


Hippocampal Volume in Psychiatric Diagnoses: Should Psychiatry Biomarker Research Account for Comorbidities?

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Abstract

Background: Many research papers claim that patients with specific psychiatric disorders (major depressive disorder, posttraumatic stress disorder, borderline personality disorder, alcohol use disorder, and others) have smaller hippocampi, but most of those reports compared patients to healthy controls. We hypothesized that if psychiatrically matched controls (psychiatric control, matched for demographics and psychiatric comorbidities) were used, much of the biomarker literature in psychiatric research would not replicate. We used hippocampus and amygdala volume only as examples, as these are very commonly replicated results in psychiatry biomarker research. We propose that psychiatry biomarker research could benefit from using psychiatric controls, as the use of healthy controls results in data that are not disorder-specific.

Method: Hippocampus/amygdala volumes were compared between major depressive disorder, sex-/age-/race-matched healthy control, and psychiatric control (N = 126/group). Similar comparisons were performed for posttraumatic stress disorder (N = 67), borderline personality disorder (N = 111), and alcohol use disorder (N = 136).

Results: Major depressive disorder patients had smaller left ($p = 8.79 \times 10^{-3}$) and right ($p = 3.13 \times 10^{-3}$) hippocampal volumes than healthy control. Posttraumatic stress disorder had smaller left ($p = 0.018$) and right ($p = 8.64 \times 10^{-4}$) hippocampi than healthy control. Borderline personality disorder had smaller right hippocampus ($p = 7.90 \times 10^{-3}$) and amygdala ($p = 1.49 \times 10^{-3}$) than healthy control. Alcohol use disorder had smaller right hippocampus ($p = 0.034$) and amygdala ($p = .024$) than healthy control. No differences were found between any of the four diagnostic groups and psychiatric control.

Conclusion: When psychiatric controls were used, there was no difference in hippocampal or amygdalar volume between any of the diagnoses studied and controls. This strategy (keeping all possible relevant variables matched between experimental groups) has been used to advance science for hundreds of years, and we propose should also be used in biomarker psychiatry research.

Keywords

brain morphometry, hippocampus volume, psychiatry research, major depressive disorder, alcohol use disorder, borderline personality disorder, posttraumatic stress disorder, amygdala volume, comorbidity

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Introduction

Magnetic resonance imaging (MRI) brain volumetry may be an important approach to discovering biomarkers of mental disorders. Structural alterations in subcortical regions have been demonstrated in many disorders, including major depressive disorder (MDD), posttraumatic stress disorder (PTSD), borderline personality disorder (BPD), and alcohol use disorder (AUD). In MDD, PTSD, BPD, and AUD, the hippocampus and amygdala are commonly studied due to their central role in memory and emotional regulation.^{1–4} Identifying the disease-specific structural

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changes that accompany common psychiatric conditions provides useful insight for understanding pathology and developing targeted therapies.

Reduction of hippocampal volume in MDD is a widely replicated finding⁵ and recently, an Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium study confirmed this on a very large sample.⁶ They evaluated volumetric subcortical data from 20 study sites, comparing 1902 MDD adult patients to 7658 healthy controls (HCs). Interestingly, this study could not replicate previous reports of amygdalar volume reductions when comparing MDD to HC. In fact, the hippocampus was the only subcortical structure they found to be significantly reduced in their MDD sample. Reduced hippocampal volume is also the most commonly reported volumetric finding in PTSD patients compared to HC⁷⁻¹⁹ including in another massive ENIGMA consortium effort.²⁰

The hippocampus and other limbic regions are popularly studied in conjunction with several other psychiatric disorders as well. However, this literature has been somewhat inconsistent. For example in BPD, several studies found significant bilateral volume reductions in the hippocampus compared to HC²¹⁻²⁸ as well as significant bilateral volume reductions in the amygdala.^{22,24-27} However, there have also been several dissenting studies: three found no significant volume reductions in the hippocampus²⁹⁻³¹ and six found no significant reduction in amygdala volumes^{29,30,32-35} in BPD versus HC.

Additionally, several studies have shown subcortical volumetric decreases in AUD. The hippocampus is particularly susceptible to atrophy in both adolescents³⁶ and adults.^{36,37} Similar trends emerge for amygdala gray matter volume.^{4,37-39} While the relationship between structural changes and AUD is well-documented, studies are often confounded by psychiatric comorbidity. Several psychiatric illnesses may act synergistically with AUD to exacerbate reduction in cortical and subcortical brain volumes.⁴⁰ For example, AUD patients with comorbid anxiety have smaller subcortical volumes than those without.⁴¹ This phenomenon is corroborated by a meta-analysis that found less gray matter loss in cases of AUD without comorbidity.⁴² These findings, as well as the reports of hippocampal reductions across psychiatric disorders, suggest these reductions may not be diagnosis-specific. It is possible that volumetric reductions may be the result of some traits many of these patients have in common or that the etiologies are different, but the end result (e.g., reduced hippocampal size) are the same.

Psychiatry research has been severely criticized as the slowest advancing field in medical research. The research domain criteria (RDoC⁴³) has been established to help with this problem by changing psychiatry research from categorical to dimensional and from diagnoses-based to

symptom-based. We propose that using controls matched for all possible known or suspected variables that can affect the measure of interest is also important. Thus, we propose it would be advantageous to use psychiatrically matched controls when studying psychiatric disorders. In clinical investigations, control populations minimize potential confounding effects on a measured outcome. Usually, affected patients are carefully matched to HC across many dimensions (age, sex, etc.) to isolate the effects of a single variable. However, in psychiatric research, patients and controls are generally not matched for comorbid psychiatric illnesses, or more commonly comorbidities are excluded for within the study. Consequently, many studies are not studying ecologically valid samples, as most patients with a psychiatric illness are likely to have another. Also, when comparing to HC, one cannot account for the many heterogeneous features a person with mental illness often has such as specific symptoms, childhood trauma, eating problems, sleep problems, and so on. This problem of using HC is present in the recent ENIGMA study of MDD.⁶ While its large sample size lends validity to the finding of decreased hippocampal volume in MDD, controls were not matched for psychiatric comorbidity. Therefore, volume reduction of the hippocampus may be generalizable across many diagnoses and not correlate with MDD specifically. We propose that this is a common methodological error that should be avoided in psychiatry research, as it may produce misleading results that perpetuate an incomplete understanding of mental illness.

In this study, we investigated volumetric differences previously described in MDD, BPD, PTSD, and AUD. We studied populations of ecologically valid MDD (n = 126), BPD (n = 111), PTSD (n = 67), and AUD (n = 136) patients. To account for the high prevalence of comorbidities, we utilized psychiatric control (PC) groups that were matched for age, gender, and race as well as all comorbid psychiatric disorders. For comparison to previous studies, we also included HC groups matched for age, sex, and race. We compared the average hippocampal and amygdalar volumes of these groups using a standardized imaging analysis method (Freesurfer 6.0, <http://surfer.nmr.mgh.harvard.edu>) with the hypothesis: Hippocampal and amygdalar volume reductions may be observed between MDD, BPD, PTSD, and AUD patients and HC, but this difference will not exist when patients with each diagnosis are compared to controls matched for psychiatric comorbidities.

Methods

Healthy Controls

HC were recruited from the community (N = 141). They had no history or current diagnosis of mental illness as

confirmed by the MINI International Neuropsychiatric Interview and had no contraindications for MRI.⁴⁴ The average age of the HC was 33.0 ± 12.0 years with 57.4% being males (81/141) and 80.9% being Caucasian (114/141).

Psychiatric Patients and Clinical Measures

Psychiatric patients (PPs; $N = 518$) were recruited from the Menninger Clinic in Houston, TX, as a part of the McNair Initiative for Neuroscience Discovery—Menninger/Baylor (MIND-MB) research study.^{45–48} All PPs were eligible if they were mentally stable enough to participate, with no contraindications for MRI. All participants gave signed, informed consent (procedures were approved by the institutional review board). PP had a variety of psychiatric conditions including mood, anxiety, personality, and substance use disorders, with over 80% diagnosed with comorbid psychiatric disorders. They remained at the clinic for several weeks while receiving treatment (medication, psycho-educational groups, 24-h nursing care, individual and group psychotherapy, addictions management, and structured interpersonal and recreational activities). Note that treatment was not relevant to this study. The MIND-MB study collected demographic, clinical, and neuroimaging data. Demographic data relevant to our study (age, gender, and race) and psychiatric

diagnoses from the Structured Clinical Interview for DSM-IV disorders axis I⁴⁹ and II⁵⁰ were collected. We also collected assessments on several psychiatric characteristics including (1) depression (Patient Health Questionnaire module for depression⁵¹ (PHQ-9)), (2) anxiety (generalized anxiety disorder scale⁵² (GAD-7)), (3) emotion regulation (difficulties in emotion regulation scale⁵³), (4) history of trauma (Stressful Life Events Screening Questionnaire⁵⁴), and (5) alcohol/substance use (World Health Organization Alcohol, Substance, and Smoking Involvement Test⁵⁵ (ASSIST)). The PHQ-9 and GAD-7 specifically assess symptoms over the past two weeks and ASSIST assesses use over the past three months. All of these measures represent total scores (higher scores indicate a more severe rating) from respective scales and were obtained near the time of scanning. The average age of PP was 31.0 ± 12.3 years with 56.0% being males (290/518), and 87.3% being Caucasian (452/522; Figure 1).

Matching Control Groups to Patient Groups of Interest

Four patient groups of interest were formed based only on the diagnosis of a specific disorder of interest: MDD (single or recurrent; $N = 126$), BPD ($N = 111$), AUD (alcohol abuse or dependence disorder; $N = 136$), and PTSD ($N = 67$). On average, patients in each of these groups had two other psychiatric disorders in addition

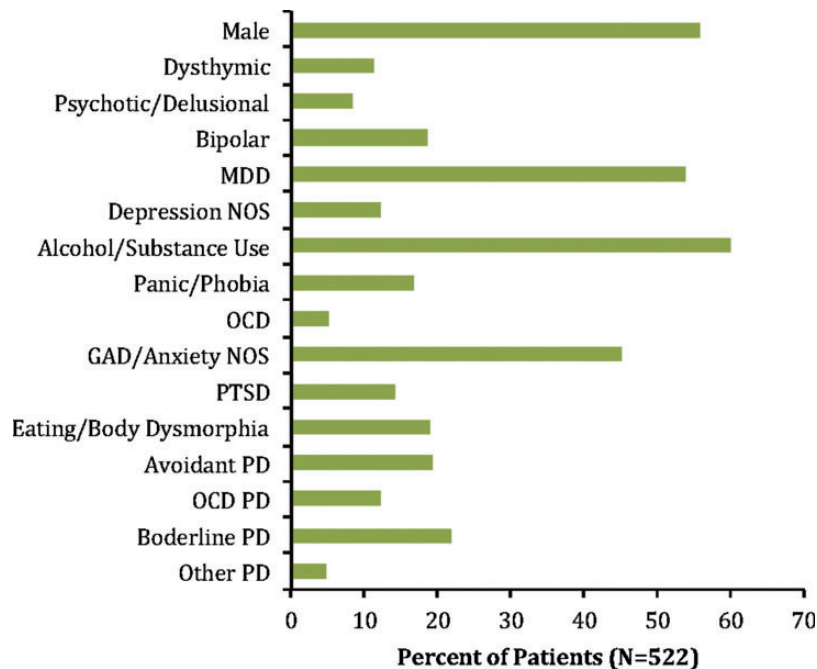


Figure 1. Characteristics of psychiatric patients. Broad categories of psychiatric disorders from the Structured Clinical Interview for the DSM-IV are shown to demonstrate the general prevalence of disorders within or psychiatric sample (note this is just for visualization as groups were matched on all possible psychiatric disorders, not just those shown). GAD: generalized anxiety disorder; MDD: major depressive disorder; NOS: not otherwise specified; OCD: obsessive compulsive disorder; PD: personality disorder; PTSD: posttraumatic stress disorders.

to the diagnosis of interest. Note that some patients in these groups could, therefore, be in more than one group. For each patient group of interest, a HC group of the same size was matched based on demographic characteristics (age, sex, and race). A group of PCs of the same size was also matched for demographic characteristics and all other past and current diagnoses of any psychiatric disorder. Group matching for both HC and PC was performed using a Euclidean distance-matching algorithm. This algorithm matched patients to controls (HC and PC separately) in a one-to-one manner, calculating the Euclidean distance between each pair (in multidimensional space) such that the sum of all paired distances was minimized. The number of dimensions in the algorithm was equal to the number of features desired to match for. Features used in distance matching were demographic characteristics when matching to HC and demographic characteristics plus psychiatric diagnoses (past and current) when matching to PC. Prior to placing the features in the algorithm, they were normalized using z -scores (there was no missing data). All matching was coded in Python (version 3); code is available upon request to authors. Following matching, we analyzed between group differences on all features using t tests for age and chi-squared tests for all other variables to ensure the groups were not significantly different for any feature ($p > 0.05$, no multiple comparisons corrections). Any feature that was still significantly different between groups was controlled for during statistical analysis. The end result was 12 total groups (with some participants in more than one group) because each of 4 groups of interest had a matching HC group and a matching PC group. For each group of interest, HC, and PC, the Euclidean distance-matching algorithm produces samples that do not significantly differ in any feature (each feature being either a demographic characteristic or a diagnosis). There was one exception to this (depression not otherwise specified (Depress)) which was dealt with by using a covariate.

Neuroimaging Acquisition and Analysis

Participants were scanned in a 3T Siemens Trio MR scanner in the Center for Advanced Magnetic Resonance Imaging at the Baylor College of Medicine in Houston, TX, as close to admission to the clinic as possible. A ~ 4.5 -min structural MPRAGE sequence (echo time = 2.66 ms, repetition time = 1200 ms, flip angle = 12° , 256×256 matrix, 160 one mm axial slices at $1 \times 1 \times 1$ mm voxels) was collected. FreeSurfer version 6.0 (<http://surfer.nmr.mgh.harvard.edu>) was used to perform all preprocessing and automated volumetric segmentation using the T1-weighted structural images. FreeSurfer segments regions of interest (ROIs) with probabilistic brain mapping based on the Aseg atlas.⁵⁶

The Aseg atlas was used to obtain bilateral amygdalar and hippocampal ROIs as well as total intracranial volume (ICV). We controlled for ICV by dividing each patient's individual ROI volume (mm^3) by his or her total ICV.

Statistics

Student's t tests were used to compare groups of interest to HC and to PC on volumetric measures of the right and left hippocampus and amygdala. Volumetric measures were also compared in the same fashion for HC and PC. The exception to this was when comparing MDD to PC because they were statistically different for a diagnosis of depression not otherwise specified (Depress), so an analysis of covariance (ANCOVA) was used with Depress as the covariate. Since we had a strong a priori hypothesis of lower hippocampal and amygdalar volumes between groups of interest and HC, no multiple comparisons were made to account for comparisons across these four ROIs.

Additional correlations (Pearson's) were explored between hippocampal and amygdalar volumes in PPs (groups of interest and each PC group) for the other five clinical measures listed above (depression, anxiety, emotion regulation, history of trauma, and alcohol/substance use) to investigate the effects of these common psychiatric characteristics. Partial correlations were performed to control for age and sex. Volumes were divided by ICV prior to statistical analysis. We also investigated these correlations across our entire PP population. All statistical analyses were performed in SPSS (SPSS, Inc., Chicago, IL). We consider these correlations an exploratory analysis, as no multiple comparison corrections were performed.

Results

Group Matching

Each group of interest was matched to HC such that they were not significantly different for any demographic characteristic. The group of interest was matched to PCs such that they were not significantly different for any demographic characteristic or psychiatric diagnosis (past or current). The only group that had any characteristic that was significantly different between matched groups was MDD versus their matched PC group. These groups were significantly different for a diagnosis of depression not otherwise specified (Depress: $\chi^2 = 65.31$; $p = 6.41 \times 10^{-16}$; PC: 56/126; MDD: 2/126).

They were also significantly different for current mood alcohol disorder ($\chi^2 = 4.07$; $p = 0.044$; PC: 4/126; MDD: 0/126).

Group Comparisons for Hippocampal and Amygdalar Volumes

Figure 2 shows results from *t* tests between groups. eTable 1 gives the full statistical results in more detail. Note that MDD versus PC used *Depress* as a covariate in an ANCOVA. Current mood alcohol disorder was not included as a covariate because there were only 4 of 126 individuals with the diagnosis, and we did not believe there was enough power to affect the result. The effect of *Depress* is shown in eFigure 1. There was a significant effect of *Depress* for the left hippocampus. However, the individuals with *Depress* had higher volume averages for the left hippocampus, indicating that the lower volume found in MDD and PC groups was not due to the diagnosis of *Depress*. Note the higher volumes in *Depress* patients were not due to age. Importantly, no significant differences were found between PC and group of interest.

Correlations Between Psychiatric Traits and Volumes

Because there were no meaningful differences in volume between PC and groups of interest and both groups seemed to be generally lower than HC, we investigated whether these differences were due to some common psychiatric traits we had measures for (full results shown in eTables 2 to 5). Exploratory correlations showed only two nominally significant correlations between groups of interest and volumes: right amygdala/anxiety in BPD and right hippocampus/depression in PTSD (Figure 3). One correlation was also shown for PC group (controlling for BPD) between the right hippocampus and depression ($r = 0.192$, $p = 0.042$). To investigate correlations between PC, we performed the same correlations but for all PPs (full results shown in eTable 6). Significant negative correlations were found for the amygdala and depression/anxiety scores (Figure 4). Note these findings are preliminary, as they would not survive multiple comparisons corrections.

Discussion

One reason we studied hippocampal size is that the available data are extremely robust, and it is not our intention to try to “refute” previous findings. However, we showed that when compared to PC matched for not only sex, age, and race but also psychiatric comorbidities, there is no difference in hippocampal volume between groups of interest (MDD, PTSD, BPD, and AUD) and controls. This should not be too surprising since the PC control groups are expected to have several patients with psychiatric diagnoses known to have smaller hippocampi than HC. The take-home message from our work is that we cannot say, for example, “MDD patients have

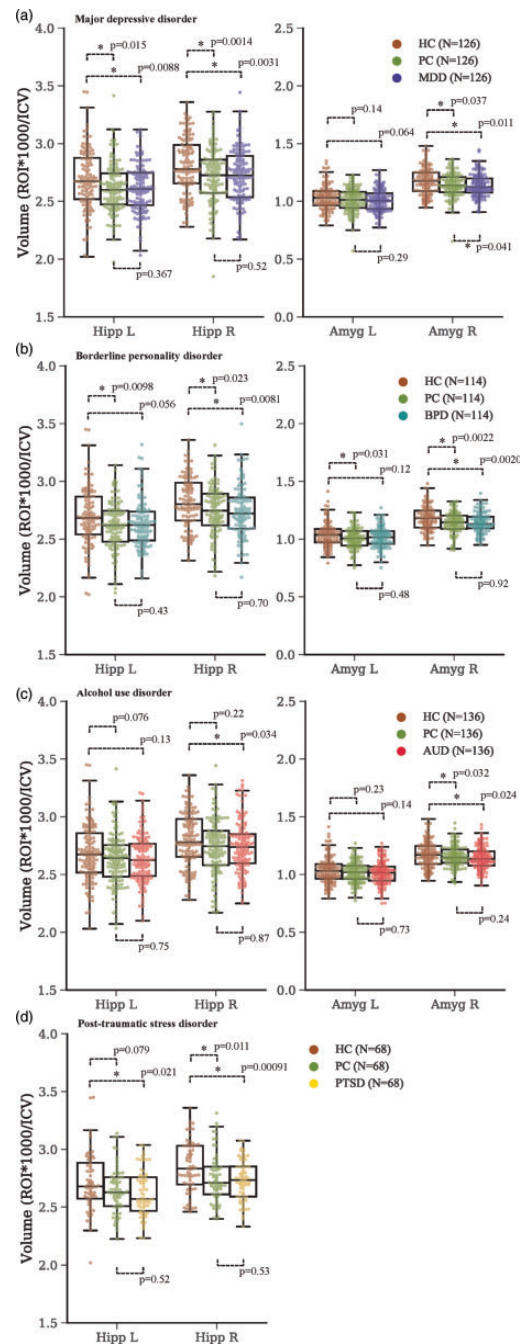


Figure 2. Hippocampal and amygdalar volumes for all groups. (a) Major depressive disorder; (b) Borderline personality disorder; (c) Alcohol use disorder and (d) Post-traumatic stress disorder. Boxplots show median value as horizontal line within boxes, the top line of the boxes is the upper quartile (75% of the data lies below this line), the bottom line of the boxes is the lower quartile (25% of the data lies below this line), whiskers represent the rest of the range of the data that is outside the interquartile. Points that are outside the whiskers are considered outliers. All data points are shown jittered within the boxplots. * $p < 0.05$. Amyg: amygdala; AUD: alcohol use disorder; BPD: borderline personality disorder; HC: healthy control; Hipp: hippocampus; ICV: total intracranial volume; L: left; MDD: major depressive disorder; PC: psychiatric control; PTSD: posttraumatic stress disorder; R: right; ROI: region of interest.

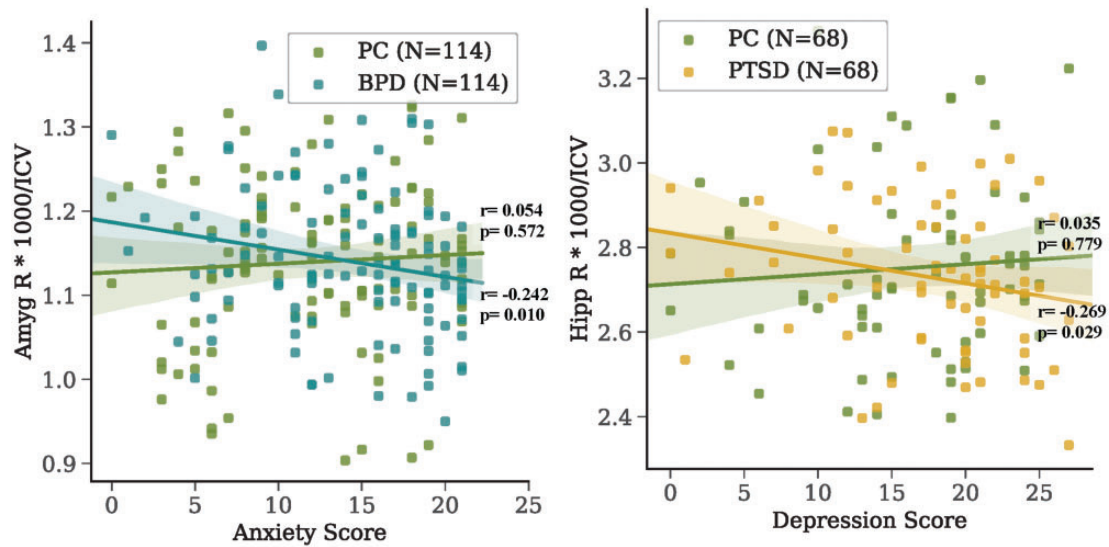


Figure 3. Correlations between psychiatric traits and volumes within each patient group. Pearson correlation r and p values are shown for each line of best fit ($p < 0.05$, no multiple corrections). Volumes were divided by ICV and scaled by 1000. Amyg: amygdala; BPD: borderline personality disorder; Hipp: hippocampus; ICV: total intracranial volume; PC: psychiatric control; PTSD: posttraumatic stress disorder; R: right.

smaller hippocampi than controls” without possible incurring in a flaw: Such statement is only true if the controls are not matched for psychiatric comorbidities.

Psychiatry has arguably been the slowest growing branch of medicine for a long time. For example, while most causes of death tend to decrease over time, death by suicide rates have stayed steady or even increased.⁵⁷ There are many reasons why this may be the case, and the National Institute of Mental Health has established the RDoC⁴³ as a general strategy to try to help solve these problems. The RDoC approach is based on symptoms instead of diagnoses and on dimensional instead of categorical approaches. We propose an additional approach that we believe has the potential to help accelerate psychiatry research using controls matched not only for demographics but for comorbidities (or alternatively, psychiatric symptoms).

Studies in psychiatry research use several approaches for comparing populations. One is to carefully recruit patients suffering from a specific illness (we can use MDD as an example), but that are not comorbid with any other psychiatric illness (e.g., recruiting MDD patients with no anxiety, personality, or substance use disorders). One problem arising from such approach is that the studied samples are unlikely to be ecologically valid, and psychiatrists are unlikely to see such “clean” patients in the clinic. A second problem from that approach is that perhaps there are features shared among different psychiatric diagnoses (or symptoms) such that MDD patients may have, for example, smaller hippocampi, but also do other PPs that are not depressed. Another approach is to compare patients

with MDD to HC. In this case, the MDD sample may be representative, but any conclusions may be the result of variables other than MDD. This approach is still widely used and in our view causes enormous confusion in the field. A better approach that is also used is to compare patients with one condition (such as MDD) to patients with another condition (such as bipolar disorder), or to compare, for example, suicidal patients to nonsuicidal patients that are equally depressed. However, these can still be confounded by comorbidities.

There is a widely accepted scientific tenet that states: When comparing two groups for a variable of interest, keep all other possible relevant variables matched between the two groups. Psychiatry research has not commonly followed such a tenet, resulting in confusing conclusions that, we believe, are one of the many reasons why psychiatry research advances slower than other medical fields. Thus, we strive to compare groups in which one variable of interest is different between both groups while keeping all other possibly relevant variables not significantly different between groups (or at least statistically accounted for).

We have shown that when all psychiatric comorbidities are accounted for, neither MDD nor BPD, PTSD, or AUD show decreased hippocampal size. However, when the psychiatric illness groups were compared to HC, we did find smaller hippocampal volume as expected from the vast literature available. In our view, given our results, it is perhaps incorrect to state that MDD is associated with decreased hippocampal volume: No one in other scientific fields would accept such a conclusion if the observed difference disappears

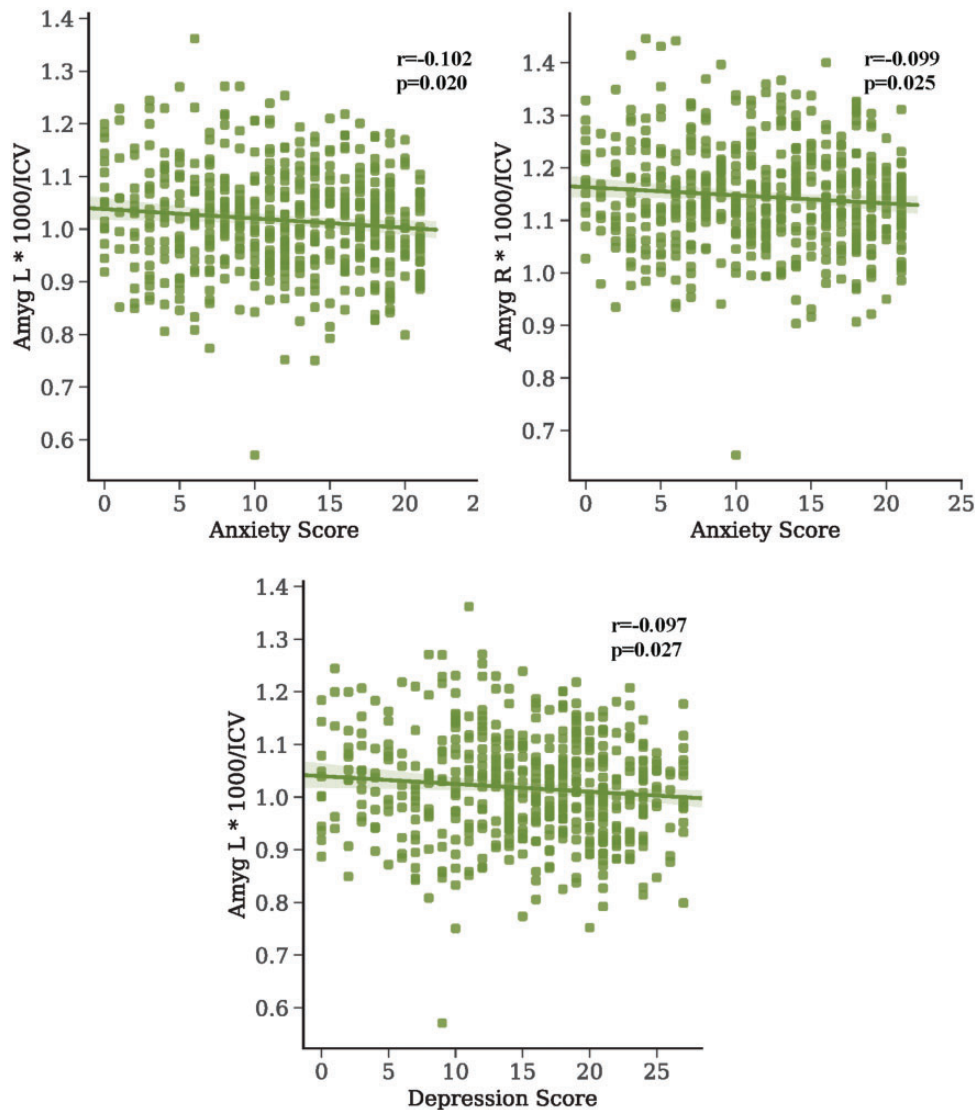


Figure 4. Correlations between psychiatric traits and volumes across psychiatric patients. Correlations between psychiatric traits and volumes were performed for all psychiatric patients ($N = 518$). Pearson correlation r and p values are shown for each line of best fit ($p < 0.05$, no multiple corrections). Volumes were divided by ICV and scaled by 1000. Amyg: amygdala; ICV: total intracranial volume; L: left; R: right.

when relevant variables are matched between groups. No one would say “MDD patients are shorter than controls”: We know males are in average taller than females and significantly less likely to be MDD patients, so the statement may somehow be true but probably meaningless. We think the statement “MDD patients have smaller hippocampi than controls” is similarly flawed even if data are clearly very strong, as we have shown that to find that result one must use a control group not matched for variables known (e.g., PTSD) or hypothesized (e.g., being a PP) to be important.

Two limitations must be noted. First, we used hippocampal size in MDD (one of the most replicated results in psychiatry biomarker research) just as an obvious

example of what we believe is a widespread problem in psychiatry biomarker research. However, the generalizability of our results is unknown, and this will need additional studies. In that sense, we propose that it would be safer to match groups as we did, but it is possible that other biomarkers are less sensitive to choice of controls. Second, although we believe that matching using diagnoses is far superior to comparison with HC, we believe that it would likely be even better to match groups using dimensional symptoms instead of diagnoses.

Thus, we postulate that future studies could use psychiatrically matched controls (for diagnoses as we did in this report, or probably better, for dimensional symptoms) to be more relevant.

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Supplemental Material

Supplemental material for this article is available online.

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