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Neuroimaging biomarkers in bipolar disorder

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1. ABSTRACT

There is an urgent need to identify objective biomarkers for the assessment of bipolar disorder, to improve diagnosis and prognostic evaluation. Neuroimaging is a particularly promising approach. We review here the structural and functional neuroimaging studies carried out on bipolar disorder. These studies have led to the development of neurobiological models of bipolar disorder assuming cortical-limbic dysregulation. Dorsal brain structures are thought to decrease in volume and activity in bipolar disorder, reducing inhibition of the ventral-limbic network and enhancing emotional responses. These models also assume abnormal prefrontal-subcortical limbic connectivity. This abnormal connectivity has been identified by both diffusion tensor imaging studies (anatomical connectivity) and functional MRI (functional connectivity). However, studies are currently limited by the heterogeneity of the patients included. Future research should include studies to validate biomarkers for the assessment of bipolar disorder and studies of large and well characterized samples of patients with bipolar disorder.

2. INTRODUCTION

Bipolar disorder (BD) is a severe chronic mental illness that affects about 1% of the population. The diagnosis of bipolar disorder is currently based entirely on clinical evaluation, without any possibility of confirming the diagnosis by laboratory tests. Recent neurobiological studies have raised hopes that it may be possible to identify biomarkers of BD (1). Such biomarkers would improve both the diagnosis and assessment of BD.

Tremendous progress has recently been made in the neuroimaging of bipolar disorder, for several reasons. First, new imaging techniques and analysis methods are being developed and existing techniques refined. These new methods include high-strength magnetic fields (3 and 7 Tesla), diffusion tensor imaging and tractography algorithms, event-related fMRI, analyses of functional connectivity, MRI spectroscopy and the combined use of genetics and neuroimaging — the so-called "imaging genetics" approach. Second, sample sizes have greatly increased in MRI studies. Third, better clinical

characterization of patients has resulted in better delineation of their underlying neurobiology. Recent neuroimaging studies have therefore increased our understanding of the physiopathology of BD, creating a solid basis for current neurobiological models of BD (2, 3).

Despite these advances, imaging biomarkers for BD have been described only for groups of patients. There are still no valid and reproducible individual biomarkers of BD, the predictive value of the biomarkers described remains low and several issues remain unexplored.

In this review, we will explore existing studies exploring the anatomical and functional neuroimaging of BD (section 3). We will then review the neurobiological models developed from these imaging studies (section 4). The exploration of brain networks connectivity is a promising new approach that may make it possible to distinguish between bipolar and unipolar depression (section 5). Finally, we will examine the potential of neuroimaging approaches in BD and their potential clinical applications, particularly in terms of predictive biomarkers (section 6). This review will be essentially restricted to adult bipolar disorder, as pediatric bipolar disorder seems to have different underlying mechanisms (4).

3. STRUCTURAL AND FUNCTIONAL BIOMARKERS OF BIPOLAR DISORDER

3.1. Structural imaging biomarkers

The first neuroimaging studies in BD investigated anatomical changes in the brains of patients with BD, by computed tomography (CT) and structural (T1 and T2) magnetic resonance imaging (MRI). No change in total brain volume was found in patients with BD, by contrast to what has been reported for schizophrenia, although this remains a matter of debate. However, meta-analyses revealed an association between BD and lateral ventricle enlargement (5, 6). It further seems that total white matter volume is altered in contrast to gray matter volume. This white matter volume decrease is present at the onset of bipolar disorder (7).

White matter changes are the most consistent, reproducible structural abnormalities observed in the neuroimaging of BD. An increase in the frequency of white matter hyperintensities (WMH) on T2 images has repeatedly been reported in patients with BD (6). These WMH are located in the deep white matter and in the periventricular areas, and have been identified in BD patients during their first episode (8). White matter hyperintensities have been proposed as a potential endophenotype of bipolar disorder (9) (for more data on this topic, see section 5.1). Such WMH do not seem to be present in unipolar depression, except in late-life depression (10).

Changes in the volumes of gray matter structures involved in emotional processing (prefrontal cortex (PFC), cingulate cortex, amygdala, insula, thalamus) have been identified (5, 11). A recent meta-analysis (11) identified regions consistently reduced in BD, including the anterior cingulate cortex and the insula. The amygdala, a key limbic region, is also frequently affected. The amygdala is located in the medial and anterior part of the temporal lobe and plays an important role in the automatic regulation of emotion processing. In BD, a recent meta-analysis revealed that the amygdala is smaller in children with BD than in healthy children, whereas it is larger in adults with BD than in healthy controls (12). Furthermore, a meta-regression analysis revealed a positive correlation between age and amygdala volume in patients with BD (13). Several explanations of this phenomenon have been put forward, including an abnormal course of development of this structure in adolescence and early adulthood (14) or differences in amygdala volume as a function of age at onset of bipolar disorder (13). Such increase of volume with age may be linked either to the pathophysiological course of BD or to concomitant factors such as comorbidities, medication or repetition of episodes (13). Longitudinal studies are required to elucidate this issue.

A very recent meta-analysis investigated the specificity of the gray-matter changes in BD (11). The authors included 42 schizophrenia studies and 14 studies on BD. Decreases in gray matter volume were limited in extent in patients with BD and were restricted to the anterior cingulate cortex (perigenual and subgenual cingulate cortex) and bilateral insula. In schizophrenia, gray matter volume decreased in a wider range of regions. The only region of gray matter reduction specific to bipolar disorder was located in the anterior cingulate cortex.

3.2. Functional imaging biomarkers

Recent functional imaging studies in BD have been based mostly on fMRI, as the spatial resolution of PET is low and magnetoencephalography is not yet widely used. The diagnostic criteria for BD suggest that the capacity to regulate emotional state is impaired in these patients. Most fMRI studies have explored the neural networks underlying emotional processing in patients with BD. The paradigms used in the different studies include explicit and implicit affect recognition tasks (15-20), emotional go/no go tasks (21, 22), emotional Stroop tasks (23, 24), emotional memory tasks (25) and emotional face-matching paradigms (26, 27). The results obtained are quite disparate, but generally indicate that patients with BD display hyperactivity of a ventral-limbic brain network encompassing structures such as the amygdala, the parahippocampal gyrus, the subgenual cingulate cortex, the ventrolateral prefrontal cortex, the orbitofrontal cortex (OFC), the caudate nucleus and the thalamus. By contrast, hypoactivity of dorsal brain structures, such as the inferior and medial frontal gyrus, the dorsal and posterior cingulate cortex and the precuneus, has been reported in patients with BD (for a specific review of these studies see (3)). Such emotional tasks have been used to explore unipolar depression, with much more complex results that in bipolar disorder (28) and in schizophrenia, reporting underrecruitment of limbic regions (29).

Functional neuroimaging studies of BD have made use of non emotional cognitive tasks, as impaired executive functioning has been described in BD, even when

the patients are in euthymic state (30). Such studies (31, 32) have provided evidence of an increase in activity in ventral-limbic brain structures during purely cognitive-attentional tasks (sustained attention, working memory) in euthymic bipolar patients with preserved behavioral performances. This suggests that patients with BD attach an emotional valence to a task for which no processing of emotional information is required, providing additional support for the hypothesis that emotional reactivity is generally heightened in BD patients (33).

In contrast, patients with schizophrenia have reduced activation in dorsolateral prefrontal cortex and anterior cingulate cortex during executive tasks, but without any evidence of increased activity in limbic regions (34).

Even though we and others have tried to summarize results of various fMRI studies in bipolar disorder, we must note that the discrepancies between the tasks used limit the range of the common findings between studies. Furthermore, longitudinal studies and explorations of first-episode patients are required in order to assess the evolution of the functional findings in the course of the disease.

3.3. Heterogeneity of results

Heterogeneous results have been obtained in the structural and functional neuroimaging of BD. However, the main source of this heterogeneity in the results of neuroimaging studies of BD is the heterogeneity of the clinical samples, which probably confounds the observed results. The clinical characteristics of the patients studied are diverse, with, for example, different subtypes of BD (e.g., types I and II, rapid cycling) and differences in age at onset (early, intermediate, late), thymic state, inclusion or exclusion of patients with comorbid psychiatric disorders, such as psychotic features, comorbid alcohol dependence, anxiety disorders or comorbid medical conditions. No difference in brain anatomy or function has yet been associated with some of these clinical features (e.g.(35)), but decreases in gray and white matter volumes have been observed in recovering alcoholic patients without BD (36) even after long periods of abstinence. The inclusion of patients with lifetime substance abuse or dependence may therefore have a major impact on the results. Another major confounding variable is psychotropic medication. Several authors have observed a neurotrophic effect of lithium and other mood stabilizers (37, 38). Similarly, changes in brain volume have been associated with the use of antipsychotic drugs (39). Lithium and valproate are known to influence fMRI activation patterns in patients with BD (40). The heterogeneity of results from fMRI studies may also result from the use of different activation tasks, making it difficult to compare findings directly.

Another factor contributing to the observed heterogeneity is the limited sample sizes used in these studies. In a meta-analysis (6), type I error (false-positive error rate) for typical neuroimaging studies of bipolar disorder was estimated at 0.34. The type II error rate is also high (e.g. 70% when measuring the lateral ventricular volume with 25 patients and 33 controls). Typical studies include groups of 20 to 30 patients and controls, but a larger number of subjects is required to obtain sufficient power.

4. NEUROBIOLOGICAL MODELS OF BIPOLAR DISORDER

Based on previous structural and functional neuroimaging studies in BD, several authors have developed putative neurobiological models of bipolar disorder. As bipolar disorder is primarily associated with emotional symptoms and disturbances, these models have focused mostly on emotional processing and its cognitive control. We review here models of the regulation of emotional processing in healthy controls and in patients with bipolar disorder.

4.1. Models of normal emotional processing

Investigations of emotional reactivity, its regulation and its underlying pathophysiological mechanisms in bipolar disorder require the identification of different stages of emotional processing. The identification of these stages is also important for the interpretation and comparison of published results.

Emotional processing is not a uniform process, and has been divided into various stages (3): (1) early emotional processing, including the pre-attentive stage, attention allocation and sensory perception; (2) emotional responses with automatic emotional response, experience and expression of emotion (3) emotional regulation, involving the initiation of new emotional responses or the alteration of existing responses (41) (see Figure 1). These three stages involve both different and common neural networks.

Early emotional processing depends principally on the attentional resources allocated. It has consistently been shown that emotional stimuli and mechanisms of selective attention modulate each other (42). It has been shown that the limbic system, including the amygdala in particular, mediates this increase in attentional load on emotional stimuli (43). The amygdala exerts this effect through amygdala-cortical connections (sensory and associative cortices; (44)). The prefrontal cortex, including the VMPFC in particular, also modulates responses to emotional stimuli by modifying the priority level of stimulus processing (43).

The amygdala, along with other subcortical structures, such as the ventral striatum, is crucial for the generation and experience of emotion (3). Amygdala activation is more specifically associated with the generation of negative emotional responses, whereas other subcortical regions, such as the ventral striatum, are more strongly linked to positive emotions.

Emotional regulation involves several mechanisms, such as reappraisal, suppression, inhibition, extinction, reversal and the maintenance of representations. Emotional appraisal networks can be modulated by

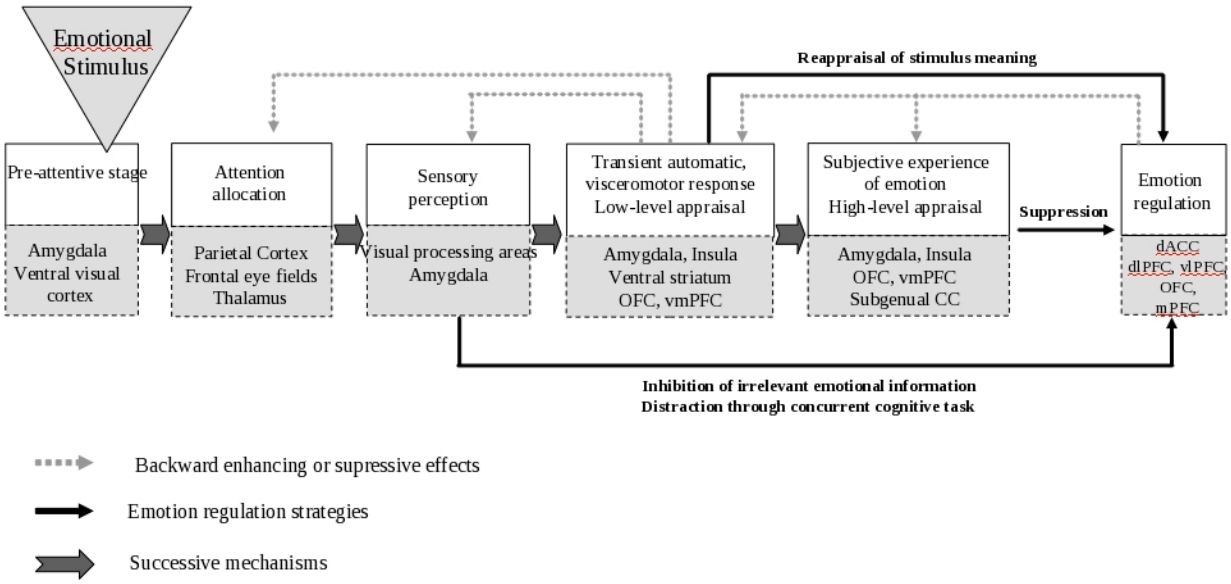

Figure 1. Mechanisms and stages of normal emotional processing, with brain areas involved in these stages. OFC: orbitofrontal cortex; vmPFC: ventromedial prefrontal cortex; CC: cingulate cortex; dACC: dorsal anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; mPFC: medial prefrontal cortex (modified from 3)

"higher-level" cognitive networks, such as the PFC, OFC and cingulate cortex, which exert top-down control on the limbic system, including the amygdala in particular (41, 45, 46). Phillips *et al*. (2) suggested that different neural networks are involved in automatic (anterior and subgenual cingulate cortex, OFC and hippocampus) and voluntary emotion regulation (ventrolateral prefrontal cortex, dorsolateral prefrontal cortex).

4.2. Models of emotional dysregulation in BD

Most of the proposed models for emotional dysregulation in bipolar disorder have focused on the abnormal production of emotional responses and defective emotion regulation. They involve cortical-limbic dysregulation with enlarged and/or hyperactive subcortical and ventral-limbic brain areas (amygdala, OFC, ventral PFC, anterior and subgenual cingulate cortex). This would result in an increase in sensitivity to the emotional significance of stimuli and an increase in the production of affective states. Furthermore, dorsal brain structures (dorsolateral and dorsomedial prefrontal cortex, dorsal anterior cingulate gyrus) are thought to decrease in volume and activity in BD and may therefore fail to inhibit the ventral-limbic network, leading to enhanced emotional responses (47, 48). A similar pattern of increased limbic activity is also observed in unipolar depression (49) whereas decreased limbic activity is generally observed in schizophrenia (29).

More recent models focusing on emotional regulation in BD have distinguished between the automatic and voluntary regulation of emotions (2). In BD, both structural and functional neuroimaging studies have suggested that abnormalities occur predominantly in the ventromedial prefrontal cortical regions and limbic regions involved in automatic emotional regulation. The authors of this model assume that these abnormalities underlie the mood instability observed in BD. This model also assumes the existence of abnormal prefrontal-subcortical limbic connectivity (see paragraph 5). However, only a few neuroimaging studies have investigated and compared different strategies of emotional regulation directly. Thus, there remains little empirical evidence concerning the nature and quality of deficiencies in emotional regulation and their neural correlates in BD.

5. CONNECTIVITY IN BIPOLAR DISORDER

In recent years, the development of two new neuroimaging techniques (diffusion tensor imaging MRI and fMRI connectivity analyses; (50)) has made it possible to investigate neural connectivity in BD. This condition is increasingly viewed as a disorder of both structural and functional connectivity.

5.1. Anatomical connectivity (DTI)

As previously stated, the most reliably replicated finding of neuroimaging studies on BD is a high rate of white matter hyperintensities, within the deep white matter and in periventricular areas. These white matter changes have been identified as a possible trait marker and endophenotype of bipolar disorder (9), as they are present from the onset of the disease. They are of physiopathological significance in BD, as they are associated with a poor prognosis (51) and cognitive decline (30) and seem relatively specific of BD. Furthermore, the genetic risk of bipolar disorder has been associated with white matter changes (52). Nevertheless, the exact significance of these white matter changes remains unclear, and it has been

suggested that they may reflect changes in anatomical connectivity.

A recently developed technique, diffusion tensor imaging (DTI), can be used to explore connectivity and white matter *in vivo*, providing information about both macrostructure (tracts) and microstructure (local organization; (53)). DTI explores the features of water diffusion in the brain. Water diffusion in the brain is restricted principally by axons and myelin sheaths. DTI therefore explores the integrity of white matter in voxels, giving a fractional anisotropy (FA) value for each voxel. Fractional anisotropy is correlated with the integrity and coherence of white matter. Decreases in FA have been associated with edema, demyelination and brain inflammation. DTI also provides information about mean diffusivity (generally expressed as ADC, or apparent diffusion coefficient) and the principal direction of diffusion in each voxel. This principal direction of diffusion within a voxel is thought to be parallel to the principal direction of the white matter tract in this voxel. These data allow a step-by-step reconstruction of white matter tracts in the whole brain and the comparison of these tracts between groups (54). In sum, DTI can be used to explore white matter and brain connectivity, in terms of both macrostructure (with tractography) and microstructure (with FA and ADC).

The first DTI-based studies in patients with BD reported a decrease in FA in frontal regions of interest (ROIs) (55-57), interpreted by the authors as axonal disorganization, a loss of coherence and, thus, changes in structural connectivity. This decrease in frontal FA has been confirmed and extended by larger whole-brain studies, which have identified diffuse decreases of FA in the corpus callosum, the fornix and in the prefrontal, limbic and striatal regions (58-61). These changes occur in key intra- and interhemispheric tracts, such as the fronto-occipital fasciculus (FOF), the inferior longitudinal fasciculus (ILF), the superior longitudinal fasciculus (SLF), the cingulum, the corpus callosum and the uncinate fasciculus (UF). DTI can also be used to evaluate these tracts and to evaluate their characteristics. Using this technique, we reconstructed the UF in a group of 16 euthymic patients with bipolar disorder and 16 healthy controls. We found that there was a significantly higher number of reconstructed fibers in the left hemisphere in patients with BD, consistent with an increase in anatomical connectivity in the left uncinate fasciculus (62). Two other DTI-based studies (63, 64) confirmed these changes to the uncinate fasciculus in BD. Connectivity changes in the UF are of particular interest, as this structure connects critical limbic areas of the brain, such as the amygdala, the subgenual cingulate cortex and the orbitofrontal cortex. It has been suggested that this brain circuit is misconnected or dysregulated in bipolar disorder (see section 4), and that this probably underlies the observed hyperactivity of the corresponding brain areas and the mood instability and inability to regulate emotional states in patients with BD. Possible increases in anatomical connectivity found with DTI are of particular interest as they are likely to be specific of BD as similar studies in schizophrenia or unipolar depression found no area of increased anatomical connectivity (65, 66).

DTI studies of BD have generated some converging results, but some inconsistencies have been found between the empirical findings of such studies. Some studies have reported an absence of change in FA (67), whereas others have reported an increase in FA in the corpus callosum (68), UF or in more diffuse brain regions (69, 70). The heterogeneity observed in DTI studies of bipolar disorder may result from the clinical diversity of samples, as previously discussed, or the recent nature of DTI, for which methodologies have yet to be standardized. Some DTI studies have used processing software developed for classical anatomical MRI, yielding to some potential issues (71). Specific techniques and software have thus been developed to process DTI data (71). Additionally, the exact nature of anatomical connectivity changes in first-episode patients still needs to be more extensively assessed.

It has been suggested that the expression of symptoms of bipolar disorder may result from dysfunctions of discrete brain networks, such as the anterior limbic network (2, 72). This model is supported by connectivity data and by genetic studies of bipolar disorder. Some allelic variants of neuregulin-1 have been repeatedly associated with bipolar disorder (73-78). Neuregulin-1 is crucial for neuronal migration, synapse formation, oligodendrocyte differentiation, neuronal myelination and, thus, brain connectivity. Interestingly, several groups have reported that neuregulin-1 variants are associated with differences in FA, as measured by DTI, in the frontal medial area (79) and anterior cingulate cortex(80).

5.2. Functional connectivity (fMRI)

In addition to DTI-based studies of anatomical connectivity, new analytical techniques for exploring functional connectivity by fMRI have recently been developed. Functional connectivity (FC) is the "temporal correlations between spatially remote neurophysisological events" (81). It provides insight into the degree to which different parts of brain networks are functionally coupled together, during the performance of a task or at rest (82). FC methods can be used to identify the brain areas communicating with each other during visual, emotional, language and motor-related functions (82, 83). The use of FC methods to analyze brain connectivity at rest has led to identification of the so-called "default-mode network" (DMN) (83). The DMN includes the precuneus/posterior cingulate cortex, medial prefrontal cortex, and medial, lateral and inferior parietal cortex (84). This network is activated at rest and deactivated during goal-oriented behavior. Studies of functional connectivity within this network have already yielded interesting results in other mental disorders, such as schizophrenia, demonstrating increases in connectivity within the DMN (85). By contrast, effective connectivity (EC) is defined as "the influence one neural system exerts over another either directly or indirectly" (81). EC includes directional data concerning the relationships between two areas.

Only a few studies have investigated FC or EC, either at rest or during cognitive and emotional tasks, in patients with BD. These studies have generated converging evidence to suggest that the connectivity between amygdala/hippocampus and ventral prefrontal/perigenual cortex is altered in BD (86). During an emotion-labeling task, patients with bipolar disorder displayed significantly

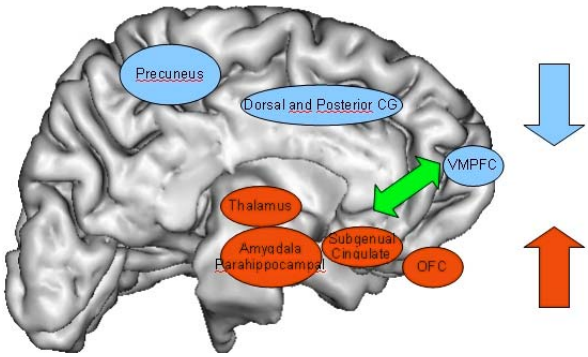

Figure 2. Proposed neurobiological model of BD on a sagittal medial view of left hemisphere (modified from 2) In red: increased activity in ventral-limbic regions; in blue: decreased activity in dorsal regions; disrupted connectivity between both networks (green). VMPFC : ventromedial prefrontal cortex; CG : cingulate gyrus; OFC : Orbitofrontal Cortex.

higher levels of effective connectivity between the right parahippocampal gyrus and the right subgenual cingulate cortex (87). During a male-female determination task with emotional interference, Wang *et al*. reported lower functional connectivity between the amygdala and the perigenual anterior cingulate cortex in patients with BD than in healthy controls (88). Almeida *et al.* reported that patients with bipolar and unipolar depression had different patterns of effective connectivity between the amygdala and orbitomedial prefrontal cortex during emotional intensity labeling tasks (89). Similarly, the same group described abnormal bilateral amygdala-orbitofrontal cortical functional connectivity in patients with BD: these patients had a significantly higher FC between the right amygdala and orbitofrontal cortex, whereas depressed female patients with BD had a significantly higher FC between the left amygdala and orbitofrontal cortex, these differences not being observed in patients in remission (90).

Even at rest, abnormalities in functional connectivity have been identified in patients with BD. The first study to investigate resting state connectivity abnormalities in BD found that patients with this disorder had significantly lower perigenual cingulate connectivity to the amygdala, thalamus and pallidostriatum than unaffected subjects (91). Similarly, Chepenik *et al.* reported a lower level of connectivity between the amygdala and ventral prefrontal cortex in patients with BD (92). One very recent study reported abnormalities within the DMN in manic patients, with abnormal recruitment of the parietal cortex, whereas patients with schizophrenia displayed greater recruitment of the basal ganglia and frontopolar cortex (93).

These converging results showing changes in amygdala/prefrontal connectivity are consistent with the proposed neurobiological models of BD reviewed above, all of which assume that the ventro-limbic network involved in the processing and regulation of emotions is dysfunctional in BD patients (see Figure 2). Nevertheless, the exact nature of connectivity changes in first-episode patients and their evolution still need to be more assessed. Furthermore, regarding both anatomical and functional connectivity techniques, we should keep in mind that these are recent techniques, still under development. The interpretation of the results should thus be cautious.

5.3. Linking structural and functional connectivity: bipolar disorder as a connectivity disorder?

With the development of structural and functional connectivity exploration techniques, new avenues of research and advanced theories have been developed based on information from different types of imaging, which is used to construct unified models of aberrant large-scale brain networks in mental disorders, such as BD (50, 94). Several studies have shown that resting-state functional connectivity (as measured with fMRI) is positively correlated with structural connectivity (as measured with DTI) (94-97). Multimodal approaches of this type are particularly useful in pathological conditions, as one technique alone may not be specific and sensitive enough for use as an individual biomarker (94), additional information from other modes of imaging therefore increasing the accuracy of the test.

Only one study has used both structural (DTI) and functional (fMRI) connectivity measurements for the same sample of patients with BD (88). This study reported lower functional connectivity between the amygdala and the perigenual anterior cingulate cortex (pACC) in patients with BD than in healthy controls. Interestingly, it also reported a positive correlation between pACC-amygdala functional connectivity and FA in ventrofrontal white matter, including the region of the UF. The authors suggested that disruption of the structural integrity of white matter bundles linking the pACC and amygdala might contribute to the pACC-amygdala functional coupling deficit. This study highlights the importance of merging data from different sources to reveal the roles of particular structures or brain networks in the pathophysiology of mental disorders.

6. PERSPECTIVE

6.1. Individual biomarkers in bipolar disorder

Neuroimaging studies of BD have yielded some interesting and convergent results supporting current neurobiological models of BD. However, the diagnostic biomarkers identified in these studies cannot yet be used by clinicians, because they have been validated at group level, but not at individual level. Valid diagnostic biomarkers must be sensitive and specific, with positive predictive value (PPV) and negative predictive value (NPV).

However, it will probably be possible to identify biomarkers suitable for individual use in the diagnosis of BD in the next few years, due to advances in bioinformatics involving the development of machine learning algorithms. In such algorithms, the computer discovers (in a supervised or unsupervised design) and learns from a "learning dataset" (group information supplied to the computer), the

rules for distinguishing the MRI scans of patients from those of healthy controls, based on various mathematical methods (e.g. support vector machine algorithms). The computer then applies these rules to new datasets, for the automatic classification of patients and healthy subjects within the sample.

Proof-of-concept for such approaches has already been demonstrated in schizophrenia and autism. In 2005, Davatzikos and colleagues (98) applied such an automated classification technique to T1 MRI scans from 69 patients with schizophrenia and 79 healthy controls. They achieved a classification accuracy of 81%. They have also used a similar method to predict disease transition: using T1 MRI scans from at-risk subjects, they were able to predict transition to psychosis four years later, with an accuracy of 82% (99). Similar computerized approaches have been used in autism (100). Some groups are developing techniques for classifying subjects on the basis of their fMRI data (101), cortical folding patterns (102) or DTI data. Very promising results have been obtained in schizophrenia, but replication studies in independent samples and cross-validation against other clinically relevant diagnoses such as major depression and schizophrenia, are required.

Such classification approaches have not been used in BD. Previous neuroimaging studies have suggested that neuroanatomical changes in bipolar disorder are more subtle than those in schizophrenia and autism, but the application of machine learning approaches nonetheless appears worthwhile in this patient group. Such approaches may make it easier to distinguish between patients with BD and healthy controls, but may also facilitate differentiation between different subtypes of BD and between unipolar and bipolar depression. Differences between unipolar and bipolar depression have already been observed for fMRI and DTI (89, 103, 104). Finally, machine learning approaches may help to predict the course of the illness or the response to treatment (medication or psychotherapy), both of which are highly relevant in clinical research.

6.2. Imaging genetics of bipolar disorder

With the increasing power of genetics and the new techniques used in neuroimaging, a new field, called imaging genetics, has emerged in recent years (105, 106). Imaging genetics assesses the impact of allelic variation on brain structure and function. It is based on the assumption that brain structure and function 1) are under strong genetic control (106) and 2) represent an intermediate phenotype. In the future, such approaches and the results they generate should facilitate elucidation of the functional role of risk gene variants and the identification of trait and vulnerability markers of mental illnesses. For example, 5-HTT promoter polymorphism has been associated with susceptibility to mood disorders in stressful conditions (107). Brain imaging studies exploring the impact of the s-allele have repeatedly demonstrated that this risk allele increases the reactivity of the amygdala to negative emotional stimuli (see (108) for a meta-analysis of this effect). This modulation of amygdala reactivity by this gene may account for the greater reactivity to negative events in subjects carrying this risk allele.

A few genes, including those encoding CACNA1C and neuregulin-1, have recently been repeatedly associated with BD. CACNA1C is a subunit of a voltage-gated calcium channel. Variants of CACNA1C were found to be associated with BD in a collaborative genome-wide analysis of 4387 patients and 6209 healthy controls (109). The impact of CACNA1C allelic variation was largely unknown until recent neuroimaging studies revealed that carriers of the CACNA1C risk allele in a group of healthy controls displayed stronger limbic (right amygdala) activation in response to reward (110). The same risk allele also seems to be associated with larger cerebral gray matter volume (111, 112), although this result requires replication, as another group reported an effect on brainstem gray matter, but not on cerebral gray matter (112).

Similarly, as reported above, neuregulin-1 variation has been associated both with BD (73-78) and changes in frontal and cingulum FA (79, 80).

The impact of susceptibility gene factors on brain structure and function can also be assessed by studying the healthy relatives of patients with BD. Such studies are difficult to perform, due to recruitment constraints, but they generate unique information. They make it possible to identify endophenotypes of BD — intermediate phenotypes associated with the genetic risk factors of bipolar disorder. White matter changes have been identified as a potential endophenotype of bipolar disorder (9). Recent studies have shown that genetic predisposition to BD is associated with low FA throughout the white matter regions (60). In gray matter, the reported deficits in healthy relatives of patients with BD are located in caudate volumes (113) and include increases in left insula and left cerebellum (114) and left parahippocampal gyrus (115) volumes. However, most studies have yielded negative results (113, 116-122). Healthy first-degree relatives of patients with BD have shown to be unable to suppress activation in the orbitofrontal cortex, superior parietal cortex, precuneus and insula during cognitive tasks, whereas such suppression is observed in healthy controls (123, 124). During a facial emotion processing task, first-degree relatives have been shown to display strong medial prefrontal cortical and subcortical (putamen and amygdala) activation, similarly to that observed in patients with BD (125). All these patterns may represent potential endophenotypes of bipolar disorder.

In conclusion, neuroimaging studies of BD have led to the formulation of neurobiological models based on dysfunctional connectivity between prefrontal and subcortical regions. Nevertheless, several issues remain unresolved, mostly due to the differences between the samples used in different studies. Two types of clinical differences may represent bias in existing studies: those linked to different pathophysiological processes (e.g. type I vs type II, rapid cycling) and those associated with the evolution of the disease (medication, substance abuse, number of episodes). The existing transversal studies cannot solve this issue. We yet do not know which abnormalities are vulnerability biomarkers, biomarkers

present before onset, after onset or associated with the evolution of the disease. No biomarker suitable for the diagnosis of BD in individual patients is yet available.

Based on the reviewed studies and the problematic issues and technical advances in neuroimaging research in BD, we make the following suggestions for future research aiming to identify neuroimaging biomarkers of BD:

1) The inclusion of a large (N > 200) number of patients. This would make it possible to compare data between subgroups of patients with sufficient statistical power (e.g. bipolar I versus bipolar II, psychotic features versus non-psychotic, etc...). It would also make it possible to take into account confounding variables, such as alcohol abuse/dependence. Multisite studies would also facilitate the development of individually usable biomarkers.

2) The inclusion of longitudinal cohort of patients, who would be scanned at the 1st episode (1st manic episode) and rescanned a few years later. This design would dramatically increase statistical power (as subjects could act as their own controls), and would make it possible to carry out a precise clinical evaluation of the confounding factors. Longitudinal approaches might also be useful for predicting the onset of disease in high-risk subjects (126).

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