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Increased grey matter volumes in the temporal lobe and its relationship with cognitive functioning in euthymic patients with bipolar disorder

D. Porta-Casteràs [a,b,c], M. Vicent-Gil [a,d], M. Serra-Blasco [d,e], G. Navarra-Ventura [f,g,h], B. Solé [d,i], L. Montejo [d,i], C. Torrent [d,i], A. Martinez-Aran [d,i], V. De la Peña-Arteaga [a], D. Palao [b,c,d], E. Vieta [d,i], N. Cardoner [a,c,d,*], M. Cano [a,d]

[a] Sant Pau Mental Health Research Group, Institut d'Investigació Biomèdica Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
[b] Mental Health Department, Unitat de Neurociència Traslacional, Parc Tauli University Hospital, Institut d'Investigació i Innovació Sanitària Parc Taulí (I3PT), Barcelona, Spain
[c] Department of Psychiatry and Forensic Medicine, School of Medicine Bellaterra, Universitat Autònoma de Barcelona, Barcelona, Spain
[d] CIBERSAM, Carlos III Health Institute, Madrid, Spain
[e] Programa eHealth ICOnnecta't, Institut Català d'Oncologia, Barcelona, Spain
[f] Research Institute of Health Sciences (IUNICS), University of the Balearic Islands (UIB), Palma (Mallorca), Spain
[g] Health Research Institute of the Balearic Islands (IdISBa), Son Espases University Hospital (HUSE), Palma (Mallorca), Spain
[h] CIBERES, Carlos III Health Institute, Madrid, Spain
[i] Bipolar and Depressive Disorders Unit, Hospital Clinic, Institute of Neurosciences, University of Barcelona, IDIBAPS, Barcelona, Spain

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ABSTRACT

Background: Bipolar disorder (BD) is characterized by episodic mood dysregulation, although a significant portion of patients suffer persistent cognitive impairment during euthymia. Previous magnetic resonance imaging (MRI) research suggests BD patients may have accelerated brain aging, observed as lower grey matter volumes. How these neurostructural alterations are related to the cognitive profile of BD is unclear.
Methods: We aim to explore this relationship in euthymic BD patients with multimodal structural neuroimaging. A sample of 27 euthymic BD patients and 24 healthy controls (HC) underwent structural grey matter MRI and diffusion-weighted imaging (DWI). BD patient's cognition was also assessed. FreeSurfer algorithms were used to obtain estimations of regional grey matter volumes. White matter pathways were reconstructed using TRACULA, and four diffusion metrics were extracted. ANCOVA models were performed to compare BD patients and HC values of regional grey matter volume and diffusion metrics. Global brain measures were also compared. Bivariate Pearson correlations were explored between significant brain results and five cognitive domains.
Results: Euthymic BD patients showed higher ventricular volume ($F(1, 46) = 6.04$; $p = 0.018$) and regional grey matter volumes in the left fusiform ($F(1, 46) = 15.03$; $pFDR = 0.015$) and bilateral parahippocampal gyri compared to HC (L: $F(1, 46) = 12.79$, $pFDR = 0.025$/ R: $F(1, 46) = 15.25$, $pFDR = 0.015$). Higher grey matter volumes were correlated with greater executive function ($r = 0.53$, $p = 0.008$).
Limitations: We evaluated a modest sample size with concurrent pharmacological treatment.
Conclusions: Higher medial temporal volumes in euthymic BD patients may be a potential signature of brain resilience and cognitive adaptation to a putative illness neuroprogression. This knowledge should be integrated into further efforts to implement imaging into BD clinical management.

1. Introduction

Bipolar disorder (BD) currently affects over 40 million people worldwide (GBD, 2019). Due to its early onset, chronicity, and recurrent symptomatology, the work productivity and quality of life of patients are severely affected (Fagiolini et al., 2013). Even during periods when clinical remission is achieved (i.e., euthymia), cognitive impairment is observed in >30% of these patients (Cullen et al., 2016; Martínez-Arán

* Corresponding author at: Sant Pau Mental Health Research Group, Institut d'Investigació Biomèdica Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Street Sant Antoni M. Claret 167, Pavilion 18, Barcelona 08025, Spain.
E-mail address: ncardoner@santpau.cat (N. Cardoner).

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et al., 2004; Tsapekos et al., 2021). These cognitive symptoms include difficulties in attention, verbal learning and memory, executive function, and social cognition, and pose a major obstacle to functional recovery (Sanchez-Moreno et al., 2017). Moreover, recent research has found a threefold increased risk of dementia in BD patients (Velosa et al., 2020), suggesting a concerning long-term neurodegenerative process (Musat et al., 2021).

The aetiology of the cognitive impairment in euthymic BD patients remains unclear. Although the impact of residual mood disturbances (Grunze and Born, 2020) and the use of psychotropic medication (Xu et al., 2020) are noteworthy, recent research suggests these cognitive impairments are not exclusively explained by these two factors (Cullen et al., 2019; Keramatian et al., 2021). In line with this idea, some cognitive impairments have also been observed in unaffected relatives of BD patients (Arts et al., 2008; Kjærstad et al., 2021). These findings suggest that an impaired cognitive endophenotype may be observable prior to illness onset, and could signal an increased genetic vulnerability to develop BD (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2019; Cattarinussi et al., 2022; Cullen et al., 2016; Woznica et al., 2022). The apparent state-independence of this cognitive pattern in BD (Leboyer et al., 2023; Villarreal et al., 2019) highlights its relevance as a distinguishable stable trait among these patients (Teixeira et al., 2019). In this regard, cognitive symptoms have been suggested as a potential prognostic marker (Bonnín et al., 2010). Recent literature has shown the impact of these cognitive deficits (e.g., in verbal memory and executive function) as predictors of future manic episodes in euthymic BD patients (Woznica et al., 2022). Similarly, affected cognitive profiles of BD patients are being explored as potential biomarkers of vulnerability to severe functional loss (Burdick and Millett, 2021). Cognitive impairments in BD are therefore an emerging treatment target (Miskowiak et al., 2022), though research exploring their relationship with structural brain changes is still limited.

Magnetic resonance imaging (MRI) offers a non-invasive up-to-date method to investigate the neurobiological underpinnings of psychiatric disorders (Gray et al., 2020). However, identifying BD imaging biomarkers is still challenging due to its cyclic nature and clinical heterogeneity. Consequently, there is a growing interest in evaluating more stable neural correlates, which could be only related to trait-like alterations observable in euthymic BD patients. Interestingly, this approach may partially avoid the influence of affective symptomatology on cognitive performance. In this sense, exploring state-independent alterations could foster the development of neurobiological diagnostic signatures, a step towards cost-effective precision psychiatry strategies during real clinical practice (Salagre et al., 2018). Previous neuroimaging research has consistently revealed that BD patients show a widespread pattern of grey matter alterations across the brain, including regions involved in emotion, cognition, and reward processing. Specifically, several studies have found that BD patients present lower grey matter metrics (either volume or thickness) in prefrontal, temporal, and insular cortices as well as in amygdala, hippocampus, and thalamus (Angelescu et al., 2021; Ching et al., 2022; Hibar et al., 2018; Hibar et al., 2016). These structural abnormalities, together with the cognitive impairment characteristic of BD patients, have been integrated under the "neuroprogression framework". This model proposes that both pathological phenomena develop in parallel during the disease's course (Librenza-Garcia et al., 2021), and reflect a cumulative neuronal loss resulting from an exacerbated induced stress during recurrent affective episodes, especially mania (Berk et al., 2011). Nonetheless, it is worth noting that pharmacological treatment has also been reported to significantly impact on cognitive performance (Vieta et al., 2018; Xu et al., 2020), and it may induce changes in neural structure (Hibar et al., 2018; Hozer et al., 2020). Therefore, pharmacological treatment has been postulated as one of the main modulators of BD neuroprogression (Cullen et al., 2019).

In contrast to the above, some recent studies do not fully support the idea of a progressive loss of grey matter (Abé et al., 2022) and cognitive function (Samamé et al., 2022) in all BD patients. These studies have identified significantly higher grey matter volumes in BD patients (Macoveanu et al., 2021; Zhang et al., 2021) and long-term cognitive trajectories with no significant differences to healthy controls (Samamé et al., 2022). Interestingly, current research suggests that this lack of consistency may arise from unaccounted heterogeneity in BD cognitive profiles (Macoveanu et al., 2021), differences in treatment response (Rodríguez-Ramírez et al., 2021) as well as a putative neuroprotective effect of lithium (Hozer et al., 2020). For example, higher dorsomedial prefrontal cortex (dmPFC) thickness has been observed in cognitively impaired BD patients compared to cognitively preserved ones and healthy participants (Macoveanu et al., 2021). In addition, recent approaches employing metrics of predicted brain age (in contrast to chronological age) suggest early-stage BD patients may present a delayed brain maturation, which converged with an accelerated neuropsychological impairment (Chakrabarty et al., 2022). Moreover, a recent multicentric study found that BD patients undergoing treatment with lithium had increased grey matter volumes compared to patients without such treatment (Hozer et al., 2020).

Similar inconsistencies arise when exploring structural connectivity in bipolar patients. Diffusion-weighted imaging (DWI) is an MRI-based technique that allows us to infer the microstructural integrity of white matter tracts through metrics of water diffusion. Early research within this field proposed a fronto-limbic dysconnectivity as one of the key alterations in BD (O'Donoghue et al., 2017; Wang et al., 2008). However, recent meta-analytical and consortia-driven efforts suggest that white matter alterations are more widespread (Cheon et al., 2022; Favre et al., 2019). Interestingly, this pattern of white matter alterations was positively correlated to an earlier age of onset, longer illness duration, and antipsychotic and anticonvulsant medications, while they were negatively correlated to lithium prescription (Benno et al., 2016; Favre et al., 2019). Moreover, this profile of white matter abnormalities has also been observed in unaffected relatives of BD patients (Bora et al., 2021), as well as in the early stages of BD (Zovetti et al., 2023). These findings suggest that white matter alterations may be part of a heritable endophenotype rather than a component of neuroprogression. Although the available research is still inconclusive, a relationship between white matter microstructure alterations and poor cognitive performance has been suggested (Masuda et al., 2020).

In this study, we aim to assess the structural underpinnings of euthymic BD patients by means of a multimodal neuroimaging assessment, as well as to evaluate their association with the cognitive performance of this population. We will analyse DWI metrics and grey matter volumes to assess white matter integrity and regional volumetric alterations. Our focus will be on comparing euthymic BD patients with age- and gender-matched healthy controls (HC). This multimodal approach will provide novel insight into the neurobiological correlates of the cognitive heterogeneity in BD. Additionally, it will further define structural features of BD in euthymic state, which are essential steps towards establishing the scientific background necessary for implementing imaging markers in clinical practice.

2. Experimental procedures

2.1. Participants

We recruited twenty-seven adult euthymic patients with BD (17 Type I and 10 Type II) from the Mood Disorders Outpatient Unit of Parc Tauli University Hospital (Sabadell, Barcelona) and the Bipolar and Depressive Disorders Unit of Hospital Clinic (Barcelona). Euthymic status was assessed by a senior psychiatrist with an extensive experience in mood disorders. The Hamilton Depression Rating Scale (HDRS-17 (Hamilton, 1960)) and the Young Mania Rating Scale (YMRS (Young et al., 1978)) were used to assess potential residual depressive and manic symptomatology, respectively. None of the patients could exhibit manic

symptoms (YMRS<12, mean score = 1.59), and only subsyndromal depressive symptoms were allowed (HDRS-17 < 15, mean score = 6.15).

As a comparison sample, we recruited twenty-four HC from both the hospital and the local community through a recruitment campaign. The healthy controls were matched to the euthymic BD patients in terms of age and gender distribution. Participants from the HC group underwent a medical anamnesis and the Structured Clinical Interview for DSM-IV Axis I Disorders non-patient version (First and Gibbon, 2004) to rule out the possibility of current or lifetime psychiatric disorders and the use of psychotropic medication.

Exclusion criteria for both groups included: (1) presence or history of severe medical, neurological, intellectual, psychiatric disorders (other than BD in patients), substance abuse or dependence (except nicotine), and (2) contraindication to MRI scanning or abnormal MRI upon visual inspection. Regarding the patients' group, comorbidities of impulse control disorders and eating disorders were not considered an exclusion criterion as long as BD was the main diagnosis and the primary reason for seeking assistance before euthymia. The main sociodemographic and clinical characteristics of both groups are summarized in Table 1. In order to better describe the medication load of BD patients, antipsychotic (Danivas and Venkatasubramanian, 2013), antidepressant (Hayasaka et al., 2015), and benzodiazepine (Ashton, 2002) doses were converted to their equivalents in chlorpromazine, fluoxetine, and diazepam, respectively.

The study protocol received the approval of the Institutional Review Board of the Parc Tauli University Hospital and the Hospital Clinic of Barcelona, and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate in the study.

Table 1
Sociodemographic and clinical characteristics of the study sample.

	Bipolars (n = 27)	Healthy Controls (n = 24)	Between-group differences †
Age, years: mean (±SD)	48.49 (9.19)	43.75 (7.93)	−1.96 (p = 0.055)
Gender, male: n (%)	13 (48%)	15 (60%)	0.53 (p = 0.467)
Bipolar diagnosis, Type I: n (%)	17 (63%)	–	–
Eating disorder: n (%)	2 (7%)	–	–
Kleptomania: n (%)	1 (4%)	–	–
YMRS: mean (±SD)	1.59 (±2.60)	1.00 (±1.73)	−0.92 (p = 0.357)
HDRS-17: mean (±SD)	6.15 (±2.76)	3 (±3.23)	−3.71 (p ≤0.001)
WHO-5: mean (±SD)	10.31 (±3.87)	15.78 (±3.68)	5.05 (p ≤0.001)
Lifetime psychotic symptoms: n (%)	12 (44%)	–	–
Age at onset, years: mean (±SD)	29.69 (±11.03)	–	–
Duration of illness, years: mean (±SD)	18.80 (±11.62)	–	–
Number of drugs: mean (±SD)	3.89 (±0.49)	–	–
Typical antipsychotics: n (%)	0	–	–
Atypical Antipsychotics: n (%)	20 (74%)	–	–
Anticonvulsants: n (%)	18 (66%)	–	–
Lithium: n (%)	17 (63%)	–	–
Doses of psychotropic drugs (milligrams/day)			
Chlorpromazine equivalents	n = 20 278 (±362)	–	–
Fluoxetine equivalents	n = 16 45 (±19)	–	–
Diazepam equivalents	n = 14 19 (±10)	–	–

YMRS = Young Mania Rating Scale; HDRS = Hamilton Depression Rating Scale; WHO-5 = World Health Organization Well-Being Index.
† Continuous variables analyzed by t-tests; categorical variables analyzed by X^2 test.

2.2. Neuropsychological assessment

Patients underwent a neuropsychological battery. Raw scores were extracted and transformed into T-scores using normative data. Then, the following five cognitive indexes were created: Attention and working memory (Wechsler Adult Intelligence Scale (WAIS-III(Wechsler, 1997): Digit Span), verbal memory (California Verbal Learning Test (CVLT (Delis et al., 1987))), visual memory (Rey-Osterrieth Complex Figure Test (ROCF(Rey, 1941)), executive function (Stroop Colour and Word Test(SCWT(Stroop, 1935)), Phonetic Verbal Fluency Test (FAS (Borkowski et al., 1967)), Trail Making Test (TMT(Partington and Leiter, 1949): Part B, Wisconsin Card Sorting Test (WCST(Grant and Berg, 2001))) and processing speed (WAIS-III (Wechsler, 1997): Digit Symbol-Coding, TMT (Partington and Leiter, 1949): Part A) **(Table S1)**.

2.3. Imaging acquisition and preprocessing

Imaging data were acquired with a 3-T scanner (Philips Ingenia, Best, The Netherlands) equipped with a 32-channel head coil 54 days on average after the neuropsychological assessment. Acquisition parameters for the high-resolution T1-weighted three-dimensional turbo field echo anatomical image were as follows: number of slices = 240; slice thickness = 0.75 mm; flip angle = 8°; field of view = 240 × 240 mm; matrix size = 352 × 352 pixels; in-plane resolution = 0.68 × 0.68 mm^2; echo time = 4.6 ms; repetition time = 9.8 ms. Diffusion-weighted images were obtained using a single-shot echo-planar sequence with 32 non-colinear directions. The scanning parameters were b-value = 1000 s/mm^2; matrix size = 112 × 112 pixels; number of slices = 66; slice thickness = 2.20 mm; flip angle = 90°; field of view = 230 × 230 mm; in-plane resolution = 2.05 × 2.05 mm^2; echo time 90 ms; repetition time = 9000 ms; phase-encode direction = P- > A. A reverse phase-encode polarity sequence (i.e., phase-encode direction = A- > P) was acquired for DWI distortion correction. In addition, a fluid-attenuated inversion recovery (FLAIR) sequence was acquired to discard brain pathology and optimized T1-weighted images preprocessing. The imaging parameters were as follows: number of slices = 137; slice thickness = 2.4 mm; flip angle = 90°; field of view = 240 × 240 mm; matrix size = 240 × 240 pixels; in-plane resolution 1 × 1 mm^2; echo time = 254 ms; repetition time = 4800 ms.

T1-weighted images were processed using the automated cortical reconstruction and volumetric segmentation procedures implemented in FreeSurfer version 7.2 (http://surfer.nmr.mgh.harvard.edu/). Briefly, FreeSurfer "recon-all" pipeline includes skull-stripping, bias field correction, intensity inhomogeneity correction, automated Talairach transformation, segmentation of subcortical white matter and grey matter, tessellation of the white matter-grey matter boundary, pial surface delimitation (optimized with FLAIR data), inflation and registration to a spherical atlas and cortical parcellation. Grey matter volumes for each of the 92 brain regions included in the Desikan-Killiany and Aseg atlases were extracted. Global measures of total grey matter, white matter, and ventricular volume were also computed for each participant. We used Freeview to control for quality as well as manually edit the images using the standard pipelines recommended by the FreeSurfer documentation. After inspecting and editing each image, we did not need to exclude any participants.

Afterwards, DWI images were processed using TRACULA (Yendiki, 2011) (TRActs Constrained by UnderLying Anatomy), a FreeSurfer tool enabling an automatic reconstruction of major white matter pathways by means of global probabilistic tractography based on neighboring anatomical structures (Maffei et al., 2021). From each of the 42 pathways reconstructed, the weighted average of 4 diffusion metrics was

extracted as indicators of white matter integrity: Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD). Reconstructed pathways were visually inspected to discard tracts with aberrant trajectories. Tracts that were not correctly reconstructed for >90% of the participants or participants with errors in >10% of the tracts were excluded from further analyses. This led to the exclusion of 3 participants and 3 tracts (i.e., bilateral fornix and right corticospinal tract). Two additional participants were excluded due to either missing DWI data or observable white matter abnormalities. A total of 23 bipolar patients and 23 HC were deemed suitable for DWI analyses.

2.4. Statistical analysis

Statistical analyses were conducted using R version 4.1.0 (R Core Team R Foundation for Statistical Computing, 2021), and data normality distribution was tested using Shapiro-Wilk Tests.

2.4.1. Surface-based morphometry

ANCOVA analyses were performed to assess between-group differences in grey matter volume in each region, controlling for total grey matter, sex and age as confounding covariates. Results were considered significant when surpassing a false discovery rate corrected threshold of pFDR <0.05, accounting for 92 multiple comparisons (i.e., 92 brain regions included in the Desikan-Killiany and Aseg atlases). To test for a potential differential effect of total grey matter volume or total intracranial volume (TIV) as covariates, analyses were rerun, controlling for TIV, sex, and age. Moreover, to assess the possible impact of lithium medication on regional grey matter volume between-group comparisons, an ANCOVA model was fit, including total grey matter volume, sex, age, and current lithium treatment as covariates.

Additionally, three independent ANCOVA analyses were conducted to explore differences in patient's total grey matter, white matter, and ventricular volume controlling for TIV, sex and age.

2.4.2. Diffusion-weighted imaging

Between-group differences in diffusion metrics (i.e., FA, MD, AD, and RD) in each reconstructed white matter tract were assessed by means of independent samples *t*-tests. Results were considered significant when surpassing a false discovery rate corrected threshold of pFDR <0.05, accounting for 156 multiple comparisons (i.e., 39 tracts × 4 metrics).

2.4.3. Relationship with neuropsychological performance

The relationship between neuroimaging variables (i.e., brain volumetric and diffusion alterations) and neuropsychological performance (i.e., five cognitive domains) in patients with BD was tested using Pearson partial correlation analyses, controlling for sex and age. An exploratory statistical significance was set at a threshold of $p < 0.05$.

3. Results

3.1. Surface-based morphometry

Euthymic BD patients showed higher grey matter volumes in the left fusiform gyrus ($F(1, 46) = 15.03$; pFDR = 0.015; $\eta_p^2 = 0.246$) and the bilateral parahippocampal gyrus (Left: $F(1, 46) = 12.79$; pFDR = 0.025; $\eta_p^2 = 0.218$ / Right: $F(1, 46) = 15.25$; pFDR = 0.015; $\eta_p^2 = 0.249$) compared to matched HC (Fig. 1). These results did not reach statistical significance after controlling for TIV or lithium treatment. No brain regions were detected to have lower grey matter volumes in BD patients compared to HC.

In addition, euthymic BD patients exhibited a higher total ventricular volume ($F(1, 46) = 6.040$; $p = 0.018$; $\eta_p^2 = 0.116$), although no significant differences were observed in total grey matter volume ($p = 0.672$) and total white matter volume ($p = 0.999$).

3.2. Diffusion-weighted imaging

We did not identify any statistically significant difference between euthymic BD patients and HC.

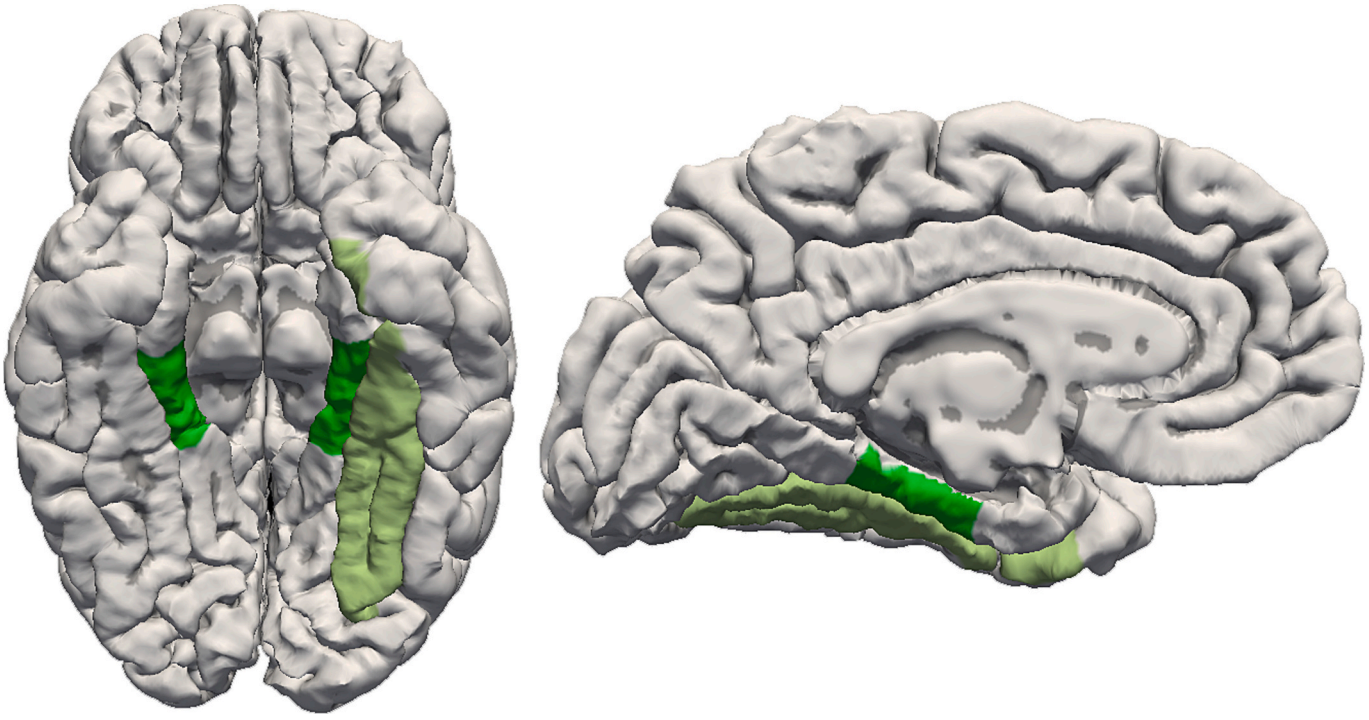

Fig. 1. Brain regions showing higher grey matter volume in BD compared to HC: parahippocampal gyrus is displayed in green and fusiform gyrus in light green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Relationship with neuropsychological functioning

Euthymic BD patients showed scores one standard deviation below normative data in the verbal memory domain. Scores in the lower range of normality were also observed for executive function and visual memory **(Table S1)**.

When correlating neuropsychological performance with those brain volumes showing differences in surface-based morphometry analysis, we observed that executive function of euthymic BD patients was positively correlated with the left fusiform ($r = 0.530$; $p = 0.008$; Fig. 2A) while left parahippocampal correlation only reached a trend-level significance ($r = 0.395$; $p = 0.056$). Post hoc disaggregated analyses evaluating the relationship between the left fusiform gyrus and the individual cognitive measures included in the executive function domain (Table S1) showed a positive correlation with the four components of the executive function domain, with only the cognitive flexibility measure reaching statistical significance by itself ($r = 0.482$; $p = 0.017$).

3.4. Statistical power estimation

We computed a statistical power estimation using G-Power (Faul et al., 2009). Our sample ($n = 51$) would require results with large effect sizes ($f > 0.40$) to reach the statistical significance achieved in our ANCOVA analysis. It should be noted that the smaller effect size detected in our ANCOVA analyses was $\eta_p^2 = 0.218$ ($f = 0.527$). In addition, the largest effect size reported in our ANCOVA analyses ($\eta_p^2 = 0.249$) reached a statistical power of 0.80. Adjusting our alpha value for the number of comparisons conducted in our study, our ANCOVA analyses would require results with an effect size over $f = 0.049$ to maintain an appropriate power of 0.80. Regarding correlational analyses between grey matter volumes and cognitive functioning, we have achieved an adequate statistical power of 0.80 for correlations with large effect sizes ($r = 0.50$).

4. Discussion

The present study examined the neurobiological underpinnings of euthymic BD patients and their relationship with five cognitive domains (i.e., attention and working memory, verbal memory, visual memory, executive function, and processing speed). In terms of grey matter volumes, BD patients exhibited higher volumes in the left fusiform gyrus, as well as the bilateral parahippocampal gyrus in comparison to HC. Additionally, BD patients displayed a higher total ventricular volume although no brain regions presented lower grey matter volumes. No significant between-groups differences were found in diffusion metrics. Importantly, executive function positively correlated with grey matter volumes of the left fusiform gyrus and left parahippocampal gyrus, potentially reflecting the adaptative value of the observed volumetric differences.

Our analyses of regional grey matter volumes did not find any individual structure with a significantly lower volume in euthymic BD patients compared to HC. Nevertheless, the overall result of higher total ventricular volume in BD patients may be consistent with previous results indicating widespread lower grey matter volumes and cortical thickness (Angelescu et al., 2021; Ching et al., 2022; Hibar et al., 2018; Hibar et al., 2016). Importantly, an increased total ventricular volume was the only significant neuroimaging feature observed in the largest longitudinal mega-analysis to date in BD (Abé et al., 2022). These findings suggest that ventricular volume may be a highly consistent indicator of global changes in grey and white matter (Grewal et al., 2023). Several authors interpret these results as a potential sign of accelerated brain aging in BD (Van Gestel et al., 2019; Zovetti et al., 2023), a phenomenon that may be shared with schizophrenia and neurodegenerative conditions such as multiple sclerosis, mild cognitive impairment, and dementia (Kaufmann et al., 2019). Recent efforts to translate this global alteration into a single metric have employed machine learning models trained with extensive datasets in order to measure, for each individual patient, to what extent the age predicted by the brain differs from the chronological age (i.e., predicted age difference; PAD) (Blake et al., 2023; Van Gestel et al., 2019). Using these models, BD patients showed a higher PAD (predicted brain age > chronological age), supporting the hypothesis of an accelerated brain-aging (Blake et al., 2023).

However, our results of regional structural alterations in BD point in an apparently opposite direction, with euthymic BD patients exhibiting higher grey matter volumes in the left fusiform gyrus and bilateral parahippocampal gyrus and no significant difference in white matter integrity compared to HC. At this point, it should be noted that our regional grey matter statistical analyses were controlled by total grey matter volume. This approach subtracted the hypothetical effect of a global grey matter volume alteration and increased the sensitivity of our tests to volumetric regional differences relative to total volume (Peelle et al., 2012). This methodological standard may have led to different findings from those reported by studies assessing absolute (not corrected) differences in grey matter volume or grey matter volumes controlled by TIV (Angelescu et al., 2021; Hibar et al., 2018). Indeed, it is possible that earlier cross-sectional neuroimaging studies may have

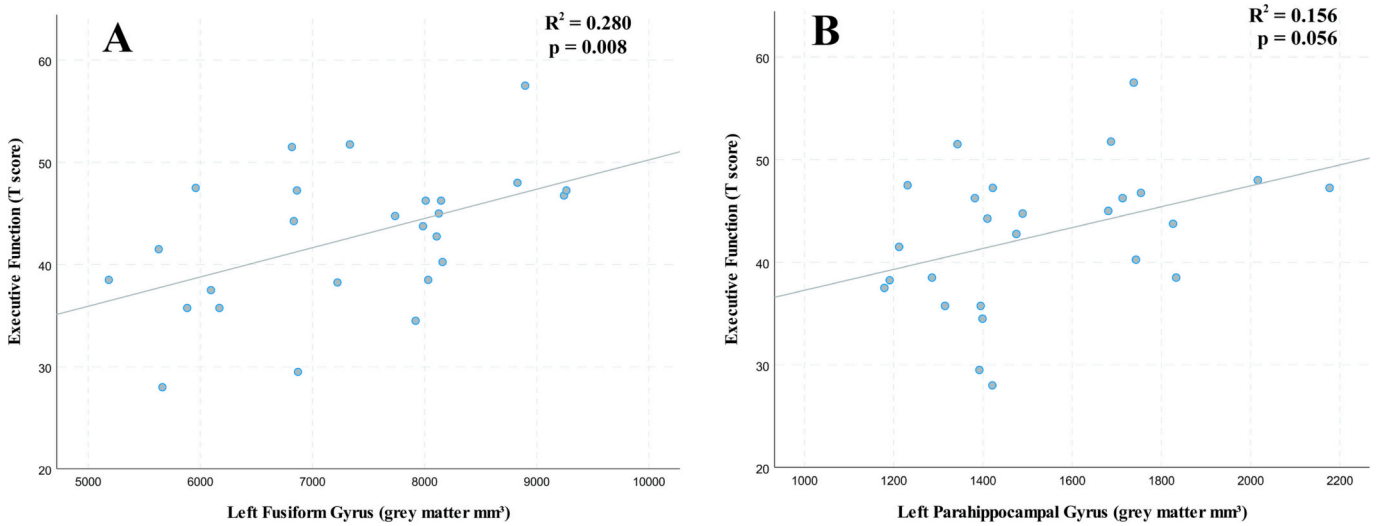

Fig. 2. Grey matter volume in the left fusiform gyrus (A) and the left parahippocampal gyrus (B) related to executive function in bipolar disorder.

experienced a masking effect on their regional findings due to the influence of bipolar disorder on overall grey matter volume, as indicated by our complementary analysis using TIV as a covariate. Consistent with our results, the largest longitudinal neuroimaging study to date suggested that both the fusiform and parahippocampal gyri may be the only brain regions with slower cortical thinning in BD patients compared to HC (Abé et al., 2022). This longitudinal finding, together with the previously indicated implications of controlling for total grey matter volume in our analyses, suggests that a plausible explanation for our cross-sectional results of higher grey matter volumes in euthymic BD may be a specific regional resilience within a model of accelerated brain aging. Interestingly, Abé et al. (2022) proposed lithium, a first-line mood-stabilizing treatment in BD (Bartoli, 2023), as a potential causal agent of brain regional resilience in a context of neuroprogression. While compelling, this interpretation raises further questions regarding the neurobiological mechanism underlying these grey matter volumetric differences as well as its adaptive or maladaptive nature.

Although our research design does not allow us to shed light on the specific neurobiological causes of the structural grey matter alterations in BD, 17 out of 27 patients in our sample were actively receiving lithium as a pharmacological maintenance treatment. In addition, between-group grey matter volumetric differences in our sample did not survive the inclusion of lithium medication as a covariate. Therefore, one potential interpretation for the higher grey matter volumes showed by euthymic BD patients is the neuroprotective properties of lithium (Abé et al., 2020; Hozer et al., 2020; Torshin et al., 2022; Van Gestel et al., 2019). Besides its disease-modifying properties in BD, lithium has also recently been placed as a potential pharmacological candidate for cognitive decline in dementia due to its procognitive and neuroprotective effects (Terao et al., 2022). Moreover, previous neuroimaging research has indicated that lithium-medicated BD patients show a lower discrepancy between brain and chronological age, with no significant differences compared to HC, whereas no lithium-medicated patients exhibited higher PAD (Van Gestel et al., 2019). Regional grey matter volumetric analyses have also consistently supported this hypothesis, and found higher grey matter volume and/or thickness in both cortical (Hibar et al., 2018; Hozer et al., 2020) and subcortical regions (Hibar et al., 2016), including but not restricted to the temporal lobe. However, further research including serum levels of lithium (Hsu et al., 2022), years of exposure to lithium, and exploring the clinical phenotype of patients' responsiveness to lithium is warranted to disentangle the relationship of lithium with neuroimaging findings in euthymic BD patients.

Regarding the relationship between brain measures and the five cognitive domains evaluated (i.e., attention and working memory, verbal memory, visual memory, executive function, and processing speed), our findings support the notion that higher volume in the fusiform and parahippocampal gyri is associated with greater executive function in euthymic BD patients. To our knowledge, this is the first study exploring the adaptive nature of higher grey matter volumes in BD. Indeed, our finding emerges as a potential compensatory neurobiological mechanism to conserve cognitive function despite a putative neuroprogression. Previous research has focused on frontal alterations (i.e., lower grey matter volumes or thickness and functional hypoactivation) as an attempt to elucidate the neurobiological underpinnings of BD cognitive symptoms (Macoveanu et al., 2021). However, even though executive functions are thought to rely more heavily on prefrontal regions (Friedman and Robbins, 2022), detrimental brain-aging related changes in executive function are also linked to the integrity of grey matter in the temporal lobe (Manard et al., 2016). Similarly, research on aging in the general population suggests that medial temporal gyrus' grey matter measurements are among the best predictors of preserved cognition later in life (Saboo et al., 2022). Therefore, our finding of a significant relationship between a higher temporal grey matter volume and a greater executive performance in BD patients may be reflecting a neurostructural adaptation induced as a response to a frontal dysfunction in cognitive tasks. Following this line of thought, these results may be indicative of a temporal lobe adaptive compensatory mechanism to accelerated brain aging as an effort to preserve executive functions in BD.

5. Limitations

Our study has several limitations. First, our small sample size may have led to modest statistical power to detect discreet differences between BD patients and HC. This drawback should be particularly considered when interpreting the negative results observed in diffusion metrics. However, we were still able to identify significantly higher regional grey matter volumes in euthymic BD patients. Second, our DWI sequence with only 32 non-colinear directions, although acceptable by current standards (Kincses et al., 2020), may also have led to a poor signal-to-noise ratio limiting our capacity to replicate previous diffusion results. Third, although our sample was close to being free from psychiatric comorbidities and residual symptoms, non-neurological/non-severe health issues were not accounted for. In this sense, obesity is highly prevalent in BD and recent research suggests that its impact on grey matter and cognition considerably overlaps with BD effect (McWhinney et al., 2023). Fourth, medication is the usual “elephant in the room” when comparing patients and controls (Ilzarbe and Vieta, 2023). Although we have comprehensively described the active medication at the moment of evaluation, a larger sample and a more detailed registry (e.g., current dosage, serum levels and years in treatment) would be required in future research aiming to assess the impact of pharmacotherapy over BD brain structure, by stratifying according to treatments such as lithium that has well-described effects on brain grey matter. Finally, longitudinal measurements across affective states of BD, even though challenging, would provide a more accurate view of the neurobiological traits of BD (Vieta and Angst, 2021).

6. Conclusions

Our findings revealed that euthymic BD patients show a higher regional grey matter volume in the parahippocampus and the fusiform gyrus compared to HC. In combination with a ventricular enlargement and considering our methodological approach (i.e., controlling for total grey matter volume), these findings may suggest a regional brain resilience to a putative global neuroprogression effect in BD patients. Importantly, this is the first study to highlight the potential adaptive nature of these higher grey matter volumes due to their association with a more preserved executive function in BD. This research provides proof of the neurobiological correlates of the executive function observed in BD. Further research is warranted to characterize the impact of this mechanism on disease trajectory and explore the role of medication, especially lithium, in this neural adaptation.

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Ethical statement

We declare all experiments on human participants were conducted following the ethical principles included in the Declaration of Helsinki and received the approval of the Institutional Review Board of the Parc Tauli University Hospital and the Hospital Clinic of Barcelona All participants gave written informed consent to participate in the study.

CRediT authorship contribution statement

D. Porta-Casteràs: Data curation, Formal analysis, Investigation, Writing – original draft, Visualization. **M. Vicent-Gil:** Investigation, Writing – review & editing. **M. Serra-Blasco:** Investigation, Writing – review & editing. **G. Navarra-Ventura:** Investigation, Writing – review & editing. **B. Solé:** Investigation, Writing – review & editing. **L. Montejo:** Investigation, Writing – review & editing. **C. Torrent:** Investigation, Writing – review & editing. **A. Martinez-Aran:** Investigation, Writing – review & editing, Funding acquisition, Conceptualization. **V. De la Peña-Arteaga:** Writing – review & editing. **D. Palao:** Funding acquisition. **E. Vieta:** Funding acquisition, Writing – review & editing. **N. Cardoner:** Conceptualization, Funding acquisition, Writing – review & editing. **M. Cano:** Supervision, Writing – review & editing.

Declaration of competing interest

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Merck, Novartis, Orion Corporation, Organon, Otsuka, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. Other authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2024.110962.

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