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Impact of monoamine-related gene polymorphisms on hippocampal volume in treatment-resistant depression

Phillips JL, Batten LA, Tremblay P, Aldosary F, Du L, Blier P. Impact of monoamine-related gene polymorphisms on hippocampal volume in treatment-resistant depression.

Objective: In major depressive disorder (MDD), single nucleotide polymorphisms (SNPs) in monoaminergic genes may impact disease susceptibility, treatment response, and brain volume. The objective of this study was to examine the effect of such polymorphisms on hippocampal volume in patients with treatment-resistant MDD and healthy controls. Candidate gene risk alleles were hypothesised to be associated with reductions in hippocampal volume.
Methods: A total of 26 outpatients with treatment-resistant MDD and 27 matched healthy controls underwent magnetic resonance imaging and genotyping for six SNPs in monoaminergic genes [serotonin transporter (*SLC6A4*), norepinephrine transporter (*SLC6A2*), serotonin 1A and 2A receptors (*HTR1A* and *HTR2A*), catechol-O-methyltransferase (*COMT*), and brain-derived neurotrophic factor (*BDNF*)]. Hippocampal volume was estimated using an automated segmentation algorithm (FreeSurfer).
Results: Hippocampal volume did not differ between patients and controls. Within the entire study sample irrespective of diagnosis, C allele-carriers for both the NET – 182 T/C [rs2242446] and 5-HT_{1A} – 1019C/G [rs6295] polymorphisms had smaller hippocampal volumes relative to other genotypes. For the 5-HTTLPR (rs25531) polymorphism, there was a significant diagnosis by genotype interaction effect on hippocampal volume. Among patients only, homozygosity for the 5-HTTLPR short (S) allele was associated with smaller hippocampal volume. There was no association between the 5-HT_{2A}, *COMT*, and *BDNF* SNPs and hippocampal volume.
Conclusion: The results indicate that the volume of the hippocampus may be influenced by serotonin- and norepinephrine-related gene polymorphisms. The NET and 5-HT_{1A} polymorphisms appear to have similar effects on hippocampal volume in patients and controls while the 5-HTTLPR polymorphism differentially affects hippocampal volume in the presence of depression.

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Keywords: hippocampal volume; magnetic resonance imaging; major depressive disorder; single nucleotide polymorphism

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Significant outcomes

- Single nucleotide polymorphisms in the norepinephrine transporter and serotonin 1A receptor genes were associated with hippocampal volume in patients with major depressive disorder and controls.
- Homozygosity for the short (S) allele of the serotonin transporter polymorphism (5-HTTLPR) was associated with smaller hippocampal volume in patients with major depressive disorder, suggesting an effect of the risk allele only in the presence of depression.

Limitations

- Given the small sample size the results should be interpreted with caution.
- Genetic effects on hippocampal volume are likely the result of the interaction of multiple genes and the study did not investigate gene–gene interaction effects.

Introduction

A number of studies have recently been conducted to investigate the pharmacogenetics of antidepressant response; namely, how an individual's genetic makeup affects how he or she responds to antidepressant drugs. Of particular interest for major depressive disorder (MDD) are single nucleotide polymorphisms (SNPs) in genes involved in the synthesis, transport, signal transduction, and degradation of monoamines as the monoaminergic systems are the primary targets of all currently available classes of antidepressants. Genetic variation within the monoaminergic system has been shown to be associated with susceptibility to the development of mood disorders, alterations in patients' response to treatment (1), and various imaging phenotypes (2).

Most depressed patients will fail to achieve complete remission upon a first trial of antidepressant treatment and are left with no response or significant residual symptoms. The potential consequences of continuing depressive symptoms include decreased recovery rates as the length of depressive episodes increase and greater likelihood of future depressive episodes (3). Given the lengthy duration required to evaluate the effects of an antidepressant trial, there is a need to identify drugs with a higher probability of success to avoid further treatment delay in resistant patients. At least some of the variation in pharmacological outcome in MDD is thought to have a genetic basis (1); thus, a treatment-resistant sample may be rich in risk alleles for candidate genes involved in antidepressant response.

Monoamine-related gene polymorphisms have also been associated with various characteristics measured using neuroimaging (2). A recent large magnetic resonance imaging (MRI) study of healthy individuals revealed an inverse association between hippocampal volume and severity of self-reported depressive symptoms (4). Moreover, meta-analyses of cross-sectional MRI studies have found reduced volume of the hippocampus among MDD patients relative to controls (5–9). While few studies have specifically targeted treatment-resistant samples, two papers have reported hippocampal volume reduction in this patient population (10,11). Recent findings suggest that genetic factors may modulate stress-related changes in hippocampal volume in depression (12). Furthermore, hippocampal volume is associated with various clinical factors related to treatment course, including patients' age of disease onset (13), number of previous depressive episodes and duration of illness (8), treatment responsiveness (14), speed of treatment response (15), and remission status (16).

The present study investigated the relationship between certain monoamine-related gene variants and hippocampal volume in patients with treatment-resistant depression and healthy controls. The focus was on monoamine-related genes as antidepressants that enhance serotonin and/or norepinephrine neurotransmission have also been shown to increase brain-derived neurotrophin factor (BDNF) and increase neurogenesis in the hippocampus, which in turn may have effects on hippocampal volume. Genes were selected based on their involvement in the mechanism of action of antidepressant drugs and previous evidence of their potential association with treatment response in MDD. Among these were genes encoding monoamine transporters: *SLC6A4* [serotonin transporter (5-HTT)], *SLC6A2* [norepinephrine transporter (NET)]; serotonin receptors: *HTR1A* (5-HT_{1A}), and *HTR2A* (5-HT_{2A}); a monoamine metabolic enzyme: *COMT* (catechol-O-methyltransferase); and *BDNF*.

Aims of the study

The aims of this study were to examine the prevalence of monoamine-related polymorphisms in a sample of patients with treatment-resistant depression relative to healthy controls, and to compare gene effects on hippocampal volumes in patient and control groups. Candidate gene risk alleles were hypothesised to be associated with reductions in hippocampal volume.

Materials and methods

Participants

A total of 28 outpatients with treatment-resistant depression (aged 18–65 years) were recruited from the Mood Disorders Research Unit at the Royal Ottawa Mental Health Centre (Ottawa, Ontario, Canada). This patient sample was previously reported by Phillips et al. (17,18). Diagnosis of MDD was established by psychiatric consultation on the basis of DSM-IV criteria (19). Classification of treatment-resistance was based on current episode illness duration of at least 6 months, failure to achieve remission after treatment with at least two antidepressants of different

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classes at adequate dosage for at least 6 weeks each, and presence of depressive symptoms corresponding to a Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) (20) score ≥18 and a Montgomery-Åsberg Depression Rating Scale (21) score ≥22. Diagnosis of post-traumatic stress disorder, any psychotic disorder, anorexia nervosa, or a history of manic, hypomanic or mixed episode were exclusionary criteria for patients. All patients were receiving antidepressant treatment at time of magnetic resonance (MR) image acquisition (17).

A total of 29 age, gender, and handedness-matched healthy controls were recruited from the community through advertisement (Table 2). Controls were free of psychiatric disorders confirmed through administration of the Scheduled Clinical Interview for DSM-IV-Nonpatient Edition (22), and reported no history of mood or anxiety disorders among their first-degree relatives. Exclusion criteria for all participants were presence of major medical illnesses, neurological disorders, history of head injury with loss of consciousness, diagnosis of substance abuse or dependence, exposure to oral or intravenous steroids, IQ <80, and contraindications to MRI. Handedness was evaluated with the Edinburgh Handedness Inventory (23). According to self-report, study participants were mostly Caucasian (96%). Participants underwent MRI and blood draw for genetic testing at study inclusion. The research protocol was approved by the Research Ethics Board of the Royal Ottawa Mental Health Centre. After complete description of the study to subjects, informed written consent was obtained.

Image acquisition, processing, and analysis

T1-weighted magnetic resonance images were obtained on a 1.5 T scanner (Siemens Magnetom Symphony Systems, Siemens, Erlangen, Germany) using the same magnetisation-prepared rapid gradient echo acquisition protocol: repetition time = 1500 ms, echo time = 4.38 ms, flip angle = 15°, field of view = 250 mm, matrix size = 256 × 256, slice thickness = 1 mm. The scans of all controls ($n = 27$) and most patients ($n = 23$) were obtained on the same scanner at St-Joseph MRI (Gatineau, Quebec, Canada) while the scans of three patients were obtained at the Ottawa Hospital (Ottawa, Ontario, Canada). MRI scans were reviewed by a licensed radiologist to rule out clinically significant neuroanatomical abnormalities.

Images were processed and analysed with the FreeSurfer image analysis suite, version 4.5 (http://surfer.nmr.mgh.harvard.edu) (24,25) to automatically generate volume estimates for subcortical regions (26). The cortical reconstructions for each participant were visually inspected for inaccuracies in segmentation and manually corrected if necessary by a single rater blind to subject identity, diagnostic group, and time point. Automated hippocampal segmentation by FreeSurfer has been shown to be comparable with manual tracing (27–30). Estimates of total intracranial volume (TIV) were obtained from FreeSurfer (31).

Genotyping

DNA was isolated from whole blood for polymerase chain reaction analyses using standard phenol extraction methods. DNA was genotyped for six polymorphic variants selected based on previous evidence of potential associations between the candidate gene and MDD, and the specific SNP and treatment response in MDD patients (Table 1) (1,32). For the 5-HTTLPR (serotonin transporter-linked polymorphic region) polymorphism, participants were classified as homozygous for the long allele (L/L genotype) or short allele (S/S genotype), or heterozygous (L/S genotype). Of the two functional variants of the L allele (L_A and L_G) (33), the L_G allele expresses serotonin at levels comparable with to the S allele (34), thus L_G alleles were reclassified as S alleles. For the remaining polymorphisms, individuals were classified as homozygous for the major allele, heterozygous, or homozygous for the minor allele. *BDNF* Val/Met and Met/Met genotypes were collapsed under a single heading (Met-carrier) due to the scarcity of Met/Met homozygotes in the sample.

Statistical analysis

Comparison of demographic variables (age, gender, handedness) and TIV of patient and control groups were examined by independent samples using *t*-tests (for continuous variables) or χ^2 tests (for dichotomous variables). Distribution differences of genotype frequencies between patients and controls were examined by χ^2 test. The χ^2 test was used to assess for Hardy–Weinberg equilibrium.

Left and right hippocampal volumes of patients and controls were compared through multivariate analysis adjusted for TIV and scanner. The genotype variant

Table 1. Selected candidate gene polymorphisms

Gene	Polymorphism	dbSNP ID
Serotonin transporter – *SLC6A4*	5-HTTLPR	rs25531
Norepinephrine transporter – *SLC6A2*	NET – 182 T/C	rs2242446
Serotonin 1A receptor – *HTR1A*	$5\text{-}HT_{1A}$ – 1019C/G	rs6295
Serotonin 2A receptor – *HTR2A*	$5\text{-}HT_{2A}$ – 102 T/C	rs6313
Catechol-O-methyltransferase – *COMT*	COMT Val158Met	rs4680
Brain-derived neurotrophic factor – *BDNF*	BDNF Val66Met	rs6265

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effects on hippocampal volume in patients and controls were investigated using individual analyses of covariance (ANCOVA) for each individual genetic polymorphism, with left and right hippocampal volume as the dependent variables, diagnosis (patient or control), and genotype (homozygous for the major allele, heterozygous, or homozygous for the minor allele) as independent variables, and TIV and scanner as covariates. *Post-hoc t*-tests, Bonferroni-corrected for multiple comparisons, were used to compare hippocampal volume among resultant diagnostic or genotype groups. In the case of significant diagnosis by genotype interaction effects, separate ANCOVAs were conducted for patient and control groups with the variables and covariates as described above. All statistical analyses were conducted using PASW Statistics, version 18.0 (SPSS Inc, Chicago, IL, USA). A p value < 0.05 was considered significant for all comparisons.

Results

Complete imaging and genetic data were available for 53 study participants (26 patients and 27 controls). Two participants were excluded following MR image acquisition, one patient due to poor quality MRI data, and one control subject due to evidence of brain tumour. In addition, two subjects (one patient and one control) were excluded for failure to provide blood samples. Patient and control groups did not differ significantly on age, gender, or handedness (Table 2).

Genotype frequencies did not differ between patient and control groups (Table 3). All polymorphisms were in Hardy–Weinberg equilibrium ($p > 0.05$).

Table 2. Demographic, clinical, and volumetric characteristics of study participants

Characteristics	Group (mean) (± SD)*		
	Patients ($n = 26$)	Controls ($n = 27$)	p value†
Age (years)	46.0 (10.4)	45.4 (10.7)	0.83
Gender (n) (male : female)	8 : 18	9 : 18	0.84
Handedness (n) (right : left)‡	22 : 4	24 : 3	0.65
Age at illness onset (years)	30.3 (13.8)		
MADRS score	34.6 (7.0)		
No. depressive episodes (A/B/C)§	10/6/10		
Total intracranial volume (mm^3)	1526 600 (163 300)	1536 100 (123 200)	0.81
Left hippocampal volume (mm^3)	4305 (458)	4373 (356)	0.60
Right hippocampal volume (mm^3)	4369 (377)	4406 (383)	0.69

MADRS, Montgomery-Åsberg Depression Rating Scale (20).

* Unless otherwise indicated.

† Independent samples t-test or χ^2 test.

‡ Handedness was measured using the Edinburgh Handedness Inventory (19).

§ Number of episodes before the study enrolment expressed as categories: A = 1–2 episodes, B = 3–4 episodes, C = 5+ episodes.

Patients and controls did not differ in TIV (Table 2). Multivariate analysis adjusted for TIV and scanner revealed no significant main effect of diagnosis on hippocampal volume in the left [$F(1,52) = 0.27$, $p = 0.60$] or right hemisphere [$F(1,52) = 0.16$, $p = 0.69$]. This indicates that patient and control groups had similar hippocampal volumes (Table 2).

In the entire study sample, multivariate ANCOVA revealed no significant main effect of 5-HTTLPR genotype on left or right hippocampal volumes (Table 4), indicating similar hippocampal volumes among individuals with 5-HTTLPR L/L, L/S, and S/S genotypes. There were, however, significant diagnosis by 5-HTTLPR genotype interactions for the left and right hippocampus (Table 4), indicating that 5-HTTLPR genotype had differing effects on hippocampal volume in the patient and control groups. ANCOVA conducted separately on patients and controls indicated significant main effects of 5-HTTLPR genotype on hippocampal volumes in both groups. In controls, there was a significant main effect of 5-HTTLPR genotype on right hippocampal volume [$F(2,26) = 5.38$, $p = 0.01$]),

Table 3. Genotype distributions of monoamine-related gene polymorphisms in patients and controls

SNP (group)	Genotype (n) (%)			p value*
5-HTTLPR	L/L	L/S	S/S	
All participants	14 (26.4)	22 (41.5)	17 (32.1)	
Patients	9 (34.6)	9 (34.6)	8 (30.8)	0.39
Controls	5 (18.5)	13 (48.2)	9 (33.3)	
NET – 182 T/C	T/T	T/C	C/C	
All participants	34 (64.1)	19 (35.9)	0 (0.0)	
Patients	15 (57.7)	11 (42.3)	0 (0.0)	0.34
Controls	19 (70.4)	8 (29.6)	0 (0.0)	
5-HT_{1A} – 1019C/G	C/C	C/G	G/G	
All participants	15 (28.3)	27 (50.9)	11 (20.8)	
Patients	8 (30.8)	13 (50.0)	5 (19.2)	0.92
Controls	7 (25.9)	14 (51.9)	6 (22.2)	
5-HT_{2A} – 102 T/C	T/T	T/C	C/C	
All participants	17 (32.1)	23 (43.4)	13 (24.5)	
Patients	7 (26.9)	10 (38.5)	9 (34.6)	0.24
Controls	10 (37.0)	13 (48.1)	4 (14.9)	
COMT Val158Met	Val/Val	Val/Met	Met/Met	
All participants	16 (30.2)	24 (45.3)	13 (24.5)	
Patients	8 (30.8)	10 (38.4)	8 (30.8)	0.51
Controls	8 (29.6)	14 (51.9)	5 (18.5)	
BDNF Val66Met	Val/Val	Val/Met	Met/Met	
All participants	40 (75.5)	12 (22.6)	1 (1.9)	
Patients	21 (80.8)	5 (19.2)	0 (0.0)	0.38
Controls	19 (70.4)	7 (25.9)	1 (3.7)	

5-HT_{2A}, serotonin 2A receptor; 5-HTTLPR, serotonin transporter-linked polymorphic region; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; 5-HT_{1A}, serotonin 1A receptor; NET, norepinephrine transporter; SNP, single nucleotide polymorphism.

* Compared with the control group by χ^2 test.

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Table 4. Investigations of genotype variant effects on hippocampal volume in patients and controls*

		Diagnosis			Genotype			Diagnosis × genotype		
Gene	Hemisphere	*F*	*df*	*p* value	*F*	*df*	*p* value	*F*	*df*	*p* value
5-HTTLPR	L	1.03	1,52	0.32	0.60	2,52	0.56	6.35	2,52	0.004
	R	1.06	1,52	0.31	1.12	2,52	0.34	4.65	2,52	0.015
NET – 182 T/C	L	0.07	1,52	0.79	4.41	1,52	0.04	0.01	1,52	0.92
	R	0.02	1,52	0.90	3.89	1,52	0.055	0.95	1,52	0.34
5-HT_{1A} – 1019C/G	L	0.01	1,52	0.94	1.76	2,52	0.19	1.01	2,52	0.35
	R	0.02	1,52	0.89	5.88	2,52	0.005	1.00	2,52	0.38
5-HT_{2A} – 102 T/C	L	0.43	1,52	0.52	0.52	2,52	0.60	0.05	2,52	0.95
	R	0.53	1,52	0.47	0.69	2,52	0.51	0.52	2,52	0.60
COMT Val158Met	L	0.12	1,52	0.73	0.55	2,52	0.58	0.04	2,52	0.96
	R	0.06	1,52	0.82	0.36	2,52	0.70	0.02	2,52	0.98
BDNF Val66Met	L	0.11	1,52	0.74	0.03	1,52	0.86	0.06	1,52	0.81
	R	0.19	1,52	0.66	0.01	1,52	0.94	0.04	1,52	0.84

5-HT_{1A}, serotonin 1A receptor; 5-HT_{2A}, serotonin 2A receptor; 5-HTTLPR, serotonin transporter-linked polymorphic region; BDNF, brain-derived neurotrophic factor; COMT, catechol-O-methyltransferase; L, left; NET, norepinephrine transporter; R, right; SNP, single nucleotide polymorphism.

* Individual analyses of covariance for each genetic polymorphism, with left and right hippocampal volume as dependent variables, diagnosis, and genotype as independent variables, and total intracranial volume and scanner as covariates.

with Bonferroni-corrected *post-hoc t*-tests revealing 8.7% larger right hippocampal volume among controls with two copies of the 5-HTTLPR S allele relative to those with only one copy (5-HTTLPR L/S genotype; $p = 0.01$; Fig. 1a). The effect of the 5-HTTLPR genotype on left hippocampal volumes in the control group did not reach statistical significance [$F(2,26) = 2.67$, $p = 0.09$]. In patients, there was a significant main effect of 5-HTTLPR genotype on left hippocampal volume [$F(2,25) = 3.55$, $p = 0.04$], with Bonferroni-corrected *post-hoc t*-tests revealing 10.9% smaller left hippocampal volume among patients with the 5-HTTLPR S/S genotype relative to 5-HTTLPR L/S genotype ($p = 0.04$; Fig. 1b), while the effect of the 5-HTTLPR genotype on right hippocampal volumes was not significant [$F(2,25) = 1.17$, $p = 0.33$].

Multivariate ANCOVA revealed a significant main effect of NET – 182 T/C genotype on left hippocampal volumes in study participants and a near significant effect on the right hippocampus (Table 4). *Post-hoc* Bonferroni-corrected *t*-tests revealed 4.7% larger left hippocampal volume among NET – 182 T/C T/T homozygotes relative to T/C heterozygotes ($p = 0.04$; Fig. 2).

There was also a significant main effect of 5-HT_{1A} – 1019C/G genotype on right hippocampal volumes in study participants (Table 4). *Post-hoc* Bonferroni-corrected *t*-tests revealed significantly larger right hippocampal volume among individuals with the 5-HT_{1A} – 1019C/G G/G genotype relative to C/C homozygotes (8.9% larger; $p = 0.005$) and C/G heterozygotes (6.2% larger; $p = 0.03$; Fig. 3).

Individual ANCOVAs for 5-HT_{2A} – 102 T/C, COMT Val158Met, and BDNF Val66Met revealed

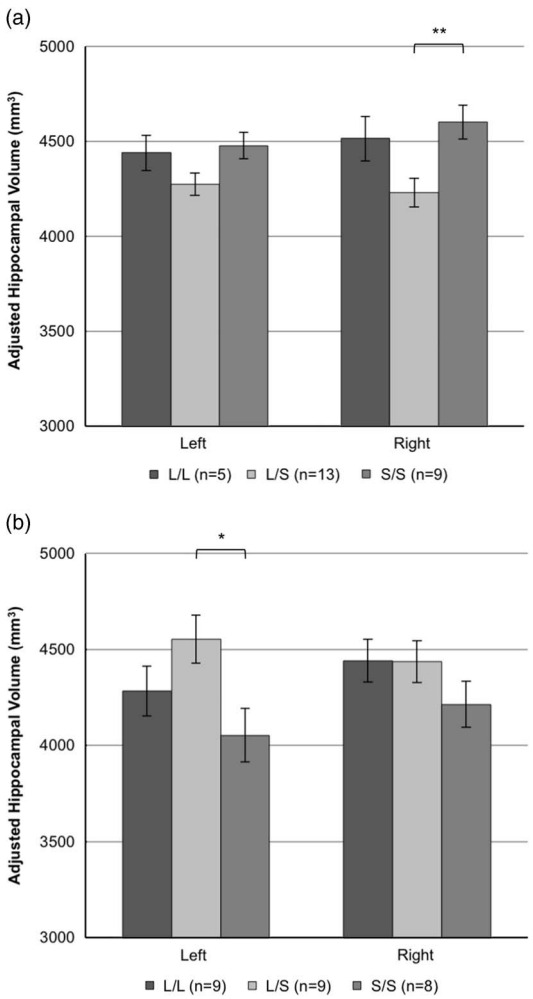

Fig. 1. Total intracranial volume-adjusted left and right hippocampal volumes by 5-HTTLPR genotype in (a) controls ($n = 27$), and (b) patients ($n = 26$). The data are expressed as mean and standard error of the mean. *$p < 0.05$; **$p < 0.01$.

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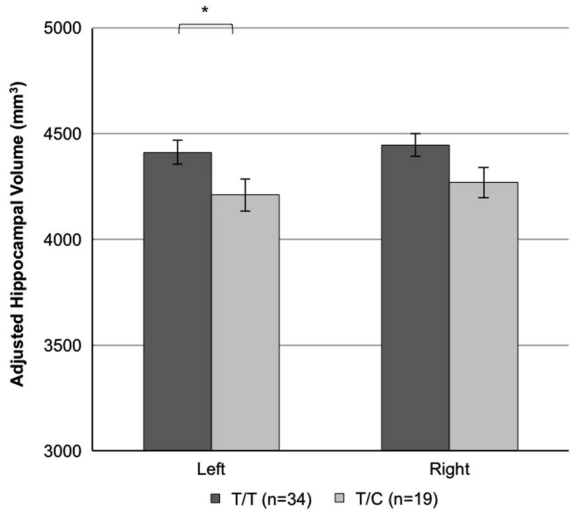

Fig. 2. Total intracranial volume-adjusted left and right hippocampal volumes by NET – 182 T/C genotype in study participants ($n = 53$). The data are expressed as mean and standard error of the mean. *$p < 0.05$.

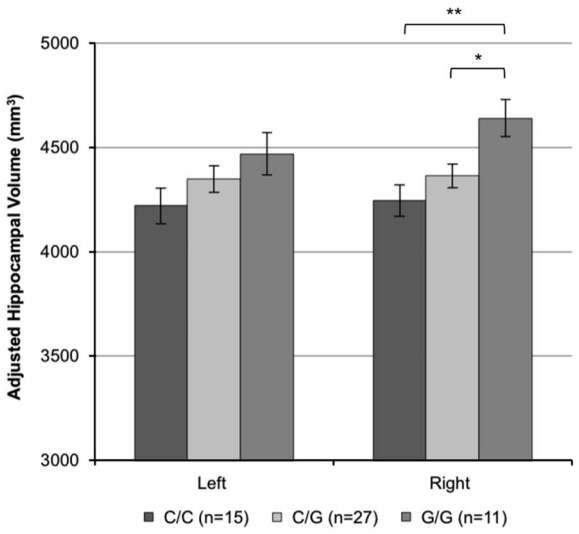

Fig. 3. Total intracranial volume-adjusted left and right hippocampal volumes by 5-HT_{1A} – 1019C/G genotype in study participants ($n = 53$). The data are expressed as mean and standard error of the mean. *$p < 0.05$; **$p < 0.01$.

no significant main effects or diagnosis by genotype interaction effects on hippocampal volume (Table 4).

Discussion

Two main findings emerged from this pilot study: first, there was no identified effect of illness on hippocampal volumes; and second, three of the monoaminergic SNPs were associated with hippocampal volume. There was a relationship between homozygosity for the 5-HTTLPR S allele and reduced hippocampal volume among patients, and in the entire study sample, the NET – 182 T/C and 5-HT_{1A} – 1019 G/C SNPs were associated with hippocampal volume.

Despite overall findings of hippocampal volume reduction in MDD patients by meta-analyses (6,9), when all studies comparing patients and controls are considered, about half have failed to find differences in hippocampal volume (12). This discrepancy may result from failure to consider genetic variation and may explain the lack of hippocampal volume differences between patients and controls in this study.

The 5-HTTLPR S allele is associated with reduced transcriptional activity of the 5-HTT promoter and diminished serotonin activity (35). Several lines of evidence suggest that the short variant of 5-HTTLPR confers vulnerability to the development of depression, especially, in the presence of stressful life events (36). A meta-analysis has reported poorer and more delayed response to selective serotonin reuptake inhibitors among MDD patients homozygous for the 5-HTTLPR S allele (32). In the current study, homozygosity for the S allele was associated with reduced hippocampal volumes in patients but not in controls. While some studies have failed to find an association between 5-HTTLPR and hippocampal volume (37,38), several other studies have found interactions between this SNP and other clinical and physiological factors that affect hippocampal volume. For example, S/S homozygosity has been reported to be associated with reduced hippocampal volume in elderly MDD patients with an early (≤50 years) age of onset (39); in the present study, the patient sample had mean age of onset of 30 years (Table 2). Such individuals would be expected to have experienced multiple depressive episodes over a longer duration, which may correlate with greater exposure to elevated glucocorticoid levels (40) thought to contribute to hippocampal volume reductions (41). This theory is consistent with the findings of other studies that have documented associations between the 5-HTTLPR S allele and reduced hippocampal volume with higher waking cortisol levels (42), the presence of childhood stress (43,44), and the diagnosis of depression (45). Thus, the effects of the 5-HTTLPR S allele on hippocampal volume may be moderated by a gene-by-environment interaction, in which the polymorphism alone is insufficient to affect hippocampal volume in the absence of an environmental stressor such as a depressive episode.

NET – 182 T/C had an effect on hippocampal volume in the full study sample. The NET – 182 T/C polymorphism is in the promoter region of the gene that encodes the norepinephrine transporter (46), considered a candidate gene for major depression. However, its functional consequences remain unknown and a recent meta-analysis failed to

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confirm an association between the polymorphism and MDD (47). Like the 5-HTT, the NET is a major target of certain antidepressants including tricyclics, norepinephrine reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors (SNRIs). The C(−182) allele has been associated with poorer response to milnacipran (an SNRI) compared with the T(−182) allele among MDD patients (48); however, associations between NET polymorphisms and antidepressant responsiveness have not been widely replicated (1). In the present study, C(−182) allele-carriers had smaller hippocampal volumes relative to T/T homozygotes. Associations between this polymorphism and hippocampal volume have not been previously reported in the literature.

Similar to NET − 182 T/C, the 5-HT_{1A} − 1019C/G polymorphism had an effect on hippocampal volume irrespective of diagnosis. 5-HT_{1A} − 1019C/G has been shown to alter receptor expression, with the G(−1019) allele in the *HTR1A* promoter region failing to bind repressors Deaf1, Hes1, and Hes5, leading to upregulation of presynaptic 5-HT_{1A} autoreceptor expression (49,50). The G(−1019) allele has been associated with MDD and suicide (50,51), and among MDD patients, reduced treatment response to serotonergic antidepressants (1), increased amygdala reactivity (52), and in patients with comorbid MDD and borderline personality disorder, reduced amygdala volume (53). There is a high concentration of 5-HT_{1A} receptors in the dentate gyrus and it is via these receptors that serotonergic antidepressants are thought to influence adult neurogenesis (54). Since the G(−1019) allele is associated with fewer postsynaptic 5-HT_{1A} receptors (55), one would expect a reduction in hippocampal neurogenesis in association with the G allele (51), which could have consequences for hippocampal volume. In the present study, however, G/G homozygotes had larger hippocampal volumes than individuals with one or two copies of the C allele. Given that a relatively small proportion of the total volume of the hippocampus is represented by the dentate gyrus, and that the magnitude of adult neurogenesis in the human hippocampus is probably too low to account for volume changes within the hippocampus itself (56,57), alterations to neurogenesis alone would be unlikely to explain the volume effects of 5-HT_{1A} − 1019C/G.

Findings of NET − 182 T/C and 5-HT_{1A} − 1019C/G effects on hippocampal volume in both patients and controls independent of a diagnosis of MDD, suggest an association with development. Serotonin plays a role in the regulation of brain development and acts as a trophic factor as well as a neurotransmitter [for review see Gaspar et al. (58)]. 5-HT_{1A} receptor activation affects early postnatal dendritic maturation in the hippocampus (59), in particular affecting the length and number of dendritic spines in hippocampal neurons (60). The effects of these particular polymorphisms on hippocampal development are unknown but it is possible that they may affect neurodevelopmental processes that have consequences for hippocampal volume in adults.

A limitation of the present study is the relatively small sample size. While the focus of this paper was to investigate the effects of various monoamine-related SNPs on hippocampal volume, the candidate genes selected generally have only modest associations with MDD diagnosis and treatment response and therefore much larger sample sizes are required to replicate association studies. Further, the genetic effects on hippocampal volume are likely the result of the interaction of multiple genes in addition to environmental influences and the study was underpowered to investigate gene–gene interaction effects on hippocampal volume. For these reasons, the findings of this study should be considered preliminary and further research is necessary.

The present data indicate that hippocampal volume may be influenced by serotonin- and norepinephrine-related gene polymorphisms. We provide evidence that the NET and 5-HT_{1A} polymorphisms appear to exert their effects on hippocampal volume similarly in patients and controls; while the 5-HTTLPR polymorphism differentially affects hippocampal volume in the presence of depression. Given the putative role of both the hippocampus and of monoamine-related candidate genes in depression and antidepressant response, it will be beneficial to elucidate how these various factors interact in order to potentially identify valid markers of depression and predictors of treatment response.

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Conflicts of Interest

P.B. received grant funding and/or honoraria for lectures and/or participation in advisory boards for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Euthymics, Forest, Janssen, Lundbeck, Merck, Otsuka, Pfizer, Pierre Fabre, Servier, Shire, Takeda, and Valeant. P.T. has served as a consultant to Lundbeck. All other authors declare no conflicts of interest.

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