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Neuroimaging Data in Bipolar Disorder: An Updated View

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1. Introduction

BD is a prevalent mood disorder, often comorbid with other medical and psychiatric conditions and frequently misdiagnosed (Altamura et al., 2011a). Intense emotional states that occur in BD comprise manic, hypomanic, mixed or depressive episodes. According to the Diagnostic and Statistical Manual of Mental Disorders, IVth edition, text revision (DSM-IV–TR; American Psychiatric Association, 2000), BD spectrum ranges from cyclothymia to Bipolar I, Bipolar II Disorder and Not Otherwise Specified (NOS) forms. BD can also be conceptualized as a gradual change in mood scale, which ranges from severe depression to severe mania with an intermediate euthymic state or balanced mood.

Dysthymia is a chronic state of mild low mood occurring for a minimum of two years. At the other end of the scale there is hypomania and severe mania. An alternative and broader dimensional approach conceptualizes BD as a continuum, between unipolar depression, schizoaffective disorder (which is considered by some authors a subcategory of BD) and schizophrenia. This theory may be supported from a clinical point of view by the fact that, sometimes, during severe manic, mixed or depressive episodes, bipolar patients experience psychotic symptoms, such as hallucinations or delusions. It is also supported by the presence of morphometric alterations of frequent observation among major psychoses, such as enlarged ventricles and white matter volume reductions in the left and temporoparietal regions (Czobor et al., 2007).

In BD, symptomatic states are frequently associated with poor working functioning and social impairment. Bipolar patients, moreover, have higher suicide rates than the general population and among the highest of psychiatric patients. In a recent study on factors predicting suicide in BD, white race, family history of suicide, and previous cocaine abuse were considered predictive of suicidal behaviour (Cassidy, 2011). Usually BD develops in early adulthood/late teens, with an age of onset ranging from 15 to 50 years (Cassano et al., 2006).

International treatment guidelines for BD recommend the use of mood stabilizers - either in monotherapy or in association - as the gold standard in both acute and long-term therapy. The concept of stabilization, in fact, has been stressed as the ultimate objective of the treatment of BD, given the chronic and recurrent nature of the illness, which accounts for its significant levels of impairment and disability (Altamura et al., 2011b). Beyond the

aforementioned core mood symptoms and clinical features of BD, over the last decade, neurocognitive dysfunction has been stressed as another nuclear dimension of BD and, possibly, a marker of its underlying pathophysiology (Lewandowski et al., 2010). There is accumulating evidence that individuals with BD have neurocognitive impairment that persists even during euthymia: the degree of impairment is more severe in patients with depressive symptoms, with functions associated with processing speed and attentional control being particularly implicated (Chaves et al., 2011; Van der Werf-Eldering et al., 2010). In addition, in older euthimic adults with BD, resting-state corticolimbic dysregulation was related to sustained attention deficits and inhibitory control, which could reflect the cumulative impact of repeated affective episodes upon cerebral metabolism and neurocognitive performance (Brooks et al., 2011). Cognitive impairment in BD is influenced by the severity of illness (Yates et al., 2010).

In addition, neuropsychological and imaging studies in BD suggested the presence of cognitive deficits and subtle magnetic resonance imaging (MRI) changes in limbic areas that may persist over euthymia. However, other studies are inconsistent with this claim. For example, a recent study did not identify any difference between BD patients and controls in levels of cognition over a two-year period, indicating that BD doesn't have a significant adverse impact on cognition (Delaloye et al., 2011).

Neuroimaging has recently gained an important role both in clinical practice and research of psychiatric disorders, including BD. Structural imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have contributed to a deeper understanding of the structural changes in the brain in the context of psychiatric disorders. Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Functional Magnetic Resonance Imaging (fMRI) and Diffusion Tensor Imaging (DTI) are techniques which measure changes in response to cognitive demand and/or connectivity between brain regions. As such, these approaches provide an opportunity for investigating the neural bases of behavioural and cognitive impairment in psychiatric populations, including BD.

2. Structural neuroimaging

2.1 Computed Tomography (CT)

In the last two decades, the first important data about neuroanatomic abnormalities in BD were obtained by means of CT. More recently, the widespread use of MRI has brought several advantages over CT, particularly in terms of higher resolution of images of subcortical regions (Steffens, 1998). Although a typical pattern of abnormality has not been identified yet (Supprian, 2004), several brain structures were found to be affected in patients with BD according to imaging studies.

CT provides excellent imaging data and rapid image acquisition at relatively low cost, it is widely available and more easily tolerated by patients, remaining the imaging modality of first choice in many clinical situations (Dougherty et al., 2004).

CT consists of a series of slices or tomograms. Its measurements are performed at the periphery of the body. The image of each slice is acquired by means of an X-ray source and detectors positioned at 180 degrees on the other side of the body. By spinning the source and the detectors on one plane of the head, data are collected from multiple angles. A computer then processes X-ray attenuation measured from different points and uses specific algorithms to create a structural image within the plane. Ionic and non-ionic intravenous

contrasts can be used to improve the visualization of certain normal or abnormal structures (Dougherty et al., 2004).
The measurement of total brain volume and ventricular volumes has been the aim of the first investigations using CT in psychiatric disorders. In this perspective, less consistent results have been found for affective disorders compared to schizophrenia and dementia (Beyer et al., 2002). The limited number of controlled CT studies focused on bipolar patients, in fact, showed heterogeneous findings. These include increased lateral ventricle size compared to controls (Andreasen et al., 1990; Nasrallah et al., 1982; Pearlson et al., 1984) or, in contrast, non significant differences between patients and controls (Dewan et al., 1988; Schlegel et al., 1987; Young et al., 1999). A larger third ventricle has been reported as well (Dewan et al., 1988; Schlegel et al., 1987). Studies on cortical alterations in BD revealed that there was no significant difference between patients and controls with respect to the level of cortical atrophy (Iacono et al., 1988; Rieder et al., 1983; Schlegel et al., 1987). However, a positive correlation between increased cortical sulcal widening and age of onset/age of first manic episode has been observed in bipolar patients in a subsequent study (Young et al., 1999). Volumetric changes in the cerebellum have been also reported, including higher rates of atrophy in bipolar patients (Nasrallah et al., 1982), even though the research of these abnormalities is limited.
In synthesis, some studies using CT in bipolar patients found an increased lateral ventricles size. In addition, cortical atrophy (which was not statistically different from controls), atrophy in the cerebellum as well as a larger third ventricle have also been reported.

2.2 Magnetic Resonance Imaging (MRI)

MRI takes advantage of the magnetic properties of the atomic constituents of the tissues in order to create an image of the different parts of the body. Every MRI scanner has a static magnet; its strength usually ranges from 1.5 to 3 Tesla. A steady magnetic field is generated as an electric current passes through the coils. In order to have a nuclear magnetic resonance signal, only atomic nuclei with unpaired protons and/or neutrons can be used. Medical MRI uses essentially hydrogen (^1H) as it is widely diffused in the human body and it has only one proton in its nucleus. Each proton has its own magnetic field or dipole moment, induced by the rotation around its axis. When an externally magnetic field is applied, protons' magnetic dipoles tend to align and to oscillate around the longitudinal axis of the applied field (this phenomenon is called precession) (Dougherty et al., 2004).
An horizontal radio frequency (RF) pulse is applied perpendicularly to the longitudinal axis of the external magnetic field with the aim to create a transverse component to the magnetization vector. This induces the generation of an electric current which is transduced into an MRI image. T1 is the "longitudinal" relaxation time and it indicates the time required to regain longitudinal magnetization following RF pulse. T2 is the "transverse" relaxation time that measures how long the resonating protons precess "in phase" following a 90° RF pulse. Due to the T1 and T2 relaxation properties in MRI, differentiation between various tissues in the body is possible (Jezzard et al., 2001).
Despite intensive research, to date no pathognomonic structural MRI finding has been correlated with affective disorders in general and to BD in particular. There are many heterogeneous data (Table 1) revealing a variety of structural alterations in bipolar patients (Dougherty et al., 2004). It must be considered, moreover, that some of these differences may be referred to the effects of medications (Van der Schot, 2009). For instance, chronic lithium treatment may prevent volume loss in treated patients because of its neuroprotective action

(Manji et al., 2000). Furthermore, genetic and/or environmental factors involved in BD may influence some brain abnormalities. In this perspective, decreases in white matter have been associated with the genetic risk of developing BD, whereas important environmental correlations have been found in relation to cortical gray matter volume (Van der Schot, 2009).
Brain abnormalities reported by fMRI studies in patients with BD include changes in cortical volumes, cerebral white matter, cortical and prefrontal gray matter. Enlargement of the ventricles, dimensional modifications of the amygdala, nuclei of the basal ganglia, corpus callosum and cerebellum have also been detected.
Main findings on lobar volumes concern frontal, temporal and insular cortex. Results on frontal lobes are quite discordant. In fact, they were found to be smaller (Coffman et al., 1990; Schlaepfer et al., 1994) or of the same size as controls (Strakowski et al., 1999). With respect to temporal lobes, no differences (Johnstone et al. 1989), bilateral reduction of volume (Altshuler et al., 1991) or loss of normal symmetry were found. Even in terms of loss of symmetry of the temporal lobes findings were sometimes discordant. In fact, a study reported a larger right temporal lobe than the left one in male bipolar patients (Swayze et al., 1992) and another study observed a larger left temporal lobe (Harvey et al., 1994). Voxel-based morphometric (VBM) MRI studies showed an increased gray matter in the insular cortex (Lochhead et al., 2004) or non significant differences in this region (McDonald et al., 2005; Nugent et al., 2006; Scherk et al., 2008a). An inverse correlation has been observed between the volume of the anterior insular cortex and the lifetime number of depressive episodes (Takahashy, 2010).
Bipolar patients, in particular those with late onset, were found to have a higher incidence of subcortical hypertensities (Dupont et al., 1990; Figiel et al., 1991; McDonald et al., 1991; Norris et al., 1997; Soares & Mann, 1997; Stoll et al., 2000; Swayze et al.,1990; Videbech, 1997). On the other hand, another study (Botteron & Figiel, 1997) identified an increased rate of white matter hyperintensity in relatively young individuals.
Lateral ventricular enlargement has been observed in BD and associated with multiple episodes of mania (Strakowski et al., 2002). A larger third ventricle was reported in elderly depressive patients and in cases of first manic episode (Strakowski et al., 1993). Likewise, correlations have been found between third ventricle volume and psychotic symptoms, advanced age, late onset of the disease, male gender and positive dexamethasone suppression test (Benabarre et al., 2002).
Studies on alterations of the amygdala in bipolar patients reported heterogeneous results, showing normal (Swayze et al., 1992), smaller (Pearlson et al., 1997) or larger volumes (Altshuler et al., 1998). More recent studies documented an increased volume in the right amygdala (Bremner et al., 2000), in bilateral amygdala in first episode subjects (Frodl et al., 2002) and loss of normal symmetry (Mervaala et al., 2000). The heterogeneity of the adult studies may be referred to the different age of subjects. It is still unclear, however, the positive correlation between increased amygdala volume and age (Usher, 2010).
A greater caudate volume as well as asymmetries among the structures of the basal ganglia were found in male bipolar patients (Aylward et al., 1994). Another study focused on the caudate volume in manic subjects in their first episode, reporting no significant differences vs healthy controls (Strakowski et al., 1999). The alterations may be attributed to a secondary effect of neuroleptic drugs (Benabarre et al., 2002). Studies examining alterations of the corpus callosum found volume reduction in bipolar patients, correlated with greater global neuropsychological dysfunction (Coffman et al., 1990). Finally, significant reduction of the cerebellar posterior vermis area was reported in patients with BD (DelBello et al., 1999).

Central nervous system structure involved	Main MRI alterations in BD
Frontal lobes	Reduced or unchanged volume
Temporal lobes	Reduced or unchanged volume Loss of the symmetry
Insular cortex	Increased gray matter or no changes
Subcortical areas	Increased hyperintensities
Lateral ventricles	Increased (association with number of episodes of mania)
Third ventricle	Increased
Amygdala	Larger, smaller or unchanged volume Loss of normal symmetry
Caudate nucleus	Increased or unchanged volume
Corpus callosum	Reduced volume
Cerebellar posterior vermis	Reduced

Table 1. Main MRI findings in BD.

2.3 Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS) is an MRI complement and serves as a non-invasive tool for tissue characterization. While MRI uses the signal from hydrogen protons to create a visual representation of the tissues, proton MRS (^{1}H- MRS) uses this information to determine the concentration of brain metabolites such as N-acetyl aspartate, choline, creatine and lactate in the examined tissue (Gujar et al., 2005).

MRS has been principally used for the diagnosis of some metabolic disorders, especially those of the central nervous system. MRS has not an optimal specificity, but in association with MRI and clinical data can be very helpful. Indeed, the main purpose of this technique is to obtain biochemical information from any part of the body in a non invasive way, i.e. not by means of radioactive tracers or electromagnetic radiation (Dougherty et al., 2004).

In psychiatry, MRS can be employed to assess the activity of different neurotransmitters, membrane and second messenger metabolism. The uniqueness of MRS is to provide an overview of the biochemical pathology of BD. Studies using proton MRS (^{1}H- MRS) reported increased glutamate and GLX (glutamate, GABA and glutamine) levels in the dorsolateral prefrontal cortex, frontal lobes, basal ganglia and gray matter of medication-free bipolar subjects and in patients with acute mania (Yildiz-Yesiloglu & Ankerst, 2006). Abnormal levels of N-acetyl aspartate, choline and myo-inositol have also been reported (Scherk et al., 2008b). N-acetyl aspartate seems to be reduced in the prefrontal cortex and hippocampus in bipolar individuals. Choline levels were found to be increased in the striatum and anterior cingulate cortex and can be normalized or decreased after treatment with antidepressants and lithium (Moore et al., 2000). Myo-inositol levels were increased in individuals with mania and euthymia and, on the contrary, reduced in bipolar depression.

Studies using phosphorus MRS (^{31}P- MRS) have found phase-specific alterations of phospholipid membranes, high energy phosphates and intracellular brain pH in BD. In particular, a number of investigations reported a reduced intracellular cerebral pH in bipolar subjects which has been associated with the increased levels of lactate observed in some ^{1}H- MRS studies. Both conditions are indicative of a shift from oxidative phosphorylation to glycolysis. There is also a ^{31}P- MRS based-report of decreased levels of phosphocreatine and of phosphomonoesters in BD (Kato et al., 1995).
Stork and Renshaw proposed a cohesive model that puts together the majority of MRS findings. They hypothesized that the impaired oxidative phopshorilation, the decreased cellular energy and the altered membrane metabolism could be due to an underlying altered mitochondrial metabolism in BD (Stork & Renshaw, 2005).
Main MRS findings in BD are synthetized in Table 2.

Technique		**Main alterations**
^{1}H- MRS	N- acetyl aspartate	Reduced levels
	Choline	Increased levels
	Glutamate, GABA and Glutamine	Increased levels
	Myo-inositol	Increased levels in mania and euthymia and reduced levels in bipolar depression
	Lactate	Increased levels
^{31}P- MRS	Phosphocreatine	Reduced levels
	Phosphomonoesters	Reduced levels
	Intracellular brain pH	Reduced levels

Table 2. Main MRS findings in BD.

3. Functional neuroimaging

The major limitation of structural neuroimaging techniques is that they are suitable for studying diseases associated with morphologic alterations, such as neurologic conditions. For this reason, they are only partially useful in psychiatric disorders which are characterized by behavioral abnormalities due to neurochemical impairment. In this perspective, PET (Abraham & Feng, 2011) and fMRI represent the gold standard for brain imaging aimed to assess cognitive performance (Glower, 2011). Electroencefalography, Event-Related Potentials and Magnetoencephalography are less specific and, therefore, mostly used to exclude neurological conditions in clinical practice or for research purposes (Cohen & Cuffin, 1983). Medication, drug or alcohol abuse and genetic/epigenetic influence represent major confounding factors (Nakama et al., 2011; Schulte et al., 2010). On the other side, following the biopsychosocial model for psychiatric disorders, functional neuroimaging could help understanding the complex interaction between environmental stressors, genetic risk and precipitating events in the plasticity of neural circuitry and consequently in clinical symptoms.

Functional neuroimaging attempts to explain psychiatric disorders by means of degenerative or developmental model of illness and/or in terms of hypometabolism.
In fact, elevated activity of the hippocampus or of the ventral prefrontal cortex as well as dorsolateral prefrontal cortex hypofunction are recurrent themes in literature (Savitz & Drevets, 2009).

3.1 Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT)

PET imaging is a direct measure of a radioactive decay due to cerebral metabolism of a radioactive substance or radionuclide. Different body tissues are characterized by different consumption rates of radionuclides (Ter-Pogossian et al., 1975; Vyas et al., 2011). Radionuclides used in clinical practice are usually major compounds of biologic molecules (18-Fluorine in the form of 18-Fluorodeoxyglucose or FDG for measuring glucose metabolism, 15-Oxygen for measuring blood flow, 11-Carbon or 13-Nitrogen common in diagnostic PET procedures). The nuclide is introduced in the patient and the radioactive decay is measured (Phelps et al., 1975): in particular, the positron emitted by nuclides has a collision with electrons producing a gamma photon which is measured by the PET camera (Roncali & Cherry, 2011). PET can measure both blood flow and glucose metabolism, often used as surrogate measures of neuronal synaptic activity. A first line comparison is between the neuroligand uptake in target regions and reference area while a more complex analysis can compare blood flow or glucose uptake in the same subject in different states, i.e. while resting or during a cognitive performance. Both ways provide useful data for research and clinical analysis; anyway, a major limitation is the use of a radioactive nuclide. Specifically, targeted PET radioligands are used to investigate neurotransmitter systems (Weisel, 1989). Cerebral PET has its major use in neurological disease: excluding primary or secondary oncologic lesions, evaluation of dementia, confirming epilepsy or assessing the state in cerebrovascular disease (Cavalcanti et al., 2011; Mazzuca et al., 2011; Person et al., 2010; Quigley et al., 2010; Salas and Gonzales, 2011).
SPECT works capturing orbiting electrons without a positron-electron collision, but by means of an emission of a single photon by the SPECT nuclide. Main nuclides used in SPECT are 123-Iodine, 33-Technetium or 133-Xenon. Single photons are selected with the use of multiple collimators.
PET and SPECT studies in depressive disorders have shown that blood rate and flow are increased both in BD and in unipolar depression in the frontal lobes during depressive episodes. However, they are increased during mania in the dorsal cingulate cortex, striatal regions, and the nucleus accumbens, as well as in limbic structures of the temporal lobes and reduced in dorsolateral prefrontal cortex, possibly reflecting its loss of modulatory control over limbic structures (Gonul et al., 2009).
With respect to neurotransmitters, serotonin (5-HT) transporter was found to have an increased density in the thalamus (Laje et al., 2010), dorsal cingulate cortex, medial prefrontal cortex and insula of depressed BD patients. 5-HT has been implicated in mania as well: in particular, individuals with current mania had significantly lower 5-HT2 receptor binding potential in frontal, temporal, parietal and occipital cortical regions, with more prominent changes in the right cortical regions compared to controls (Yatham et al., 2010, 2002a, 2002b). With regards to 5-HT1A receptor, bipolar depressed patients were found to show higher 5-HT1A in raphe nuclei and forebrain (Sullivan et al., 2009). An interesting use of PET consists of assessing the role of serotonin in major depressive episodes comparing

BD vs unipolar depression. In fact, both unipolar and bipolar depression were associated with elevated 5-HT transporter binding in the insula, thalamus and striatum, but showed distinct abnormalities in the brainstem (Cannon et al., 2007).
With respect to dopamine, D1 receptor binding potentials were found to be reduced in frontal cortex, even though striatal D2 receptor density was normal in all phases of non-psychotic BD (Bauer, 2003; Suhara et al., 1992).
In synthesis, PET and SPECT studies have shown in BD a loss of modulatory control of the cortex over limbic structures, reflected by specific phase-dependent modifications of blood rate and flow. Alterations of neurotransmitters involved in the pathogenesis of BD have also been reported, particularly with respect to serotonin transporter, serotonin receptor density and dopamine receptor density.

3.2 Functional Magnetic Resonance Imaging (fMRI)

FMRI is the most used technique in brain mapping and in psychiatric research due to its non-invasive technology, wide availability, high spatial and temporal resolution and the lack of ionizing radiation that allows the clinician to repeat functional exams over time as well as in different phases of illness. FMRI, in fact, is suitable for studying bipolar patients' performances on the same cognitive tasks during depressed, manic or euthymic phases. It can also compare brain activity during symptom exacerbation as well as over periods of remission.
One limit of fMRI is that it gives limited information on subcortical structures. Spatial resolution remains anyway highly relevant for the study of psychiatric diseases, given the clear correlation between cortical dysfunction and many psychiatric symptoms. Another limit consists of the increased variance of the results obtained with this technique in psychiatric patients (Dougherty et al., 2004).
FMRI measures changes in blood flow in areas of the central nervous system (Konarsky et al., 2007). The hemodynamic response reflects neural activity in the brain or spinal cord as neurons have no reserve for oxygen or glucose and they need to rapidly increase blood flow when necessary. A Blood-oxygen-level dependent (BOLD) signal is measured by fMRI. From a physiological perspective, hemoglobin is diamagnetic when oxygenated (oxyhemoglobin) and paramagnetic when deoxygenated (deoxyhemoglobin) producing different signals that are higher when coming from activated areas. Actually, an increase in cerebral blood flow produces changes in oxygen consumption resulting in increased BOLD signals (Bandettini, 2003).
Studies with fMRI in bipolar patients showed various alterations of the activity in different regions of the cortico-limbic pathways responsible for emotional regulation: amygdala, thalamus, striatum, portions of the prefrontal cortex and anterior cingulated cortex. Studies, however, were limited by the small samples size and by the possible interference of the medication. The increased activation of amygdala, striatum and thalamus were the most constant findings among the different studies (Cerullo et al., 2009).
Increased amygdala and subcortical activity to emotional stimuli, in particular negative stimuli, as well as reduced activity of the prefrontal cortical regions during cognitive performances are common to all phases of BD, suggesting that they may be trait features of the disease (Phillips & Vieta, 2007). Other additional frontal and temporal regions were found to be activated, maybe as a compensatory mechanism (Townsed et al., 2010).
FMRI studies in bipolar patients also suggest the presence of phase-dependent abnormalities. In fact, bipolar depression is associated with attenuated bilateral orbitofrontal

or elevated left orbitofrontal activity. Right dorsolateral prefrontal cortical activity was found to be reduced, while the increased left prefrontal activity seems to be a state marker of bipolar depression (Altshuler et al., 2008).
The few studies with fMRI on manic patients report an increased activity of the amygdala, insular cortex and subcortical areas in response to negative emotional stimuli. Ventral striatal activity was found to be elevated at rest and during motor tasks. On the other hand, ventral prefrontal activity was found to be attenuated during cognitive performances (Altshuler et al., 2005; Elliott et al., 2004). In addition, bilateral orbitofrontal attenuation has been reported in mania and may represent a trait feature of the disorder as it is also present during bipolar depression (Altshuler et al., 2008).

BD Phase	Central nervous system structures involved	Main fMRI alterations
Bipolar depression	Orbitofrontal cortex	Activity reduced bilaterally or increased on the left
	Prefrontal cortex	Reduced right activity; Increased left activity
Mania	Amygdala Insula Subcortical areas	Increased activity in response to negative stimuli
	Ventral prefrontal cortex	Reduced activity during cognitive performances
	Orbitofrontal cortex	Reduced activity bilaterally
Euthymia	Ventral prefrontal cortex Anterior cingulate gyrus	Reduced activity during attentional tasks
	Dorsolateral prefrontal cortex	Increased (i.e. during attentional tasks) or reduced activity (i.e. in response to fearful stimuli, during working memory tasks)
	Subcortical areas	Increased activity during performance or working memory tasks
	Amygdala	Increased activity in response to fearful stimuli
	Striatum	Increased activity in response to fearful stimuli; Significantly increased activity in response to reward stimuli

Table 3. Main fMRI findings in BD.

Findings on euthymic bipolar patients are more consistent and have pointed out reduced activity in dorsal, ventral prefrontal cortical regions and dorsal regions of the anterior cingulate gyrus during performance of attentional tasks. Dorsolateral prefrontal cortical activity was found to be, on the contrary, increased. Other studies have reported reduced dorsolateral prefrontal cortex activity in euthymic individuals during working memory and verbal encoding tasks (Deckersbach et al, 2006; Monks et al., 2004). Increases in activity

within subcortical regions associated with emotion processing rather than working memory or attention have also been detected in remitted, euthymic individuals with BD during performance of a continuous performance task (Strakowski et al., 2004) and working memory task (Adler et al., 2004). Other studies investigated the response of the activity of these structures to fearful expressions in remitted bipolar patients. Results showed an increased activity in the amygdala and in the striatum and, on the other hand, a reduction of the dorsolateral prefrontal cortex activity (Phillips & Vieta, 2007). Of note, striatal activity in response to potentially rewarding stimuli was found to be significantly elevated. Other emotional stimuli led to decreased dorsolateral prefrontal cortical activity. These two patterns may underlie mood instabilities in euthymic patients, especially in those with comorbidities (Hassel et al., 2008).

In synthesis, fMRI findings in bipolar patients are heterogeneous: they may be present in all phases of BD and/or can be phase-dependent. Among the formers, the most significant data include an increased activity of the amygdala and of the subcortical areas to negative stimuli and a reduced activity of the prefrontal cortex during cognitive tasks. Bipolar depression has been associated with modifications of the activity of the orbitofrontal and prefrontal cortex. In mania, specific alterations include an increased activity of the striatum at rest and during motor tasks and a reduction of the prefrontal cortex activity during cognitive performances. There are several studies on euthymic patients showing modifications of the activity of the prefrontal cortex during attentional or working memory tasks. Structures implicated in the emotional processing seem to be involved as well: in fact, modifications of the activity of the amygdala, striatum and dorsolateral prefrontal cortex in response to different emotional stimuli have been reported.

3.3 Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) is an MRI application developed in order to investigate white matter connections between regions of interest. These connections provide information on functional activity between areas of the central nervous system. DTI is particularly useful to detect white matter lesions or dysfunction (Versace et al., 2008).

There are few studies with DTI in BD, most of them based on the promising results from MRI research showing microstructural alterations in white matter in various neocortical areas and in the corpus callosum. In particular, fractional anisotropy, the most sensitive DTI marker which reflects fiber density, axonal diameter and myelination in white matter, was found to be decreased significantly in the ventral part of the corpus callosum in patients with BD (Heller et al., 2011). Other interesting results coming from DTI revealed that gray matter concentration was reduced in BD in the right anterior insula, head of the caudate nucleus, nucleus accumbens, ventral putamen and frontal orbital cortex. Other studies pointed out that BD patients showed abnormalities within white matter tracts connecting the frontal cortex with the temporal and parietal cortices and the fronto-subcortical circuits (Lin et al., 2011). White matter abnormalities seem to persist by the time of remission even after the first manic episodes (Chan et al., 2010), suggesting that disruption of white matter cortical-subcortical networks as well as projection, associative and commissural tracts may be a hallmark of the illness (Heng et al., 2010) involving prefrontal and frontal regions, associative and commissural fibres.

Some recent studies reported that certain variants of BD may be due to an increased functional or effective connectivity between orbitofrontal and temporal pole structures in the dominant hemisphere. The orbitofrontal cortex codifies the value of different stimuli,

allowing goal and sub-goal structuring. Moreover, it is involved in reward prediction. On the other hand, the temporal pole seems to be activated in basic semantic processes with person-emotion linkages associated with narrative. BD patients have a deficit of performance on visuospatial and constructional praxis which suggests an atypical localization of cognitive functions. This atypical localization and the hyperconnectivity between specific regions could be responsible for the enhanced creativity and writing ability observed in BD probands (McCrea, 2008).

Recently, abnormalities in perigenual anterior cingulate cortex-amygdala functional connectivity during emotional processing have been found in BD (Wang et al., 2009). Similar findings have been reported even in children and adolescents with BD, concluding that in these subjects significant white matter tract alterations were present in regions involved in emotional, behavioural and cognitive regulation. In addition, these results suggest that alterations in white matter are present early in the course of disease in familial BD (Barnea-Goraly et al., 2009; Kavafaris et al., 2009). An impaired fiber density in anterior corona radiata (as detected with a decreased fractional anisotropy) was detected in BD in pediatric age and in Attention Deficit and Hyperactivity Disorder suggesting a possible link between the two disorders (Pavuluri et al., 2008).

DTI studies can allow to detect a possible overlap between BD and schizophrenia. In fact, reduced integrity of the anterior limb of the internal capsule, uncinate fasciculus and anterior thalamic radiation regions is common to both schizophrenia and BD suggesting an overlap in white matter pathology, possibly relating to risk factors common to both disorders (Sussman et al., 2008).

Concerning antidepressants and mood stabilizers, these compounds seem to have neuroprotective effects and are not likely to explain white matter abnormalities, even though minor effects cannot be excluded (Bruno et al., 2008). Anyway, microstructural abnormality in the white matter has been associated with a low remission rate of major depression.

In synthesis, DTI provides information on functional connectivity between regions of the central nervous system. DTI studies on bipolar probands showed a reduced gray matter in areas such as putamen, caudate nucleus, nucleus acumbens, insula and orbitofrontal cortex. As concerns white matter, connections between orbitofrontal cortex, temporal, parietal corteces and the frontosubcortical circuits were found to be altered during mania and also over euthymia, as possible traits of BD. DTI findings have interesting implications on the association between BD and creativity. The hyperconnectivity between specific regions and the atypical localization of cognitive functions seem to be correlated to the enhanced creativity and writing ability of BD subjects. On the other hand, the atypical localization of cognitive functions could underlie the visuoconstructional praxis deficit present in BD.

4. Conclusions

Since the introduction of CT, researchers focused their efforts in elucidating the connection between psychiatric diseases and the presence of structural cerebral alterations through neuroimaging. CT pioneered this research without providing, however, a complete answer. Actually, a growing body of evidence has been accumulated in literature as newer techniques such as MRI and functional imaging (i.e., SPECT, PET, fMRI) have been introduced revealing much about the biological underpinnings of neuropsychiatric disorders. Neuroimaging research in BD has already produced several data documenting the involvement of different cortical and subcortical regions in different phases of the

illness. In particular, published studies explored structural and functional abnormalities present in BD and tried to establish specific correlations with outcome (Moore et al., 2001; Wingo et al., 2009, Bearden, 2010) as well as difficult-to-treat conditions such as treatment resistant forms (Regenold et al., 2008).

The possibility to study cognitive function in BD through fMRI represents another major acquisition of neuroimaging in psychiatric research. The attainment of this goal can be facilitated by identifying biomarkers reflecting pathophysiologic processes in BD, namely impaired emotion regulation, impaired attention, and distractibility, which persist during depression and remission and are not common to unipolar depression (Phillips & Vieta, 2007).

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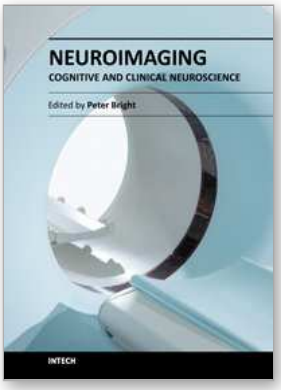

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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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