Structural and Functional Brain Correlates of Neuroprogression in Bipolar Disorder

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Abstract Neuroprogression is associated with structural and functional brain changes that occur in parallel with cognitive and functioning impairments. There is substantial evidence showing early white matter changes, as well as trajectory-related gray matter alterations. Several structures, including prefrontal, parietal, temporal cortex, and limbic structures, seem to be altered over the course of bipolar

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Curr Topics Behav Neurosci (2021) 48: 197–214
https://doi.org/10.1007/7854_2020_177
Published Online: 11 October 2020

disorder, especially associated with the number of episodes and length of the disease. An important limitation is that most of the studies used either a cross-sectional design or a short follow-up period, which may be insufficient to identify all neuroprogressive changes over time. In addition, the heterogeneity of patients with bipolar disorder is another challenge to determine which subjects will have a more pernicious trajectory. Larger studies and the use of new techniques, such as machine learning, may help to enable more discoveries and evidence on the role of neuroprogression in BD.

Keywords Bipolar disorder · Functional MRI · Neuroprogression · Structural MRI

1 Introduction

Bipolar disorder (BD) has heterogeneous trajectories, with some patients experiencing a more severe course, marked by progressive features and impairments in both cognition and functioning. The term neuroprogression has been proposed as a pathological rewiring of the brain that occurs in parallel with clinical, neurocognitive, and functioning deterioration in BD patients (Passos et al. 2016). In these cases, there is cumulative evidence that several structures and systems seem to be affected. Neuroprogression has been associated with poor clinical outcomes such as worse response to treatment (Ketter et al. 2006; Swann et al. 1999), increased comorbidity (Matza et al. 2005), functional and cognitive impairments (Kessing 2004; Rosa et al. 2012; Torres et al. 2007), and higher suicide and hospitalization risk (Goldberg and Ernst 2002; Hawton et al. 2005). Refractory trajectories, which include difficulty to treat acute episodes, persistence of symptoms between episodes, or the emergence of mood episodes or cycling during optimal treatment, have been associated with an end-stage presentation of BD (Berk et al. 2007, 2014; Gitlin 2001; Poon et al. 2012). Among the factors contributing to these changes, the number of episodes seems to be the most robust aspect associated with clinical deterioration (Martino et al. 2016).

Although not all patients present a progressive course, it is paramount to understand factors that might be associated with neuroprogression. Among the distinct pathways that the clinical course of BD can assume, identifying those patients who will experience clinical and neurocognitive deterioration is a critical need. In addition, a better understanding of these processes will enable effective and targeted interventions with the aim of improving outcomes in patients with BD. Neuroimaging studies aim to shed light on some of the brain changes occurring over time, the factors associated with those changes, and its consequences for those suffering from BD.

In the current chapter, we will review findings from structural and functional neuroimaging studies that aimed to study brain changes in patients with BD associated with neuroprogression.

2 Structural Aspects of Neuroprogression in Neuroimaging

Changes in brain structures in bipolar disorder patients, when compared to controls, were shown by several cross-sectional and longitudinal studies, with patterns compatible with neuronal loss in cortical and subcortical tissues (Hibar et al. 2016). Most of the evidence comes from cross-sectional studies, which may limit definite conclusions about the directionality of the findings.

There is evidence pointing to a white matter pathology in earlier stages and gray matter loss in more advanced stages (López-Larson et al. 2002). A meta-analysis of eight studies assessing magnetic resonance imaging (MRI) in patients with first-episode BD found a reduction in total intracranial and white matter volumes, with no significant changes being observed for gray matter and whole brain volumes (Vita et al. 2009). Cortical thinning has been described in several brain regions, including the cingulate cortex, prefrontal cortex, fusiform cortex, and limbic structures, among others, with some studies finding an inverse correlation of duration of illness with cortical thickness of some regions, such as the left middle frontal cortex (Lyoo et al. 2010). These earlier changes in white matter may indicate that abnormal connectivity between regions may play a significant role in the onset of disorders, with more structural changes, predominantly in the gray matter, presenting over its clinical course and trajectory.

2.1 Evidence from Cross-Sectional Studies

2.1.1 Brain Volume and General Findings

A study comparing multiple-episode and first-episode BD found that the lateral ventricles were larger in those individuals with multiple episodes, which was associated with a higher number of manic episodes. Additionally, the authors also reported a smaller total cerebral volume (Strakowski et al. 2002). A voxel-based morphometry meta-analysis including 660 BD patients compared to 770 healthy controls showed gray matter reduction that was more pronounced in chronic illness, in the basal ganglia, subgenual anterior cingulate cortex (ACC), and amygdala, with lithium promoting an enlargement of these areas (Bora et al. 2010). Differences in the frontal, temporal and parietal cortex, amygdala, thalamus, globus pallidus, striatum, and hippocampus, among others, were also described comparing patients with healthy subjects (Hibar et al. 2018; Strakowski et al. 1999). An inverse correlation was also found between length of illness and gray matter volumes in

BD, but not in unipolar depression and healthy controls (Frey et al. 2008). There is also evidence pointing to a lower gyrification index (GI) in patients with late-stage BD and a correlation between the GI and the stage of the disorder (Cao et al. 2016). A study comparing 63 patients with first manic episode and healthy controls found no significant volumetric differences between the two groups (Arumugham et al. 2017), which reinforces the hypothesis of gray matter pathology being associated with the trajectory of the disorder. Longer duration of illness was associated with lower total gray matter volumes even when controlling for confounding factors, suggesting a cumulative loss over time (Gildengers et al. 2014).

2.1.2 Prefrontal Cerebral Cortex

Bipolar patients hospitalized for a manic episode showed smaller bilateral prefrontal gray matter volumes that were more noticeable in the middle and superior subregions when compared to healthy controls, with no significant differences in white matter content (López-Larson et al. 2002). A decreased gray matter density in frontolimbic areas has been associated with poor clinical outcomes (Doris et al. 2004). Extensive prefrontal cortex thinning was also found by a meta-analysis of whole-brain voxel-based morphometry studies including 1720 subjects with BD, suggesting that this region plays a major role in the pathophysiology of BD (Lu et al. 2019). A small study ($n = 12$) with BD type I patients found a significant reduction of gray matter volume (GMV) in the right subgenual prefrontal cortex, with positive family history and sex being associated with the GMV (Sharma et al. 2003). A reduction of the subgenual prefrontal cortex was also observed in pediatric bipolar disorder patients with a history of first-degree relatives with a mood disorder (Baloch et al. 2010). A study with BD type II patients also showed significant thinning in the PFC, including the left perigenual ventromedial cortex, bilateral dorsomedial PFC, and bilateral dorsolateral PFC. However, no association was found with medication, mood state, illness duration, or family history (Elvsåshagen et al. 2013). The prefrontal gyrification index was reduced in ventral and dorsal regions of the PFC of BD patients when compared to controls, but not when compared to schizophrenia patients.

Moreover, those reductions were associated with cognitive impairments and reduced IQ (McIntosh et al. 2009). A study with patients experiencing a rapid-cycling course found reductions of the GMV in the bilateral medial orbital prefrontal cortex, ventromedial prefrontal cortex, and limbic regions when compared to controls and in the ventromedial prefrontal cortex when compared to BD patients without rapid cycling (Narita et al. 2011). Finally, a vertex-wise whole-brain analysis found reduced cortical thickness associated with executive function in BD type II patients in lateral prefrontal and occipital regions (Abé et al. 2018).

2.1.3 Cingulate Cortex

A decreased left ACC volume was found in untreated BD patients when compared to healthy controls and lithium-treated patients, while there was no difference between healthy controls and lithium-treated subjects (Sassi et al. 2004). Another study also found a decrease in the left ACC volume, with an inverse correlation of the ACC volume with the number of hospitalizations (Delvecchio et al. 2019). When comparing patients with a more severe presentation and poorer outcomes, another study found an abnormal gray matter density widespread on the cingulate cortex (Doris et al. 2004). In younger patients, a study reported smaller mean volumes in the left anterior, left posterior, and right posterior cingulate cortex when compared to controls (Kaur et al. 2005). Nevertheless, several studies, including a meta-analysis, pointed to an enlargement of the cingulate cortex when compared to controls, suggesting a possible compensatory mechanism (Lu et al. 2019).

2.1.4 Temporal-Limbic Structures

Temporal lobe clusters gray matter loss was also reported and significantly associated with reductions in full-scale IQ and performance IQ (Moorhead et al. 2007). A study with BD type II patients found significant thinning of the superior middle and inferior temporal gyrus but without association with illness duration, family history, medication, or mood state (Elvsåshagen et al. 2013). Cortical gray matter was found to be reduced in BD patients in the temporal study by another large study, finding associations with medication use (Hibar et al. 2018). BD patients treated with antipsychotics were found to have larger bilateral temporal lobe whiter matter volumes when compared to those not taking antipsychotics and healthy controls. Hyper perfusion of left frontal and temporal cerebral areas was found in BD patients, suggesting an over-activation of these regions (Agarwal et al. 2008).

A study stratifying patients in early, intermediate, and late stage as a function of the number of lifetime episodes found smaller hippocampus in late-stage patients when compared to healthy controls, as well as worse performances in the California Verbal Learning Test (CVLT) for intermediate- and late-stage patients (Cao et al. 2016). Anterior limbic regions also had the most robust decrease in gray matter in a meta-analysis comparing BD and HC, with a more robust decrease being associated with a longer duration of illness (Bora et al. 2010). Hippocampal volumes were decreased in a study with adolescents with BD, with negative correlations being found between the duration of the disorder and positive correlations between duration of medication use and levels of neurotrophins, such as NGF and BDNF (Inal-Emiroglu et al. 2015). In older adults with BD (mean age 57 years), a study showed smaller hippocampal and right amygdala volumes after controlling for intracranial volume, with the hippocampus but not the amygdala volume being negatively associated with the duration of depressive and manic episodes (Wijeratne et al. 2013). However, a study with males with BD, schizophrenia, and healthy

controls found larger amygdala volumes of BD patients when compared to the two other groups (Altshuler et al. 2000), and a study of BD patients recently remitted from a manic episode found no difference in the amygdala volume when comparing to healthy controls (Arumugham et al. 2017). Another study, with euthymic patients with BD type I patients older than 50 years, found that the right and left hippocampal volume was negatively associated with inflammatory markers, including the tumor necrosis factor receptor-1 (sTNF-R1) and the soluble interleukin (IL)-2 receptor (sIL-2r) (Tsai et al. 2019). There is cumulative evidence that persistent inflammation plays a major role in bipolar disorder and neuroprogression (Kapczinski et al. 2008).

2.1.5 Other Brain Structures

A study comparing young individuals with bipolar disorder and healthy controls found a trend for smaller vermis V2 areas of the cerebellum in patients that was inversely correlated with the number of mood episodes in the male patient group (Monkul et al. 2008). Other studies also showed smaller cerebellum volumes for multiple-episode BD. Mills et al. compared first-episode and multiple-episode bipolar patients, and healthy controls, and found smaller vermis subregions V2 and V3 in patients with multiple episodes (Mills et al. 2005), while the V3 area was also found to be significantly smaller in multiple-episode patients with prior manic episodes and hospitalizations when compared to first-episode patients (DelBello 1999). Cerebellar loss in gray matter was also reported and associated with the number of manic and depressive episodes (Moorhead et al. 2007).

Altered myelination was also suggested in the development and course of BD. Lower signal intensity for the corpus callosum in all callosal subregions was reported for BD patients, although no effects of length of illness were found (Brambilla et al. 2004), and for first-episode BD with higher YMRS scores (Atmaca et al. 2007). The corpus callosum and total white matter volumes were also reduced in a study including patients in early and late stages, although gray matter was only altered in late stage, suggesting an early role for the demyelination process in BD (Duarte et al. 2018). Another study found a reduced posterior corpus callosum volume in late-stage women with BD type I when compared to early-stage type I BD and healthy controls, after controlling for confounding factors (Lavagnino et al. 2015). A PET-SCAN study found decreased cortical volume extending from the prefrontal cortex ventral to the genu of the corpus callosum, a region associated with the medication of emotional and autonomic responses to social stimuli and modulations of neurotransmitter system implicated in mood disorder treatment (Drevets et al. 1997). A DTI study also showed aberrations in several white matter structures in young patients, including the corpus callosum, in fibers connecting the fornix to the thalamus, and bilateral parietal and occipital corona radiata, in adolescents with BD (Barnea-Goraly et al. 2009). These findings are consistent with the hypothesis that white matter changes may occur early at the onset of the disease. In contrast, gray matter changes are more associated with the course of the disorder and, therefore, implicated in the clinical aspects of neuroprogression and deterioration.

Intracortical myelin (ICM) has recently been studied in the context of BD, with evidence for an association of verbal memory function with ICM and age-related deficits in adults with BD type I, including a correlation with age of onset and an inverse correlation with duration of illness and manic episodes (Sehmbi et al. 2018). Depressive episodes, however, were not associated with ICM signal in the study. This points to a role of ICM in cognitive dysfunction in BD since verbal memory impairment is one of the main findings in individuals with BD (Martínez-Arán et al. 2004) and suggests a role for ICM on neuroprogression.

Shape differences in the caudate heads and putamen were also observed for drug-naïve patients but not for treated subjects when compared to healthy subjects (Hwang et al. 2006). A systematic review including 508 subjects also analyzed hypoperfusion and showing widespread resting hypoperfusion in the cingulate gyrus, frontal, and anterior temporal regions when compared to healthy controls (Toma et al. 2018). A large study with 1837 patients found cortical thinning in bilateral frontal, temporal, and parietal regions, with longer duration of illness being associated with reduced cortical thickness in frontal, medial parietal, and occipital regions. Authors also found an association of several medications, such as lithium, anticonvulsants, and antipsychotics, with cortical thickness and brain surface area (Hibar et al. 2018). Finally, a pioneering study of blood-brain barrier imaging showed that patients with extensive BBB leakage had more severe depression and anxiety and a more chronic course of illness (Kamintsky et al. 2020).

2.2 Evidence from Longitudinal Studies

2.2.1 Brain Volume and General Findings

A study comparing remitted first manic episode patients, patients with recurrence of the episode, and healthy subjects, showed that the group with recurrence had a greater GMV loss when compared to those in remission, including left frontal and bilateral temporal regions (Kozicky et al. 2016). Loss of gray matter over time was also observed in longitudinal studies, with follow-ups up to 4 years that have been associated with deterioration in cognition and more pernicious illness courses (Moorhead et al. 2007).

2.2.2 Prefrontal Cerebral Cortex

Gray matter volume seems to be reduced at baseline in the frontal gyrus and right superior frontal gyrus in BD when compared to controls, but no reductions were found after a 2-year follow-up (Farrow et al. 2005). In adolescents diagnosed with BD and followed for 2 years, there seems to be a progressive bilateral reduction of GMV in both ventral and rostral portions of the PFC when compared to controls (Kalmar et al. 2009). Decreases of the GMV after 3–34 months of the initial scan

were seen in the superior frontal gyrus in adults diagnosed with BD when compared to healthy controls (Lisy et al. 2011). Gene variants of the brain-derived neurotrophic factor (BDNF) such as the valine methionine were shown to be associated with a greater reduction in the gyrification index of the PFC that is more pronounced in the left hemisphere (Mirakhur et al. 2009). The role of BDNF as a neuroprotective factor with lower levels being associated with inflammation and neuroprogression is supported in the literature (Kapczinski et al. 2008).

Nevertheless, a study following first-episode psychosis found no difference in the PFC between BD patients and controls (Arango 2012). Some studies reported a progressive increase of GMV in the ventrolateral PFC in young BD patients (Gogtay et al. 2007; Lisy et al. 2011). Medial or orbital PFC seems to be decreased in patients with psychotic illnesses, including BD (Pantelis et al. 2003), although in young patients, there is evidence of increase in the GMV of the medial PFC in the left hemisphere (Gogtay et al. 2007). A study that followed bipolar disorder patients for 6 years found that those with a higher number of manic episodes had a significant decreased in frontal cortical volume in the dorsolateral and prefrontal inferior frontal cortex (Abé et al. 2015). The short period of follow-up of most studies may be an explanation for these contradictory results, since a longer follow-up may be needed to detect changes associated with neuroprogression.

2.2.3 Cingulate Cortex

A study of first-episode psychosis, including BD patients, found a gray matter deficit in the anterior cingulate cortex (Farrow et al. 2005). A reduced GMV in the ACC was also observed in young adults that developed psychotic illnesses (Pantelis et al. 2003), and bilateral GMV loss was shown in the ACC and the left posterior cingulate gyrus in young BD patients (Gogtay et al. 2007), and progressive losses of GMV when comparing adolescent and adult patients (Kalmar et al. 2009; Lyoo et al. 2010). These losses were shown to be reversible with lithium therapy (Lyoo et al. 2010; Moore et al. 2009).

2.2.4 Temporal-Limbic Structures

There are conflicting results regarding temporal lobe structures. Increased GMV was observed in medial and superior temporal gyri at 3–33 months (Lisy et al. 2011) and 4–8 years follow-up (Gogtay et al. 2007), while reduction of GMV in the temporal lobe was associated with reduced full-scale IQ and mainly verbal IQ (Moorhead et al. 2007). Reduced GMV was also observed in the left fusiform gyrus in high-risk subjects that went on to develop psychotic episodes, including BD patients (Pantelis et al. 2003).

The amygdala seems to be structurally altered in earlier phases of BD: a study showed reduced GMV in adolescents in a 2-year follow-up (Blumberg et al. 2005), with another study showing no difference over time in adult BD (Moorhead et al.

2007). In older patients, a 2-year follow-up also showed no difference between amygdala volume of BD and healthy control subjects (Delaloye et al. 2011). Changes found in the hippocampus include reductions of GMV in the left parahippocampal gyrus after the onset of psychosis (Pantelis et al. 2003); progressive loss of GMV in the left hippocampus and fusiform gyrus (Moorhead et al. 2007); increased GMV in the hippocampus of BD patients (Delaloye et al. 2011; Lisy et al. 2011); and an increased volume that was associated with lithium treatment and improved verbal memory (Yucel et al. 2007).

3 Functional Aspects of Neuroprogression in Neuroimaging

Currently, the knowledge of the functional changes of the brain as a consequence of neuroprogression in bipolar disorder remains limited. A major thrust of the work thus far has focused on biochemical and structural correlates, while fewer studies have examined the functional consequences of brain aging. Nonetheless, there have been some attempts to address this issue. For instance, a review comprising 12 longitudinal studies on functional neuroimaging found evidence for increased positive coupling with the insula and negative coupling with prefrontal regions as patients progressed from manic to depressed state. In brief, the insula is a region that separates the frontal and parietal lobes from the temporal lobe and plays a role in processing a number of basic emotions (Lim et al. 2013).

Moreover, in a motor task designed to assess long-term neural activity in frontal subcortical regions, strong ACC activation was found in those who were in remission from depression, suggesting that decreases in the activation of this region may be related to vulnerability to depression in BD. However, more than half of the studies within this review were gathered from pediatric samples, which limit the applicability of such findings in the context of abnormal brain aging. Apart from this, another study has compiled evidence on differences in the brain's response across distinct functional tasks and patient age groups (Schneider et al. 2012).

Currently, long-term longitudinal functional neuroimaging studies have yet to be conducted in the context of neuroprogression. Such studies will be important to assess the extent and probable mechanisms of brain changes as a result of bipolar disorder progression. Furthermore, it will be beneficial moving forward to control for clinical characteristics long thought to precipitate accelerated brain aging, such as the number of mood episodes, chronicity, severity, and medication use, to name a few.

Nonetheless, one way to extrapolate from existing data is to summarize findings from cross-sectional studies comparing BD cases to HC participants across varying age groups. For instance, a comprehensive meta-analysis from 2014 identified several significant differences between HC and BD in pediatric ($n = 21$) and adult samples ($n = 73$) using the activation likelihood estimation (ALE) technique (Wegbreit et al. 2014). Briefly, ALE is a robust quantitative method for pooling neuroimaging meta-analyses, as described elsewhere (Kirby and Robinson 2017).

Here, youth with BD exhibited significant hyper-activation in the right amygdala, left prefrontal cortex (PFC), and precuneus, as well as hypo-activation in the right pregenual ACC and caudate (Wegbreit et al. 2014). The authors indicated that this suggests potentially unique brain alterations between youth and adults with bipolar disorder.

Conversely, adults with BD generally exhibited hyper-activation in left inferior frontal gyrus (IFG), left pgACC, and right pallidus and significant hypo-activation in bilateral putamen, bilateral IFG, right lingual gyrus, and inferior parietal lobe compared to HC. Contradictory results such as both hyper- and hypo-activation in a region are a result of ALE methods, which measure convergence across studies. They indicate that a significant number of studies supported both directions of activation within a region. One salient detail from these findings is that BD youth exhibited hypo-activation in the pgACC while adults exhibited the opposite direction of activation compared to HC, a pattern that is directly converse to what is observed in HC (Weathers et al. 2012). This suggests that the development of the primary role of the ACC (error detection and conflict monitoring) is aberrant in childhood, resulting in increased compensation in adulthood reflected by hyper-activation of the region.

However, it is difficult to draw meaningful conclusions on the functional markers of neuroprogression by merely comparing BD and HC cases alone. Instead, the clinical characteristics of the patients should be closely considered, alongside the age range of the sample. For instance, Wegbreit et al. (2014) compared BD adults with BD youth in terms of regional activations for different types of functional tasks. For emotional face processing tasks, BD youth exhibited significant hyper-activation in the right amygdala compared to BD adults, replicating previous findings (Kim et al. 2012) that were excluded from this analysis due to data unavailability. For other emotional paradigms, BD youth exhibited significant hyper-activation in the left IFG and precuneus and significant hypo-activation in the pgACC for non-emotional paradigms compared to BD adults. This last result was retained when all studies were pooled, indicative of a trait deficit in BD youth when compared to both HC youth and BD adults. In a recent study of neural responses to emotional face presentations, BD youth ($n = 24$) exhibited hyper-activation in the PFC and lingual gyrus in comparison with BD adults ($n = 33$) as well as hypoconnectivity in the medial PFC and amygdala-temporoparietal junction (Kryza-Lacombe et al. 2019). Neither of these patterns were seen in comparisons of HC youth vs HC adults. These results seem indicative of a pattern of abnormal functional neurodevelopment in BD and may indicate "scarred" or compensatory mechanisms.

Notably, the aforementioned results do not appear to be explicitly affected by mood state, medications, or select comorbidities (ADHD and ODD). However, given the general limitation of limited sample size in these studies, these assurances have not been well-tested and seem to be provisional, at best.

More recently, new evidence on the disease burden of bipolar disorder and its relationship with functional changes has been measured with fMRI. Comparisons between first-episode and multi-episode bipolar disorder showed lower activation of several regions of the brain for multi-episode bipolar disorder, such as the

ventrolateral prefrontal cortex and orbitofrontal cortex (Borgelt et al. 2019). Using spectroscopy, the authors also identified lower concentrations of glutamate and N-acetylaspartate in the anterior cingulate cortex of the multi-episode group. Individuals included in the study experienced one or more manic or mixed episodes, but the duration and severity of them were not included in the analysis. Another limitation of the study is the lack of information on the type of past episodes, as patients with more recurrent manic episodes than depressive ones might present a different progression of the disorder.

Studies on functional neuroprogression in BD are significantly limited in terms of adjusting for certain confounders. Although the above studies contend that their results are not significantly affected by mood state, a review on the topic suggests that functional activations across mood states vary by region (Townsend and Altshuler 2012), i.e., hypo-activation in PFC tends to be trait-dependent while functional changes in the amygdala are more state-dependent. To consider this more rigorously in the context of neuroprogression, functional differences across the life span should be considered within each mood state. Additionally, effects of medication are usually investigated in terms of current use, not lifetime, and are generally found to be non-significant. However, a recent review on the topic suggests this may be due to methodological problems, and when considering the data in aggregate, medication use may affect prefrontal activation in patients with BD (Laidi and Houenou 2016). A recent meta-analysis found that age of onset is associated with more severe depression, latency to treatment, substance use, and comorbid anxiety; however, there were none of the expected associations with greater severity of psychotic symptoms (Joslyn et al. 2016). Regardless, these are all factors that may influence brain activation and should be systematically considered.

The primary recommendation of this section for future studies is the conduction of large, longitudinal investigations of functional changes in BD across the life span. They would ideally follow individuals across significant life transitions (e.g., adolescence to adulthood, adulthood to older age) while taking into consideration mood state, lifetime and current medication use, and differing ages of onset which may correlate with overall illness severity across individuals. Furthermore, there is a growing need for prospective studies using state-of-the-art neuroimaging techniques to aid in our understanding of the neural correlates of neuroprogression.

4 Challenges (Limitations) and Perspectives

One of the major limitations is that most of the data we have available comes from cross-sectional studies, which hinders the establishment of causality. Nevertheless, a number of longitudinal studies also seem to support structural and functional changes to the brain that occur in parallel to distinct and unfavorable clinical trajectories, especially in gray matter. Another major challenge is to identify which patients will develop these changes and what are the distinct endophenotypes

associated with neuroprogression. Studies with bipolar offspring, for example, may offer valuable insight about the trajectory of the disorder, including prodromal phases, baseline cognition and functioning, and its changes over time, as well as changes in the clinical presentation or development of treatment resistance. Nevertheless, one could still argue that these cohorts may capture specific subtypes of BD, but not all of them.

The reason for conflicting results in the field may go beyond the discussion of whether neuroprogression occurs. One reason for that may be that we are looking at BD through the lens of categorical diagnosis that is elaborated through symptom phenomenology alone. If several different endophenotypes of the disorder exist, they may be diluting the effect of one another. Moreover, we cannot be sure which of these phenotypes are being included in the studies and in which proportion, so multiple studies that are looking at the same bipolar disorder "label" may be looking at multiple different neurobiological entities that roughly manifest with the same symptomatology.

Group-level results, including patients based merely on the DSM-V criteria, may overlook these distinctions, given the heterogeneous presentation of BD. In this light, approaches that consider these changes at the individual level, such as machine learning, may help to pinpoint what subjects are presenting a neuroprogressive course. Therefore, a closer look at what these cases have in common may enable the discovery of endophenotypes and relevant environmental factors that interact and contribute to more severe trajectories. Predicting which cases may have a neuroprogressive trajectory will enable timely and tailored-made interventions that can prevent cognitive and functioning impairments, reduce the number of episodes, and avoid treatment refractoriness.

Finally, assuming that distinct presentations exist, the greatest challenge in the study of structural and functional neuroprogression changes in the brain of BD patients is the need for a sample large enough to capture a representative amount of patients, followed up by a long period of time and using multimodal assessments. This will enable us to detect progressive trajectories and/or subtypes associated with progression. In addition, assessing multiple neurobiological, cognitive, and functional levels, such as neuroimaging, cognitive testing, and blood biomarkers, may help to pinpoint which events have a greater contribution to neuroprogression in BD, how they interact with the biological blueprint of the patients, and which structural and functional changes follow, as well as its clinical consequences for patients.

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