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Mini Review

Neuroimaging Studies of Brain Structure in Older Adults with Bipolar Disorder: A Review

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ABSTRACT

Bipolar disorder (BD) is a common mood disorder that can have severe consequences during later life, including suffering and impairment due to mood and cognitive symptoms, elevated risk for dementia and an especially high risk for suicide. Greater understanding of the brain circuitry differences involved in older adults with BD (OABD) in later life and their relationship to aging processes is required to improve outcomes of OABD. The current literature on gray and white matter findings, from high resolution structural and diffusion-weighted magnetic resonance imaging (MRI) studies, has shown that BD in younger age groups is associated with gray matter reductions within cortical and subcortical brain regions that subserve emotion processing and regulation, as well as reduced structural integrity of white matter tracts connecting these brain regions. While fewer neuroimaging studies have focused on OABD, it does appear that many of the structural brain differences found in younger samples are present in OABD. There is also initial suggestion that there are additional brain differences, for at least a subset of OABD, that may result from more pronounced gray and white matter declines with age that may contribute to adverse outcomes. Preclinical and clinical data supporting neuro-plastic and -protective effects of mood-stabilizing medications, suggest that treatments may reverse and/or prevent the progression of brain changes thereby reducing symptoms. Future neuroimaging research implementing longitudinal designs, and large-scale, multi-site initiatives with detailed clinical and treatment data, holds promise for reducing suffering, cognitive dysfunction and suicide in OABD.

KEYWORDS: bipolar disorder; aging; gray matter; white matter; neuroimaging; brain structure

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ABBREVIATIONS

BD, Bipolar Disorder; OABD, Older Adults with Bipolar Disorder; GM, Gray Matter; WM, White Matter, DTI, Diffusion Tensor Imaging; FA; Fractional Anisotropy

INTRODUCTION

Bipolar disorder (BD) is a common disorder, with an estimated lifetime prevalence of 2.4% [1]. In addition to the profound suffering from its symptoms, BD carries high rates of comorbidity and suicide [2]. While the onset of BD typically occurs before the age of 25 years [3], it persists throughout the life-course and, for at least a portion of those with the disorder, the illness evolves with age, being associated with a greater risk for cognitive impairment, dementia, and an especially high rate of suicide ideation and attempts in older adults with BD (OABD) [4–7]. Compared to BD in younger adults, BD in older adults has been associated with more severe depressive episodes [8], and greater rates of episode recurrence [9,10]. These severe clinical outcomes in OABD, alongside rapidly aging populations across the globe [11], give new impetus to understand aging and the brain in BD [12]. Here we define OABD as individuals with BD and an age of 40 years or more, as an age of 40 years provides a more comprehensive picture of BD during later life that is more able to encompass individuals with a later onset of the illness [10]. Moreover, as this is a review of structural neuroimaging, it considers work suggesting that the brain begins to undergo age-related gray and white matter declines during the fourth decade of life [13,14], which is especially pertinent to OABD given hypotheses suggesting that it may be characterized by accelerated aging processes [15–17].

Numerous neuroimaging studies of BD have characterized differences in brain structure, although participants have primarily been in the second through fifth decades of life [18]. There is a growing body of research examining brain structure in OABD and potential effects of aging processes. This mini-review will explore the neuroimaging literature on gray matter (GM) and white matter (WM) findings in OABD, their relationship with medication use and aging processes, and future directions for the field.

GRAY MATTER IN BIPOLAR DISORDER

Three key metrics have been used to assess GM structure in BD: volume and its components in the cortex, thickness and surface area. Cortical thickness is defined as the distance between the cortex's inner GM-WM boundary and outer pial GM surface; cortical surface area is defined as the surface area of the cortex's outer pial surface. As cortical thickness and surface area have differing genetic and environmental contributions [19], investigations of these GM metrics in BD are providing intriguing insights into the underlying neurobiology of the illness. Measures of cortical

gyrification have also been studied in BD, but to a lesser extent and rarely in OABD.

The largest structural neuroimaging literature in BD is on studies of GM volume in individuals mostly below the age of 40 years, with findings converging in subcortical and cortical areas that subserve emotion processing and regulation. Lower subcortical GM may be a particularly early difference associated with BD. In adolescents and young adults with BD, lower GM volume in the amygdala is one of the most consistently reported results [20–23]. GM differences have also been reported in other subcortical regions, albeit with some variable findings, such as the hippocampus, striatum, thalamus and cerebellum [23–29]. Lower cortical GM in ventral prefrontal areas are also some of the most frequently reported findings in BD [30], and progressive decreases in adolescents and young adults with BD suggest an underlying neurodevelopmental pathophysiology [31,32]. GM volume decreases have also been reported in lateral and medial dorsal frontal cortices, and, although less frequently studied, in insular and temporopolar cortices [33–38]. Lower cortical thickness has been reported in these regions, while cortical surface area differences have been inconsistent [34,36,37,39,40]. These findings suggest that in BD, anterior cortical GM reductions are predominantly driven by factors that lower cortical thickness, providing a potential lead about underlying pathophysiology.

While there are substantially fewer neuroimaging studies focusing on OABD, most investigations of OABD echo the results in younger samples as they show lower GM volume in structures that subserve emotion processing and regulation, including the dorsolateral and ventromedial prefrontal cortex, hippocampus, amygdala, and striatal regions [41–45]. However, there are studies with conflicting and negative findings [46–49], and it is noteworthy that the majority of the samples in these neuroimaging studies have been comprised of 20 or fewer individuals with BD [42–44,47–49]. In addition to differences across studies in imaging methods, subject heterogeneity may have contributed to the discrepant findings.

Given that OABD is associated with a greater risk for cognitive impairment, a small number of studies have attempted to investigate how GM properties relate to cognition in OABD, however no consistent relationships have so far been detected [43,46,49]. Similarly, given the greater risk for dementia associated with OABD, two studies have directly compared the GM properties of individuals with frontotemporal dementia and OABD. The disorders showed similar GM reductions within insular and anterior cingulate cortices, but also showed differences in the involvement of regions within prefrontal and posterior cortices, with OABD showing more prominent GM reductions within the ventrolateral prefrontal cortex, and individuals with frontotemporal dementia showing more prominent GM reductions within dorsolateral prefrontal and orbitofrontal cortex, as well as temporal, occipital and parietal cortices

[42,49]. However, these studies were limited in sample size, including only 13-16 individuals with BD, so should be viewed with caution. Future studies directly investigating commonalities between OABD-related and dementia-related GM reductions are warranted, as they may elucidate why OABD confers a greater risk for dementia.

WHITE MATTER IN BIPOLAR DISORDER

WM deficits are increasingly implicated as integral in the pathophysiology of BD, with supportive lines of evidence from neuroimaging studies [50], such as initial studies consistently reporting greater numbers of WM hyperintensities within periventricular and deep WM [51–53] in both younger and older individuals with BD [54].

More recently, diffusion tensor imaging (DTI) has been used to study BD, due to its sensitivity to the microstructural integrity of WM tracts. A commonly used metric from DTI is fractional anisotropy (FA). FA measures whether water diffusion within WM tracts is more restricted towards moving in the direction of the tracts with high FA inferring greater water diffusion along the WM tract and therefore greater WM integrity. DTI-based studies have shown lower FA across numerous WM tracts in BD [50,55–57], particularly within the frontotemporal emotion regulation system [30]. The corpus callosum is one of the WM tracts most studied, with findings in BD reported most often in the genu, which provides connections between the right and left ventral prefrontal cortices [58–64]. Of tracts providing intra-hemispheric connections, in BD, lower FA has been found in the uncinate fasciculus [65–69], a tract that provides the major connections between the ventral prefrontal cortex and the amygdala [70]. Progressive differences in FA in the uncinate fasciculus, observed in a longitudinal study of adolescents and young adults with BD, suggest developmental contributions to uncinate WM pathology [50].

While a greater number of WM hyperintensities has frequently been reported in OABD and in younger samples, it appears that WM hyperintensities may be more abundant in OABD particularly within deep WM [54]. Furthermore, the causes underlying WM hyperintensities in BD may be related to age and comorbidities. In OABD, and particularly in those with a later onset of BD, it is thought that cardiovascular and metabolic comorbidities that have high rates in OABD [10,71,72], may contribute to WM hyperintensities [54]. However, more studies directly assessing these associations, and of the specific mechanisms involved, in OABD are needed [73].

Furthermore, studying OABD using DTI methods is a burgeoning area, with several studies showing FA decreases in similar areas as in younger samples with BD, including ventral corpus callosum, and uncinate fasciculus [74,75]. In addition to contributions to emotion dysregulation in BD, contributions to cognitive deficits are implicated by negative correlations between cognitive performance across multiple domains, including working memory, information processing, executive function,

and attention, with FA in the corpus callosum and uncinate fasciculus [76–78]. As cognitive decline is a feature for some individuals with BD during later life, that causes suffering, impaired functioning, and is associated with poor prognosis [79], elucidating disturbances in these key WM tracts may be integral to preventing some of the severe clinical outcomes associated with BD during later life.

MEDICATIONS AND BRAIN STRUCTURE IN BIPOLAR DISODER

An intriguing avenue of research is on the potential for mood-stabilizing medications to have neuroplastic and neuroprotective effects. This is supported by preclinical data demonstrating that mood-stabilizing medications, with lithium being most studied, upregulate molecular factors that promote plasticity and down-regulate factors that promote cell death [80]. Neuroimaging findings in individuals with BD are consistent with these effects, such as lithium-associated increases in GM volume of the amygdala and hippocampus [45,81,82], and in WM FA [57,83–86]. Moreover, in OABD, there is a growing body of work suggesting that lithium use is associated with a lower risk for developing dementia [5,87]. Together, these findings suggest that lithium may have neuroplastic and neuroprotective effects within the brain in OABD that could potentially reverse and/or prevent progression of detrimental age-related processes [45,81,82]. However, randomized control trials are required to confirm these effects.

While lithium has been the most studied medication in imaging studies of BD, varying effects of other medications have been reported. For example, antipsychotic medications, which are highly prescribed for OABD [88], have been associated with more extensive GM reductions in younger individuals with BD [23,26,34,89]. The relationship between antipsychotic medication use and WM structure in BD, however, is less clear with some studies finding reduced FA within the corpus callosum [57] and others finding no effects [69,83,90]. Far less work has focused on brain structure and antipsychotic medication use in OABD. One study of a sample of 54 individuals with BD found that antipsychotic medication use was associated with lower overall GM volume across the brain and particularly within the hippocampus [91], however, it is yet to be replicated. Moreover, randomized controlled trials that longitudinally investigate the effects of antipsychotic medications on brain structure in BD have not been conducted, and it is therefore difficult to establish causality.

AGING PROCESSES AND BRAIN STRUCTURE IN BIPOLAR DISORDER

While differences at the group-level in GM and WM structure appear to be present in OABD, it is still unclear whether the illness is associated with differences in brain aging processes. It has been proposed that BD is characterized by accelerated biological aging [15–17], a hypothesis supported by findings in BD of more pronounced markers of biological

aging such as shorter telomeres [92], greater markers of oxidative stress [93], and reduced mitochondrial DNA copy numbers [94]. Moreover, findings of group differences showing lower GM properties and FA in BD have been used to suggest that accelerated aging of the brain may also be a characteristic of the illness [15–17], given that these structural properties decline during typical aging [95–99]. However, as many of these differences in GM and WM have also been found in younger samples, their causes may be neurodevelopmental rather than related to aging.

While few in number, studies investigating the relationship between brain structure and age in BD have been equivocal, with most failing to find age-related differences associated with the illness [47,100–102]. The largest longitudinal investigation of GM structure in BD, involving a sample of 307 individuals with BD, who had a mean age of 40 years, recently found no evidence of accelerated cortical thinning in BD. Moreover, studies investigating age-related differences in DTI-based WM properties in adults with BD have been unclear, with some failing to identify age-related differences associated with the illness [101,103]. More recent brain-based age-prediction models suggest that BD may show subtle indications of greater brain age [104,105] though these are yet to be supported by longitudinal evidence, which are required to support hypotheses surrounding effects of aging processes in BD.

The age of BD onset may be a particularly salient factor in attempting to understand brain structure and aging, specifically in OABD. The definition of late-onset BD has varied substantially across studies, with studies defining it as occurring after the age of 60 years [53], 50 years [106,107], 40 years [10], and others as low as in the late twenties [108]. Given that in around 50% of cases, the onset of BD occurs below the age of 25 years [3], an age of onset above 25 years does appear to mark a meaningful difference in onset that may have a different underlying neurobiology [3,109,110], and although prior studies have tended to use later age cutoffs, findings from studies using younger age of onset cutoffs are emerging [108,110–112]. A later onset of BD has frequently been associated with greater cognitive impairment across many cognitive domains in OABD [4,113–117], and it has been suggested that a later onset of BD may be associated with a greater level of WM differences, with one study finding that late onset BD was associated with a greater number of WM hyperintensities and another finding that a later onset of BD was associated with lower FA within multiple WM tracts, including the corpus callosum [53,54,107,108,118]. To date, few studies have investigated the effects of age of BD onset on GM properties in OABD. Interestingly, findings have been identified using measures of gyrification, with two studies showing that a later onset of BD was associated with lower levels of cortical folding [111,112]. This is intriguing given that lower levels of cortical folding have previously been proposed as a potential marker for Alzheimer's disease [119,120], and suggests that future imaging work should consider other structural neuroimaging metrics such as

gyrification measures when studying OABD. Together, while few in number and limited by small samples, these studies implicate age of BD onset as a key clinical factor that may interact with aging processes within the brain in OABD and may be involved in the severe clinical outcomes experienced by some individuals with BD during later life, such as cognitive impairment.

FUTURE DIRECTIONS

Crucial areas for further study of OABD include neuroimaging investigations of larger samples of individuals with comprehensive demographic and clinical data, and with longitudinal designs necessary to clarify aging-related processes. Moreover, given the heterogeneity of BD, in both its clinical presentations and in its outcomes, more work is needed to identify differences between individuals with BD, to find neurobiological mechanisms that are specific to key clinical phenotypes of the illness during later life, such as differences associated with BD-type (e.g., BDI or II), presence of psychosis, cognitive impairment, age of illness onset, and risk for dementia. Promising new initiatives that involve large scale, international multi-site data harmonization approaches, such as in the Global Aging and Geriatric Experiments in BD (GAGE-BD) consortium [121], are likely to be indispensable in harnessing datasets with enough clinical detail and statistical power to further our understanding of differences between individuals with BD during later life, and to provide more specific and effective interventions.

AUTHOR CONTRIBUTIONS

NR, HPB, and LMV conceived the content of the paper and wrote the paper.

CONFLICTS OF INTEREST

HPB has consulted for the Milken Institute. All other authors have no conflicting interests to declare.

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