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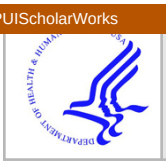

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Author manuscript
Psychiatr Ann. Author manuscript; available in PMC 2018 October 25.

Published in final edited form as:
Psychiatr Ann. 2010 March ; 40(3): 154–159. doi:10.3928/00485713-20100303-09.

Tackling the Kraepelinian Dichotomy: a Neuroimaging Review

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Background

The description of Schizophrenia and Bipolar Disorder as disparate clinical entities arose from a Kraepelinian distinction in the time period from the late 19th to early 20th century, which soon became known as the Kraepelinian Dichotomy. Over the years, many studies were conducted to gain further insight as to whether or not this distinction continued to hold true. The increase in interest in the study and impact of the phenomenology associated with psychiatric illness in the 1980's led to the Kraepelinian Dichotomy being operationalized in the third revision of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM) (1). The Kraepelinian Dichotomy continues to be engrained in psychiatric practice and yet the age-old debate as to whether or not the dichotomy "holds true" persists. The current article reviews the existent neuroimaging literature on this topic in an effort to illustrate the neurobiological evidence that either supports or refutes this dichotomy. The article concludes with related recommendations as to suggested revisions to the current categorical nosology of the DSM IV-TR.

Despite Kraepelin's initial conceptualization, he later acknowledged that Schizophrenia and Bipolar Disorder may indeed share some overlapping clinical features. Kraepelin began to appreciate that it was not individual symptoms that would distinguish Schizophrenia and Bipolar Disorder, but rather the pattern of their presentation that would provide these clinical delineations. While Kraepelin believed Schizophrenia to be associated with a gradual and progressive cognitive and functional decline, he believed manic-depression to be more representative of a course of intermittent decline in functioning interwoven with periods of return to baseline and full recovery of illness. Kraepelin found, through his studies of

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Financial Disclosures
The authors declare no potential conflict of interest.

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families, that indeed what he termed Dementia Praecox (Bleuler later renamed this as Schizophrenia) and Manic Depression (later differentiated into various mood disorders including Bipolar illness and Depression)(2, 3) appeared to be inherited traits based on the similarities in course and outcome among generations within families.

Some clinicians of the era debated the idea of a mutually exclusive or dichotomous characterization of these debilitating illnesses. In a more integrative fashion, Kasanin introduced the term Schizoaffective Disorder with its inherent overlap between mood and psychotic symptoms. Some clinicians and researchers continue to argue that given the significant clinical overlap, a certain degree of shared biological (and likely associated genetic) predisposition is likely present. Indeed, Kraepelin's discussions on the ability of these disorders to "breed true" emphasized the inherited nature of these syndromes, providing evidence of his foresight of the need to identify biological features of these illnesses to gain a mechanistic understanding of their similarities and differentiation.

Despite some early questions and debate as to the degree of overlap between these clinical illnesses, the increase in genetic and family studies over the past two to three decades has resulted in the re-ignition of this age-old debate. The extent of clinical overlap between Schizophrenia and Bipolar Disorder that were identified in research studies support the overlap that was readily apparent from clinical practice. Some of the factors involved in this overlap include epidemiological factors (i.e. age of onset, sex distributions, and prevalence) and clinical presentations (i.e. Schizophrenia with superimposed mood symptoms and psychotic presentations of Bipolar Disorder). Until recently, however, there has been limited research involving neurobiological phenotypes of this overlap.

We set out to review the literature that explores this issue by reviewing studies that specifically compared and contrasted the various imaging findings between Schizophrenia and Bipolar Disorder. While the bulk of the neuroimaging literature comparing and contrasting the findings amongst these two clinical paradigms relates to volume comparisons derived from anatomical studies (i.e. post mortem anatomy, structural magnetic resonance imaging (MRI)), the evolution of functional neuroimaging research paradigms has resulted in a slow but gradual increase in the numbers and quality of studies that compare and contrast the brain function between these two debilitating illnesses.

Methods

An extensive literature review of original research articles comparing neuroimaging findings in Schizophrenia and Bipolar Disorder was conducted using PubMed. In all articles reviewed here, diagnoses were to be made based on the DSM version that was current at the time of article submission. A post-mortem anatomical study was also included to represent earlier work and as a reference to compare more recent neuroimaging findings against. The literature search was further narrowed by including only those original research articles whose paradigms were based on the following neuro-imaging techniques: structural Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET), and functional Magnetic Resonance Imaging (fMRI). Of the approximately 80 original research articles obtained

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form our intensive search (“Brain Imaging Bipolar Schizophrenia”; MRI Bipolar Schizophrenia”, PET Bipolar Schizophrenia”, “fMRI Bipolar Schizophrenia”, “Functional Bipolar Schizophrenia”) the results were narrowed down to approximately 20 articles based on methodological soundness and quality of research. The results were further organized categorically based on imaging modality and then further subdivided based on regional findings. These findings are outlined in the attached table (Table 1) under the following categories: Post-Mortem, MRI, MRS, DTI, PET, and fMRI. This was not intended to be a thorough review of neuroimaging for each individual disorder, but rather, an outline of findings from studies that specifically compared Schizophrenia and Bipolar Disorder and which possibly had related these findings to those of healthy controls.

Additionally, to further investigate whether the Kraeplinian Dichotomy and the associated neuroimaging findings “hold true,” some studies focusing on genetic studies have been included. Where possible, comparisons of neuronal circuitry from a systems based approach to neuroimaging has been highlighted. However, despite these efforts, the bulk of the studies comparing these two illnesses involved anatomical comparisons from structural MRI.

Results

The majority of articles identified involved comparing and contrasting the brain structure in individuals with Schizophrenia and Bipolar Disorder with that of healthy controls (Table 1). While there has been some work done in PET imaging (Table 1), investigating the differences in the various receptor systems specifically across these diagnostic boundaries, this volume of this research is not great – perhaps due to the ethical concerns of withholding treatment from this clinically unstable group of individuals.

A post-mortem study (4) investigating diagnostic comparisons of neuronal somal size within the layers of the insular cortex, has determined that schizophrenic subjects have a reduction in neuronal somal size within a particular layer of the insula as compared to bipolar subjects.

The structural MRI studies reviewed (Table 1) show consistent evidence that in Schizophrenia there is a reduction in hippocampal volumes and an increase in ventricular size compared to patients with Bipolar Disorder. However, there is less consistency regarding frontal and subcortical changes in terms of replication of findings, presence or absence of lateralization, and clinical association.

In an MRS investigation (5) (Table 1), although no difference in metabolites between diagnostic categories was detected, Bipolar subjects on lithium treatment evidenced elevated NAA/PCr-Cr in the basal ganglia region as compared to healthy controls, an effect that could be confounded by the effects of medication.

Of the fMRI studies reviewed (Table 1), a common theme emerged indicating activation differences in the prefrontal cortex between subjects with Bipolar Disorder and subjects with Schizophrenia. These differences do not appear to be limited to psychotic presentations of mood episodes and include subjects with Bipolar Disorder Type I in general. Of particular interest is that these differences occurred across a variety of tasks including emotional prosody, sentence completion, and verbal fluency. It should be noted that one study

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identified a link between the effect of genotype for neuroreglin-1 and activation under a verbal fluency task, with effect of genotype being associated with greater deactivation in the left precuneus across diagnostic boundaries (Schizophrenia, Bipolar Disorder, and healthy controls). This study additionally identified an association between effect of genotype and activation that appeared to separate out with clinical categories (inferior frontal gyrus in subjects with high risk for Schizophrenia; posterior orbital gyrus in subjects with high risk for Bipolar Disorder).

We identified and selected two PET studies that specifically compared the neurobiology of Schizophrenia and Bipolar Disorder I (Table 1). One of these studies directly measured particular receptor or transporter binding potentials, and the second study used PET to measure cerebral blood flow. Zubieta et al found differences in the concentration of vesicular monoamine transporters (VMAT2), as measured with the radiotracer [^{11}C]DTBZ, reflecting aminergic synaptic density, between schizophrenic and bipolar subjects in the thalamus, as well as between Bipolar Disorder and healthy subjects (6)(7). In another study that investigated the diagnostic differences in blood flow in the superior temporal cortex, no effects of diagnosis were found (8).

There has been little work done to date examining the differences in measures of white matter tracks and neuronal connectivity between Schizophrenia and Bipolar Disorder. However, one recent study investigating connectivity with diffusion tensor imaging found that although patient groups and controls had differences in fractional anisotropy compared to healthy controls, these differences did not hold for comparisons across the diagnostic categories of Schizophrenia and Bipolar Disorder (9) (Table 1).

Conclusion

The neurobiological/neuropsychological domains affected in Bipolar Disorder have been identified as being more widespread and more closely related to Schizophrenia than originally expected. However, the degree of severity of these changes is disparate, with Schizophrenia resulting in a typically more severe neuropsychological deterioration than that of Bipolar Disorder. The convergence that is seen within endophenotypes (i.e. neuroimaging data) associated with certain phenotypic domains (i.e. psychosis) suggests the presence of a dimensional pattern of illness. However, the existence of overlap with Schizophrenia appears more consistent in psychotic forms of Bipolar Disorder as compared to non-psychotic Bipolar Disorder. Although on comparing respective measures of connectivity, fractional anisotropy was indeed found to be similar across diagnostic boundaries in certain brain regions (i.e. anterior limb of internal capsule, anterior thalamic radiation, and uncinate fasciculus) and with FA differences noted between either patient group and healthy controls.

Attempts to separate out these psychiatric pathologies by spectroscopic measures have not proven beneficial. Specifically, evidence of changes in the concentrations of various cellular markers (i.e. Choline, Inositol & NAA/PCr-Cr) in the basal ganglia has been observed only in bipolar patients on lithium treatment whereas concentrations in both the basal ganglia and occipital cortex were found to be similar between Schizophrenia and Bipolar Disorder. In

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addition, these similarities overlapped with those of healthy controls, suggesting that this measure may not be helpful in differentiating these psychopathologies from normalcy.

Additionally, other associations (i.e. left amygdala volume associated with verbal memory) highlight the vast differences between these illnesses and in so doing provide more support to the categorical nosology present in the current version of the DSM. Indeed, just as many non-overlapping findings are evident from our review of neuroimaging in Schizophrenia and Bipolar Disorder. Most notable are the volumetric differences in the ventricles, hippocampus, and amygdala between Schizophrenia and Bipolar Disorder that have been widely reproduced. However, if these changes were to be represented on a continuum, we wouldn't expect such disparate association with neuropsychological functioning as has been pointed out by Kilgore et al. who were unable to find differences in amygdala volume, but did find that left amygdala volume in bipolars was positively correlated to verbal memory, while conversely in Schizophrenia, it was negatively correlated to memory (10).

The PET findings illustrate the idea of partial overlap and co-existing heterogeneity of these two psychiatric illnesses with Diagnostic effects being associated with vesicular monoamine transporter (VMAT2) binding in both the thalamus (Bipolar Disorder having greater binding than Schizophrenia or healthy controls) and the Ventral Brainstem (similar binding in Bipolar Disorder and Schizophrenia, both of which are greater than that in healthy controls). Other research showed no diagnostic difference in regional cerebral blood flow measurements.

The results of the fMRI studies yield similar results - some supporting the dichotomy and others supporting a dimensional explanation. There is evidence to show that bipolar and schizophrenic subjects differentially activated portions of their insula and prefrontal cortex during sentence completion and differential activation of the prefrontal cortex during verbal fluency tasks. Additionally, tasks of emotional prosody appeared to highlight both differential activation and similarities in activation between Schizophrenia and Bipolar Disorder. Despite the fact that recent studies have suggested neuroregulin-1 as a susceptibility gene for Schizophrenia and Bipolar Disorder, the results outlined have shown regions of deactivation associated with the neuroregulin-1 gene that appear to be common to Bipolar Disorder, Schizophrenia, and healthy controls (left precuneus). Additionally, an interaction between genotype and regional activation in the prefrontal cortex is present in both Bipolar Disorder and Schizophrenia, but these regions of activation are disparate, outlining the possibility that despite a possible genetic similarity across these diagnostic paradigms, the functional implication of this genetic susceptibility appears to be somewhat disparate.

In summary, the available neuroimaging findings that have been reviewed support the presence of both an overlap and a distinction between the circuitry that appears to be involved in the pathophysiology of Schizophrenia and Bipolar Disorder. At present, the majority of available data is limited to neuroanatomical measures of both grey matter and white matter, with a recent trend towards an increase in functional studies. The findings of anatomical and functional overlap would be helpful in informing genetic association studies

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in this area. Additionally, further longitudinal neuroimaging incorporated into family studies would likely provide more evidence to support these hypotheses.

The above findings neither refute nor prove the Kraepelinian Dichotomy, but certainly provide evidence for an overlap between neurobiological factors underlying both disorders. The results of this review validate the need for the further investigation of biomarkers that will assist in the sub-classification of those psychiatric illnesses whose symptom clusters lie along the spectrum of mood and psychotic dimensions. These discoveries will likely highlight the complexity of disordered neurobiology, yielding a greater prominence to biologically driven diagnostic and treatment approaches in chronic neuropsychiatric illnesses. The key question that emerges is not surrounding the validity of the Kraepelinian Dichotomy, but rather how do we move forward in our transition away from descriptive clinical classifications and towards a diagnostic system that is aligned with the complex neurobiological underpinnings of these disorders, and more akin to clusters of biological disparities and similarities.

Acknowledgments

Funds from The Phil F. Jenkins Foundation and The Prechter Bipolar Research Fund at the University of Michigan supported this work.

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Table 1

A review of neuroimaging studies comparing Schizophrenia and Bipolar Disorder

Author	Date	Title	Journal	Type	Region	Notes
Pennington, K. et al.	2008	Evidence for redùced neùronal somal size withìn the insùlar cortex in schizophrenia, bùt not in affective disorders	Schizophr Res	Post Mortem	Insular Cortex	Cytoarchitecture of Insula is abnormal in Schizophrenia, but not in mood disorders.
Dasari, M. et al.	1999	A magnetic resonance imaging stùdỳ of thalamic area in adolescent patients with either schizophrenia or bipolar disorder as compared to healthỳ controls	Psỳchiatrỳ Res	MRI	Thalamus	Thalamic area in Bipolars is similar to that of schizophrenics. Both patient groups have less thalamic area than controls
McDonald, C. et al.	2005	Regional volùme deviations of brain strùctùre in schizophrenia and psỳchotic bipolar disorder: compùtational morphometrỳ stùdỳ	Psỳchiatrỳ	MRI	fronto-temporal neocortex, medial temporal lobe, insùla, thalamùs and cerebellùm; major longitùdinal and interhemispheric tract	Grey Matter Deficits (fronto-temporal neocortex, medial temporal lobe, insùla, thalamùs and cerebellùm) are greater than in bipolars or controls. Major longitùdinal and interhemispheric tract Deficits in shizophrenics and bipolars are similar and greater than controls.
McDonald, C. et al.	2004	Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain strùctùral endophenotỳpes	Arch Gen Psỳchiatrỳ	MRI	fronto-striato-thalamic, temporal, anterior cingùlate gỳrùs, ventral striatùm	Genetic risk for Schizophrenias assoc, w/ distribùted graỳ deficits (bilateral fronto-striato-thalamic, left lateral temporal), Genetic risk for bipolar assoc, w/ graỳ deficits (right anterior cingùlate gỳrùs and ventral striatùm); Left frontotemporal disconnectivitỳ as a geneticallỳ controlled brain strùctùral abnormalitỳ common to both disorders
McIntosh, A. M. et al.	2004	Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives	Biol Psychiatry	MRI	Anterior Thalamus (AT); Middle PreFrontal Gyrus (mPFG); Dorsal Medial Thalamus (DMT)	Anterior thalamus is similar in Schizophrenics, Bipolars, and their relatives, but smaller than controls. Schizophrenics have smaller mPFG and DMT than bipolars and controls;
McIntosh, A. M. et al.	2008	White matter tractography in bipolar disorder and schizophrenia	Biol Psychiatry	MRI	uncinate fasciculus, anterior thalamic radiation	uncinate fasciculus & anterior thalamic radiation is similar in Schizophrenics and Bipolars, both less than controls.
McIntosh, A. M. et al.	2009	Prefrontal gyral folding and its cognitive correlates in bipolar disorder and schizophrenia	Acta Psychiatr Scand	MRI	prefrontal gyrification	prefrontal gyrification is greater in controls than in either bipolars or schizophrnics (both with similar results).
McIntosh, A. M. et al.	2006	Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure	Am J Med Genet B Neuropsychiatr Genet	MRI	Prefrontal Cortex (Dorsolateral and Ventrolateral)	Genetic risk associated with decreased volume in schizophrenia, but not in bipolar disorder.
Velakoulis, D. et al.	2006	Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic	Arch Gen Psychiatry	MRI	Hippocampus	smaller bilaterally in Schizophrenics than in Bipolars or Controls.

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Author	Date	Title	Journal	Type	Region	Notes
		schizophrenia, first-episode psychosis, and ultra-high-risk individuals				
Connor, S. E. et al.	2004	A study of hippocampal shape anomaly in schizophrenia and in families multiply affected by schizophrenia or bipolar disorder	Neuroradiology	MRI	Hippocampal shape anomaly (HSA)	present in schizophrenics, but not in their relatives, Bipolars, or controls.
Strasser, H. C. et al.	2005	Hippocampal and ventricular volumes in psychotic and nonpsychotic bipolar patients compared with schizophrenia patients and community control subjects: a pilot study	Biol Psychiatry	MRI	Hippocampus, Ventricles	Ventricle volume greater in psychotic Bipolars than in non-psychotic Bipolars or controls. Hippocampal volume less in Schizophrenics than in Bipolars or controls.
McDonald, C. et al.	2006	Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives	Am J Psychiatry	MRI	ventricles, Hippocampus	Lateral & 3rd Ventricular volumes greater in Schizophrenics (and relatives) than in Bipolars or controls.
Sharma, R. et al.	1992	Proton magnetic resonance spectroscopy of the brain in schizophrenic and affective patients	Schizophr Res	MRS	Basal Ganglia	Bipolar patients had greater elevated NAA/PGr-Cr, choline/PCr-Cr and inositol/PCr-Cr ratios than schizophrenics
Zubieta, J. K. et al.	2001	Vesicular monoamine transporter concentrations in bipolar disorder type I, schizophrenia, and healthy subjects	Biol Psychiatry	PET [11C] DTBZ	VMAT2 binding in Thalamus, Ventral Midbrain	Bipolars had greater VMAT2 binding in the Thalamus but similar binding in the Ventral Brainstem as compared to schizophrenics
Dye, S. M. et al.	1999	No evidence for left superior temporal dysfunction in asymptomatic schizophrenia and bipolar disorder. PET study of verbal fluency	Br J Psychiatry	PET (rCBF)	Temporal	rCBF is reduced in the STC in all groups.
Mechelli, A. et al.	2008	The effects of neuregulin1 on brain function in controls and patients with schizophrenia and bipolar disorder	Neuroimage	fMRI, Genetic	Relation of PFC activation to neuroregulin1	Interaction found (rIFG, high risk, schizophrenia) (rPOG, high risk, bipolar disorder)
McIntosh, A. M. et al.	2008	Prefrontal function and activation in bipolar disorder and schizophrenia	Am J Psychiatry	fMRI	insula and dorsal prefrontal cortex activation	Difference in OFC & Ventral Striatum recruitment in Bipolars and Schizophrenics
Curtis, V. A. et al.	2001	Differential frontal activation in schizophrenia and bipolar illness during verbal fluency	J Affect Disord	fMRI	Frontal Lobe	Bipolars have different frontal response patterns (during verbal fluency tasks) than Schizophrenics
McIntosh, A. M. et al.	2008	Prefrontal function and activation in bipolar disorder and schizophrenia	Am J Psychiatry	fMRI	Insular Cortex, Dorsal Prefrontal Cortex	Activation during Hayling task differentiated Bipolars from Schizophrenics and Controls
Mitchell. R. L. at al.	2004	Neural response to emotional prosody in schizophrenia and in bipolar affective disorder	Br J Psychiatry	fMRI	Temporal Lobe	Bipolars and Schizophrenics show left-lateralization of Temporal Lobe response to emotional prosody
Sussmann, J. E. et al.	2009	White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging	Bipolar Disord	DTI	anterior limb of internal capsule (ALIC), anterior thalamic radiation (ATR), uncinate fasciculus (UF)	Reduced integrity of the ALIC, ATR, UF regions in both bipolars and schizophrenics as compared to controls.

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Author	Date	Title	Journal	Type	Region	Notes
Fornito, A. et al.	2009	Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder	Curr Opin Psychiatry	MRI Review		Results point to the gross complexity, regional heterogeneity present in both bipolar disorder and schizophrenia