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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.

The ultimate aim is to help the translation of most relevant research findings into every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, 4 key-words, one Table or Figure and up to ten references).

Paolo Brambilla, *Section Editor*

# Twin studies for the investigation of the relationships between genetic factors and brain abnormalities in bipolar disorder

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The pathogenesis of bipolar disorder (BD) is to date not entirely clear. Classical genetic research showed that there is a contribution of genetic factors in BD, with high heritability. Twin studies, thanks to the fact that confounding factors as genetic background or family environment are shared, allow etiological inferences. In this work, we selected twin studies, which focus on the relationship between BD, genetic factors and brain structure, evaluated with magnetic resonance imaging. All the studies found differences in brain structure between BD patients and their co-twins, and also in respect to healthy controls. Genetic effects are predominant in white matter, except corpus callosum, while gray matter resulted more influenced by environment, or by the disease itself. All studies found no interactions between BD and shared environment between twins. Twin studies have been demonstrated to be useful in exploring BD pathogenesis and could be extremely effective at discriminating the neural mechanisms underlying BD.

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Bipolar disorder (BD) is a severe psychiatric disorder with a prevalence of 1–2%, with recurring episodes varying from psychosis to mania or major depression. It has a deep social impact due to increased suicide risk and poor quality of life, and is often associated with disability and chronicity, especially if there is a delay in treatment (Altamura *et al*. 2010, 2015). Many neuroimaging studies demonstrated brain abnormalities in patients affected by BD, afflicting both white and gray matter (Bellani *et al*. 2016; Maggioni *et al*. 2016). In particular, the inter-hemispheric connectivity, primarily fronto-limbic and callosal connectivity, results to be disrupted (Brambilla *et al*. 2009; Sprooten *et al*. 2016) and subcortical abnormalities have also been recently reported (Hibar *et al*. 2016). Furthermore, gray

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matter thickness and volume are heavily affected (Houenou *et al*. 2012; Hanford *et al*. 2016), especially in prefronto-temporal areas.

The pathogenesis of this disease is not entirely clear yet, but there is evidence of a predominant contribution of genetic factors to the risk for BD, with a very high heritability estimated around 85% (McGuffin *et al*. 2003). Classical genetic research involving families, twins and also adoptions showed that genes are strictly related to the risk of developing BD (Craddock & Sklar, 2013). Over the last years, the study of twins has proven to be particularly effective in biomedical etiological research. Monozygotic (MZ) twins are genetically identical and dizygotic (DZ) twins share 50% of their genes; also, both MZ and DZ twins share environmental factors in utero as well as within the family in early infancy. For these reasons, twin studies allow etiologic inferences to be made without the confounding effect of unmeasurable factors such as genetic background, intrauterine or perinatal exposures, or family environment. Thus, the main challenges associated with case-control studies are overcome when dealing with twins (McGue *et al*. 2010).

Discordant-twin studies, in particular, could be crucial for the understanding of the interplay between these factors (Fagnani *et al*. 2014). In this review, we address twin studies, which focus on magnetic resonance imaging (MRI) of the brain and BD. Ten studies met our inclusion criteria (i.e., MR imaging, twin pairs affected by BD, comparison with healthy twin pairs, focus of work on genetic influence on BD). Their main findings are summarised in Table 1.

Based on the assumption that environmental factors are shared by MZ and DZ twins to the same extent ('Equal Environments Assumption') (Neale & Cardon, 1992), a higher similarity observed in MZ twins suggests genetic influences on the trait under study. Consequently, the comparison of BD-affected twins with healthy control (HC) twins could help in shedding light on the mechanisms of the disease. Noga *et al*. (2001) compared a small sample (6 pairs) of discordant MZ twins to MZ HC and showed that left caudate was larger in BD and co-twins, suggesting genetic effects, and right caudate was larger only in BD, implying environmental factors. Kieseppä *et al*., in two works (2002, 2003), found evidence of genetically-induced decreased left white matter and environment-related decreased frontal white matter, while no significant results were found for gray matter, in a dataset comprising around 30 BD-affected twins. Bearden *et al*. (2011) focused on the white matter and found callosal thinning, area reduction and different ventral curvature in patients with BD ($n = 21$) compared with both co-twins ($n = 19$) and controls ($n = 34$), while co-twins had no differences with controls. This suggests that differences in corpus callosum are disease- rather than genetically-induced.

The only study, which analysed fMRI task activation found no difference in BD twins or their co-twins, in respect to controls during word generation, while it found relevant results in schizophrenia (Costafreda *et al*. 2009).

A more formal description of the genetic and environmental estimates that can be obtained with the classical twin model involves three factors, namely additive genetic (A), common (i.e., shared by twins) environmental (C) and unique (i.e., individual-specific) environmental (E) factors, under the so-called ACE model. This model allows one to partition the total variance in liability to a given disease (e.g., BD) in the three components A, C and E; in particular, the proportion of total variance due to the A component is named 'heritability'. Such a decomposition requires structural equation model (SEM) fitting, which has limited applications in clinical contexts due to the large sample size needed to achieve adequate statistical power (Wolf *et al*. 2013). The SEM approach has been employed in five of the studies considered in this review, and all of them found no significant role of common environment.

Considering a population of around 200 twins at baseline (MZ and DZ, both discordant and concordant for BD, details in Table 1) and 100 twins at follow-up, Bootsman *et al*. (2015) found a phenotypic and genetic association of BD with smaller subcortical volumes at baseline. Volume change over time had low heritability, but high association with unique environment. Interestingly, most of the other studies, which used the ACE model found only environmental influences on gray matter, while they detected genetic effects on white matter. Van der Schot *et al*. (2010) demonstrated, in a sample of around 200 individuals (49 affected twin pairs and 67 healthy twin pairs), that genetic factors are involved in white matter density of superior longitudinal fasciculus, while cortical gray matter volume decrease was related only to unique environmental factors. Another work of the same group (Van der Schot *et al*. 2009) showed that the genetic risk of developing BD was associated with decreases in white matter volumes, while gray matter was highly related to unique environment. This indicates that genes involved in BD could contribute to white matter loss found in BD patients and their co-twins, while gray matter decrease is probably related to the illness itself. Hulshoff *et al*. (2012) found relevant genetic factors in both BD and SCZ, related to smaller white matter volume and thickness: thinner in parahippocampus and right orbitofrontal cortex, thicker in temporoparietal and left superior motor cortices. In this case, gray

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**Table 1.** *Selection of twin studies on BD investigating brain structure and function with MRI*

| Title | Dataset | Methods | Results |
|---|---|---|---|
| Bootsman *et al.* (2015) | Baseline: 99 twins (pairs: 15 MZ discordant, 9 MZ concordant, 20 DZ discordant, 4 DZ concordant. 1 unmatched BD patient, 2 co-twins) 129 HC twins (pairs: 37 MZ, 25 DZ, 2 MZ unmatched twins, 3 DZ unmatched twins)<br>Follow-up: 48 twins (pairs: 10 MZ discordant, 2 MZ concordant, 6 DZ discordant, 2 DZ concordant. 1 unmatched patient, 2 MZ co-twins, 5 DZ co-twins) 52 HC twins pairs (pairs: 13 MZ, 8 DZ, 6 MZ unmatched twins, 8 DZ pairs and 4 DZ unmatched twins) | MRI @ 1.5 T<br>Voxel size: $1 \times 1 \times 1.2$ mm$^3$<br>Subcortical volumes obtained with FreeSurfer (correction GLM for lithium)<br>SEM, ACE model | Lithium use was associated with bigger volume of thalamus and putamen.<br>No common environment influences for BD.<br>BD phenotypically and genetically associated with smaller volumes of the thalamus, putamen and nucleus accumbens at baseline.<br>No association with volume change over time.<br>High heritability of subcortical volumes at baseline.<br>Low heritability of volume change. High association of volume change with unique environment |
| Vonk *et al.* (2014) | 53 BD-affected twin pairs (9 MZ concordant, 15 MZ discordant, 4 DZ concordant and 25 DZ discordant pairs) 51 HC twin pairs | MRI @ 1.5 T<br>Voxel size: $1 \times 1 \times 1.6$ mm$^3$<br>Manual ROI tracing<br>SEM, ACE model | No common environment influences for BD.<br>Dermatoglyphic a–b ridge count (ABRC) has genetic association with total brain volume, total cortical volume, cortical GM and WM volumes.<br>ABRC is related to the genetic risk of developing bipolar disorder |
| Hulshoff *et al.* (2012) | 310 individuals from 158 (152 complete and 6 incomplete) twin pairs (26 discordant for SCZ (13 MZ and 13 DZ), 49 with BD (9 MZ and 4 DZ concordant; 14 MZ and 22 DZ discordant), 83 HC twin pairs (44 MZ, 39 DZ) | MRI @ 1.5 T<br>Voxel size: $1 \times 1 \times 1.2$ mm$^3$<br>Cortical thickness and gray and WM volumes.<br>Correction for lithium use<br>SEM, ACE model | No common environment influences for BD.<br>Relevant genetic factors for both illnesses related to smaller WM volume.<br>Phenotypical correlations in both illnesses for thinner left and right parahippocampal gyrus, right orbitofrontal and right medial occipital cortices.<br>Genetic factors in both diseases, except for occipital lobe where there are only environmental factors.<br>Smaller GM volume related only to environmental factors both illnesses (not significant).<br>Abnormalities in cortical thickness shared by patients with SCZ and patients with BD and by their co-twins |
| Bearden *et al.* (2011) | 21 patients with BD (4 MZ), 19 of their non-BD co-twins, 34 control twin individuals (8 MZ) | MRI @ 1.0 T<br>Voxel size: $0.98 \times 0.98 \times 1.2$ mm$^3$<br>Three-dimensional callosal surface.<br>Neurocognitive correlates of callosal area differences were additionally investigated in a subsample of study participants | Smaller area in BD *v.* controls and *v.* co-twins.<br>Difference in: genu, anterior midbody, posterior midbody (only BD *v.* controls) splenium (only BD *v.* controls).<br>Thinner genu and splenium *v.* co-twins and HC.<br>Co-twins did not differ from controls<br>Differences in ventral curvature *v.* controls and co-twins, dorsal *v.* co-twins (trend *v.* controls).<br>No differences between co-twins and controls |

*Continued*

**Table 1.** *Continued*

| Title | Dataset | Methods | Results |
|---|---|---|---|
| van der Schot *et al.* (2010) | 232 subjects: 49 BD-affected twin pairs (8 MZ concordant, 15 MZ discordant, 4 DZ concordant, 22 DZ discordant) 67 HC twin pairs (39 MZ and 28 DZ) | MRI @ 1.5 T<br>Voxel size: $1 \times 1 \times 1.2$ mm$^3$<br>VBM + SEM, with and without correction for Lithium use<br>SEM, ACE model<br>Cross-twin/cross-trait correlations as a basis for decomposition | No common environment influences for BD.<br>Genetic factors related to the association between density and bipolar disorder in the right medial frontal gyrus and the right insula.<br>Genetic factors involved in WM density of superior longitudinal fasciculus.<br>Environmental factors negatively associated with liability for BD in all regions. Positive association only in right inferior frontal gyrus |
| van der Schot *et al.* (2009) | 234 subjects including 50 affected twin pairs (9 MZ concordant; 15 MZ discordant; 4 DZ concordant; 22 DZ discordant) and 67 HC pairs (39 MZ and 28 DZ) | MRI @ 1.5 T<br>Voxel size: $1 \times 1 \times 1.6$ mm$^3$<br>Brain volumes.<br>Phenotypic and cross-twin/cross-trait correlations<br>SEM, ACE model | No common environment influences for BD.<br>Genetics associated with liability related to WM volume decrease except for the occipital lobe.<br>Unique environmental factors, including the effects of illness, lead to decreased cortical GM volume |
| Costafreda *et al.* (2009) | 41 MZ pairs and 50 singletons: 39 SCZ patients, 10 unaffected MZ twins, 28 BD patients, 7 unaffected MZ twins, 48 HC | MRI @ 1.5 T<br>Voxel size: not reported (7 mm thickness)<br>fMRI verbal fluency task | No differences in activation for BD and healthy co-twins *v.* HC |
| Kieseppä *et al.* (2003) | 24 twins (8 MZ) with BP I, 15 healthy co-twins, and 27 HC twins | MRI @ 1.0 T<br>Voxel size: $0.4492 \times 0.4492 \times 5$ mm$^3$<br>Manual ROI tracing | Decreased left WM volume in BD and co-twins *v.* controls<br>Decreased frontal right WM volume in BD *v.* HC and co-twins.<br>No decrease in GM.<br>Increase in frontal and temporal CSF in BD *v.* HC and co-twins |
| Kieseppä *et al.* (2002) | 28 bipolar twins (23 BD patients, 5 schizoaffective), 22 healthy co-twins, 34 HC | MRI @ 1.0 T<br>Voxel size: $0.4492 \times 0.4492 \times 5$ mm$^3$<br>Manual ROI tracing | CSF increase in sulcal volumes in BD and co-twins *v.* controls<br>Larger ventricular volumes and decrease in frontal WM in BD *v.* HC and co-twins |
| Noga *et al.* (2001) | 6 discordant MZ pairs, 6 MZ HC twin pairs | MRI @ 1.5 T<br>Voxel size:$2 \times 1.5 \times 1.5$ mm$^3$<br>Manual ROI tracing | No difference in basal ganglia volume<br>Larger right caudate in BD twins *v.* co-twins and controls<br>Left caudate larger in BD and co twins *v.* controls |

MZ, monozygotic; DZ, dizygotic; BD, bipolar disorder; HC, healthy controls; SCZ, schizophrenia; SEM, structural equation modelling; WM, white matter; GM, gray matter; MRI, magnetic resonance imaging; ROI, region of interest.

matter was influenced, although not significantly, by environmental factors. Vonk *et al*. (2014) found an indirect genetic relationship between the genetic risk of developing BD and brain, white matter and cortical volumes: these quantities were genetically related with the dermatoglyphic-derived ridge count, and this was related with the risk of BD.

In summary, twin studies demonstrated that there are strong genetic factors involved in the pathogenesis of BD, which also influence white matter, which in turn is involved in brain connectivity. Interestingly, corpus callosum seems to be disease-related. Gray matter, on the contrary, seems more affected by environmental effects or by the disease itself. These results have been found employing different methodologies (VBM, ROI-based studies, automatic estimation of cortical thickness and brain volumes), which allow the study of brain morphology from many points of view. It would be beneficial to introduce more recent techniques as cortical folding or gyrification also in twin studies, to reach a more comprehensive understanding of brain characteristics. A future use of the twin design should be encouraged, especially exploiting the potential of population-based Twin Registries, which could help in the identification of high numbers of BD concordant and discordant pairs, thus facilitating the complex modelling of the genetic and environmental etiological mechanisms.

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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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