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Review

Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: Review of the evidence

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ABSTRACT

Longitudinal studies of biological domains in bipolar disorder (BD) are crucial in determining if such baseline changes are progressive. We reviewed reported studies of longitudinal brain structural/functional magnetic resonance imaging (MRI) and neuropsychological changes in BD through November 2012. Longitudinal brain structural MRI studies suggest cortical and subcortical abnormalities within networks subserving emotional regulation. There is evidence of neuroprogressive loss of gray matter volume in prefrontal and anterior cingulate cortex and the subgenual region, with less consistent findings in temporal and subcortical regions. Abnormal amygdala neurodevelopment is noted in adolescent onset BD and possible changes in hippocampus require further evaluation. The fewer reported longitudinal functional MRI studies suggest neurobiological changes in activation patterns involving fronto-limbic circuitry which relate to different illness phase and mood states. Early onset pediatric/adolescent BD may signify a more malignant course of illness in which extensive and executive neurocognitive deficits are found early and may persist, with some potential for improvement during remission and perhaps with treatment. Future studies should include larger samples, combine investigational modalities, incorporate genetic profiles, consider standardization of assessments and collaborative ventures across institutions, selection of more homogeneous subgroups and track neurobiological changes longer to clarify trajectories of changes.

Contents

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention-deficit hyperactivity disorder; BD, bipolar disorder; DTI, diffusion tensor imaging; Eu, euthymia; GMV, grey matter volume; GP, globus pallidus; Li, lithium; MRI, magnetic resonance imaging; PFC, prefrontal cortex; ROI, region-of-interest; SCZ, schizophrenia; SGC, subgenual cortex; TBSS, tract-based spatial statistics; VBM, voxel-based morphometry; WMV, white matter volume.

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1. Introduction

Bipolar disorder (BD) is a prevalent, complex and often disabling or even fatal, major psychiatric disorder characterized by a fluctuating course that includes manic, depressive, and mixed episodes, with intervals of varying levels of euthymic remission. Manic episodes are characterized by elevated and often irritable mood, prevalent psychotic features, and increased energy, flight of ideas and rapid speech, overactivity and disinhibited behavior that contributes to high rates of recurring hospitalization. Depressive episodes are characterized by lack of interest, loss of appetite, insomnia, fatigability and suicidal thoughts, with a very high rate of completed suicides. Early mortality is also associated with fatal accidents, effects of substance-abuse, or other forms of violence; later excess mortality is associated with intercurrent medical illnesses. BD has been subdivided into types I (with mania) and II (recurrent depression with hypomanic phases). Both types can be severe and disabling, and are associated with similarly high rates of suicide. Type I BD is one of the most robust diagnoses among major or psychotic disorders (Salvatore et al., 2009, 2011).

BD has a high degree of familial risk of unipolar as well as bipolar mood disorders that correlate with younger onset, and genetic contributions to its etiology are strongly suspected (Goodwin and Jamison, 2007; McGuffin et al., 2010; Byerley and Badner, 2011; Baldessarini et al., 2012a). This background has encouraged studies of the neurobiology of the disorder, including applications of modern brain-imaging technologies. Most reported studies of this type are cross-sectional, and findings are often not compared with other diagnostic groups to test for specificity of findings. Moreover, long-term or longitudinal assessments of neurobiological and neuropsychological abnormalities have rarely been documented.

Cross-sectional neuroimaging studies in BD have documented structural and functional abnormalities in cortical, subcortical, and limbic brain systems (Strakowski et al., 2005; Green et al., 2007; Langan and McDonald, 2009). Specific brain regions implicated include the dorsolateral and lateral orbitofrontal-temporal areas known to be involved in emotional regulation, attention, learning and memory, and the anticipation and interpretation of complex information (Bechara and Damasio, 2000; Frey and Petrides, 2000; Perlstein et al., 2002; Beer et al., 2006; Knudsen, 2007; Pomarol-Clotet et al., 2012). Meta-analyses of voxel based morphometry studies in BD found that the most consistent abnormalities involved gray matter reduction in anterior insula, inferior frontal cortex and anterior cingulate cortex (ACC) (Bora et al., 2010). In addition, abnormal neuronal activity in the cortical and subcortical regions of the brain has been documented in cross-sectional functional neuroimaging studies. Compared to healthy controls, persons diagnosed with BD generally have been found to have higher activation in prefrontal cortex (PFC) (Adler et al., 2004; Chang et al., 2004), temporal cortex (Adler et al., 2004; Green et al., 2007), basal ganglia (Adler et al., 2004), thalamus (Chang et al., 2004), and amygdala (Strakowski et al., 1999, 2004). Manic BD patients showed greater activity in anterior cingulate cortex (Blumberg et al., 2000; Rubinsztein et al., 2001; Chang et al., 2004; Gruber et al., 2004) and basal ganglia (Blumberg et al., 2000; Caligiuri et al., 2003), and lower activity in the right-ventral-PFC (Blumberg et al., 2003). In contrast, depressed BD patients generally have demonstrated decreased blood flow in the PFC region, especially the subgenual cortex (SGC) (Drevets et al., 1997), and increased circulation in amygdala, striatum, and thalamus (Drevets, 2001; Savitz and Drevets, 2009).

Neurocognitive impairments have been reported among BD patients involving executive functions, attention, learning and memory, verbal fluency, and processing speed (Bora et al., 2009; Burdick et al., 2006, 2010; Depp et al., 2008; Tabarés-Seisdedos et al., 2008; Wingo et al., 2009a; Harvey et al., 2010). Neurocognitive impairments identified among BD subjects from different age groups include executive functioning (Zubieta et al., 2001; Malhi et al., 2007; Mur et al., 2007; Martinez-Aran et al., 2008), verbal memory (Zubieta et al., 2001; Martinez-Aran et al., 2008) and attentional deficits (Wilder-Willis et al., 2001; Clark et al., 2002) that have been replicated consistently despite high levels of variability in neuropsychological measurements. Such cognitive deficits have been largely independent of current clinical-affective states, and have been found even in euthymia, and may be more pronounced in BD I than in BD II patients (Solé et al., 2011). This evidently independent nature of potentially crippling and sometimes enduring neurocognitive deficits call for better understanding of the underlying neurobiological substrates and consideration of potentially effective therapeutic interventions. As with imaging studies, most investigations of such neurocognitive deficits in BD are cross-sectional in nature. However, longitudinal studies are needed to identify progressive neurocognitive changes as well as their relationships with clinical and other biological variables.

Deeper understanding of the longitudinal course of the several reported findings are important for several reasons. First, follow-up studies are useful to identify the trajectory of changes and deficits over time. Second, such findings may allow identification of biomarkers of BD onset, progression, and prognosis, and perhaps responses to treatment. Third, well-planned evaluation of such changes prospectively and systematically may help to distinguish meaningful findings from effects of confounders related to socio-demographic, clinical and other biological correlates, including effects of often complex and prolonged treatments.

Accordingly, in view of the need to better understand the time-course of neuroimaging and neurocognitive findings in BD, we have reviewed reported longitudinal studies examining brain structural and functional changes in brain regions in order to synthesize and