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This Section of *Epidemiology and Psychiatric Sciences* appears in each issue of the Journal to stress the relevance of epidemiology for behavioral neurosciences, reporting the results of studies that explore the use of an epidemiological approach to provide a better understanding of the neural basis of major psychiatric disorders and, in turn, the utilisation of the behavioural neurosciences for promoting innovative epidemiological research.

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Paolo Brambilla, *Section Editor*

Neuroanatomical voxel-based profile of schizophrenia and bipolar disorder

E. Maggioni[1,2], M. Bellani[3]*, A. C. Altamura[2] and P. Brambilla[2,4]*

[1] *Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari 'Aldo Moro', Bari, Italy*
[2] *Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[3] *Section of Psychiatry, AOUI Verona, Verona, Italy*
[4] *Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, Texas, USA*

Although schizophrenia (SCZ) and bipolar disorder (BD) share elements of pathology (Ellison-Wright and Bullmore, 2009), the neural mechanisms underlying these disorders are still under investigation. Up until now, many neuroimaging studies investigated the brain structural differences of SCZ and BD compared with healthy controls (HC), trying to identify the possible neuroanatomical markers for the two disorders. However, just a few studies focused on the brain structural changes between the two diagnoses. The present review summarises the findings of the voxel-based grey matter (GM) comparisons between SCZ and BD, with the objective to highlight the possible consistent anatomical differences between the two disorders. While the comparisons between patients and HC highlighted overlapping areas of GM reduction in insula and anterior cingulate cortex, the SCZ–BD comparisons suggest the presence of more generalised GM deficits in SCZ compared with BD. Indeed, in a number of studies, SCZ patients showed lower GM volumes than BD patients in fronto-temporal cortex, thalamus, hippocampus and amygdala. Conversely, only a couple of studies reported GM deficits in BD compared with SCZ, both at the level of cerebellum. In summary, the two disorders exhibit both common and specific neuroanatomical characteristics, whose knowledge is mandatory to develop innovative diagnostic and treatment strategies.

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The two major forms of psychosis, schizophrenia (SCZ) and bipolar disorder (BD), have been historically regarded as separate illnesses. However, the Kreaepelian dichotomous conceptualisation of the two disorders has been recently challenged by evidence of an intimate relationship. Indeed, SCZ and BD exhibit considerable overlaps in terms of genetic risk factors (Lichtenstein *et al*. 2009), clinical features (Fischer & Carpenter, 2009), neuropsychological impairment (Hill *et al*. 2013), as well as morphological brain changes compared with healthy controls (HC), including impaired white matter (WM) connectivity (Brambilla *et al*. 2005, 2009), ventricular enlargement

* Address for correspondence: Dr M. Bellani, Section of Psychiatry, AOUI Verona, Piazzale L.A. Scuro 10, 37134 Verona, Italy; Prof. P. Brambilla, Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via F. Sforza 35, 20122 Milan, Italy.
(Email: marcella.bellani@univr.it; paolo.brambilla1@unimi.it)

and global brain volume reduction (Arnone *et al*. 2009). These similarities contribute to raise questions on the degree of distinctiveness of the two disorders.

A comprehensive understanding of the neurobiological characteristics of SCZ and BD may help to shed light on their common and specific pathophysiological bases. A large number of region-based and voxel-based approaches has already been applied to identify the structural abnormalities associated with SCZ and BD (Arnone *et al*. 2009; Ellison-Wright & Bullmore, 2010; Yu *et al*. 2010; Bora *et al*. 2012; Selvaraj *et al*. 2012). Whole-brain voxel-based morphometry (VBM) studies highlighted overlapping areas of grey matter (GM) reduction in SCZ and BD compared with HC, mainly located in bilateral insula and anterior cingulate cortex. The same studies also provided evidence for the larger extent and magnitude of the GM deficits in SCZ than in BD, suggesting a specific involvement of dorsolateral prefrontal cortex, superior temporal cortex, medial frontal gyrus, posterior cingulate cortex and thalamus in SCZ (Ellison-Wright & Bullmore, 2010).

Having said this, it has to be noticed that most of the current knowledge of the neuroanatomical differences between SCZ and BD relies on meta-analyses of comparisons between each group of patients and HC. There are just a few studies that compared GM structure between SCZ patients and BD ones. In the present review, we focus on the VBM studies directly comparing SCZ patients to BD type I patients by providing an overview of their findings, in order to shed light on possible unique anatomical underpinnings of the two disorders.

Ten studies met the criteria for inclusion (the numerosity and clinical characteristics of the SCZ and BD groups, the type of comparison (single *v*. multi centre) and the main findings of the studies are listed in Table 1). In these studies, SCZ and BD were compared between each other and to HC, as well as to schizoaffective disorder (SAD) patients in Ivleva *et al*. (2012, 2013); Amann *et al*. (2016), and to their first-degree relatives in Ivleva *et al*. (2013). It is worth noticing that Yüksel *et al*. (2012) included SAD patients in the SCZ group. Although the clinical characteristics of patients varied from study to study, the large majority considered chronic patients (except from Farrow *et al*. 2005) and BD patients with lifetime psychosis (except from Molina *et al*. 2011; Amann *et al*. 2016). The differences in clinical symptoms and pharmacological therapies between studies represent a confounding factor that should be taken into account when interpreting their findings.

Except of Cui *et al*. (2011), which did not find significant differences between the two disorders, and Farrow *et al*. (2005), Molina *et al*. (2011), which detected reciprocal GM deficits in the two groups, the other studies only found regions of GM reduction in SCZ compared with BD. Although the regions interested by these deficits were rather heterogeneous across studies, the overall results provide further proof of the greater GM damage associated with the SCZ pathology.

As mentioned above, volumetric deficits in BD compared with SCZ were detected only in two studies (Farrow *et al*. 2005; Molina *et al*. 2011). The singularity of these findings may be partially related to the much smaller number of BD patients compared to SCZ ones (8 of BD *v*. 25 of SCZ in Farrow *et al*. (2005), 19 of BD *v*. 38 of SCZ in Molina *et al*. (2011)) characterising the two datasets. In the follow-up study by Farrow and colleagues (2005), after 2 years from illness onset, BD patients showed less GM in the left temporal cortex, right occipital cortex and left cerebellum. Cerebellar deficits emerged also in chronic BD patients *v*. chronic SCZ patients (Molina *et al*. 2011). The authors additionally found lower GM volume in BD than in SCZ in left anterior cingulate, which is in line with the hypothesis that genetic risk for BD is associated with anterior cingulate deficits (McDonald *et al*. 2004).

With regard to the GM deficits associated with SCZ, a variety of cortical and subcortical regions emerged from the BD–SCZ comparisons. Three studies found in SCZ patients GM reductions at the level of cerebellum (Molina *et al*. 2011; Ivleva *et al*. 2013; Amann *et al*. 2016), and basal ganglia (McDonald *et al*. 2005; Brown *et al*. 2011; Ivleva *et al*. 2013).

A number of works reported hippocampal (McDonald *et al*. 2005; Nenadic *et al*. 2015*a*; Brown *et al*. 2011) amygdalar (McDonald *et al*. 2005; Brown *et al*. 2011) and thalamic (McDonald *et al*. 2005; Molina *et al*. 2011; Ivleva *et al*. 2013; Nenadic *et al*. 2015*a*) deficits in SCZ when compared with BD. Given the key function of these structures in learning, memory, attention and information transmission, the GM deficits of these structures in SCZ patients seem to be consistent with the relevant cognitive impairment associated with SCZ (Andreasen *et al*. 1994; Brambilla *et al*. 2013).

At the cortical level, a GM reduction in the frontal gyri was found to characterise SCZ compared with BD from the first phases of the illness (Farrow *et al*. 2005; McDonald *et al*. 2005; Molina *et al*. 2011; Ivleva *et al*. 2013; Nenadic *et al*. 2015*a*). Some studies reported lower GM volume in SCZ than in BD in the temporal lobe, mainly in insula and temporal gyri (McDonald *et al*. 2005; Ivleva *et al*. 2013; Nenadic *et al*. 2015*a*, *b*). A few works also reported occipito-parietal deficits associated with SCZ, mainly in lingual gyrus and precuneus (McDonald *et al*. 2005; Ivleva *et al*. 2012), as well as deficits in cingulum (Ivleva *et al*. 2013) and

Table 1. *Selection of studies comparing SCZ and BD in terms of GM volume using voxel-based approaches*

Study	No. of SCZ patients	No. of BD patients	Study type	Findings
Farrow *et al.* (2005)	25 (2 years after psychosis onset)	8 (BD type I, 2 years after psychosis onset)	SC	BD < SCZ: left uncus, middle temporal gyrus and amygdala, right lingual gyrus and left cerebellum. SCZ < BD: left precentral/inferior frontal gyrus, right medial frontal gyrus, bilateral inferior and middle frontal gyrus
McDonald *et al.* (2005)	25	37 (BD type I, all with lifetime psychosis)	SC	SCZ < BD: bilateral inferior and middle frontal gyri, middle and superior temporal gyri, insula, precentral gyrus, precuneus and caudate nucleus. Right postcentral gyrus, amygdala, hippocampus, parahippocampal gyrus, putamen and thalamus
Molina *et al.* (2011)	38	19 (BD type I, 10 with lifetime psychosis)	SC	SCZ < BD: right anterior and posterior cerebellum, right pulvinar thalamus, bilateral medial frontal cortex, left precentral frontal cortex. BD < SCZ: bilateral anterior cerebellar lobe, left anterior cingulate cortex
Brown *et al.* (2011)	17	15 (BD type I)	SC	SCZ < BD: right hippocampus, putamen and amygdala
Cui *et al.* (2011)	23	24 (BD type I)	SC	SCZ *v.* BD: no significant differences
Ivleva *et al.* (2012)	19	17 (BD type I, all with lifetime psychosis)	SC	SCZ < BD: left precuneus and left lingual gyrus
Yuksel *et al.* (2012)	58 (21 with schizoaffective disorder)	28 (BD type I, all with lifetime psychosis)	SC	SCZ < BD: bilateral subgenual cortex
Ivleva *et al.* (2013)	146	115 (BD type I, all with lifetime psychosis)	MC	SCZ < BD: frontal, temporal, parietal, occipital, cingulate cortex, insula, thalamus, basal ganglia and cerebellum
Nenadic *et al.* (2015*a*, *b*)	$n = 34$	17 (BD type I, all with lifetime psychosis)	SC	SCZ < BD: bilateral medial, dorsolateral and ventrolateral prefrontal cortex, thalamus, insula, superior and medial temporal lobes, posterior hippocampus
Amann *et al.* (2016)	$n = 45$ (20 with acute symptoms, 25 stabilised)	$n = 45$ (BD type I, 32 with lifetime psychosis)	SC	SCZ < BD: left and right cerebellum

SC, single centre; MC, multi centre; SCZ, schizophrenia; BD, bipolar disorder; GM, grey matter.

subgenual cortex (Yuksel *et al.* 2012). The widespread GM deficits emerged from these studies may be related to the lower WM metabolism in frontal, parietal and temporal areas characterising SCZ in comparison with BD (Altamura *et al.* 2013).

In summary, the findings of the above SCZ–BD comparisons suggest the presence of GM differences between the two disorders, mainly consisting of volumetric deficits in SCZ compared with BD. While a minority of studies found GM deficits in BD, repeatedly in the cerebellum, most of them detected in SCZ GM reductions in fronto-temporal cortex, thalamus and hippocampal-amygdalar region, supporting the hypothesis that fronto-striato-thalamic and temporal deficits are present in SCZ (McDonald *et al.* 2004).

The above GM changes may reflect partially different aetiologies, changes in the illness progression over years, different medication effects, or a combination of these factors. A plausible explanation comes from post-mortem examinations (Selemon & Rajkowska, 2003), which found in dorsolateral prefrontal cortex altered packing with increased neuronal density in SCZ, as opposed to decreased neuronal density in BD, suggesting specific anatomical underpinnings for

the two disorders. Future research in this direction, using novel morphometric parameters (such as local gyrification (Nenadic *et al*. 2015*b*) and labelled cortical distance (Ratnanather *et al*. 2014)) and advanced multimodal processing techniques (such as support vector machine algorithms), opens the door to the development of instruments with higher diagnostic specificity. Significant evidence on SCZ and BD can also come from trans-diagnostic analyses that look at common dimensions of functioning across the two disorders (e.g., Goodkind *et al*. 2015), in line with the recent Research Domain Criteria.

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Conflict of Interest

None.

Ethical Standard

The authors declare that no human or animal experimentation was conducted for this work.

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