Abstract

Background: Schizophrenia (SZ) and bipolar disorders (BD) are often correctly diagnosed only years after the initial manifestations. Brain imaging may provide support for early differential diagnosis, but is complicated by marked heterogeneity of results between studies. Obesity, dyslipidemia and insulin resistance (IR) are frequent in psychiatric disorders and may contribute to brain alterations/heterogeneity. We studied BD and SZ in different stages of illness and specifically investigated the effects of metabolic parameters on brain structure and function. **Methods:** In Study 1 we used machine learning algorithm to estimate the individual brain age from MRI scans of 120 participants with first episode schizophrenia (FES) and 114 controls. We calculated the brain age gap (BrainAGE) score by subtracting the chronological age from the brain age. We also performed voxel-based morphometry (VBM) study to localize obesity or psychosis related pathology. In Study 2, we acquired biochemical and cognitive measures from 100 euthymic BD patients and explored the association between IR and memory. In Study 3, we explored differences in BrainAGE in early stages of SZ (43 participants) or BD (96 offspring of BD parents) and healthy controls (HC). In Study 4, we performed MRI cerebellar volume analyses on 648 participants with SZ, BD and HC. **Results:** In Study 1, the diagnosis of FES and obesity/overweight were each additively associated with higher BrainAGE scores. VBM confirmed association between FES, higher BMI and lower GM volume. In Study 2, BD participants with IR displayed worse composite verbal memory score, while composite working memory scores were comparable in patients with or without IR. In Study 3, brain age of FES was on average 2.64 years greater than their chronological age. In contrast, participants at risk or in the early stages of BD showed comparable BrainAGE scores to HC and to their chronological age. In Study 4 patients with SZ had smaller global cerebellar GM volume compared to HC, while patients with BD did not differ from HC. **Conclusions**: Overweight/obesity may be an independent risk factor for diffuse brain alterations manifesting as advanced brain age as well as for local lower GM volumes already early in the course of psychosis. IR may contribute to worse cognitive functions in BD. These findings raise the possibility that targeting metabolic health and intervening already at the level of overweight/obesity or IR could slow neurostructural alteration and preserve brain function in SZ or BD. BrainAGE method and cerebellar volume measurements could aid in early differential diagnosis between BD and SZ.