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Brain Gyrification and Neuroprogression in Bipolar Disorder

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Bipolar disorder has a prevalence of about 1–5% worldwide and is associated with premature death by multiple causes, including cardiovascular disease, diabetes, and suicide. Less appreciated, however, is the emerging evidence suggesting that bipolar disorder may present a progressive course with neuroanatomical changes[1]. In this sense, the term neuroprogression was put forward as the pathological rewiring of the brain that takes place in parallel with the cognitive and clinical deterioration in the course of bipolar disorder[1]

Brain gyrification is an important anatomical characteristic of the human cortex. The spatial folding due to gyrification makes it possible for our brain to host more cortical neurons within a limited cranial volume than a brain without cortical gyrification. Some studies reported that the gyrification in patients with bipolar disorder was altered[2]. However, the relationship between the brain gyrification and neuroprogression in bipolar disorder was still unknown.

Previous studies on neuroprogression categorize the progressive stages of bipolar disorder according to prior numbers of manic episodes and hospitalizations, and provided valuable insights of the relationship between the brain changes and the neuroprogression of bipolar disorder[3,4]. In the current study, we used the same method to classify subjects with bipolar disorder as “BD-Late”, if they had 10 or more manic episodes and 1 or more hospitalizations due to manic or depressive episodes and as “BD-Early”, if they had 3 or less manic episodes. The remaining subjects were classified as the “Intermediate-stage” (BD-Intermediate).

Sixty-nine patients with bipolar I disorder (16 BD-Early, 38 BD-Intermediate and 15 BD-Late) according to DSM-IV and 80 healthy controls were recruited. Patients with head

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Dr. Cao designed the study, organized and processed the data, performed the analysis, and drafted the manuscript.
Dr. Passos jointly designed the study and drafted the manuscript.
Dr. Wu partly organized and processed the data, and critically edited the manuscript.
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Dr. Mwangi partly organized and processed the data, and critically edited the manuscript.
Dr. Soares designed the study, recruited the subjects, collected the data, and critically edited the manuscript.

Conflict of Interest

Dr. Soares has received grants/research support from Forrest, BMS, J&J, Merck, Stanley Medical Research Institute, NIH and has been a speaker for Pfizer and Abbott.

trauma with residual effects, neurological disorder, and uncontrolled major medical conditions were excluded. Axis-I diagnoses and clinical characteristics were assessed with the Structured Clinical Interview for DSM-IV axis-I Disorders (SCID-I). Patients with comorbidities were not excluded. However, only nine (13%) patients had comorbidities with substance abuse and 14 (20%) with PTSD, and their distribution in the three stage groups were not significantly different under χ^2 tests ($p>0.05$). Only seven percent of patients were in mania, 46% patients were in depression and 22% were euthymic at the time of the scan. The mood states were not significantly different across the three stage groups. Current dimensional mood symptoms were assessed with the Hamilton Depression Scale (HAM-D) and the Young Mania Rating Scale (YMRS). All the subjects signed written consent forms and the study was approved by local IRB committee.

We acquired structural T1-weighted scans using a Philips 1.5 Tesla MRI scanner (Philips Medical System, Andover, MA, USA) with a three-dimensional axial fast field echo sequence. The parameters were as reported previously[3]. The average cortical gyrification of all subjects was the average of local gyrification index (GI) at each cortical surface vertex estimated using the Freesurfer software suite version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). The GI is the ratio of the cortical surface area to an envelope surface that smoothly contains the brain[5].

We used the general linear model and the Spearman's correlation to estimate the effect of stages (HC, BD-Early, BD-Intermediate, BD-Late; severity from low to high) on the cortical GI and local GI on the cortical surface. We considered p-values < 0.05 significant.

We found a significant stage effect on the GI ($F(3,143)= 3.792$; $p=0.050$). Further post-hoc analysis showed that BD-Intermediate ($p=0.034$) and BD-Late ($p=0.025$) subjects had significantly lower GI than HC, while BD-Early had similar GI with HC ($p>0.05$), but these results did not survive Bonferroni correction. Furthermore, the correlation between the GI and stages of bipolar disorder was significant ($r=-0.181$, $p=0.027$, confidence interval with bootstrapping $[-0.286, -0.077]$). It is worth mentioning that illness duration was not different among groups. Surface-based analysis based on Spearman's correlation also found negative local GI changes from early to late stages at a false discovery rate (FDR) of 0.3 across the cortical surface. These results indicate progressive changes of brain gyrification in different stages of bipolar disorder, and provide evidence of the brain gyrification as a marker of bipolar disorder stages. These findings are consistent with previous findings about the pathophysiologic associations between number of episodes and hospitalization, brain alterations and cognitive impairment, and further support the neuroprogression theory[1].

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