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

PK Bolin1,2,3, SN Gosnell1,4, K Brandel-Ankrapp4, N Srinivasan5, A Castellanos1,7, and R Salas1,4,6,7

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 = 0.063). 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 comparisons 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

Received 19 April 2022; accepted 16 June 2022

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, psychiatric disorders such as depression, anxiety, and bipolar disorders; dementia; general cognitive decline; advanced aging; Rett syndrome; neurodegenerative disorders such as Alzheimer’s disease, amyotrophic lateral sclerosis, cortical basal ganglionic degeneration, multiple sclerosis, Huntington’s disease, and Parkinson’s disease; and herpes simplex encephalitis. Finally, astronauts subjected to long-duration spaceflight also appear to have exhibited brain ventricle enlargement over time, whereas controls did...
not. 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. 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. In addition, SRIs have been reported to have a key role in hippocampal neurogenesis. In addition, sertraline 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. The subventricular zone (SVZ) is also interesting, as it has been identified as a highly neurogenic region of the adult brain.

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 (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) 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), the Generalized Anxiety Disorder Scale (GAD-7), 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 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.nmr.mgh.harvard.edu). Using FreeSurfer, we segmented brain regions of interest (ROIs) with probabilistic mapping based on the Aseg (Automatic subcortical segmentation) atlas. 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 mm³) by his or her estimated total intracranial volume eTIV (also in mm³ units), to control for head size variability effects.
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,\textsuperscript{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’ 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

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.
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 < 0.05.
controls’ 90% confidence interval boundaries. 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 (Figures 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 (Figures 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 Figures 1G and H are shown in neurological convention (right side of the image is the patient’s right side). SRI+ patients’ TTLVeTIV at Time 2 has a mean of 0.00496 which was originally at 0.00511 at Time 1. The SRI+ patients’ Time 2 TTLVeTIV 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.

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

| Ventricles   | Time 1 mean (SEM) | Time 2 mean (SEM) | F     | p     | η²partial | Healthy controls mean (SEM) |
|--------------|-------------------|-------------------|-------|-------|-----------|-----------------------------|
| TTLVeTIV     |                   |                   |       |       |           |                             |
| SRI+         | 5.11 × 10⁻³ (4 × 10⁻⁶) | 4.96 × 10⁻³ (4 × 10⁻⁶) | 4.560 | 0.043* | 0.160     | 4.91 × 10⁻³ (2 × 10⁻⁶)     |
| SRI–         | 5.67 × 10⁻³ (3 × 10⁻⁶) | 5.72 × 10⁻³ (3 × 10⁻⁶) |       |       |           |                             |
| TVVeTIV      |                   |                   |       |       |           |                             |
| SRI+         | 6.85 × 10⁻⁴ (4 × 10⁻⁵) | 6.70 × 10⁻⁴ (4 × 10⁻⁵) | 3.795 | 0.063 | 0.137     | 5.81 × 10⁻⁴ (2 × 10⁻⁵)     |
| SRI–         | 6.71 × 10⁻⁴ (3 × 10⁻⁵) | 6.75 × 10⁻⁴ (4 × 10⁻⁵) |       |       |           |                             |
| TRLVeTIV     |                   |                   |       |       |           |                             |
| SRI+         | 5.04 × 10⁻³ (4 × 10⁻⁶) | 4.87 × 10⁻³ (4 × 10⁻⁶) | 6.220 | 0.020* | 0.206     | 4.66 × 10⁻³ (2 × 10⁻⁵)     |
| SRI–         | 5.20 × 10⁻³ (4 × 10⁻⁵) | 5.23 × 10⁻³ (4 × 10⁻⁵) |       |       |           |                             |

* p < 0.05, SRI+ (n = 44), SRI– (n = 25), healthy controls (n = 80). SEM: standard error of the mean; TTLV: 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.

| Ventricles   | Time 1 mean (lower bound, upper bound) | Time 2 mean (lower bound, upper bound) | Healthy controls mean (lower bound, upper bound) |
|--------------|----------------------------------------|----------------------------------------|-------------------------------------------------|
| TTLVeTIV     |                                        |                                        |                                                 |
| 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) |                                                 |
| TVVeTIV      |                                        |                                        |                                                 |
| 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) | 5.81 × 10⁻⁴ (5.54 × 10⁻⁴, 6.08 × 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) |                                                 |
| TRLVeTIV     |                                        |                                        |                                                 |
| 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) | 4.66 × 10⁻³ (4.29 × 10⁻³, 5.03 × 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 TRLVeTIV mean value of 0.00487 fell within the healthy controls’ 90% CI (0.00429, 0.00503). Compare this to SRI+ Time 1’s TRLVeTIV mean value of 0.00504, which fell slightly outside of the healthy controls’ 90% CI (0.00429, 0.00503) originally.
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-hour nursing 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 duloxetine,74 paroxetine,75 vortioxetine,76 and desvenlafaxine77). In 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 measures 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 treatment79 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.

Acknowledgments

This material is partly the result of work supported with resources and the use of facilities at the Michael E. DeBakey VA Medical Center, Houston, TX. These data included herein were collected through the use of facilities and resources at The Menninger Clinic, Houston, Texas USA. The authors thank the Core for Advanced MRI at Baylor College of Medicine, Dr Charles Neblett, and research participants. “We thank Elise N. Denghausen, Vanessa N. Heredia, and Puneetha Goli for help with editing. We also thank Kieran Paddock, Danna Ramirez, and Michelle Patriquin for providing the medications data from The Menninger Clinic.”

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the American Foundation for Suicide Prevention,
Office of Research and Development, National Alliance for Research on Schizophrenia and Depression, Robert and Janice McNair Foundation, (grant number SRG-2-125-14, I01CX000994, I01CX001937, 19295, MIND-MB).

ORCID iDs
PK Bolin https://orcid.org/0000-0002-2018-2070
N Srinivasan https://orcid.org/0000-0001-7906-846X
R Salas https://orcid.org/0000-0002-1105-566X

References
1. Cockerell OC, Iino Hayes N, Sylvester R. The neurological risks of playing association football. *J RSM Open*. 2021;12(11):2054270421105558.
2. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauropathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709–735.
3. Graham NS, Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. *J Neurol Neurosurg Psychiatry*. 2019;90(1):1221–1233.
4. Shima S, Shikano T, Kitamura T, et al. Depression and ventricular enlargement. *Acta Psychiatr Scand*. 1984;70(3):275–277.
5. Scott ML, Golden CJ, Ruedrich SL, et al. Ventricular enlargement in major depression. *Psychiatry Res*. 1983;8(2):91–93.
6. Engel K, Bandelow B, Gruber O, et al. Neuroimaging in anxiety disorders. *J Neural Transm (Vienna)*. 2000;116(6):703–716.
7. Pearlson GD, Veroff AE. Computerised tomographic scan changes in manic-depressive illness. *Lancet*. 1981;2(8244):470.
8. Fears SC, Schur R, Sjouwerman R, et al. Brain structure-function associations in multi-generational families genetically validated using the Alzheimer disease neuroimaging initiative database. *Brain*. 2008;131(Pt 9):2443–2454.
9. Nestor SM, Rupsingh R, Borrie M, et al. Ventricular enlargement as a possible measure of Alzheimer’s disease progression validated using the Alzheimer’s disease neuroimaging initiative database. *Brain*. 2008;131(Pt 9):2443–2454.
10. Ott BR, Cohen RA, Gogvavata A, et al. Brain ventricular volume and cerebrospinal fluid biomarkers of Alzheimer’s disease. *J Alzheimers Dis*. 2010;20(2):647–657.
11. Darad M, Manera AL, Zinnman L, et al. Cerebral atrophy in amyotrophic lateral sclerosis parallels the pathological distribution of TDP43. *Journal of Brain Communications*. 2020;2(2):fca061.
12. Scarmeas N, Chin SS, Marder K. Cortical basal ganglionic degeneration. *Sci Aging Knowledge Environ*. 2001;2001(1):dn1.
13. Sinnecker T, Ruberte E, Schädelin S, et al. New and enlarging white matter lesions adjacent to the ventricle system and thalamic atrophy are independently associated with lateral ventricular enlargement in multiple sclerosis. *J Neurol*. 2020;267:192–202.
14. Dalton CM, Brex PA, Jenkins R, et al. Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2002;73:141–147.
15. Hobbs NZ, Barnes J, Frost C, et al. Onset and progression of pathologic atrophy in Huntington disease: a longitudinal MR imaging study. *American J Neuroradiol*. 2010;6:1036–1041.
16. Lewis MM, Smith AB, Stynor M, et al. Asymmetrical lateral ventricular enlargement in Parkinson’s disease. *Eur J Neurol*. 2009;16:475–481.
17. Mak E, Su L, Williams GB, et al. Longitudinal whole-brain atrophy and ventricular enlargement in nondemented Parkinson’s disease. *Neurobiol Aging*. 2017;55:78–80.
18. Racette BA, Esper GJ, Antenor J, et al. Pathophysiology of parkinsonism due to hydrocephalus. *J Neurol Neurosurg Psychiatry*. 2004;75:1617–1619.
19. Apostolova LG, Beyer M, Green AE, et al. Hippocampal, caudate, and ventricular changes in Parkinson’s disease with and without dementia. *J Mov Disord*. 2010;25:687–695.
20. Camicioli R, Sabino J, Gee M, et al. Ventricular dilatation and brain atrophy in patients with Parkinson’s disease with incipient dementia. *J Mov Disord*. 2011;26(8):1443–1450.
21. Conradi CD, Zheng M, van Rootien N, et al. Microglia and a functional type I IFN pathway are required to counter HSV-1-driven brain lateral ventricle enlargement and encephalitis. *J Immunol*. 2013;190(6):2807–2817.
22. Van Ombergen A, Jillings S, Jeurissen B, et al. Brain ventricular volume changes induced by long-duration spaceflight. *Proc Natl Acad Sci U S A*. 2019;116(21):10531–10536.
23. Roberts DR, Truman R DCI, Brown HR, Collins MA, Eckert DA. Longitudinal change in ventricular volume is accelerated
in astronauts undergoing long-duration spaceflight. Aging Brain. 2021;1:1–8.

34. Feng R, Wang H, Wang J, et al. Forebrain degeneration and ventricle enlargement caused by double knockout of Alzheimer’s presenilin-1 and presenilin-2. Proc Natl Acad Sci U S A. 2004;101(21):8162–8167.

35. Olopade FE, Shokunbi MT, Siren AL. The relationship between ventricular dilatation, neuropathological and neurobehavioural changes in hydrocephalic rats. Fluids Barriers CNS. 2012;9(1):19.

36. LeMay M. CT changes in dementing diseases: a review. AJR Am J Roentgenol. 1986;147(5):963–975.

37. Gorman AM. Neuronal cell death in neurodegenerative diseases: recurring themes around protein handling. J Cell Mol Med. 2008;12(6A):2263–2280.

38. Martin LJ. Neuronal cell death in nervous system development, disease, and injury (review). Int J Mol Med. 2001;7(5):455–478.

39. Laskaris LE, Di Biase MA, Everall I, et al. Microglial activation and progressive brain changes in schizophrenia. Br J Pharmacol. 2016;173(4):666–680.

40. Nemati S, Abdallah CG. Increased cortical thickness in patients with major depressive disorder following antidepressant treatment. Chronic Stress (Thousand Oaks). 2020;4:1–6.

41. Alenina N, Kлемpert F. The role of serotonin in adult hippocampal neurogenesis. Behav Brain Res. 2015;277:49–57.

42. Gould E. Serotonin and hippocampal neurogenesis. Neuropsychopharmacology. 1999;21:46–51.

43. Duan W, Peng Q, Masuda N, et al. Sertraline slows disease progression and increases neurogenesis in N171-82Q mouse model of Huntington’s disease. Neurobiol Dis. 2008;30(3):312–322.

44. Garcia-Verdugo JM, Doetsch F, Wichterle H, et al. Architecture of the subventricular zone: in search of the stem cells. J Neurobiol. 1998;36(2):234–248.

45. van Vliet IM, de Beurs E. [The MINI-internation neuropsychiatric interview. A brief structured diagnostic psychiatric interview for DSM-IV en ICD-10 psychiatric disorders]. Tijdschr Psychiatr. 2007;49(6):393–397.

46. Gosnell SN, Meyer MJ, Jennings C, et al. Hippocampal volume in psychiatric diagnoses: should psychiatry biomarker research account for comorbidities? Chronic Stress (Thousand Oaks). 2020;4:247054702096799.

47. Gosnell SN, Oh H, Schmidt J, et al. Right temporal pole volume reduction in PTSD. Prog Neuropsychopharmacol Biol Psychiatry. 2020;100:109890.

48. Gosnell SN, Crooks KE, Robinson M, et al. Subcortical brain morphometry of avoidant personality disorder. J Affect Disord. 2020;274:1057–1061.

49. Gosnell SN, Curtis KN, Velasquez K, et al. Habenular connectivity may predict treatment response in depressed psychiatric inpatients. J Affect Disord. 2019;242:211–219.

50. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613.

51. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–1097.

52. First M, Gibbon M. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). Vol. 2. John Wiley & Sons, Inc. 2004. 134–143.

53. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(3):341–355.

54. Fischl B. FreeSurfer. Neuroimage. 2012;62(2):774–781.

55. W JL, WR C, HC W, et al. Normalization of cerebral volumes by use of intracranial volume: implications for longitudinal quantitative MR imaging. AJNR Am J Neuroradiol. 2001;22:1483–1489.

56. Kempton MJ, Underwood TS, Brunton S, et al. A comprehensive testing protocol for MRI neuroanatomical segmentation techniques: evaluation of a novel lateral ventricle segmentation method. Neuroimage. 2011;58(4):1051–1059.

57. Berger RL, Hsu JC. Bioequivalence trials, intersection-union tests and equivalence confidence sets. 1996;11(4):283–318.

58. Bjorkholm C, Monteggia LM. BDNF - a key transducer of antidepressant effects. Neuropsychopharmacology. 2016;102:72–79.

59. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59(12):1116–1127.

60. Jiang DG, Jin SL, Li GY, et al. Serotonin regulates brain-derived neurotrophic factor expression in select brain regions during acute psychological stress. Neural Regen Res. 2016;11(9):1471–1479.

61. Autry AE, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev. 2012;64(2):238–258.

62. Peng Q, Masuda N, Jiang M, et al. The antidepressant sertraline improves the phenotype, promotes neurogenesis and increases BDNF levels in the R6/2 huntington’s disease mouse model. Exp Neurol. 2008;210(1):154–163.

63. Miranda M, Morici JF, Zanoni MB, et al. Brain-Derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. Front Cell Neurosci. 2019;13:363.

64. Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. Neuropsychopharmacology. 2001;25(6):836–844.

65. Akter M, Kaneko N, Sawamoto K. Neurogenesis and neuronal migration in the postnatal ventricular-subventricular zone: similarities and dissimilarities between rodents and primates. Neurosci Res. 2021;167:64–69.

66. Reed MB, Vanicek T, Seiger R, et al. Neuroplastic effects of a selective serotonin reuptake inhibitor in relearning and retrieval. Neuroimage. 2021;236:118039.

67. Yohn CN, Shifman S, Garino A, et al. Fluoxetine effects on intracellular serotonin levels in plasma and platelets after fluoxetine treatment in depressive patients. J Clin Psychopharmacol. 2002;22(2):131–136.

68. Weikop P, Kehr J, Scheel-Kruger J. The role of alpha1- and alpha2-adrenoceptors on venlafaxine-induced elevation of...
extracellular serotonin, noradrenaline and dopamine levels in the rat prefrontal cortex and hippocampus. *J Psychopharmacol.* 2004;18(3):395–403.

71. Kitaichi Y, Inoue T, Nakagawa S, et al. Sertraline increases extracellular levels not only of serotonin, but also of dopamine in the nucleus accumbens and striatum of rats. *Eur J Pharmacol.* 2010;647(1–3):90–96.

72. Culpepper L. Escitalopram: a new SSRI for the treatment of depression in primary care. *Prim Care Companion J Clin Psychiatry.* 2002;4(6):209–214.

73. Invernizzi R, Velasco C, Bramante M, et al. Effect of 5-HT1A receptor antagonists on citalopram-induced increase in extracellular serotonin in the frontal cortex, striatum and dorsal hippocampus. *Neuropharmacology.* 1997;36(4–5):467–473.

74. Kihara T, Ikeda M. Effects of duloxetine, a new serotonin and norepinephrine uptake inhibitor, on extracellular monoamine levels in rat frontal cortex. *J Pharmacol Exp Ther.* 1995;272(1):177–183.

75. Nakayama K. Effect of paroxetine on extracellular serotonin and dopamine levels in the prefrontal cortex. *Naunyn Schmiedebergs Arch Pharmacol.* 2002;365(2):102–105.

76. D’Agostino A, English CD, Rey JA. Vortioxetine (braintellix): a new serotonergic antidepressant. *P T.* 2015;40(1):36–40.

77. Deecher DC, Beyer CE, Johnston G, et al. Desvenlafaxine succinate: a new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther.* 2006;318(2):657–665.

78. Woelfer M, Li M, Colic L, et al. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J Biol Psychiatry.* 2020;21(9):696–710.

79. Strawn JR, Mills JA, Suresh V, et al. Combining selective serotonin reuptake inhibitors and cognitive behavioral therapy in youth with depression and anxiety. *J Affect Disord.* 2022;298(Pt A):292–300.

80. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med.* 2014;174(3):357–368.