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The Kraepelinian Dichotomy Viewed by Neuroimaging

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The Kraepelinian dichotomy between schizophrenia (SZ) and bipolar disorder (BD) is being challenged by recent epidemiological and biological studies. We performed a comparative review of neuroimaging features in both conditions at several scales: whole-brain and regional volumes, brain activity, connectivity, and networks. Structural volumetric neuroimaging studies suggest a common pattern of volume decreases, but networks studies reveal a clearer distinction between BD and SZ with an altered connectivity generalized to all brain networks in SZ and restricted to limbic, paralimbic, and interhemispheric networks in BD.

Key words: schizophrenia/bipolar disorder/Kraepelinian dichotomy/connectivity/neuroimaging

Introduction

The dichotomy described between schizophrenia (SZ) and bipolar disorder (BD) is still present in the most recent classifications (DSM5, CIM-10) but remains controversial, with disputed boundaries, weak diagnostic validity, and limited promise for biological significance. It is increasingly recognized that SZ and BD not only share environmental and genetic risk factors, but also medication and neurobiological mechanisms.[1] Following the concept that the boundaries between SZ and BD may not be so clear, brain imaging is a useful tool to examine the overlap as well as specific patterns in cerebral structures of patients with SZ or BD. Structural T1 MRI provides extensive information on differences in several brain regions between patients with SZ and BD on one hand and healthy individuals on the other hand, but also between SZ on one hand and BD patients on the other hand. Other imaging techniques are also valuable, such as diffusion tensor imaging (DTI) which allows examining white matter integrity and resting state functional magnetic resonance imaging (rs-fMRI) to assess regional interactions in brain circuits.

BD and SZ: From Volumes to Circuits?

Reviewing brain imaging studies to explore the different and shared features of SZ and BD has yielded heterogeneous results, depending on various factors such as populations included, the techniques used, and the neural scale being studied. We will therefore here focus on the most relevant and consistent neuroimaging results in both conditions, favoring meta-analytical results whenever available.

Brain Volumes

The first neuroimaging studies explored total brain volumes. In SZ, meta-analyses revealed that intracranial and whole brain volumes are reduced compared to controls, including at the onset of the disease.[2,3] In parallel, ventricles are enlarged, total grey matter volume decreased, with contradictory findings in white matter. In BD, a parallel meta-analysis of MRI studies at the onset of the disease found a largely similar pattern with a decrease in intracranial, whole brain, total grey, and white matter volumes but not in ventricular volumes.[3] Effect sizes of the decrease in whole brain volumes are usually larger in SZ than BD. In both conditions, number of episodes, duration of illness, antipsychotic medication, and poorer functional outcome are associated with decreases in grey and white matter volumes and enlargement of ventricles.[4]

Studies of regional brain volumes showed robust reductions in gray matter volume and/or density throughout cortical and subcortical structures in SZ, with the most substantial deficits in the frontotemporal

regions, including the hippocampal-amygdala complex, dorsolateral and medial prefrontal cortex, and superior temporal cortex.[5] In BD, recent meta-analyses have also described gray matter reductions in the prefrontal, anterior cingulate, insular, and temporal cortices, overlapping with those observed in SZ, albeit less extensively.[5] In addition, studies reported more frequently in SZ than in BD a decrease in dorsolateral prefrontal, parietal, or occipital cortical volumes. The level of between-studies heterogeneity is more important in BD than in SZ. Studies have reported either decreased[6] or unchanged[7] volumes of hippocampus in BD depending on number of episodes, psychotic features, and lithium medication. Recent models of clinical staging of SZ and BD may explain discrepancies between studies.[8] But to date, there has not been any clear attempt to examine imaging evidence of these models.[9] Similarly, amygdala enlargement has been reported in adult patients with BD and amygdala shrinkage has been reported in children and adolescents with BD.[10]

Brain Activity

Numerous studies have explored brain activation in SZ and BD but few direct comparisons have been conducted, and, in addition, these studies generally used different paradigms for SZ and BD. Tasks used were based on known neuropsychological deficits in these conditions (cognitive and executive tasks in SZ and emotional processing tasks in BD).

Brain regional activity is usually assessed with fMRI using the blood oxygenation level-dependent (BOLD) technique. BOLD is based on the neurovascular coupling: it assumes that an increase in the regional blood flow is a marker of heightened regional cerebral activity. fMRI studies in SZ have consistently shown abnormal activation of prefrontal regions such as the dorsolateral and ventrolateral prefrontal cortex, dorsal and anterior cingulate cortex, and in the thalamus and parietal cortex. More specifically, studies of executive function or episodic memory in SZ have revealed this typical prefrontal pattern[11] with either hyper- or hypoactivation, depending on the cognitive load of the task. This has been interpreted as an inefficient prefrontal cognitive processing in SZ. Another clinical dimension frequently explored with fMRI in SZ is the theory of mind, defined as the ability to understand the potential mental states and intentions of others. It represents a crucial aspect of social cognition, with a high impact on the capacity to interact within the social world. Alterations in critical regions for social cognition such as the temporo-parietal junction, the superior temporal sulcus, and the medial prefrontal cortex have been reported.[12]

Because of the prevailing emotional symptoms in BD, functional neuroimaging studies mostly used emotional processing paradigms such as emotional labeling or Go/NoGo. They provided evidence for alterations in regions associated with the experience and regulation of emotions. Patients exhibited a decreased activation in regions associated with the regulation of emotions (middle and inferior prefrontal and parietal) and an increased activation in ventral limbic brain regions that mediate the experience of emotions and generation of emotional responses (amygdala and parahippocampal gyrus).[13] However, such a mechanistic model appears overly reductionist as tasks exploring other processes such as reward processing yield similar results.[14]

Among the different paradigms used, facial emotion processing tasks have been used in both SZ and BD. A recent meta-analysis identified as much as 29 studies and found clear differences between SZ and BD: patients with SZ showed under-activation throughout the regions implicated in facial affect processing network and increased activation in visual processing regions (cuneus). Patients with BD showed overactivation within the parahippocampus/amygdala and thalamus and reduced engagement within the ventrolateral prefrontal cortex.[15]

Finally, direct comparisons with volumetric anatomical studies are not straightforward since a vast majority of fMRI studies use template-derived analyses, not so commonly used in structural imaging.

Brain Connectivity and Networks

Based on the theories of disconnection first postulated by Wernicke and Bleuler and the notion that major psychiatric disorders may not arise from focal brain abnormalities, there has been a recent interest in explorations of brain connectivity in SZ and BD. Theories of disconnection assume that some aspects of SZ are best understood in terms of abnormal interactions between different cerebral areas.

SZ has even been conceptualized as a "connectivity disorder."[16] Connectivity refers to the structural and functional links between brain regions. Structural connectivity not only relies on white matter, mainly axons, but also on synapses. Long-range structural connectivity can be assessed in vivo by DTI. Functional connectivity (FC) is the "temporal correlations between spatially remote neurophysiological events."[17] It provides insight into the degree to which different parts of brain networks are functionally coupled together.

Structural Connectivity. DTI allows the exploration of microstructural features of white matter tracts. Fractional anisotropy (FA), its most used variable, is correlated with the integrity and coherence of white matter. Decreases in FA have been associated with edema, demyelination, and brain inflammation. In SZ, large clusters of FA decreases

have been identified,[18] especially in frontal and temporal regions and also in most of the long-range white matter tracts such as the corpus callosum, the fornix, the arcuate fasciculus, the corticospinal tract, the cerebello-thalamo-cortical circuits, and the limbic tracts.[19] These decreases in FA are associated with and thought to underlie cognitive abnormalities and many of the clinical dimensions in SZ such as hallucinations, dissociative symptoms, or negative symptoms.[20] Their presence in first-episode patients and healthy relatives of patients led some authors to suggest that FA decreases as putative endophenotypes for SZ.[21]

In BD, similar alterations in structural connectivity have been found, but to a smaller spatial extent. Decreases in FA have been found in emotional regulation-related regions such as in white matter adjacent to the parahippocampus and the subgenus cingulate.[22] The uncinate fasciculus, linking the prefrontal areas to ventral limbic regions (such as the amygdala and hippocampus), is particularly altered,[23] along with the cingulum and corpus callosum.[24] Results in other tracts are more heterogenous. The alteration in prefrontal-limbic connectivity is thought to underlie the emotional dysregulation present in patients with BD.

Functional Connectivity. FC has been studied both during task and at rest. Similar to activation studies, in SZ, FC studies used working memory or executive tasks and showed an altered FC not only in frontotemporal networks[25,26] but also in most of the task-related brain networks.[27] In BD, most of the FC studies used affective paradigms focusing on the corticolimbic connectivity and identified altered FC between the anterior limbic cortices and the amygdala[28,29] in patients, generally decreased, but dependent on the age of onset, emotional valence, and state of the patients.

The use of rs-fMRI is very appealing in the comparison of SZ and BD as it is easily feasible in both populations, is not task performance dependent, and it allows a direct comparison of results between populations and studies. Most of the networks evidenced during tasks are also detectable at rest. In addition, the default-mode network (DMN), encompassing the medial prefrontal cortex, the posterior cingulate, the precuneus, and the hippocampus, preferentially activates at rest. Despite some heterogeneity between the numerous studies, compared with healthy controls, patients with SZ generally exhibited increased connectivity within the DMN[30]; default-mode abnormalities were associated with symptoms of SZ and abnormal connectivity with task-positive networks in several studies.[31] In BD, the spatial extent of DMN has been found altered[32] but few studies reported altered connectivity within the DMN, independently of a history of psychosis.

Regarding other networks, abnormal FC within the networks in charge of the emotion regulation has been identified in BD, in particular for the ventral lateral and medial prefrontal-limbic connectivity.[33–35] In SZ, prefrontal cortex, cortical-subcortical, and within auditory/language networks FC have been reported altered,[36] generally lowered.

Several studies compared patients with SZ and BD using rs-fMRI. A very recent exploration compared 19 patients with BD and 18 patients with SZ and computed FC between 266 regions of interest throughout the brain. Both patient groups had significantly lower connectivity in the paracingulate gyrus and right thalamus but only patients with SZ also had significantly lower connectivity in the temporal occipital fusiform cortex, left caudate nucleus, and left thalamus compared with healthy controls.[36]

Recent analytical techniques, derived from the graph theory, allow studying and describing the topological properties of brain networks based on rs-fMRI data. Graph metrics have shown that the normal human brain is highly similar to a "small-world" network, with high levels of clustering among nodes of the networks and short path lengths between nodes of the different brain networks.[37] Such studies in patients with SZ revealed reduced clustering and small-worldness along with reduced probability of high-degree hubs in medial parietal, premotor, and cingulate regions.[38] These metrics correlated with behavioral performance on a verbal fluency task. This decreased small-worldness is present both at rest and during task, indicating a consistent tendency towards a more random organization of brain networks.[39] To our knowledge, no such fMRI-based graph study is available in BD. One group, using DTI-derived graph metrics, found impaired inter-hemispheric but relatively preserved intra-hemispheric integration in BD, with nodal network abnormalities in the limbic system.[40]

A very recent study tested whether alterations in global brain signal, often discarded as a meaningless baseline in fMRI study, were present in SZ and BD. Using a very large sample (161 patients with SZ, 73 with BD, and 220 controls), they showed that patients with SZ exhibited increased global brain BOLD signal variability that was associated with symptomatic levels. Both findings were absent in patients with BD. The authors additionally designed a computational model of rs-fMRI to understand this finding. The modeling results show that changes in global signal may have their origin in an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) actions.[41] Alterations in metabolism of glutamate and GABA are evidenced in SZ by magnetic resonance spectroscopy studies while findings are more equivocal in BD.[42,43]

In summary, whole-brain DTI studies identified a widespread pattern of decreased structural connectivity in SZ, while altered connectivity in BD was restricted to limbic and interhemispheric bundles. FC studies paralleled these findings of a more extended decreased connectivity in SZ than in BD.

Psychotic Features

BD with psychotic features is considered by some authors as an intermediate subtype of BD between SZ and BD without psychotic features. The inclusion of various proportions of patients with BD with psychotic features between studies may bias some of the previous results. Recently, a multisite consortium has studied, with multimodal MRI, a large sample of patients with SZ, schizoaffective disorder, and BD with psychotic features. This consortium largely confirmed the findings described in the previous paragraphs with widespread gray matter reductions across the brain of patients with SZ or schizoaffective disorder, while these reductions were restricted to the frontotemporal areas in BD.[44] With DTI, many regions revealed decreases in FA for SZ but not for psychotic BD, even though a direct comparison between both patients groups yielded no differences.[45] Similarly, during rs-fMRI, the same group identified 5 networks connected differentially depending on the diagnosis. The paralimbic circuit was specifically altered in patients with BD, with an increased FC between multiple regions involved in emotion processing such as the mesial temporal cortex, amygdala, parahippocampus, hippocampus, subgenual cingulate, ventrolateral prefrontal cortex, orbitofrontal cortex, and insula. They also reported a decreased FC between fronto-premotor and meso/paralimbic networks specific to SZ. These networks may be related to large-scale brain networks in charge of several domains such as planning, affective flattening, and cognitive control. Both patients groups also shared affected FC between networks associated with self-referential processing, executive attention, orientation, and goal-directed top-down processing, all of which are compromised in both SZ and BD.[46]

To our knowledge, no large-scale multimodal MRI study comparing patients with SZ and BD with and without psychotic features has yet been published.

Conclusion: Evidence for Diagnostic Specificity?

Numerous genetic and epidemiologic findings have questioned the strict dichotomy of SZ and BD. Structural volumetric neuroimaging studies suggest that patients with SZ and BD share a common pattern of volume decreases, though to a larger extent in SZ. Nevertheless, whole-brain studies of networks reveal a clearer distinction between BD and SZ with an altered connectivity in BD restricted to limbic, paralimbic, and interhemispheric connections. In contrast, patients with SZ suffer from a generalized altered connectivity.

Consistently with these differences, multivariate machine learning algorithms achieve to distinguish patients with SZ and BD with a good accuracy using whole-brain information. In such algorithms, the computer learns from a "learning dataset", the rules for distinguishing the MRI scans of 2 groups (patients with BD and SZ), based on various mathematical methods. The computer then applies these rules to new datasets. Using structural MRI, Schnack et al trained an algorithm able to separate patients with SZ and BD with an average accuracy of 88% and used it on another dataset with a classification accuracy of 66%.[47] These results tend to support the specificity of some brain features in SZ and BD.

We may thus hypothesize that SZ is primarily be a global "disconnectivity disorder" affecting indifferently all brain networks, while BD would primarily be a disorder affecting emotion processing networks. Developmental longitudinal studies of at-risk subjects for SZ and BD might help validate and refine this hypothesis.

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