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Impact of genetic variants on hippocampal volume among individuals with schizophrenia and bipolar disorders

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ABSTRACT

Background and Hypothesis: Hippocampal volume reduction is a consistent finding in schizophrenia (SCZ) and bipolar disorder type I (BP-I), yet the role of genetic factors remains unclear. We investigated the influence of DISC1 (rs821616), AKT1 (rs1130233), COMT (rs4680), and GSK-3β(rs334558) polymorphisms on hippocampal morphology.

Study Design: Seventy-one participants (25 SCZ, 22 BP-I, 24 healthy controls, HC) underwent 1.5T MRI and genotyping. Bayesian multilevel models estimated associations between corrected hippocampal volume, diagnosis, hemisphere, and genetic variants.

Study Results: Both SCZ and BP-I showed significantly smaller hippocampal volumes compared with HC (Average Marginal Effects: SCZ vs HC = −1.38; BP-I vs HC = −1.46; probability of direction [PD] = 100%). Rightward asymmetry was preserved across groups. The COMT AA genotype was associated with lower hippocampal volume (AME = −0.67; PD = 99%), while DISC1 AT carriers showed moderate reductions (AME = −0.37; PD = 96%). GSK-3β contributed to variability but not mean volume, and AKT1 showed no clear effects.

Conclusions: Hippocampal atrophy is a shared marker of SCZ and BP-I, with preserved lateralization. COMT and DISC1 variations appear to modulate hippocampal volume, supporting their role in psychosis vulnerability.

Abbreviations

SCZ = Schizophrenia
BP-*I* = Bipolar Disorder type I
HC = Healthy Controls
MRI = Magnetic Resonance Imaging

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MPRAGE = Magnetization Prepared Rapid Gradient Echo
ROI = Region of Interest
WBV = Whole Brain Volume
SNV = Single Nucleotide Variant
HRMA = High Resolution Melting Analysis
RFLP = Restriction Fragment Length Polymorphism
PCR = Polymerase Chain Reaction
$MgCl_2$ = Magnesium Chloride
dNTP = Deoxynucleotide Triphosphates
GE = General Electric
ABI = Applied Biosystems Instruments
BPRS = Brief Psychiatric Rating Scale
GAF = Global Assessment of Functioning
M.I.N.I. = Mini International Neuropsychiatric Interview
DISC1 = Disrupted in Schizophrenia 1
COMT = Catechol-O-Methyltransferase
GSK-3β = Glycogen Synthase Kinase 3 Beta
AKT1 = *v*-Akt Murine Thymoma Viral Oncogene Homolog 1
DNA = Deoxyribonucleic Acid
brms = Bayesian Regression Models using Stan (R package)
PSIS-LOO—CV = Pareto-Smoothed Importance Sampling Leave-One-Out Cross-Validation
CrI = Credible Interval
PD = Probability of Direction
AME = Average Marginal Effect
AMP = Average Marginal Prediction
R^2 = Coefficient of Determination

1. Introduction

The hippocampus is crucially involved in episodic memory consolidation, spatial navigation, and affective regulation (Al Bazzal et al., 2025). Recent multimodal imaging studies confirm its central role in large-scale cognitive networks and its vulnerability to pathological processes in psychiatric disorders (Girelli et al., 2024; Luo et al., 2023).

Structural abnormalities in the hippocampus have been consistently observed in psychiatric disorders, notably schizophrenia (SCZ) and bipolar disorder type I (BP-I) (Brosch et al., 2022; Sato et al., 2021). Meta-analyses indicate significant hippocampal volume reductions in individuals with SCZ which suggest neurodevelopmental disruptions and impaired neuroplasticity (van Erp et al., 2016). In BP-I, findings on volumetric alterations have been conflicting. Some studies reported intermediate volumes between those of SCZ and healthy controls (HC), while others did not detect significant differences—possibly hinting at differential influences of disease phase, pharmacological treatment, and/or illness duration (Angelescu et al., 2021; Hibar et al., 2016; Kempton et al., 2011; Ohi et al., 2022)

Interpretations of findings are complicated by known hemispheric asymmetry of the hippocampus, a well-documented phenomenon in healthy individuals. The right hippocampus is generally larger and more commonly involved in spatial processing, while the left is engaged to a greater extent in verbal memory functions (Pedraza et al., 2004). Differences in hippocampal asymmetry, particularly left-sided volume reductions, has been reported in SCZ (Okada et al., 2016; Roeske et al., 2021; Wang et al., 2001). There is also some evidence of lateralization abnormalities in BP-I, though it remains relatively understudied (Miskowiak et al., 2025).

Genetic influences on hippocampal morphology are of particular interest in SCZ and BP-I, given the hippocampus' central role in neurodevelopmental trajectories and its susceptibility to dysregulation in affective and psychotic states. Candidate gene studies highlight variants within pathways critical for neuronal migration, synaptic integrity, and neurotransmission. DISC1 (rs821616) has been associated with hippocampal structural abnormalities and increased SCZ risk, consistent with its role in neuronal migration and synaptic organization (Mahoney et al., 2023; li and H, 2009). Similarly, AKT1 (rs1130233), a component of the PI3K/AKT/GSK3 cascade, has been linked to hippocampal volume differences and cognitive function (Zheng et al., 2012; Tan et al., 2008). The COMT Val158Met polymorphism (rs4680), affecting dopamine catabolism, has been shown to influence hippocampal–prefrontal functional connectivity and neuroanatomical variability (Honea et al., 2009; Ma et al., 2021). GSK-3β (rs12630592), a downstream effector of AKT1, is implicated in hippocampal plasticity and vulnerability to mood disorders (Inkster et al., 2009). Together, these variants index complementary and biologically plausible mechanisms relevant to hippocampal integrity, spanning dopaminergic modulation, neurodevelopmental scaffolding, and intracellular signalling pathways involved in neuronal survival and synaptic plasticity. The present study therefore adopted a hypothesis-driven candidate-variant approach, rather than an exploratory genetic screen. Given the modest sample size and the increased risk of false-positive findings when testing a large number of variants, analyses were intentionally restricted to a small set of a priori selected polymorphisms. This strategy improves interpretability, limits multiple-testing burden, and allows targeted hypotheses on hippocampal volume and lateralization across diagnostic groups.

This study aimed to compare absolute and differential hippocampal volumes in patients with schizophrenia, bipolar disorder type I, and healthy controls, and to assess their association with genetic variants in DISC1 (rs821616), AKT1 (rs1130233), COMT (rs4680), and GSK-3β (rs12630582). Our hypotheses were that: (i) SCZ and BP-I would exhibit reduced hippocampal volumes relative to HC, with more pronounced deficits in SCZ; (ii) hippocampal asymmetry would be altered in SCZ, with reduced or reversed left-right differences, and to a lesser extent in BP-I; (iii) risk alleles would display an association with degrees of hippocampal volume reductions and altered asymmetry. It is important to clarify that the hypothesis regarding risk alleles refers to their potential association with hippocampal atrophy (i.e., volume reduction and altered asymmetry), rather than with the risk of disease per se, which has not been consistently demonstrated for all variants or across both disorders.

2. Methods

2.1. Patient selection

Twenty-five patients with SCZ, twenty-two patients with BP-I, and twenty-four HC were enrolled in the study. All subjects were recruited at the Psychiatric Unit in the Hospital of Conegliano (Treviso, Italy). Patients were selected using the following inclusion criteria: age 18–55, major Axis I disorders, according to DSM-IV TR criteria, within the bipolar-schizophrenic spectrum, onset of illness before the age of 35, duration of illness longer than three years. Healthy control subjects exhibited no past or present psychiatric, neurological, or medical disorders, and reported no positive family history of psychiatric disorders. Presence of an organic central nervous system disorder (e.g., epilepsy, traumatic brain injury, infectious, toxic, or cerebrovascular disease), alcohol or substance dependence or abuse within the previous 12 months, significant current active medical problems, and contraindications to MRI scanning were all exclusion criteria. At the time of the study, most patients received a stable medication regimen including typical and atypical antipsychotics, mood stabilizers (e.g., lithium and anticonvulsants), and benzodiazepines, while HC did not receive any medication. The research was approved by the local ethics committees (Treviso, ULSS 2); subjects were enrolled after receiving a complete description of the study procedures and providing written informed consent.

2.2. Clinical assessments

Psychiatric and medical assessments included a complete past and present history, by performing a mental status examination, and by conducting a structured Mini International Neuropsychiatric Interview

(M.I.N.I.) (Sheehan et al., 1998) to obtain diagnoses according to DSM-IV TR criteria. The M.I.N.I. was also administered in the control group to rule out the presence of current or past psychiatric conditions. Severity of symptoms was assessed using the Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993) and the Global Assessment of Functioning (GAF) (Lewis, 1994). Patients were evaluated when clinically stable since at least 6 months.

2.3. MRI imaging procedures

MRI acquisitions have been performed using a 1.5 T MRI scanner (Achieva XR; Philips Medical Systems) in the Neuroradiology Unit of the Hospital of Conegliano (Treviso, Italy). Whole-brain T1-weighted three-dimensional images (magnetization-prepared rapidly acquired gradient-echo, MPRAGE) were acquired in the sagittal plane for volumetric measurements (using the following acquisition protocol: TR = 10 msec, TE = 4 msec, TI = 300 msec, flip angle = 8°, slice thickness = 1.25 mm, matrix size = 256 × 256 × 192, voxel resolution 1 × 1 × 1.25 mm). The imaging data were transferred from the MRI unit to a PC workstation and analysed using Analyze software (version 10.0, Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA). The volumes of brain regions of interest (ROIs) were estimated using unbiased stereological point-counting methods.. Coronal sections were sampled at regular intervals (every 1.0 mm for the hippocampus and every 20 mm for the whole brain) following a systematic random sampling procedure. A 3 × 3 mm^2 point grid was used for hippocampal measurements and a 20 × 20 mm^2 grid for whole-brain volume estimation, with sampling parameters optimized to obtain at least 150 point hits per structure, yielding a coefficient of error below 5 %. Hippocampal boundaries were traced according to established anatomical landmarks using a validated segmentation protocol, with simultaneous visualization of coronal, sagittal, and axial planes. Whole-brain volume included both grey and white matter above the superior border of the pons, excluding cerebellum and cerebrospinal fluid (Perini et al., 2017). A ratio of the absolute hippocampal volume to whole brain volume was used for comparison purposes. These ratio scores were referred to as corrected volumes (Jack et al., 1989). Ratio of right/left hippocampal volume, expressed as a percentage, was chosen as an additional measure (*100 * (right hippocampal volume – left hippocampal volume)/left hippocampal volume*) of the differences in lateralization (laterality index) (Szabo et al., 2001).

2.4. Genotype analysis

DNA samples were collected at the time of assessment in all participants. Genomic DNA was extracted from saliva using Oragene DNA Self-Collection kits (DNA Genotek Inc., Ottawa, Canada). The seven single nucleotide variants (SNV) were analyzed using different techniques: High Resolution Melting Analysis (HRMA), Restriction fragment Length Polymorphism (RFLP) and Sanger sequencing. PCR was performed in 25 μl reactions and primers were designed with Primer 3 Plus website (http://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi). RFLP and Sanger sequencing were performed using 20–50 ng of DNA, 0.75 U of AmpliTaq Gold™ DNA Polymerase (Applied Biosystems, Waltham, MA), 10 × PCR Gold-buffer, 1.5 mM MgCl2, 0.2 mM dNTP Mix and 0,25 μM of each primer. PCR conditions were the following: incubation 10 min at 95 °C, 40 cycles of 95 °C for 30 s, annealing temperature (ranging from 56 °C or 60 °C according to the different primer pairs) for 40 s, and 72 °C for 1 min, followed by a final extension step at 72 °C for 10 min. For RFLP analysis, PCR products were further digested using 1 U of the specific restriction enzyme (New England BioLabs, Ipswich, MA), according to manufacturer instructions, and then products were separated by agarose or polyacrylamide gel electrophoresis. For Sanger sequencing, amplicons were purified with the Illustra ExoProStar 1-Step kit (GE Healthcare Life Sciences, St. Louis, MO) and sequenced with the BigDye Terminator v3.1 cycle sequencing kit (Life Technologies) and the ABI 3500Dx Sequencer (Applied Biosystems). HRMA was carried out on a Rotor-Gene 6000 (Corbett Life Sciences) according to Favaro et al., 2013 (Favaro et al., 2013). The melt-curve analysis allowed the specific detection of genotypes.

Catechol-O-Methyltransferase (COMT; rs4680) is an enzyme that degrades catecholamines like dopamine. The A allele (Met variant) reduces enzymatic activity, leading to higher synaptic dopamine, which affects prefrontal and hippocampal function (Mashhour et al., 2025). Disrupted-in-Schizophrenia 1 (DISC1; rs821616) encodes a scaffold protein involved in neuronal migration, cytoskeletal dynamics, and synaptic organization (Duff et al., 2013; Ishizuka et al., 2006). The T allele disrupts protein–protein interactions and has been linked to altered neurodevelopmental trajectories and increased schizophrenia risk. Glycogen Synthase Kinase 3 Beta (GSK-3β; rs334558) is a serine/threonine kinase originally identified for its role in glycogen metabolism, but also crucial in regulating neuroplasticity, inflammation, and apoptosis. The T allele increases promoter activity and has been associated with enhanced stress sensitivity and psychiatric vulnerability (Lovestone et al., 2007). v-Akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1; rs1130233) codes for a serine/threonine kinase central to the PI3K/AKT signalling pathway, which governs cell survival, neurogenesis, and synaptic modulation. The A allele has been associated with reduced AKT1 expression, altered hippocampal structure, and increased sensitivity to environmental stressors (Devine et al., 2025). These genes were selected based on their roles in neurodevelopment, neuronal metabolism, dopamine signalling, and cellular stress regulation—pathways critical for hippocampal integrity and function (Wijtenburg et al., 2019). Hardy–Weinberg equilibrium was assessed for each polymorphism in the control group using an exact test appropriate for small sample sizes.

2.5. Statistical analyses

Bayesian multilevel generalized linear models were used to investigate the association between corrected hippocampal volume (left and right, nested into individuals) and clinical, demographic, and genetic predictors. The outcome was modelled using a lognormal distribution to account for right- skewed data, then re-run on z-transformed values for ease of interpretation. Using the 2.22.0 version of the *brms* R package (Bürkner, 2017), we tested models of increasing complexity, entering demographic covariates (sex, age, education, hemisphere), then clinical group, followed by genetic variants (GSK-3β, DISC1, AKT1, COMT) and ultimately interaction terms informed by prior hypotheses (e.g., group × hemisphere, COMT × hemisphere). All models included varying intercepts for participant. In addition, we tested whether the variability of hippocampal volumes (standard deviation, or sigma) varied as a function of group and GSK-3β genotype. Model comparisons was based on out-of-sample predictive accuracy (PSIS-LOO—CV). In addition, prior sensitivity analysis were conducted on the uninformative default priors, using the *priorsense* package (Kallioinen et al., 2024). This overall approach is robust against overfitting and false positive results, allowing for explicit modelling of uncertainty.

Results are reported as posterior medians with 95 % Credible Intervals (CrI) and Probability of Direction (PD), i.e. the probability that the value (or value difference) does not cross zero (Makowski et al., 2019). For rigorous interpretation of results, we also computed Average Marginal Predictions (AMPs) and Average Marginal Effects (AMEs). AMPs represent the predicted average hippocampal volume for observations at a specific covariate level (e.g. a diagnostic group or a genetic trait), maintaining other covariates at their observed distribution (Arel-Bundock et al., 2024). Whereas, AMEs estimate the average change in hippocampal volume when switching between predictor levels, or after a unit change for continuous predictors, while holding other variables constant. AMEs provide a more direct approximation of causal effects, under the assumptions of correct model specification and no unmeasured confounding. They differ from conditional effects

(common adjustment in multivariable models), which only fix covariates at reference values.

3. Results

3.1. Sample characteristics

The final sample included 24 HC, 22 individuals with BP-I, and 25 with SCZ. Demographic, clinical, genetic and volumetric data for the patient groups are presented in Table 1. Groups differed in sex distribution, with a higher proportion of females in the HC group (63 %) compared to BP-I (45 %) and SCZ (32 %). Mean age was similar across groups (HC: 37 years, BP-I: 40, SCZ: 36). Educational attainment was highest in HC (16 years), followed by BP-I (13 years) and SCZ (12 years). Age of onset and illness duration (available only for BP-I and SCZ) were comparable. Whole brain volume (WBV) was largest in HC (mean = 1007,379 mm^3), followed by BP-I and SCZ (Fig. 1). Genotype distributions in the control group did not deviate from Hardy–Weinberg equilibrium for any of the examined polymorphisms (DISC1: p= 0.818; AKT1: p= 0.351; COMT: p= 0.842; GSK-3β: p= 0.523).

3.2. Models of hippocampal volume

In the final model, the outcome was corrected hippocampal volume, modelled using a lognormal distribution both a mean and variance (sigma) component. Predictors included sex, age, hemisphere (side), diagnosis group, and four candidate genes (GSK-3β, DISC1, AKT1, COMT) as fixed effects, with random intercepts for subject. The model included the interaction between diagnosis and hemisphere (side × diagnosis) and between COMT and hemisphere to capture lateralization effects. The sigma sub-model retained group and GSK-3β as predictors to account for group-dependent variance. This specification improved model fit while maintaining parsimony and convergence. Model fit indices indicated good explanatory power: Bayesian R^2 including varying effects was 0.83 (95 % CrI, 0.75–0.88), while the marginal R^2 (fixed effects only) was 0.50 (95 % CrI, 0.39–0.58), suggesting substantial variance explained by group-level structure. LOO—CV diagnostics showed satisfactory overall fit, with 59.3 % of observations below the recommended Pareto k threshold.

Examining model parameters yielded credible effects of various factors. Corrected hippocampal volume was higher in the control group compared to individuals with BP-I (β = 0.25; 95 % CrI, 0.16 to 0.33; PD = 100 %), while less clear differences emerged between the SCZ and BP-I groups (β = 0.02; 95 % CrI, −0.06 to 0.10; PD = 73 %) A credible right-lateralization effect was found (β = 0.07; 95 % CrI, 0.03 to 0.10; PD = 99.6 %), with significant diagnosis by side interaction: the difference appeared higher in patients than in controls (β = −0.03; 95 % CrI, −0.07 to 0.00; PD = 97 %). Among genetic predictors, the COMT AA genotype was associated with *lower* hippocampal volume (β = −0.13; 95 % CrI, −0.23 to −0.04; PD = 99.7 %), with a credible COMT-by-hemisphere interaction (β = 0.05; 95 % CrI, 0.01 to 0.09; PD = 98.8 %). No strong evidence of association emerged for GSK-3β, DISC1, or AKT1 genotypes predicting mean volumes. Whereas, a greater variance of volumes (sigma) was credibly associated with the GSK-3β GT genotype (β = 0.81; 95 % CrI, 0.10 to 1.50; PD = 99 %) and the TT genotype (β = 0.81; 95 % CrI, −0.07 to 1.72; PD = 96 %), but not with diagnosis.

Model-derived Marginal Predictions and Average Marginal Effects approximate the causal effect of individual predictors (Table 2) and confirmed the large effect of patient status. AME: −1.46 for BP-I vs HC (95 % CrI −1.93 to −0.97; PD = 100 %) and −1.38 for SCZ vs HC (95 % CrI −1.83 to −0.93; PD = 100 %). Volume was also consistently higher on the right compared to the left side (mean difference = 0.38, 95 % CrI 0.27–0.46; PD = 100 %) but AMEs did not reveal meaningful interactions between diagnosis status and lateralization degree (mean differences (right – left): HC = 0.33, BP-1 = 0.43, SCZ = 0.39; all 95 % CrI 0.16–0.61; PD = 100 %).

Among genetic predictors, both COMT and DISC1 showed notable effects on mean hippocampal volume. The COMT AA genotype was on average associated with lower volumes compared to GG (AME = −0.67, 95 % CrI −1.23 to −0.12; PD = 99 %). This effect was more pronounced in the left side than the right (AME left: −0.80; 95 % CrI: −1.37; −0.24, PD 100 %; AME right: −0.55; 95 % CrI:−1.11; 0.03, PD 97 %). Whereas, DISC1 AT carriers had a reduced volume relative to AA (AME = −0.37, 95 % CrI −0.77 to 0.05; PD = 96 %) (Fig. 2). The effect of GSK-3β alleles on the variability of hippocampal volumes (sigma parameter) was confirmed by AMEs: variability was higher among GT carriers compared to GG (AME = 0.25, 95 % CrI 0.05–0.50, PD 100 %), and in those with the TT genotype (AME = 0.23, 95 % CrI −0.02 to 0.72, PD 97 %).

Table 1
Demographic, clinical and volumetric data.

Characteristic	HC *N*= 24	BP-I *N*= 22	SCZ *N*= 25
Sex %			
Female	15 (63 %)	10 (45 %)	8 (32 %)
Male	9 (38 %)	12 (55 %)	17 (68 %)
Age y			
Mean (SD)	37 (11)	40 (9)	36 (7)
Handedness %			
Right	23 (96 %)	21 (95 %)	23 (92 %)
Left	1 (4.2 %)	1 (4.5 %)	2 (8.0 %)
Years of education			
Mean (SD)	16 (3)	13 (3)	12 (3)
Age of disease onset			
Mean (SD)	-	24 (8)	23 (6)
Duration of illness			
Mean (SD)	-	16 (9)	13 (6)
BPRS score	-	32 (5)	40 (10)
Whole brain volume mm^3			
Mean (±SD)	1007.4 (119.7)	928.2 (85.1)	904.3 (73.0)
Right hippocampus mm^3			
Mean (±SD)	2791 (360)	2140 (261)	2028 (179)
Left hippocampus mm^3			
Mean (±SD)	2689 (334)	1977 (186)	2019 (290)
DISC1			
AA	11 (46 %)	15 (68 %)	13 (52 %)
TT	2 (8.3 %)	1 (4.5 %)	3 (12 %)
AT	11 (46 %)	6 (27 %)	9 (36 %)
AKT1			
GG	15 (63 %)	9 (41 %)	16 (64 %)
AA	0 (0 %)	4 (18 %)	2 (8.0 %)
AG	9 (38 %)	9 (41 %)	7 (28 %)
COMT			
GG	9 (38 %)	6 (27 %)	5 (20 %)
AA	4 (17 %)	5 (23 %)	5 (20 %)
GA	11 (46 %)	11 (50 %)	15 (60 %)
GSK-3β			
GG	9 (38 %)	7 (32 %)	10 (40 %)
TT	2 (8.3 %)	3 (14 %)	5 (20 %)
GT	13 (54 %)	12 (55 %)	10 (40 %)

Abbreviation: BPRS: Brief Psychiatric Rating Scale.

4. Discussion

This study examined hippocampal volumes across individuals with SCZ, BP-I, and HC, estimating the association with four candidate genes variants (COMT, DISC1, AKT1, and GSK-3β). Hippocampal volume reductions were found in both clinical groups relative to controls, although we did not detect robust differences between SCZ and BP-I. Furthermore, a consistent rightward asymmetry of hippocampal volume was observed across all groups, with no robust difference across diagnostic status. Genetic variation in COMT and DISC1 was associated with overall volume differences, and COMT showed evidence of lateralized effects. These findings highlight the possible relevance of genetic factors shaping hippocampal morphology in severe mental illness.

These findings align with and extend recent evidence from large-scale neuroimaging meta-analyses (Brosch et al., 2022; Jiang et al.,

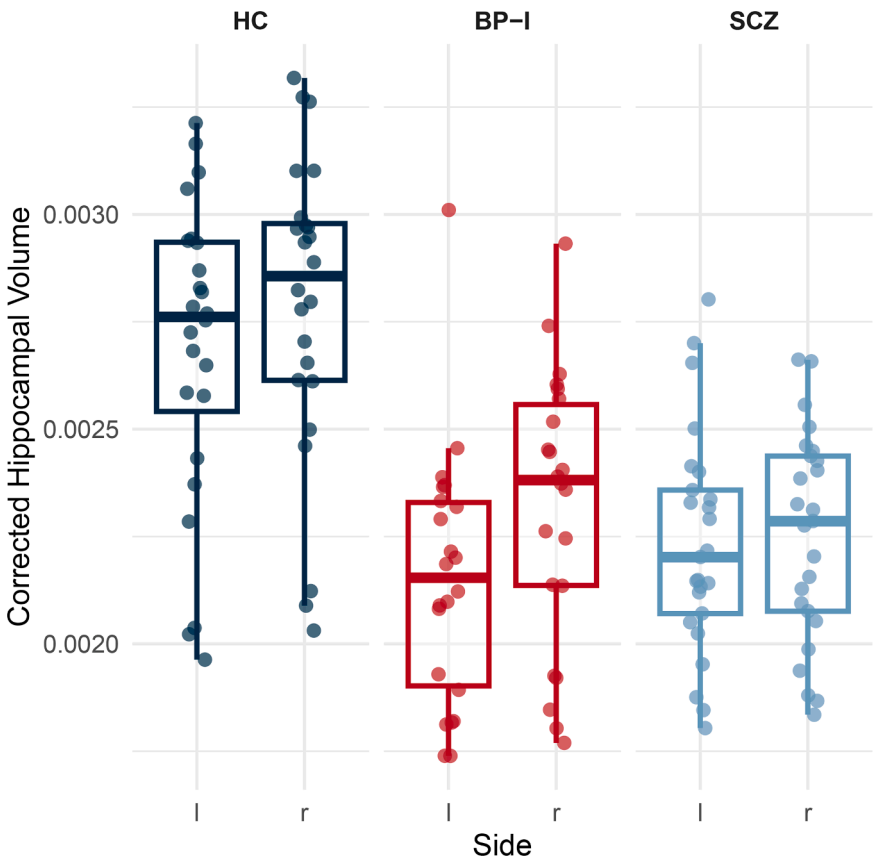

Fig. 1. Corrected hippocampal volumes by hemisphere and diagnostic group.
Boxplots represent left (L) and right (R) hippocampal volumes for each diagnostic group: healthy controls (HC), individuals with bipolar I disorder (BP-I), and individuals with schizophrenia (SCZ). Each dot corresponds to an individual participant.

2024; Navarri et al., 2022), confirming that hippocampal atrophy is a transdiagnostic structural marker of psychotic and mood disorders. Our findings are in line with the notion that hippocampal volume loss is a shared feature of SCZ and BP-I, and that the neurobiological mechanisms underlying such alterations may depend on genetic background, rather than diagnostic category (Atwood et al., 2023). From a pathophysiological perspective, hippocampal atrophy in SCZ and BP-I is hypothesized to reflect a convergence between neurodevelopmental vulnerability and acquired neurotoxic processes. Abnormalities in glutamatergic transmission, dysregulated stress response, and mitochondrial dysfunction have been implicated in progressive hippocampal damage (Catapano et al., 2025). Elevated allostatic load, reflected in chronic hypercortisolaemia and oxidative stress, may impair neurogenesis and dendritic complexity—particularly in stress-sensitive hippocampal subfields such as CA1 and dentate gyrus (Mondelli et al., 2011; McEwen and Gianaros, 2011; Dioli et al., 2019; Belvederi Murri et al., 2016).

Regarding lateralization, we observed a robust rightward asymmetry of hippocampal volume, consistent with normative neuroanatomy and prior work (Nemati et al., 2023), similar in controls and patients, unlike previous findings of abnormal lateralization (Okada et al., 2016). Interestingly, this asymmetry was not significantly diminished in SCZ or BP-I. Thus, after accounting for covariates, it suggests a degree of preservation of hemispheric asymmetry, and possibly functional specialization, even in the context of global atrophy.

The COMT Val158Met (rs4680) polymorphism predicted differences of hippocampal volume: the Met/Met (AA) genotype exhibited lower volumes, especially in the right side. This finding is consistent with prior evidence linking the Met allele to reduced enzymatic activity, increased dopaminergic tone, and impaired prefrontal-hippocampal signalling (Otsuka et al., 2019). While these features do not necessarily predict hippocampal volume in a uniform direction, they have been associated with inefficient stress regulation which might lead to increased vulnerability to hippocampal damage via excitotoxic and oxidative pathways, a mechanism that might result in lower volumes (Deslauriers et al., 2018). The DISC1 risk allele (T) was also associated with moderate reductions in hippocampal volume, particularly in heterozygous (AT) carriers. Given the role of DISC1 in cytoskeletal organization, neuronal migration, and synaptic plasticity, its impact on hippocampal integrity is biologically plausible and may exert its effects independently from patient or diagnostic status (Cukkemane et al., 2025). Finally, GSK-3β polymorphisms was not associated with a clear effect on mean hippocampal volume; however, the presence of the T risk allele (i.e., in GT and TT genotypes) was associated with greater volumetric variability. This suggests a possible role in modulating volume dispersion in the population, that might reflect the role of GSK-3β modulating the sensitivity towards downstream biological or environmental factors, such as stress responses and neuroplasticity (Cheng et al., 2016; Mondelli et al., 2011). This may therefore increase the heterogeneity of structural features among carriers; to our knowledge, this is among the first studies to examine genetic effects on structural brain variance, highlighting the potential of modelling variance alongside mean differences.

4.1. *Strengths and limitations*

The study is strengthened by the simultaneous measurement of multiple genetic variants and the robust statistical approach that allowed us to account for data heteroskedasticity, subject-level dependencies, and complex interactions. However, it is limited by a relatively small sample size—which may have limited the statistical power

Table 2
Effects of diagnosis, hemisphere, and genotype on corrected hippocampal volume.

Marginal predictions and Average Marginal Effects (AMEs)							
Factor	Level	Estimate	CI_low	CI_high	Slope	Slope_CI	PD
Diagnosis	HC	0.883	0.772	1.041			
	BP-I	−0.469	−0.601	−0.342			
	SCZ	−0.431	−0.550	−0.314			
	BP-I – HC				−1.459	[−1.93, −0.97]	100 %
	SCZ – HC				−1.380	[−1.83, −0.93]	100 %
Sex	F	0.105	−0.003	0.231			
	M	−0.088	−0.179	0.003			
	M - F				0.185	[−0.21, 0.58]	82 %
Side	left	−0.185	−0.267	−0.099			
	right	0.190	0.102	0.283			
	right - left				0.379	[0.27, 0.46]	100 %
GSK3B	GG	0.168	0.102	0.241			
	TT	−0.377	−0.598	−0.152			
	GT	−0.013	−0.133	0.119			
	GT - GG				−0.148	[−0.55, 0.25]	77 %
	TT - GG				−0.054	[−0.65, 0.56]	57 %
DISC1	AA	0.041	−0.050	0.135			
	TT	−0.193	−0.497	0.202			
	AT	−0.014	−0.123	0.106			
	AT - AA				−0.373	[−0.77, 0.05]	96 %
	TT - AA				−0.392	[−1.11, 0.34]	86 %
AKT1	GG	0.010	−0.082	0.108			
	AA	−0.039	−0.222	0.145			
	AG	0.000	−0.132	0.136			
	AA - GG				0.300	[−0.42, 1]	80 %
	AG - GG				0.007	[−0.4, 0.41]	51 %
COMT	GG	0.394	0.260	0.560			
	AA	−0.394	−0.539	−0.231			
	GA	−0.061	−0.155	0.034			
	AA - GG				−0.674	[−1.23, −0.12]	99 %
	GA - GG				−0.296	[−0.73, 0.15]	90 %

to detect subtle effects, particularly for gene-by-diagnosis or higher-order interactions. Accordingly, findings related to genetic main effects and interactions should be considered exploratory and interpreted with caution. Replication in larger, independent samples are warranted to more precisely estimate the magnitude of genetic contributions to hippocampal volume. Second, hippocampal volume was assessed at the whole-structure level and do not allow to detect specific patterns of subfield alterations (e.g., CA1 vs. dentate gyrus) (Otsuka et al., 2019). Third, hippocampal development and psychiatric vulnerability may reflect other unmeasured processes, such as epistatic interactions, or gene–environment correlations. Integration with genome-wide polygenic risk scores and environmental exposures (e.g., trauma, cannabis use, medications) is recommended for future studies. Fourth, the cross-sectional design limits causal inference regarding disease progression or the temporal dynamics of hippocampal atrophy. However, the use of AMEs and generalized Bayesian models can approximate true causal effects under specific assumptions. In addition, psychotropic medication represents an important potential confounder in the interpretation of hippocampal volume differences. Although medication classes were reported and treatments were clinically stable at the time of MRI acquisition, exposure remained heterogeneous across patients. Antipsychotics, mood stabilizers, and antidepressants have been shown to influence hippocampal structure, and some treatments may interact with the genetic pathways investigated in the present study. For example, COMT variation is closely linked to dopaminergic signalling, which is modulated by antipsychotic treatment, while GSK-3β activity is directly affected by lithium exposure. Given the cross-sectional design and the limited sample size, it was not possible to disentangle medication effects from illness- and genotype-related influences. Future longitudinal studies with larger samples and more detailed quantification of medication exposure will be required to clarify these interactions.

5. Conclusion

In conclusion, we replicated the finding of bilateral hippocampal volume reductions in schizophrenia and bipolar disorder, with preserved rightward lateralization, and found significant modulation by COMT, DISC1 and GSK-3β genotypes. These findings support a pathophysiological framework in which hippocampal atrophy reflects both neurodevelopmental liability and cumulative neurotoxic stress, interacting with genetic vulnerability factors. Rightward asymmetry, despite global atrophy, may represent a compensatory adaptation or reflect asymmetric susceptibility to pathological processes. Further research should incorporate longitudinal designs with hippocampal subfield resolution, polygenic risk scores, and multimodal imaging to delineate the temporal unfolding of structural changes and the relation to environmental factors.

CRediT authorship contribution statement

Tommaso Toffanin: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Giulia Ida Perini:** Writing – review & editing, Writing – original draft, Conceptualization. **Halima Follador:** Methodology, Investigation, Data curation. **Filippo Zonta:** Methodology, Investigation, Data curation. **Giovanni Ferri:** Methodology, Data curation. **Giorgio Pigato:** Investigation, Data curation. **Mario Angelo Pagano:** Supervision. **Nadia Scupola:** Investigation, Data curation. **Claudia Pinato:** Methodology. **Davide Calosci:** Methodology. **Maria Ferrara:** Supervision. **Angela Muscettola:** Writing – review & editing, Supervision, Methodology. **Giovanni Antonio De Bellis:** Methodology. **Chiara Montemitro:** Supervision. **Luigi Zerbinati:** Supervision. **Maria Giulia Nanni:** Supervision. **Rosangela Caruso:** Supervision. **Andrea Escelsior:** Supervision. **Alessandra Baratto:** Methodology. **Nicola Martino:** Methodology. **Eva Trevisson:** Methodology. **Daniele Olivo:** Methodology, Formal analysis, Data curation. **Fabio Sambataro:** Writing – review & editing,

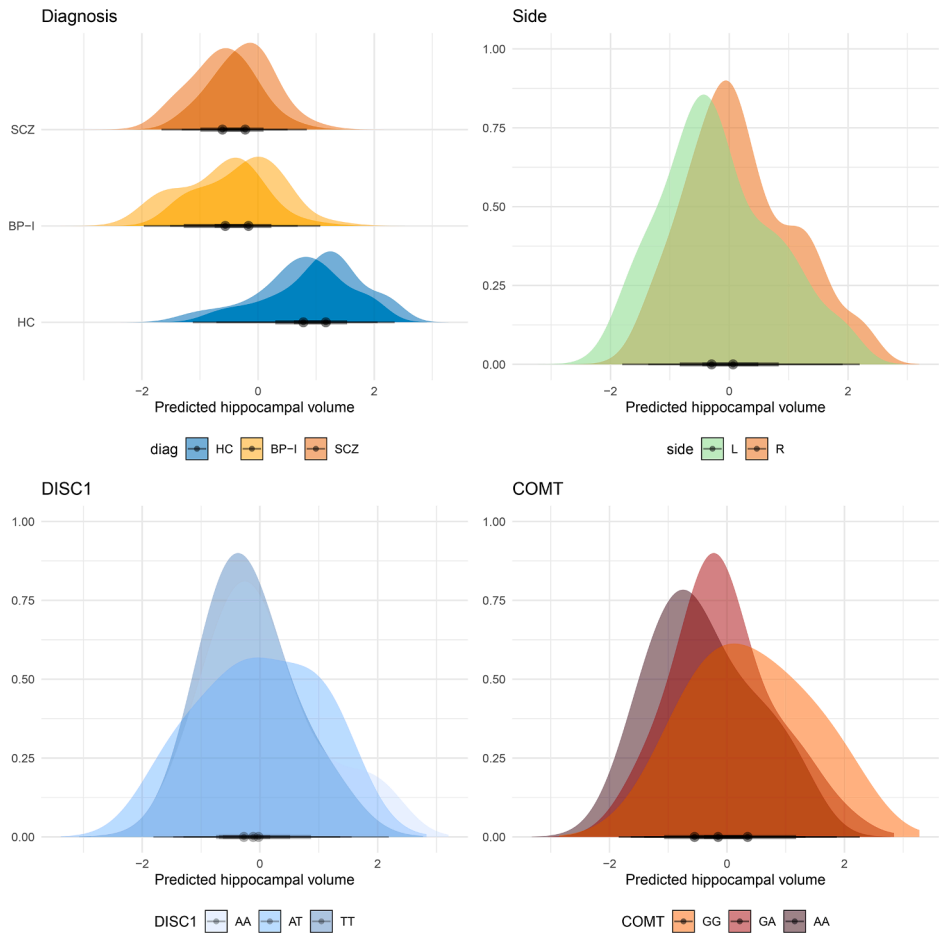

Fig. 2. Marginal predictions of corrected hippocampal volume by diagnostic group, hemisphere, and genotype.
Posterior distributions of predicted hippocampal volume are shown for diagnostic groups (top left), hemispheric side (top right), and genotypes of DISC1 (bottom left) and COMT (bottom right). Predictions are marginal, integrating over all other covariates in the model.

Methodology, Formal analysis, Conceptualization. **Luigi Grassi:** Writing – review & editing, Conceptualization. **Martino Belvederi Murri:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Giulia Ida Perini reports financial support was provided by Veneto Region. Luigi Grassi reports financial support was provided by Italian Ministry of University and Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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