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Decreased Brain Ventricular Volume in Psychiatric Inpatients with Serotonin Reuptake Inhibitor Treatment

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Abstract

Background: Brain ventricles have been reported to be enlarged in several neuropsychiatric disorders and in aging. Whether human cerebral ventricular volume can decrease over time with psychiatric treatment is not well-studied. The aim of this study was to examine whether inpatients taking serotonin reuptake inhibitors (SRI) exhibited reductions in cerebral ventricular volume.

Methods: Psychiatric inpatients, diagnosed mainly with depression, substance use, anxiety, and personality disorders, underwent two imaging sessions (Time 1 and Time 2, approximately 4 weeks apart). FreeSurfer was used to quantify volumetric features of the brain, and ANOVA was used to analyze ventricular volume differences between Time 1 and Time 2. Inpatients' brain ventricle volumes were normalized by dividing by estimated total intracranial volume (eTIV). Clinical features such as depression and anxiety levels were collected at Time 1, Time 1.5 (approximately 2 weeks apart), and Time 2.

Results: Inpatients consistently taking SRIs (SRI +, n = 44) showed statistically significant reductions of brain ventricular volumes particularly for their left and right lateral ventricular volumes. Reductions in their third ventricular volume were close to significance ($p = .068$). The inpatients that did not take SRIs (SRI-, n = 25) showed no statistically significant changes in brain ventricular volumes. The SRI + group also exhibited similar brain structural features to the healthy control group based on the 90% confidence interval comparsions on brain ventricular volume parameters, whereas the SRI- group still exhibited relatively enlarged brain ventricular volumes after treatment.

Conclusions: SRI treatment was associated with decreased brain ventricle volume over treatment.

Keywords

serotonin reuptake inhibitors, SSRI, SNRI, brain ventricles, MRI, neuroimaging biomarkers, brain volumetry, ventriculomegaly

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Introduction

There is a wealth of published research associating higher brain ventricle volume with neuropsychiatric diagnoses, neurodegenerative disorders, as well as other phenomena including traumatic brain injury;[1–3] psychiatric disorders such as depression,[4,5] anxiety,[6] and bipolar disorders;[7,8] dementia;[9] general cognitive decline;[10] advanced aging;[11–13] Rett syndrome;[14–17] neurodegenerative disorders such as Alzheimer's disease,[18–20] amyotrophic lateral sclerosis,[21] cortical basal ganglionic degeneration,[22] multiple sclerosis,[23,24] Huntington's disease,[25] and Parkinson's disease;[26–30] and herpes simplex encephalitis.[31] Finally, astronauts subjected to long-duration spaceflight also appear to have exhibited brain ventricle enlargement over time, whereas controls did

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not.[32,33] Brain ventricle enlargement generally appears to be due to the loss of neurons and/or glia, including cell death due to microglia activation and neuroinflammation.[34–39] A recent study exploring cortical thickness in Major Depressive Disorder showed that patients using the serotonin reuptake inhibitor (SRI) sertraline for eight weeks exhibited an increase in cortical thickness.[40] In addition, SRIs have been reported to have a key role in hippocampal neurogenesis.[41,42] In addition, sertaline was shown to slow disease progression and increased neurogenesis in the N171-82Q mouse model of Huntington's disease (HD): sertraline exhibited neuroprotective effects including against brain ventricular enlargement (caused by neurodegeneration) which was less pronounced in sertraline-treated HD mice compared to the vehicle-treated HD mice. Vehicle-treated HD mice exhibited greater neurodegeneration and brain ventricular enlargement over time.[43] The subventricular zone (SVZ) is also interesting, as it has been identified as a highly neurogenic region of the adult brain.[44]

Thus, we aimed to investigate whether treatment of approximately four weeks with SRIs resulted in decreased cerebral ventricular volume over time by analyzing neuroimaging data from both psychiatric inpatients who were prescribed SRIs (SRI +) and those who were not (SRI-). We hypothesized that (SRI +) patients would exhibit either less pronounced enlargement in brain ventricle volume over time compared to SRI- patients, or exhibit reduced brain ventricular volume over time whereas (SRI-) patients would not. Our goals were to evaluate the structural effects that SRIs can induce on the adult human brain, focusing on brain ventricular volume as our parameter of interest.

Materials & Methods

Participants

Our study pool consisted of controls with no history of mental illness according to the MINI International Neuropsychiatric Interview[45] (n = 80), and psychiatric inpatients (n = 81, see Table 1). All subjects participated in the McNair Initiative for Neuroscience Discovery at Menninger and Baylor (MIND-MB[46–49]) research study, which actively collected patient data from 2012 to 2017, and provided informed consent in compliance with policies and procedures approved by the Baylor College of Medicine Institutional Review Board. All Menninger Clinic psychiatric inpatients were eligible if they were mentally stable enough to participate and had no contraindications for magnetic resonance imaging. In addition to neuroimaging data the MIND-MB study collected demographic and relevant clinical information from inpatients including the following evaluations: the Patient Health Questionnaire module for depression (PHQ-9),[50] the Generalized Anxiety Disorder Scale (GAD-7),[51] which were taken as close to admission as possible and every two weeks thereafter, and psychiatric diagnoses from the Structured Clinical Interview for diagnostic and statistical manual of mental disorders (DSM)-IV Axis I and II disorders[52] which were taken as close to admission as possible. The total number of brain imaged adult psychiatric inpatients from the MIND-MB study was 518 at the time of the data collection, with 81 of those having magnetic resonance imaging (MRI) scan data at two time points, one near the time that the inpatient was admitted to Menninger (Time 1) and again approximately four weeks later (Time 2). The 81 inpatients included in the study pool were further divided into two subgroups, those inpatients prescribed and consistently taking SRIs (SRI + , n = 44) and inpatients who did not take any SRI drugs during their participation (SRI-, n = 25). Additional inclusion criteria were no contraindications for magnetic resonance imaging, and full individual capability to consent to participation. Twelve inpatients were excluded as they failed to meet the criteria of consistently taking SRIs.

Neuroimaging Acquisition and Analysis

Participants were scanned in a 3T Siemens Trio MR scanner in the Center for Advanced Magnetic Resonance Imaging at Baylor College of Medicine in Houston, TX, as close to admission to the clinic as possible, and were scanned again approximately four weeks later using the same parameters.

A ~4.5-min structural magnetization-prepared rapid gradient-echo sequence (echo time = 2.66 ms, repetition time = 1200 ms, flip angle = 12°, 256 × 256 matrix, 160 one mm axial slices at 1 × 1 × 1 mm voxels) was collected.

Preprocessing and automated volumetric segmentation of the T1-weighted structural images was performed using FreeSurfer (V6.0) (http://surfer.nm.gh.harvard.edu). Using FreeSurfer, we segmented brain regions of interest (ROIs) with probabilistic mapping based on the Aseg (Automatic subcortical segmentation) atlas.[46,53,54] We used the Aseg atlas to obtain the inpatients' brain ventricle volumes of their left and right lateral ventricles, including their inferior lateral ventricles, as well as their third ventricle, and also the estimated total intracranial volume (eTIV).

Statistics

Analysis of variance (ANOVA) was used to compare Time 1 and Time 2 volumetric data of lateral ventricle and third ventricle regions. Healthy controls were used in this study as a reference group and were matched by age and gender to the inpatients. As healthy controls were not expected to change brain anatomy within a month, only one time point of scan data was available for this group. We normalized data by dividing each subject's brain ventricle volumes (in mm^3) by his or her estimated total intracranial volume eTIV (also in mm^3 units), to control for head size variability effects.[55]

Table 1. Demographics, Clinical Characteristics, and Medications.

Characteristics	SRI + n = 44	SRI − n = 25	Healthy controls n = 80
Demographic			
Age, mean (SEM)	27.0 (1.6)	28.6 (1.9)	30.0 (0.9)
Male	63.6%	52%	65.0%
Most common diagnoses			
Major depressive disorder	25.0%	8.0%	
Substance use disorder	25.0%	36.0%	
Generalized anxiety disorder	27.3%	8.0%	
Post-traumatic stress disorder	11.4%	20.0%	
Avoidant personality disorder	31.8%	20.0%	
Borderline personality disorder	25.0%	24.0%	
Obsessive-compulsive personality disorder	15.9%	16.0%	
Dimensional measures			
Time 1 depression score, mean (SEM)	17.7 (0.9)	15.1 (1.3)	
Time 1.5 depression score, mean (SEM)	10.9 (0.8)	9.0 (1.2)	
Time 2 depression score, mean (SEM)	8.1 (0.8)	7.1 (1.1)	
Time 1 anxiety score, mean (SEM)	12.4 (0.7)	12.1 (1.3)	
Time 1.5 anxiety score, mean (SEM)	8.2 (0.8)	8.3 (1.3)	
Time 2 anxiety score, mean (SEM)	6.6 (0.7)	6.6 (1.1)	
Serotonin reuptake inhibitors (SRIs)			
Trazodone (SARI)	38.6%		
Fluoxetine (SSRI)	22.7%		
Venlafaxine (SNRI)	22.7%		
Sertraline (SSRI)	20.5%		
Escitalopram (SSRI)	11.4%		
Citalopram (SSRI)	6.8%		
Duloxetine (SNRI)	4.5%		
Paroxetine (SSRI)	4.5%		
Vortioxetine (SMS)	4.5%		
Desvenlafaxine (SNRI)	2.3%		
Most common non-SRI medications			
Anticonvulsants	45.5%	60.0%	
Antipsychotics	29.5%	40.0%	
Benzodiazepines	15.9%	16.0%	
Amphetamines	13.6%	4.0%	
NSAIDs	13.6%	16.0%	
Opiate agonists	9.1%	8.0%	
Opiate antagonists	6.8%	8.0%	

There were no statistically significant differences among the three groups in terms of demographics, diagnostics, and other non-SRI medications. The SRI + group expectedly was composed of slightly more depressed and anxiety patients, but the test statistic *p* value was still above 0.05 for the Chi-squared analysis, indicating no statistically significant differences between the SRI + and SRI- groups. Of the inpatients that used trazodone combined with another SRI such as fluoxetine, they used low-dose trazodone (50 mg to 150 mg) as a sleeping aid. There were only four inpatients in the SRI + group that used trazodone by itself, and of those four inpatients, one of them used high-dose trazodone (600 mg) intended as a treatment for depression. NSAIDs: non-steroidal anti-inflammatory drugs; SARI: serotonin antagonist and reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and norepinephrine reuptake inhibitor; SMS: serotonin modulator and stimulator.

Since FreeSurfer outputs the lateral ventricular regions into two parts consisting of the "lateral ventricles" and "inferior lateral ventricles," we combined these two, so that the right lateral ventricle and the right inferior lateral ventricle were added together,[56] and this sum was then divided by the patient's eTIV. The lateral ventricles here are thus "total left lateral ventricle" (TLLV) or the "total right lateral ventricle" (TRLV). Finally, "third ventricle volume" is referred to as TVV hereon.

As a form of equivalence testing, we used 90% confidence intervals as well to see how the inpatients' (SRI + or SRI-) mean ventricular volume/eTIV (and 90% confidence intervals) compared to the healthy controls' mean ventricular volume/eTIV (and with the healthy controls' respective

90% confidence intervals), while keeping in mind the upper and lower boundaries. For example, seeing if the SRI + 's or SRI-'s 90% confidence interval boundaries become more similar and overlapping with the healthy controls' 90% confidence interval boundaries.[57] All statistical analyzes were performed in SPSS Version 27 (SPSS, Inc., Chicago, IL).

Results

The demographics, clinical characteristics, and the list of SRIs used are shown in Table 1. The three groups did not differ in terms of age or gender, and the two inpatient groups did not significantly differ in demographic nor clinical features.

The 2 × 2 repeated-measures ANOVA (time*SRI status) showed statistically significant reductions in the brain ventricular volumes in the SRI + group from Time 1 to Time 2. The SRI- group did not exhibit statistically significant changes from Time 1 to Time 2 (Figure 1A-F, Table 2). These reductions can be seen to some extent in the slight shrinkage of the "butterfly wings" of the lateral ventricles, as shown the transverse MRI slice view of one of the SRI + patients but not in an SRI- patient (Figure 1G and H). Note that these are "raw" images as taken in the scanner without any preprocessing, so the exact angle of the head is expected to slightly differ between the first and second MRI. These images are shown only for a visual assessment, as quantification was done with Freeurfer. The example images in Figure 1G and H are shown in neurological convention (right side of the image is the patient's right side). SRI + patients' TTLV/eTIV at Time 2 has a mean of 0.00496 which was originally at 0.00511 at Time 1. The SRI + patients' Time 2 TTLV/eTIV was closer to the healthy controls' (0.00491 mean, see Table 2). Several inpatients used trazodone combined with another SRI. In that case, they used low-dose trazodone (50 mg to 150 mg) mainly as a sleeping aid. There were only four inpatients in the SRI + group that used trazodone and no other SRI. Of those four inpatients, one of them used high-dose trazodone (600 mg) intended as a treatment for depression. As an additional control, we removed three low-dose trazodone-only inpatients and repeated the analysis of SRI + versus SRI- ventricular volume. The *p* values were not significantly changed.

With the 90% confidence interval method, one can see that the SRI + group for their TRLV/eTIV mean was outside of the healthy controls' 90% confidence interval upper boundary at Time 1, but at Time 2, the SRI + group's mean TRLV/eTIV was within the healthy controls' 90% confidence interval (Table 3). This indicates that the changes in the SRI + 's brain structure (in terms of the total right lateral ventricular volume) became relatively more similar to the healthy controls' brain structure at Time 2.

Discussion

In this study, we investigated changes in TLLV/eTIV, TVV/eTIV, and TRLV/eTIV over a time of approximately four weeks (Time 1 and Time 2) in inpatients who were or were not taking SRIs. The SRI + group experienced significant reductions in their TLLV/eTIV, TVV/eTIV, and TRLV/eTIV, whereas the SRI − group experienced no significant changes in ventricular volume, in fact they exhibit slightly enlarged ventricles over time, albeit not statistically significantly (Table 2, Figure 1). The results of this study may be viewed in light of other studies that connect SRI activity with neuroplasticity/neurogenesis, wherein SRIs increase extracellular serotonin levels in the brain by blocking its reuptake, and serotonin can in turn stimulate brain-derived neurotrophic factor (BDNF) production.[58–64] Note also that neurogenesis has been reported to occur in the ventricular-subventricular zone.[65]

Previous studies have supported evidence of neuroplasticity and neurogenesis being associated with SRI use, especially in rodent models.[66,67] As mentioned earlier, a mouse Huntington disease model (neurodegeneration) showed an effect of a specific SRI on ventricular volume. . Because currently there is a lack of human studies reporting a relationship between reductions in brain ventricle volume and SRI use, we decided to pursue this analysis. We believe that our results warrant further study of the possible role of SRIs on ventricular volume.

The reduction in brain ventricle volume in the SRI + group may be due to a cumulative combined effect: The Menninger Clinic provides a supportive low-stress environment with numerous therapeutic strategies including psychotherapy, group therapy, medication, 24 h nurse care, and occupational activities, among others. Therefore, the effects of SRIs on brain ventricle volume may be a consequence of the interaction between medication and environment. Thus, future studies are needed to replicate this observation both at another inpatient sample at Menninger or a similar clinic, and in different settings including outpatients and ethnically and socioeconomically more diverse populations.

There are several limitations to this study. While sample sizes were sufficient for a statistically significant effect, larger sample sizes would help make our observations more robust. Another limitation is that the psychiatric inpatients' medication history data only included medications that they were using while being an inpatient at The Menninger Clinic. Also, while the various SRI drugs used by the SRI + inpatients can have similar effects of increasing brain serotonin levels, each drug may have slightly different effects. Since we had a limited number of inpatients for each type of SRI drug, all viable SRI + inpatients were pooled together because all SRIs raise the user's levels of extracellular serotonin (trazodone,[68] fluoxetine,[69] venlafaxine,[70] sertraline,[71] escitalopram,[72] citalopram,[73] duloxtetine,[74] paroxetine,[75] vortioxetine,[76] and desvelanfaxine[77]). In

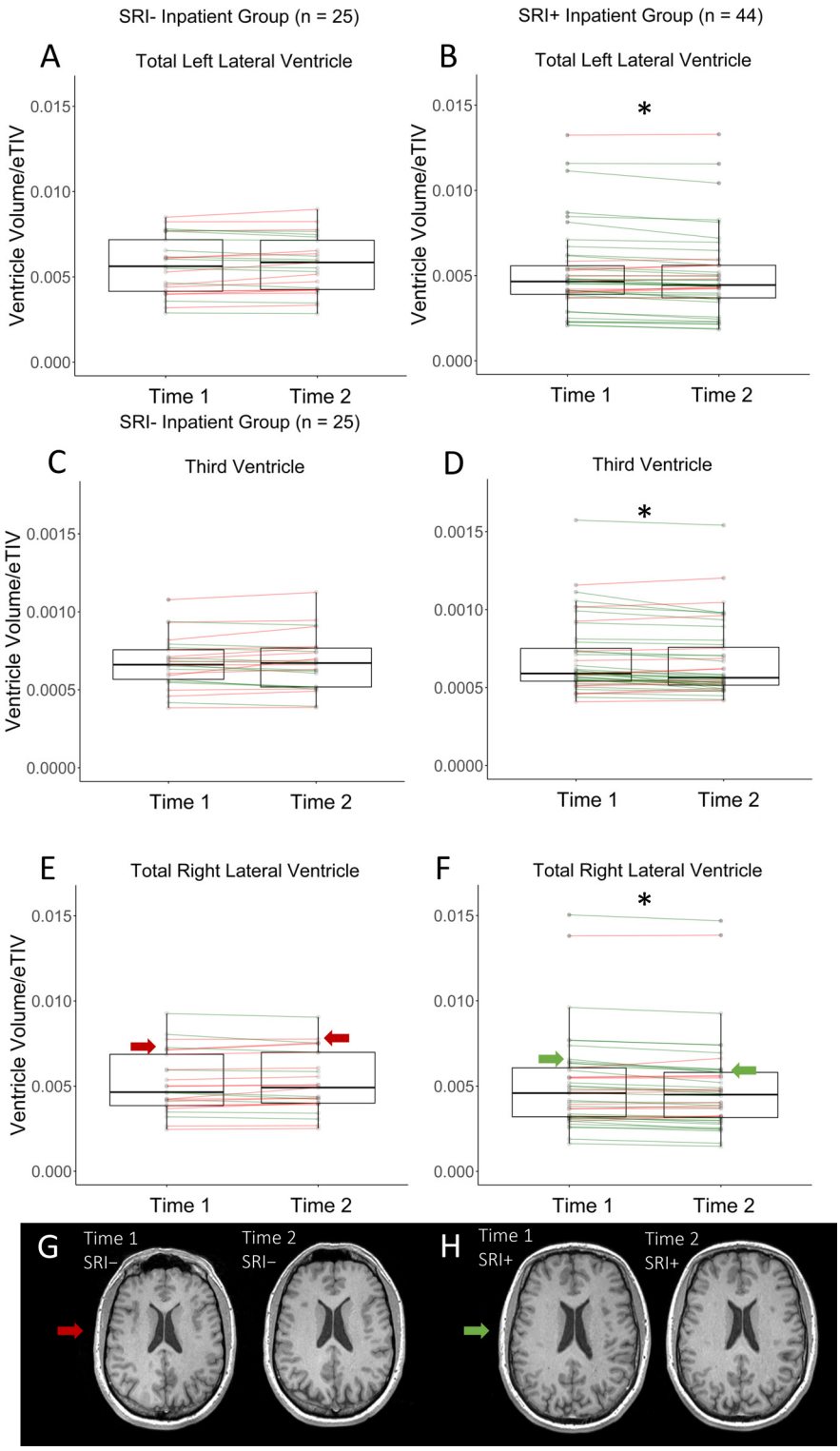

Figure 1. Ventricular volume (in mm^3/mm^3, unitless) in SRI- and SRI + inpatients, at time 1 (close to admission) and time 2 (~4 weeks later). Green lines denote inpatients whose ventricles were smaller after treatment, while red lines denote inpatients whose ventricles were larger after treatment. A, B) Left Total Lateral Ventricle; C, D) Third Ventricle; E, F) Right Total Lateral Ventricle; G) A representative section of one SRI- inpatient anatomy is shown. The slices are not perfectly exactly the same because of slight changes in the angle of the head between scans. We used the overall shape of the brain, skull, and other visual marker features to approximate as close as possible to match one-to-one from Time 1 to Time 2. The red arrows in E show the specific inpatient shown; H) A representative section of one SRI + inpatient anatomy is shown. The green arrows in E show the specific inpatient shown. * $p < .05$.

Table 2. Summary of the Results in Terms of 2 × 2 Repeated-Measures ANOVA (Time*SRI Status).

TLLV/eTIV	Time 1 mean (SEM)	Time 2 mean (SEM)	F	*p*	$\eta^2_{partial}$	Healthy controls mean (SEM)
SRI +	5.11×10^{-3} (4×10^{-4})	4.96×10^{-3} (4×10^{-4})	4.560	.043*	0.160	4.91×10^{-3} (2×10^{-4})
SRI −	5.67×10^{-3} (3×10^{-4})	5.72×10^{-3} (3×10^{-4})				
TVV/eTIV						5.81×10^{-4} (2×10^{-5})
SRI +	6.85×10^{-4} (4×10^{-5})	6.70×10^{-4} (4×10^{-5})	3.795	.063	0.137	
SRI −	6.71×10^{-4} (3×10^{-5})	6.75×10^{-4} (4×10^{-5})				
TRLV/eTIV						4.66×10^{-3} (2×10^{-4})
SRI +	5.04×10^{-3} (4×10^{-4})	4.87×10^{-3} (4×10^{-4})	6.220	.020*	0.206	
SRI −	5.20×10^{-3} (4×10^{-4})	5.23×10^{-3} (4×10^{-4})				

* $p < .05$, SRI + (n = 44), SRI − (n = 25), healthy controls (n = 80). SEM: standard error of the mean; TLLV: total left lateral ventricle; TVV: third ventricle volume; TRLV: total right lateral ventricle; eTIV: estimated total intracranial volume.

Table 3. Summary of the 90% Confidence Interval Data.

TLLV/eTIV	Time 1 mean (lower bound, upper bound)	Time 2 mean (lower bound, upper bound)	Healthy controls mean (lower bound, upper bound)
SRI +	5.11×10^{-3} (4.49×10^{-3}, 5.75×10^{-3})	4.96×10^{-3} (4.34×10^{-3}, 5.58×10^{-3})	4.91×10^{-3} **(4.52×10^{-3}, 5.30×10^{-3})**
SRI −	5.67×10^{-3} (5.09×10^{-3}, 6.24×10^{-3})	5.72×10^{-3} (5.15×10^{-3}, 6.28×10^{-3})	
TVV/eTIV			5.81×10^{-4} **(5.54×10^{-4}, 6.08×10^{-4})**
SRI +	6.85×10^{-4} (6.25×10^{-4}, 7.46×10^{-4})	6.70×10^{-4} (6.06×10^{-4}, 7.24×10^{-4})	
SRI −	6.71×10^{-4} (6.16×10^{-4}, 7.27×10^{-4})	6.75×10^{-4} (6.15×10^{-4}, 7.35×10^{-4})	
TRLV/eTIV			4.66×10^{-3} **(4.29×10^{-3}, 5.03×10^{-3})**
SRI +	5.04×10^{-3} (4.36×10^{-3}, 5.72×10^{-3})	4.87×10^{-3} (4.20×10^{-3}, 5.54×10^{-3})	
SRI −	5.20×10^{-3} (4.58×10^{-3}, 5.81×10^{-3})	5.23×10^{-3} (4.61×10^{-3}, 5.83×10^{-3})	

SRI + (n = 44), SRI − (n = 25), healthy controls (n = 80). Bolded healthy controls' 90% CI as it is the main interval of interest for comparison (higher sample size, tighter confidence interval). Note that SRI + Time 2's TRLV/eTIV mean value of 0.00487 fell within the healthy controls' 90% CI (0.00429, .00503), whereas SRI + Time 1's TRLV/eTIV mean value of 0.00504 was slightly outside of the healthy controls' 90% CI (0.00429, .00503).

addition, for future studies, it may be beneficial to image healthy controls at two time points to control for possible differences in brain ventricle volume measure between the two scans. Future studies may also want to look at other various classes of drugs that can increase BDNF levels and see if they also reduce brain ventricle volume over time. For example, it has been reported that using ketamine can help upregulate BDNF expression, and it may be interesting to see if it also can reduce brain ventricle volume over time.[78] Other future studies of interest may be to study the effects seen here with SRIs when used in combination with another form of therapy, such as combining cognitive behavioral therapy with SRI treatment[79] versus another form of therapy (eg, a meditation program) in combination with SRI treatment,[80] all the while also looking at changes in the brain ventricles over time. Finally, a follow up study would be needed to link SRI-induced ventricle volume decrease to clinically relevant measures, which our limited sample size did not allow.

In conclusion, we showed that a month of SRI treatment in psychiatric inpatients significantly decreased ventricle volume.

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