuroimaging studies may be to identify which brain structures should be targeted in such innovative *postmortem* investigations, based on the critical involvement of these brain structures in the emergence of the clinical phenotype supposedly related to the protein pathway under investigation.

In MDD with psychotic features, one such key region may be the hippocampus. There is PET imaging evidence that reductions in psychotic severity in MDD patients after treatment are directly related to increments in functional activity in the hippocampal region.[86] Psychological and neuroanatomical models of schizophrenia have long implicated abnormal hippocampal functioning specifically in the emergence of positive symptoms of the disorder (delusions and hallucinations).[43,46] It is widely known that the emergence of psychotic symptoms in schizophrenia and other psychotic disorders is mediated by increased dopamine transmission.[87–89] Recent studies in animals have demonstrated that the ventral hippocampus plays a critical role in the regulation of the functioning of the dopamine system, and altered hippocampal activity may result in dysregulated dopamine system functioning, leading to a proneness to display psychotic symptoms in humans.[44] The ventral hippocampus is also critically involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress, with abnormal hippocampal functioning being associated with increases in the release of cortisol and adrenocorticotropic hormone.[90] Dysregulation of the HPA axis is a consistent feature of MDD,[91] being most significantly associated with the psychotic form of severe MDD.[21] There is also evidence of disturbed dopaminergic activity in psychotically depressed patients in comparison to nonpsychotic MDD, possibly related to HPA dysregulation.[92] It should be noted that a model of hippocampal dysfunction possibly influencing on the emergence of psychotic symptoms both in schizophrenia and psychotic MDD does not necessarily imply the existence of similar hippocampal neuropathological processes underlying the symptoms of the 2 disorders.

One other recent model of potential interest to MDD with psychotic features hypothesizes that psychotic symptoms in general are mediated by dysfunction of the insula.[45] The insula is a critical component of the salience brain network, which also involves the anterior cingulate cortex and is primarily involved in switching between the default mode and task-related states of brain connectivity.[93] According to the insular model of psychosis, dysfunction of the insula would be associated with disruption in normal salience network activity, leading to inappropriate allocation of salience to internally generated actions (such as inner speech) and misattribution of such actions to the external environment (generating hallucinations and passivity phenomena).[45] Structural and functional imaging studies have provided extensive evidence of insular abnormalities in association with schizophrenia from early disease stages.[45,94] There have been suggestions that volumetric abnormalities of the insula in first-episode psychosis might be specific to schizophrenia and absent in affective psychoses[95]; however, the affective psychosis group in such investigation (n = 34) included a majority of patients with bipolar disorder (n = 23) rather than subjects with MDD with psychotic features, and this group was substantially smaller than the group of first-episode schizophrenia patients (n = 57). Conversely, volumetric studies of the insula in MDD have reported significantly reduced volumes of the anterior insular cortex both in currently depressed and remitted MDD patients,[96] as well as significant correlations between insular volumes and the severity of depressive symptoms in MDD patients.[97] Finally, the neuroimaging literature of MDD with psychotic features reviewed herein provide some support to a view that insular abnormalities may be critical to psychotic phenomena in psychotic MDD and in schizophrenia given the evidence that functional abnormalities of the insula may be present in patients with MDD with psychotic features in comparison with either healthy controls or subjects with nonpsychotic MDD.[64,98]

Finally, the actual *postmortem* literature mentioned above may also help to highlight other key brain regions that should be examined in even greater detail in the next generation of in vivo neuroimaging studies of MDD with psychotic features. For instance, Martins-de-Souza et al (2012) recently described a proteomic signature in the dorsolateral prefrontal cortex of psychotic MDD patients (involving proteins relevant to synaptic function,

among others) that was distinct from the findings obtained in prefrontal cortical tissue from a nonpsychotic MDD group but similar to results previously reported in proteomic investigations of schizophrenia patients.[99] This is consistent with findings of volume deficits of the dorsolateral prefrontal cortex in patients with first-episode psychotic depression with confirmed diagnosis of MDD[58] and highlights the lateral prefrontal cortex as an additional brain region of potentially critical relevance to the emergence of psychotic symptoms in MDD. The relevance of the dorsolateral prefrontal cortex in MDD with psychotic features is further emphasized by the particularly critical role of this brain region in the neurobiology of delusions,[100] a prevalent psychotic phenomenon in psychotic MDD.[101] This contrasts with the consistent link between structural changes of the superior temporal gyrus and hallucinations,[102] a clinical feature that emerges less frequently in MDD than in other severe psychotic disorders.[103]

The Potential of Functional MRI Studies

As discussed in earlier sections of this article, structural brain abnormalities as assessed with MRI vary considerably across the diagnostic categories of schizophrenia and affective psychoses. However, such anatomical distinctions do not preclude the possibility that similar patterns of functional brain changes might be detected underlying the presence of psychotic phenomena across such different psychiatric categories. This can nowadays be investigated using functional MRI (fMRI), which allows the noninvasive mapping of neural activity changes in the human brain while subjects perform motor, sensory, cognitive, or emotion-provoking tasks. Recently, it has also become possible to study human brain functioning using fMRI when subjects are not performing any particular task, and this is known as resting-state fMRI; fluctuations in regional brain activity can be detected across separate brain regions during rest, and the patterns of intercorrelation between the functioning of these regions is measured, affording quantitative indices of resting-state functional connectivity. Finally, studies using fMRI or PET can also be carried out during the transient experience of psychotic symptoms such as auditory verbal hallucinations; a recent meta-analysis of these findings concluded that the experience of auditory hallucinations in schizophrenia patients is associated with aberrant activity bilaterally in language-related areas (Broca's area, the middle and superior temporal gyri, and the inferior parietal lobule), as well as the anterior insula and hippocampus/parahippocampal gyrus.[104]

Unfortunately, the potential of fMRI methods has hardly been explored to date in investigations of psychotic MDD. There are only 2 studies that compared directly a group of subjects with MDD with psychotic features with a nonpsychotic MDD sample and healthy controls, carried out by the same research group.[98,105] One of these 2 investigations[98] used an executive functioning task involving working memory with varying levels of difficulty (*N*-back task), which in healthy subjects usually engages the lateral prefrontal cortex, hippocampus/parahippocampal gyrus, and temporoparietal cortex. The 2 groups of MDD patients showed greater activity increments relative to healthy controls in the parahippocampal gyrus, but the psychotic MDD group showed such aberrant parahippocampal activation at a lower level of task demand compared with nonpsychotic MDD patients. Also, the psychotic MDD group showed increased activity in a cluster located in the right temporoparietal junction relative to the 2 other groups, and this region showed functional connectivity with activation in the left prefrontal cortex. Finally, only the psychotic MDD group engaged the insula during task trials of higher working memory load.[98] Group differences remained unchanged when the analyses were covaried for differences in the severity of depression across the 2 MDD groups. In the companion study by the same research group using episodic verbal memory tasks,[105] only the sample of psychotic MDD patients showed reduced activity in the hippocampus, insula, and prefrontal cortex relative to healthy controls during an encoding memory task. During episodic memory retrieval, the psychotic MDD patients displayed abnormally increased prefrontal and parietal cortical activation compared with both healthy controls and nonpsychotic MDD subjects, and this was appropriately interpreted as reflecting compensatory brain activity in consequence to the encoding deficits in the psychotic MDD group. Overall, it is interesting that the 3 brain regions highlighted earlier in the present article as potentially relevant to the emergence of psychosis in MDD, namely the hippocampus, insula, and lateral prefrontal cortex, were all engaged distinctly in the group of psychotic MDD in the 2 fMRI studies discussed herein.[98,105] These findings await replication in further fMRI investigations using memory paradigms and other tasks relevant to psychotic phenomena.

The alternative strategy of investigating similarities in the patterns of brain abnormalities across schizophrenia and separate categories of affective psychoses (MDD with psychotic features and psychotic bipolar disorder) has been explored in only 1 fMRI study to date by Sommer et al (2007), which investigated lateralized functional brain activity changes during a language task.[106] It is know, from other fMRI studies specifically with first-episode, never-medicated schizophrenia patients that the typically lateralized pattern of increased brain activity during language tasks is reduced in schizophrenia, most prominently in Broca's area and Wernicke's area.[107] Sommer et al (2007) found that brain hemispheric lateralization during language processing was decreased in the overall sample of psychotic patients compared with healthy controls, regardless of diagnostic category.[106]

These results hint at the possibility that decreased language lateralization could be a functional imaging phenotype not specific to schizophrenia but instead associated also with affective psychoses.

Up until now, no resting-state fMRI study has separately investigated groups of MDD patients presenting with psychotic features. Conversely, in bipolar disorder, there is recent fMRI evidence that the proneness to display psychotic features over the disease course is directly related to reduced resting-stated medial prefrontal connectivity with other regions over the whole brain, as well as to increased connectivity specifically with the amygdala.[108]

Diagnostic Difficulties and Clinical Issues in Neuroimaging Studies of Major Depression With Psychotic Features

Current psychiatric classification systems, widely used for diagnostic ascertainment of cases in neuroimaging investigations, employ clinical criteria highly reliant on the observation of behavior and personal accounts by patients and their families and may therefore be inaccurate in many cases. One issue of particular relevance in neuroimaging studies of MDD regards to the uncertainty of the MDD diagnosis when this is based on a single assessment or a retrospective review of periods of a year or less. Rates of diagnostic change from MDD to bipolar disorder over time are known to be high,[109] and the presence of psychotic features is associated with a greater risk of such diagnostic shift.[110–112] There is also evidence of common diagnostic shifting from MDD with psychotic features to schizophrenia over time.[110,112,113] Among the studies reviewed in the present article, only a minority of investigations enrolled MDD patients with psychotic features who had an established diagnostic stability of at least 1 year.[58]

Moreover, in cross-sectional evaluations, it may be difficult to distinguish between MDD with psychotic features from schizoaffective disorder, commonly seen as an intermediate condition between major mood disorders and schizophrenia[114] and from schizophrenia, which frequently present with clinically relevant depressive symptoms.[115] Such porosity of the borders between mood disorders and schizophrenia-related disorders is highly likely to add variability to findings from neuroimaging studies of MDD with psychotic features. Future longitudinal neuroimaging investigations with repeated diagnostic assessments over several years of follow-up in representative samples may be needed in order to minimize diagnostic uncertainties and validate the ascertainment of cases to separate categories.

It should also be acknowledged that repeated depressive episodes in MDD patients may not always feature psychotic symptoms over the course of illness although recurrence of psychotic MDD is not uncommon.[111] Therefore, repeated neuroimaging assessments in longitudinal evaluations may also be useful to capture state-dependent brain changes specifically related to the emergence of psychotic features in MDD.

Finally, it is relevant to mention that variable medication usage in psychotic MDD vs schizophrenia may potentially exert influence on the different degrees of brain abnormalities detected in association with each of these diagnoses. While antipsychotic drugs have been shown to influence on the occurrence of brain tissue loss over time in schizophrenia,[116] successful treatment with antidepressants is associated with volume increases of key brain regions such as the hippocampus and dorsolateral prefrontal cortex.[37,117]

Concluding Remarks and Future Directions

The search for a specific neurobiological substrate underlying MDD with psychotic features has featured in the neuroimaging research agenda since the 1980s. However, as highlighted in the present review, well-conducted imaging studies addressing this issue directly have been overwhelmingly sparse over the following decades. At present, this prevents the use of a meta-analytic approach to quantitatively assess alterations specifically related to the presence of pychotic symptoms in MDD.

Despite such limitations, a significant proportion of the neuroimaging studies reviewed herein indicate that groups of patients with MDD with psychotic features often display structural and functional abnormalities located in brain regions unequivocally implicated in major depression and in mood disorders in general, such as the subgenual cingulate cortex.[28,42,63,64] Such findings reinforce the validity of the classification of psychotic MDD in proximity to MDD without psychotic features. There is also some neuroimaging evidence indicating that MDD with psychotic features may be associated with additional structural and functional brain abnormalities relative to nonpsychotic MDD although less prominently in comparison with the findings that concurrently emerged from the neuroimaging literature on schizophrenia.

In order to pinpoint converging brain abnormalities implicated in the emergence of psychotic phenomena across psychotic MDD and schizophrenia, further neuroimaging studies evaluating groups of recent-onset schizophrenia and psychotic MDD subjects of similarly large sizes, in comparison with the same groups of healthy controls, are eagerly awaited. These studies should drive special attention to the neural circuits that encompass the candidate brain regions highlighted in the present article, such as the hippocampal region, insula, and lateral prefrontal cortex.

If well succeeded within the next few years, such neuroimaging studies are expected to produce imaging phenotypes more firmly related to the vulnerability to display psychotic symptoms in the context of MDD. Such imaging phenotypes should then be investigated

in regard to their degree of heritability (via studies of unaffected first-degree relatives of patients with MDD with psychotic features), as well as in regard to their possible associations with specific candidate genes.[41,118,119] Moreover, because a polygenic contribution to MDD with psychotic features can be expected, future genome-wide association studies on representative samples MDD with psychotic features may afford quantitative risk scores to be subsequently used in studies investigating the relationship between robust imaging phenotypes and polygenic risk scores.[120,121]

Finally, there should also be neuroimaging studies applying a dimensional approach to the evaluation of psychosis associated with MDD, with both subthreshold and full-blown psychotic experiences rated along a continuum of severity, on a background of major depressive symptoms. There is a significant prevalence of subthreshold psychotic-like experiences in the general population[122] and in subjects with less severe major depressive episodes,[123] and there is a growing recognition that psychotic symptoms may best be viewed as falling along a continuum of severity in MDD rather than solely as a subcategory of severe MDD.[123] Interestingly, there is recent fMRI evidence indicating that individuals from the general population with quantifiable rates of psychosis proneness may display distinct patterns of brain activity changes during emotion stimulation in the insula, anterior cingulate cortex, prefrontal cortex, and amygdala.[122]

Taking advantage of continuous technological improvements in neuroimaging methods and exploring the research avenues outlined above, we may look forward to innovative forms of classifying MDD with psychotic features in the future, basing such classifications not only on clinical data but also on information about brain mechanisms underlying the symptoms and their etiological influences.

Funding

Provost's Office for Research of the University of São Paulo—Programa de incentivo à Pesquisa (2011.1.9333.1.3); CNPq-Brazil to G.F.B.

Acknowledgment

I thank Paula Squarzoni for her assistance in the organization of references for the article.

References

1. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry*. 2006;188:510–518.
2. Busatto GF, Zanetti MZ, Schaufelberger MS, Crippa JAS. *Brain Anatomical Abnormalities in Schizophrenia: Neurodevelopmental Origins and Patterns of Progression over Time*. Vol 2. New York: Springer; 2010.
3. van Haren NE, Schnack HG, Cahn W, et al. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*. 2011;68:871–880.
4. Bora E, Fornito A, Radua J, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr Res*. 2011;127:46–57.
5. Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophr Res*. 2009;108:3–10.
6. Kawashima T, Nakamura M, Bouix S, et al. Uncinate fasciculus abnormalities in recent onset schizophrenia and affective psychosis: a diffusion tensor imaging study. *Schizophr Res*. 2009;110:119–126.
7. Walterfang M, Wood AG, Reutens DC, et al. Corpus callosum size and shape in first-episode affective and schizophrenia-spectrum psychosis. *Psychiatry Res*. 2009;173:77–82.
8. Chaim TM, Schaufelberger MS, Ferreira LK, et al. Volume reduction of the corpus callosum and its relationship with deficits in interhemispheric transfer of information in recent-onset psychosis. *Psychiatry Res*. 2010;184:1–9.
9. Lehrer DS, Christian BT, Mantil J, et al. Thalamic and prefrontal FDG uptake in never medicated patients with schizophrenia. *Am J Psychiatry*. 2005;162:931–938.
10. Kühn S, Gallinat J. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. *Schizophr Bull*. 2013;39:358–365.
11. Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses. *Schizophr Bull*. 2009;35:482–490.
12. Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *Br J Psychiatry*. 2009;195:194–201.
13. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res*. 2010;117:1–12.
14. De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Curr Pharm Des*. 2012;18:486–494.
15. McDonald C, Marshall N, Sham PC, et al. Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. *Am J Psychiatry*. 2006;163:478–487.
16. Watson DR, Anderson JM, Bai F, et al. A voxel based morphometry study investigating brain structural changes in first episode psychosis. *Behav Brain Res*. 2012;227:91–99.
17. Bora E, Fornito A, Yücel M, Pantelis C. The effects of gender on grey matter abnormalities in major psychoses: a comparative voxelwise meta-analysis of schizophrenia and bipolar disorder. *Psychol Med.* 2011;42:295–307.
18. Lu LH, Zhou XJ, Keedy SK, Reilly JL, Sweeney JA. White matter microstructure in untreated first episode bipolar disorder with psychosis: comparison with schizophrenia. *Bipolar Disord*. 2011;13:604–613.
19. Whalley HC, Papmeyer M, Sprooten E, Lawrie SM, Sussmann JE, McIntosh AM. Review of functional magnetic

resonance imaging studies comparing bipolar disorder and schizophrenia. *Bipolar Disord*. 2012;14:411–431.
20. Delvecchio G, Sugranyes G, Frangou S. Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies. *Psychol Med*. 2012;43:553–569.
21. Keller J, Schatzberg AF, Maj M. Current issues in the classification of psychotic major depression. *Schizophr Bull*. 2007;33:877–885.
22. Crebbin K, Mitford E, Paxton R, Turkington D. First-episode psychosis: an epidemiological survey comparing psychotic depression with schizophrenia. *J Affect Disord*. 2008;105:117–124.
23. Gaudiano BA, Dalrymple KL, Zimmerman M. Prevalence and clinical characteristics of psychotic versus nonpsychotic major depression in a general psychiatric outpatient clinic. *Depress Anxiety*. 2009;26:54–64.
24. Hill SK, Keshavan MS, Thase ME, Sweeney JA. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. *Am J Psychiatry*. 2004;161:996–1003.
25. Tohen M, Khalsa HM, Salvatore P, Vieta E, Ravichandran C, Baldessarini RJ. Two-year outcomes in first-episode psychotic depression the McLean-Harvard First-Episode Project. *J Affect Disord*. 2012;136:1–8.
26. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry*. 2004;161:598–607.
27. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry*. 2004;161:1957–1966.
28. Hajek T, Kozeny J, Kopecek M, Alda M, Höschl C. Reduced subgenual cingulate volumes in mood disorders: a meta-analysis. *J Psychiatry Neurosci*. 2008;33:91–99.
29. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp*. 2009;30:3719–3735.
30. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *Eur Neuropsychopharmacol*. 2012;22:1–16.
31. Taki Y, Kinomura S, Awata S, et al. Male elderly subthreshold depression patients have smaller volume of medial part of prefrontal cortex and precentral gyrus compared with age-matched normal subjects: a voxel-based morphometry. *J Affect Disord*. 2005;88:313–320.
32. Cheng YQ, Xu J, Chai P, et al. Brain volume alteration and the correlations with the clinical characteristics in drug-naïve first-episode MDD patients: a voxel-based morphometry study. *Neurosci Lett*. 2010;480:30–34.
33. Du MY, Wu QZ, Yue Q, et al. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36:11–16.
34. Tu PC, Chen LF, Hsieh JC, Bai YM, Li CT, Su TP. Regional cortical thinning in patients with major depressive disorder: a surface-based morphometry study. *Psychiatry Res*. 2012;202:206–213.
35. Soriano-Mas C, Hernández-Ribas R, Pujol J, et al. Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. *Biol Psychiatry*. 2011;69:318–325.
36. Frodl T, Meisenzahl EM, Zetzsche T, et al. Hippocampal changes in patients with a first episode of major depression. *Am J Psychiatry*. 2002;159:1112–1118.
37. Arnone D, McKie S, Elliott R, et al. State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry*. 2012b.
38. Savitz JB, Drevets WC. Imaging phenotypes of major depressive disorder: genetic correlates. *Neuroscience*. 2009;164:300–330.
39. Mayberg HS, Brannan SK, Tekell JL, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry*. 2000;48:830–843.
40. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol*. 2002;12:527–544.
41. Brody AL, Saxena S, Stoessel P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. *Arch Gen Psychiatry*. 2001;58:631–640.
42. Price JL, Drevets WC. Neurocircuitry of mood disorders. *Neuropsychopharmacology*. 2010;35:192–216.
43. Weinberger DR. Cell biology of the hippocampal formation in schizophrenia. *Biol Psychiatry*. 1999;45:395–402.
44. Lodge DJ, Grace AA. Developmental pathology, dopamine, stress and schizophrenia. *Int J Dev Neurosci*. 2011;29:207–213.
45. Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *J Psychiatry Neurosci*. 2012;37:17–27.
46. Frith CD, Done DJ. Towards a neuropsychology of schizophrenia. *Br J Psychiatry*. 1988;153:437–443.
47. Arnone D, McIntosh AM, Ebmeier KP, Munafò MR, Anderson IM. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *Eur Neuropsychopharmacol*. 2012;22:1–16.
48. Wang PW, Ketter TA. Biology and recent brain imaging studies in affective psychoses. *Curr Psychiatry Rep*. 2000;2:298–304.
49. Zanetti MV, Schaufelberger MS, de Castro CC, et al. White-matter hyperintensities in first-episode psychosis. *Br J Psychiatry*. 2008;193:25–30.
50. Sexton CE, Mackay CE, Ebmeier KP. A systematic review of diffusion tensor imaging studies in affective disorders. *Biol Psychiatry*. 2009;66:814–823.
51. Rothschild AJ, Benes F, Hebben N, et al. Relationships between brain CT scan findings and cortisol in psychotic and nonpsychotic depressed patients. *Biol Psychiatry*. 1989;26:565–575.
52. Schlegel S, Kretzschmar K. Computed tomography in affective disorders. Part I. Ventricular and sulcal measurements. *Biol Psychiatry*. 1987;22:4–14.
53. Targum SD, Rosen LN, DeLisi LE, Weinberger DR, Citrin CM. Cerebral ventricular size in major depressive disorder: association with delusional symptoms. *Biol Psychiatry*. 1983;18:329–336.
54. Shiraishi H, Koizumi J, Hori M, et al. A computerized tomographic study in patients with delusional and non-delusional depression. *Jpn J Psychiatry Neurol*. 1992;46:99–105.
55. Luchins DJ, Meltzer HY. Ventricular size and psychosis in affective disorder. *Biol Psychiatry*. 1983;18:1197–1198.
56. Simpson S, Baldwin RC, Jackson A, Burns A. The differentiation of DSM-III-R psychotic depression in later life from

nonpsychotic depression: comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features. *Biol Psychiatry*. 1999;45:193–204.

57. Salokangas RK, Cannon T, Van Erp T, et al. Structural magnetic resonance imaging in patients with first-episode schizophrenia, psychotic and severe non-psychotic depression and healthy controls. Results of the schizophrenia and affective psychoses (SAP) project. *Br J Psychiatry Suppl*. 2002;43:s58–s65.
58. de Azevedo-Marques Périco C, Duran FL, Zanetti MV, et al. A population-based morphometric MRI study in patients with first-episode psychotic bipolar disorder: comparison with geographically matched healthy controls and major depressive disorder subjects. *Bipolar Disord*. 2011;13:28–40.
59. Rosa PG, Schaufelberger MS, Uchida RR, et al. Lateral ventricle differences between first-episode schizophrenia and first-episode psychotic bipolar disorder: a population-based morphometric MRI study. *World J Biol Psychiatry*. 2010;11:873–887.
60. Keller J, Shen L, Gomez RG, et al. Hippocampal and amygdalar volumes in psychotic and nonpsychotic unipolar depression. *Am J Psychiatry*. 2008;165:872–880.
61. Vassilopoulou K, Papathanasiou M, Michopoulos I, et al. A magnetic resonance imaging study of hippocampal, amygdala and subgenual prefrontal cortex volumes in major depression subtypes: melancholic versus psychotic depression. *J Affect Disord*. 2013;146:197–204.
62. Kim DK, Kim BL, Sohn SE, et al. Candidate neuroanatomic substrates of psychosis in old-aged depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23:793–807.
63. Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *Am J Psychiatry*. 2005;162:1706–1712.
64. Skaf CR, Yamada A, Garrido GE, et al. Psychotic symptoms in major depressive disorder are associated with reduced regional cerebral blood flow in the subgenual anterior cingulate cortex: a voxel-based single photon emission computed tomography (SPECT) study. *J Affect Disord*. 2002;68:295–305.
65. Nakamura M, Salisbury DF, Hirayasu Y, et al. Neocortical gray matter volume in first-episode schizophrenia and first-episode affective psychosis: a cross-sectional and longitudinal MRI study. *Biol Psychiatry*. 2007;62:773–783.
66. Schaufelberger MS, Duran FL, Lappin JM, et al. Grey matter abnormalities in Brazilians with first-episode psychosis. *Br J Psychiatry Suppl*. 2007;51:s117–s122.
67. Morgan KD, Dazzan P, Orr KG, et al. Grey matter abnormalities in first-episode schizophrenia and affective psychosis. *Br J Psychiatry Suppl*. 2007;51:s111–s116.
68. Reig S, Parellada M, Castro-Fornieles J, et al. Multicenter study of brain volume abnormalities in children and adolescent-onset psychosis. *Schizophr Bull*. 2011;37:1270–1280.
69. El-Sayed M, Steen RG, Poe MD, et al. Brain volumes in psychotic youth with schizophrenia and mood disorders. *J Psychiatry Neurosci*. 2010;35:229–236.
70. de Castro-Manglano P, Mechelli A, Soutullo C, et al. Structural brain abnormalities in first-episode psychosis: differences between affective psychoses and schizophrenia and relationship to clinical outcome. *Bipolar Disord*. 2011;13:545–555.
71. Takahashi T, Wood SJ, Soulsby B, et al. An MRI study of the superior temporal subregions in first-episode patients with various psychotic disorders. *Schizophr Res*. 2009;113:158–166.
72. Bora E, Fornito A, Radua J, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophr Res*. 2011;127:46–57.
73. Hirayasu Y, Shenton ME, Salisbury DF, et al. Subgenual cingulate cortex volume in first-episode psychosis. *Am J Psychiatry*. 1999;156:1091–1093.
74. Kubicki M, Shenton ME, Salisbury DF, et al. Voxel-based morphometric analysis of gray matter in first episode schizophrenia. *Neuroimage*. 2002;17:1711–1719.
75. Koo MS, Levitt JJ, Salisbury DF, Nakamura M, Shenton ME, McCarley RW. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. *Arch Gen Psychiatry*. 2008;65:746–760.
76. Kasai K, Shenton ME, Salisbury DF, et al. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. *Arch Gen Psychiatry*. 2003;60:1069–1077.
77. Konarski JZ, McIntyre RS, Kennedy SH, Rafi-Tari S, Soczynska JK, Ketter TA. Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. *Bipolar Disord*. 2008;10:1–37.
78. Hakak Y, Walker JR, Li C, et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc Natl Acad Sci USA*. 2001;98:4746–4751.
79. Harrison PJ, Law AJ. Neuregulin 1 and schizophrenia: genetics, gene expression, and neurobiology. *Biol Psychiatry*. 2006;60:132–140.
80. Walker RM, Christoforou A, Thomson PA, et al. Association analysis of Neuregulin 1 candidate regions in schizophrenia and bipolar disorder. *Neurosci Lett*. 2010;478:9–13.
81. Domschke K, Lawford B, Young R, et al. Dysbindin (DTNBP1)–a role in psychotic depression? *J Psychiatr Res*. 2011;45:588–595.
82. Weickert CS, Straub RE, McClintock BW, et al. Human dysbindin (DTNBP1) gene expression in normal brain and in schizophrenic prefrontal cortex and midbrain. *Arch Gen Psychiatry*. 2004;61:544–555.
83. Marballi K, Cruz D, Thompson P, Walss-Bass C. Differential neuregulin 1 cleavage in the prefrontal cortex and hippocampus in schizophrenia and bipolar disorder: preliminary findings. *PLoS ONE*. 2012;7:e36431.
84. Pennington K, Dicker P, Dunn MJ, Cotter DR. Proteomic analysis reveals protein changes within layer 2 of the insular cortex in schizophrenia. *Proteomics*. 2008;8:5097–5107.
85. Martins-de-Souza D. Proteomics tackling schizophrenia as a pathway disorder. *Schizophr Bull*. 2012b;38:1107–1108.
86. McCormick LM, Boles Ponto LL, Pierson RK, Johnson HJ, Magnotta V, Brumm MC. Metabolic correlates of antidepressant and antipsychotic response in patients with psychotic depression undergoing electroconvulsive therapy. *J ECT*. 2007;23:265–273.
87. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry*. 2012;69:776–786.
88. Pearlson GD, Wong DF, Tune LE, et al. In vivo D2 dopamine receptor density in psychotic and nonpsychotic patients with bipolar disorder. *Arch Gen Psychiatry*. 1995;52:471–477.
89. Reeves S, Brown R, Howard R, Grasby P. Increased striatal dopamine (D2/D3) receptor availability and delusions in Alzheimer disease. *Neurology*. 2009;72:528–534.

90. Sapolsky RM, Krey LC, McEwen BS. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. *Proc Natl Acad Sci USA*. 1984;81:6174–6177.
91. Frodl T, O'Keane V. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiol Dis*. 2013;52:24–37.
92. Schatzberg AF, Posener JA, Rothschild AJ. The role of dopamine in psychotic depression. *Clin Neuropharmacol.* 1995;18(Suppl 1):S66–S73.
93. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct*. 2010;214:655–667.
94. Shepherd AM, Matheson SL, Laurens KR, Carr VJ, Green MJ. Systematic meta-analysis of insula volume in schizophrenia. *Biol Psychiatry*. 2012;72:775–784.
95. Takahashi T, Wood SJ, Soulsby B, et al. Diagnostic specificity of the insular cortex abnormalities in first-episode psychotic disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33:651–657.
96. Takahashi T, Yücel M, Lorenzetti V, et al. Volumetric MRI study of the insular cortex in individuals with current and past major depression. *J Affect Disord*. 2010;121:231–238.
97. Sprengelmeyer R, Steele JD, Mwangi B, et al. The insular cortex and the neuroanatomy of major depression. *J Affect Disord*. 2011;133:120–127.
98. Garrett A, Kelly R, Gomez R, Keller J, Schatzberg AF, Reiss AL. Aberrant brain activation during a working memory task in psychotic major depression. *Am J Psychiatry*. 2011;168:173–182.
99. Martins-de-Souza D, Guest PC, Harris LW, et al. Identification of proteomic signatures associated with depression and psychotic depression in post-mortem brains from major depression patients. *Transl Psychiatry*. 2012;2:e87.
100. Corlett PR, Taylor JR, Wang XJ, Fletcher PC, Krystal JH. Toward a neurobiology of delusions. *Prog Neurobiol*. 2010;92:345–369.
101. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-year prospective follow-up study. *J Clin Psychiatry*. 2007;68:1411–1417.
102. Sun J, Maller JJ, Guo L, Fitzgerald PB. Superior temporal gyrus volume change in schizophrenia: a review on region of interest volumetric studies. *Brain Res Rev*. 2009;61:14–32.
103. Baethge C, Baldessarini RJ, Freudenthal K, Streeruwitz A, Bauer M, Bschor T. Hallucinations in bipolar disorder: characteristics and comparison to unipolar depression and schizophrenia. *Bipolar Disord*. 2005;7:136–145.
104. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry*. 2011;168:73–81.
105. Kelley R, Garrett A, Cohen J, et al. Altered brain function underlying verbal memory encoding and retrieval in psychotic major depression. *Psychiatry Res*. 2013;211:119–126.
106. Sommer IE, Vd Veer AJ, Wijkstra J, Boks MP, Kahn RS. Comparing language lateralization in psychotic mania and psychotic depression to schizophrenia; a functional MRI study. *Schizophr Res*. 2007;89:364–365.
107. van Veelen NM, Vink M, Ramsey NF, et al. Reduced language lateralization in first-episode medication-naive schizophrenia. *Schizophr Res*. 2011;127:195–201.
108. Anticevic A, Brumbaugh MS, Winkler AM, et al. Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. *Biol Psychiatry*. 2013;73:565–573.
109. Dudek D, Siwek M, Zielińska D, Jaeschke R, Rybakowski J. Diagnostic conversions from major depressive disorder into bipolar disorder in an outpatient setting: results of a retrospective chart review. *J Affect Disord*. 2013;144:112–115.
110. Ruggero CJ, Kotov R, Carlson GA, Tanenberg-Karant M, González DA, Bromet EJ. Diagnostic consistency of major depression with psychosis across 10 years. *J Clin Psychiatry*. 2011;72:1207–1213.
111. Tohen M, Khalsa HM, Salvatore P, Vieta E, Ravichandran C, Baldessarini RJ. Two-year outcomes in first-episode psychotic depression the McLean-Harvard First-Episode Project. *J Affect Disord*. 2012;136:1–8.
112. Bromet EJ, Kotov R, Fochtmann LJ, et al. Diagnostic shifts during the decade following first admission for psychosis. *Am J Psychiatry*. 2011;168:1186–1194.
113. Whitty P, Clarke M, McTigue O, et al. Diagnostic stability four years after a first episode of psychosis. *Psychiatr Serv*. 2005;56:1084–1088.
114. Peralta V, Cuesta MJ. Exploring the borders of the schizoaffective spectrum: a categorical and dimensional approach. *J Affect Disord*. 2008;108:71–86.
115. Majadas S, Olivares J, Galan J, Diez T. Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. *Compr Psychiatry*. 2012;53:145–151.
116. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*. 2011;68:128–137.
117. Smith R, Chen K, Baxter L, Fort C, Lane RD. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. *J Affect Disord*. 2013;146:414–419.
118. Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. *Mol Psychiatry*. 2011;16:604–619.
119. Cannon DM, Walshe M, Dempster E, et al. The association of white matter volume in psychotic disorders with genotypic variation in NRG1, MOG and CNP: a voxel-based analysis in affected individuals and their unaffected relatives. *Transl Psychiatry*. 2012;2:e167.
120. Terwisscha van Scheltinga AF, Bakker SC, van Haren NE, et al. Genetic schizophrenia risk variants jointly modulate total brain and white matter volume. *Biol Psychiatry*. 2013;73:525–531.
121. Whalley HC, Papmeyer M, Sprooten E, et al. The influence of polygenic risk for bipolar disorder on neural activation assessed using fMRI. *Transl Psychiatry*. 2012;2:e130.
122. Modinos G, Pettersson-Yeo W, Allen P, McGuire PK, Aleman A, Mechelli A. Multivariate pattern classification reveals differential brain activation during emotional processing in individuals with psychosis proneness. *Neuroimage*. 2012;59:3033–3041.
123. Maj M. Delusions in major depressive disorder: recommendations for the DSM-V. *Psychopathology*. 2008;41:1–3.