Archival Report

Underlying Hippocampal Mechanism of Posttraumatic Stress Disorder Treatment Outcome: Evidence From Two Clinical Trials

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ABSTRACT

BACKGROUND: The hippocampus plays an important role in the pathophysiology of posttraumatic stress disorder (PTSD) and its prognosis. Accumulating findings suggest that individuals with larger pretreatment hippocampal volume are more likely to benefit from PTSD treatment, but the mechanism underlying this effect is unknown. We investigated whether further increase in hippocampal volume during treatment explains the better prognosis of individuals with greater pretreatment hippocampal volume.

METHODS: We collected structural magnetic resonance imagesfrom patients with PTSD before and after treatment. We examined whether larger hippocampal volume moderates the effect of increased hippocampal volume during treatment on symptom reduction. Given the relatively small sample sizes of treatment studies with pre- and post-treatment magnetic resonance imaging, we focused on effect sizes and sought to replicate findings in an external sample. We tested our hypothesis in study 1 ($N = 38$; prolonged exposure therapy) and then tested whether the results could be externally replicated in study 2 ($N = 20$; ketamine infusion followed by exposure therapy).

RESULTS: Findings from study 1 revealed that increased right hippocampal volume during treatment was associated with greater PTSD symptom reduction only in patients with greater pretreatment right hippocampal volume ($p = .03$; $\eta^2 = 0.13$, a large effect). Findings were partially replicated in study 2 for depressive symptoms ($p = .034$; $\eta^2 = 0.25$, a very large effect) and for PTSD symptoms ($p = .15$; $\eta^2 = 0.15$, a large effect).

CONCLUSIONS: Elucidating increased hippocampal volume as one of the neural mechanisms predictive of therapeutic outcome for individuals with larger pretreatment hippocampal volume may help identify clinical targets for this subgroup.

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Posttraumatic stress disorder (PTSD) is associated with individual suffering and high societal costs ([1]), and treatments for PTSD, such as prolonged exposure therapy (PE), are effective only for some ([2,3]). Empirical findings suggest that individuals with high pretreatment hippocampal volume are more likely to benefit from treatment ([4]), but the mechanisms underlying this effect remain to be discovered.

Hippocampal volume in PTSD has been the focus of much research because of the central role it plays in regulating stress hormones and responses through the hypothalamic-pituitary-adrenal axis ([5]), as well as its role in the retrieval of episodic memory, particularly autobiographical memory ([6]). PTSD is characterized by volume reduction in the hippocampus, with greater PTSD symptom severity being associated with lower hippocampal volume ([7–10]). A large-scale study conducted by the ENIGMA (Enhancing Neuroimaging Genetics through Meta Analysis) consortium suggested that of all 8 subcortical structures examined (the nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, and lateral ventricle), the most robust difference between individuals with PTSD and trauma-exposed healthy control subjects (TEHCs) was hippocampal volume, with individuals with PTSD showing significantly lower hippocampal volume than TEHCs ([11]). Further analyses of the ENIGMA dataset also identified aberrations in interhemispheric structural connectivity ([12]). These findings are consistent with the neurobiological model of PTSD according to which the hippocampus subserves extinction memory recall and context-encoding during a traumatic event, and it is therefore likely to play an important role in context differentiation between cues that signal safety and those that signal threat ([13–15]).

Studies of PTSD treatment have supported the putative role the hippocampus plays in PTSD and have suggested that individuals with larger hippocampal volume are more likely to benefit from treatment ([16]). Treatment studies further suggest that smaller hippocampal volume may be specifically related to the persistence of chronic PTSD after treatment ([4,17]). Furthermore, research has shown that patients who recovered from PTSD were not characterized by smaller hippocampal volume ([4,17–19]). Although the accumulating findings suggest

that larger hippocampal volume may be key to successful treatment, the neural mechanism underlying this effect, namely which neural alterations occur during treatment in individuals with larger pretreatment hippocampal volume, is not clear.

In the current investigation, we hypothesized that the mechanism underlying the greater response to PTSD treatment of individuals with larger pretreatment hippocampal volume is an additional increase in hippocampal volume during treatment. This hypothesis is based on theories arguing for the benefit of capitalizing on strengths—the "rich get richer" phenomenon (20): individuals with already larger pretreatment hippocampal volume may benefit most from leveraging this strength, gaining further increase in hippocampal volume during treatment and therefore showing better treatment outcomes. The underlying mechanism may be extinction learning, which is key to successful PTSD treatment (21). For extinction learning to take place during treatment, patients should be engaged in recall of traumatic memories (22) via brain regions involved in autobiographical memory. During the process of extinction recall, new learning is attained, which can be translated into therapeutic gains, potentially reversing the adverse effect of PTSD on hippocampal volume. Accumulated findings suggest that an increase in hippocampal volume may be associated, at least for some patients, with greater treatment efficacy. Significant posttreatment volume increases have been reported in the bilateral hippocampus (23) and in the left parahippocampal gyrus (24). A positive correlation between symptom improvement and total hippocampal volume has also been documented (23). However, the findings are mixed (25), and other studies have failed to replicate the correlation between treatment success and changes in hippocampal volume (17).

As argued by Manthey *et al.* (25), given the mixed findings in the literature, there is no robust evidence, to date, of therapy-induced changes in the hippocampus at the group level, and much heterogeneity may exist between patients. Given the better prognosis of individuals with larger hippocampal volume pretreatment as well as the beneficial effect of increased hippocampal volume during treatment for a subset of patients, we hypothesized that only individuals with already larger pretreatment hippocampal volume are able to benefit from further increased hippocampal volume during treatment to achieve symptom reduction. The current study tested this hypothesis. We investigated whether a further increase in hippocampal volume during treatment is the mechanism underlying the

better prognosis of individuals with larger pretreatment hippocampal volume (Figure 1). Given the replication crisis and concerns about potential validity (26,27), especially in small treatment samples with repeated magnetic resonance imaging (MRI) scans, we resorted to an external validation design. Specifically, we tested our hypothesis on one sample in which PE was administered and then tested its potential replication in an independent sample in which both PE and ketamine were administered. The two treatment samples differ in treatment, methodology, and sample characteristics, representing a rigorous test of the validity and generalizability of the findings. We focused on both PTSD and depressive symptoms because of their centrality in PE (28) and ketamine (29–31) treatments, respectively.

METHODS AND MATERIALS

Samples

Study 1. Individuals with PTSD and TEHCs matched on sex, age at exposure to trauma, trauma type (interpersonal vs. noninterpersonal) and duration, race, and ethnicity were recruited through advertisements and fliers. All participants met DSM-IV (32) PTSD criterion A1 for adult traumatic events, including vehicular accidents, sexual or physical assaults, and witnessing serious injuries or deaths. Medical history, review of systems, physical examination, and laboratory tests determined the health status of all participants.

Individuals with PTSD were included in the study only following clinician diagnosis of PTSD and a Clinician-Administered PTSD Scale (CAPS) (33) score ≥50. Full inclusion and exclusion criteria for individuals with PTSD appear in Table S1. TEHC exclusion criteria were any current or past Axis I disorder and a CAPS score >19, which is considered symptomatic (33). The New York State Psychiatric Institute Institutional Review Board approved all procedures, and all participants provided written informed consent for the trial, which was registered at clinicaltrials.gov (identifier NCT01576510). Eighty-five participants consented. A total of 43 individuals did not drop out and had both pre- and posttreatment MRI scans (24 of them receiving treatment) and were therefore included in the analyses. To enlarge variability in hippocampal volume pretreatment and in changes in hippocampal volume during treatment, we used the data of both individuals with PTSD receiving PE and of TEHC individuals not receiving treatment. Thus, the TEHCs served as a control
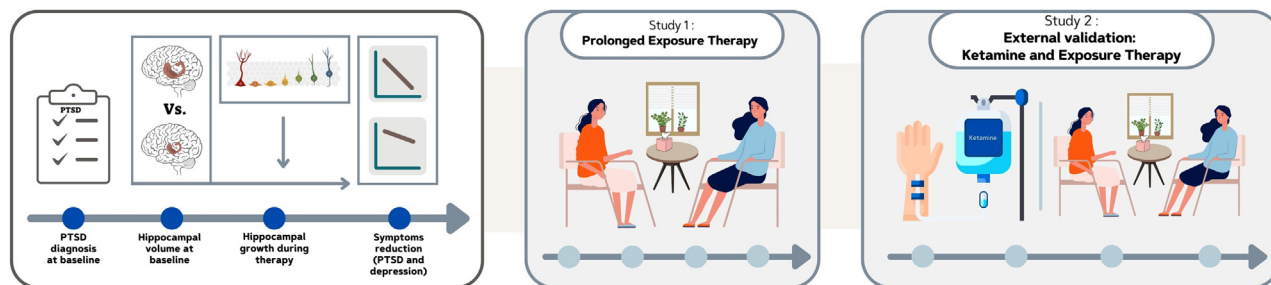

Figure 1. (Left) The proposed conceptual model according to which an increase in hippocampal volume during treatment explains the better prognosis of individuals with greater pretreatment hippocampal volume. (Middle) Study 1 (prolonged exposure therapy). (Right) Study 2 (ketamine and exposure therapy). PTSD, posttraumatic stress disorder.

to expand heterogeneity in hippocampal volume variance, enabling the capture of potential associations if they indeed exist. The sample for study 1 overlaps with the sample of Rubin *et al.* (4).

Study 2. Individuals with PTSD were recruited to participate in the study. PTSD diagnosis was established using CAPS-5 (34). Patients were excluded for acute medical illness based on medical history, physical examination, and screening laboratory test values. Possible cardiac issues were screened using electrocardiogram. The Yale University School of Medicine Institutional Review Board approved all procedures, and all participants provided written informed consent for the trial, which was registered at clinicaltrials.gov (identifier NCT02727998).

Twenty-eight individuals with PTSD consented. A total of 20 individuals (11 receiving ketamine, 9 receiving midazolam) did not drop out and had both pre- and posttreatment MRI scans and were therefore included in the analyses.

Treatments

Study 1. Individuals with PTSD started treatment with one of the two trained therapists who adhered to the standard 10-week PE protocol (35). According to the protocol, patients are required to 1) repeatedly recount the traumatic experience by describing the event in detail in the present tense with guidance from the therapist (imaginal exposure) and 2) identify and confront a range of previously avoided trauma reminders, such as specific stimuli and situations, to extinguish fear responses (in vivo exposure). Before the start of the study, therapists treated 2 pilot cases under supervision to confirm their expertise. In the course of the study, they were continuously monitored and supervised by PE experts for adherence and competence. The independent assessors used the PE integrity measure (36) to rate audiotaped sessions. For a detailed description of the design and procedure, see Rubin *et al.* (4).

Study 2. While the trauma memory was reactivated into a labile state, infusion with either ketamine, a noncompetitive NMDA receptor antagonist (0.5 mg/kg), or benzodiazepine midazolam, a positive allosteric modulator of GABA$_A$ (gamma-aminobutyric acid A) receptors (0.045 mg/kg), was administered inside the MRI scanner for 40 minutes. Twenty-four hours postinfusion, participants began daily exposure-based therapy (34) that included imaginal and in vivo exposure. The PE protocol was administered by one of the two trained therapists and was identical in its goals and therapeutic techniques to that used in study 1, but with differences in the time frame. The complete study procedure, including imaging sessions, lasted 7 days. For a detailed description of the design and procedure, see Duek *et al.* (36).

Measures

Study 1. We used CAPS-4 to assess PTSD symptoms and the Beck Depression Inventory (BDI) to assess depressive symptoms, pre- and posttreatment.

Study 2. We used the PTSD Checklist for DSM-5 (PCL-5) (37) to assess PTSD symptoms and BDI to assess depressive symptoms, pre- and posttreatment. Given that treatments lasted for 7 days, we used the 1-month posttreatment assessment of outcome in all analyses.

MRI Data Acquisition. See the Supplement.

Overview of Statistical Analyses

To test the study hypothesis, we examined whether larger hippocampal volume moderates the effect of increased hippocampal volume during treatment on symptom reduction such that increased hippocampal volume during treatment is associated with greater symptom reduction only for individuals with larger pretreatment hippocampal volume. We focused on the interaction between the baseline level of hippocampal volume and changes in hippocampal volume over the course of treatment in predicting outcome. Such an interaction between the baseline value of a given variable and changes in that variable during treatment was designed to identify the process of change in treatment associated with the best outcomes for individuals holding a given pretreatment characteristic (38,39).

Previous findings on hippocampal volume were bilateral (23) or evident in either the left or right hippocampus (24); therefore, we conducted separate analyses for right and left hippocampal volume. We conducted a set of linear regressions to adjust pre- and posttreatment left and right hippocampal volume for the relevant estimated intracranial volume. Positive values of adjusted features mean higher scores than what can be anticipated based on estimated intracranial volume. We then used the residual scores in two multiple regression analyses; the first tested the interaction between pretreatment and changes (from pre- to posttreatment) in left hippocampal volume in predicting pre- to posttreatment symptom changes, accounting for all main effects, and the second repeated the analysis focusing on the right hippocampus.

Given the small sample sizes, we focused on effect sizes, with η^2 of 0.01 meaning a small effect size, 0.06 a medium effect size, and 0.14 a large effect size (40). We first tested the study hypothesis on the sample of study 1. If confirmed (namely, showing medium-to-large effect sizes), we tested the validity of the findings externally, based on the sample of study 2.

RESULTS

The pretreatment demographics and clinical characteristics of the 2 samples appear in Table S2.

Study 1

The interaction between pretreatment right hippocampal volume and changes in right hippocampal volume during treatment showed a large effect size in predicting treatment outcome as measured by CAPS (B = −0.006, SE = 0.02, t = −0.35, p = .03; η^2 = 0.13) and a medium effect size in predicting treatment outcome using BDI (B = −0.00002, SE = 0.00002, t = −1.41, p = .16; η^2 = 0.06). Simple slope analysis of the CAPS scores suggested that for those with large right hippocampal volume, there was a significant association

between increased right hippocampal volume and greater reduction in PTSD symptoms (B = −0.05, SE = 0.05, t = −1.0, p = .04). By contrast, for those with low right hippocampal volume, there was no significant association between increased right hippocampal volume and less reduction in PTSD symptoms (B = 0.04, SE = 0.03, t = 1.33, p = .19). As shown in Figure 2, an increase in right hippocampal volume during treatment was associated with greater PTSD symptom reduction for those with greater pretreatment right hippocampal volume.

The interaction between pretreatment left hippocampal volume and changes in left hippocampal volume during treatment showed only a low-to-medium effect size in predicting treatment outcome as measured by CAPS (B = −0.00002, SE = 0.00002, t = −0.72, p = .19; η^2 = 0.05) and BDI (B = −0.00006, SE = 0.00004, t = −1.31, p = .48; η^2 = 0.01).

Study 2

The interaction between pretreatment right hippocampal volume and changes in right hippocampal volume during treatment showed a very large effect size in predicting treatment outcome as measured by BDI (B = −0.003, SE = 0.001, t = −2.31, p = .034; η^2 = 0.25) and a large effect size as measured by PCL-5 (B = −0.002, SE = 0.001, t = −1.50, p = .15; η^2 = 0.15). Simple slope analysis of the BDI scores suggested that for those with large right hippocampal volume, there was a significant association between increased right hippocampal volume and greater reduction in depressive
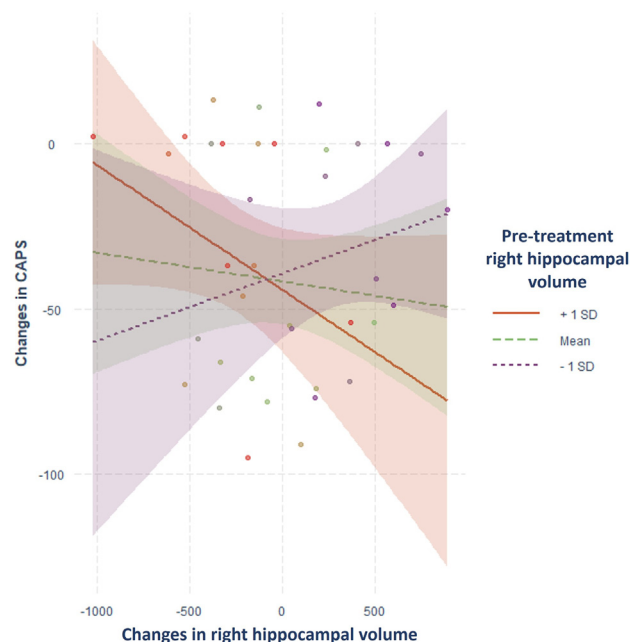

Figure 2. The interaction between pretreatment right hippocampal volume and changes in its volume in predicting Clinician-Administered PTSD Scale (CAPS) changes in study 1. Note. Low vs. high pretreatment hippocampal volume refers to 1 standard deviation (SD) above and below the mean, respectively. This categorization is for visualization only, and hippocampal volume was used as a continuous variable in all analyses.

symptoms (B = −0.57, SE = 0.25, t = −2.24, p = .04). By contrast, for those with low right hippocampal volume, there was no significant association between increased right hippocampal volume and less reduction in depressive symptoms (B = 0.04, SE = 0.21, t = 1.70, p = .11). As shown in Figure 3, an increase in right hippocampal volume during treatment was associated with greater depressive symptom reduction for those with greater pretreatment right hippocampal volume.

The interaction between pretreatment left hippocampal volume and changes in left hippocampal volume during treatment did not predict treatment outcome, using either PCL-5 (B = 0.0003, SE = 0.0004, t = 0.67, p = .51; η^2 = 0.03) or BDI (B = 0.0001, SE = 0.0003, t = 0.29, p = .77; η^2 = 0.005).

Sensitivity Analyses

Given that the findings in study 2 replicated those of study 1 mainly for depressive symptoms and less for PTSD symptoms, and because of potential differences between CAPS and PCL-5 (41) in evaluating re-experiencing, which is a core characteristic of PTSD psychopathology and a main mechanism underlying PE effects, we tested whether the re-experiencing subscale of PCL-5 would yield larger effects. Findings revealed that the interactions for the right and left hippocampus were not significant (B = −0.0007, SE = 0.0005, t = −1.43, p = .17; η^2 = 0.11) and moderately significant (B = −0.0001, SE = 0.000006, t = −1.83, p = .08; η^2 = 0.17, a large effect size), respectively.

We also tested whether findings were replicated when controlling for age and sex. For study 1, the effect size of the relevant interaction remained similar (B = −0.00008, SE = 0.00003, t = −2.43, p = .02; η^2 = 0.15, a large effect size). For study 2, the effect sizes of the relevant interaction remained relatively similar for both PCL-5 (B = −0.001, SE = 0.002, t = −0.85, p = .41; η^2 = 0.05, a medium effect size) and BDI (B = −0.002, SE = 0.002, t = −1.77, p = .09; η^2 = 0.16, a very large effect size).

Reanalyzing the data from study 2 separately for the ketamine (n = 11) and midazolam (n = 9) conditions revealed a significant effect for ketamine. The findings for ketamine suggest that the interaction between pretreatment right hippocampal volume and changes in right hippocampal volume during treatment showed a very large effect size in predicting treatment outcome as measured by BDI (B = −0.004, SE = 0.001; t = −2.75; p = .002; η^2 = 0.52). By contrast, the findings for midazolam (n = 9) yielded a nonsignificant interaction (B = −0.0008, SE = 0.001; t = −0.58; p = .58; η^2 = 0.06). A simple slope analysis of the BDI for ketamine suggested that for those with large right hippocampal volume, there was a significant association between increased right hippocampal volume and greater reduction in depressive symptoms (B = −0.61, SE = 0.20, t = −3.02, p = .02), whereas for those with low right hippocampal volume, there was an insignificant association between increased right hippocampal volume and less reduction in depressive symptoms (B = 0.19, SE = 0.17, t = 1.07, p = .32).

DISCUSSION

The findings suggest that one possible mechanism underlying the ability of individuals with greater pretreatment right
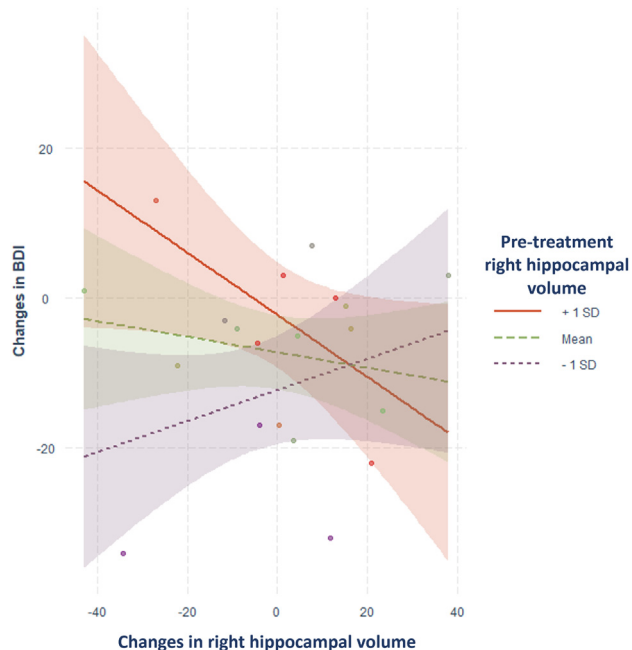
Figure 3. The interaction between pretreatment right hippocampal volume and changes in its volume in predicting Beck Depression Inventory (BDI) changes in study 2. Note. Low vs. high pretreatment hippocampal volume refers to 1 standard deviation (SD) above and below the mean, respectively. This categorization is for visualization only, and hippocampal volume was used as a continuous variable in all analyses. The differences in the changes from pre- to posttreatment within each study (Figure 2 vs. Figure 3) may be because of the specific pipeline used. For example, study 2 used a longitudinal protocol whereas study 1 did not.

hippocampal volume to show better prognosis is increased hippocampal volume during treatment. The findings of study 1 indicated that an increase in the right hippocampal volume during treatment was significantly and meaningfully associated with greater PTSD and depressive symptom reduction only for patients with greater pretreatment right hippocampal volume. The findings for both depressive symptom reduction and reduced PTSD symptoms were partially replicated in a separate external sample. Based on the findings, it can be suggested that for individuals with a relatively larger hippocampus, successful treatment for PTSD may compensate for PTSD-related neural aberrations, potentially enabling better extinction of memory recall and facilitating context differentiation. The replication of the findings in an external sample that received a different treatment composition is an important strength of the current work.

The hippocampus is considered to play an important role in PTSD pathophysiology and treatment through its involvement in memory functions (42,43) and fear-related learning processes (44,45). The findings suggest that over the course of treatment, hippocampal volume may increase through neurogenesis or show greater density, which can potentially lead to greater functional connectivity to other brain areas (46,47). This process may point to the potential of hippocampal plasticity in humans, which may have some similarities with hippocampal neurogenesis

processes that have been documented in mice (48–50). Therefore, critical aspects of impaired hippocampal function associated with PTSD may potentially be reversed as a result of successful treatment, particularly for individuals with large pretreatment hippocampal volume. This may also explain how effective treatment for PTSD produces the therapeutic response by causing new cell growth in an area of the brain known to suffer cell death and atrophy as a result of trauma. Future studies should examine whether the larger hippocampal volume may result in less activation of the amygdala during the process of reconsolidation of the traumatic memory.

Both study 1 and study 2 included exposure to trauma as part of the treatment; therefore, it is not possible to determine whether the mechanism underpinning the good prognosis for patients with larger hippocampal volume is common across other types of effective treatments for PTSD or a characteristic of exposure treatment only. One possibility is that the documented neural changes in the hippocampus in individuals with large pretreatment hippocampal volume are central to any process of recovery from PTSD. Such a conclusion is consistent with previous findings suggesting that changes were observed in the activation of brain regions considered implicated in PTSD (such as the medial prefrontal cortex, rostral anterior cingulate cortex, and amygdala) following various forms of treatment (e.g., imaginal exposure and cognitive restructuring therapy, exposure and cognitive restructuring therapy, PE and virtual reality exposure therapy, group mindfulness-based exposure therapy, and individual and group cognitive behavioral therapy) (25). Alternatively, because both treatments in the current study contained an exposure component, the observed brain alterations may be conceptualized as neural correlates of extinction learning (51,52). Future studies testing whether the current findings can be replicated with nonexposure treatment are needed to determine which of the two alternative conclusions is valid.

It is not entirely clear why the CAPS findings of study 1 were replicated in study 2 mainly for depressive symptoms. The many differences between the studies may account for the slightly different results: the different characteristics of the patient populations (including different inclusion and exclusion criteria, demographic differences), differences in treatment duration, and differences in the type of treatments provided. For example, regarding the treatment provided, the original findings of the study 2 suggest greater sensitivity to changes during treatment of depression than during treatment of PTSD symptoms (36), possibly because half of the patients in study 2 received ketamine. Accumulating findings support the potential therapeutic role of ketamine in reducing depressive symptoms (29–31) through mechanisms such as the enhancement of synaptic plasticity (30). This post hoc explanation receives support from the large effects that appeared when the ketamine condition was analyzed separately (see Sensitivity Analyses). Another possible reason for the differences between the studies may have to do with the different measures used. Study 1 used CAPS to assess PTSD symptoms, whereas study 2 used PCL-5. The literature suggests that although PCL-5 and CAPS are highly correlated in cross-sectional designs, their sensitivity to change differs, with CAPS being more sensitive to symptom reduction (41). Previous

literature suggests that the correlation between reduction in symptoms using CAPS and BDI was higher ($r = 0.9$) than the correlation between PCL-5 and BDI ($r = 0.8$) (41). This literature may provide some explanation for why the findings based on CAPS in study 1 were replicated in study 2 mainly using BDI. This post hoc reasoning received only partial support when we focused on a core PTSD characteristic, the re-experiencing scale (rather than the full PCL scale) in study 2 (see Sensitivity Analyses).

The most important limitation of the current work is the small sample size that forced us to focus mainly on effect sizes. It should be noted that the sample sizes of the randomized controlled trials we used in the current study are within the range of 8 to 39 (mean = 18.25), typically published in the literature on brain changes as a result of PTSD treatments (25). To mitigate this limitation, we conducted external validation, strengthening the potential validity of the findings. However, additional replications in large samples are needed. Such replications would also enable testing the potential effects of trauma type (7), resources activated during trauma exposure, distress experienced during the therapy session, general activity level, comorbidities with major depressive disorder, and pharmacotherapy. Such replication would also enable quantifying the size of the hippocampus (relative to the individual's estimated intracranial volume) that may indicate a better treatment prognosis, as well as the individual's characteristics that may affect such an estimate. It may also shed further light on the mechanisms underlying the current findings, answering questions like whether resources activated during trauma exposure may explain why increased hippocampal volume for those with already large hippocampal volume results in a greater reduction in symptoms. We did not use a prospective pretrauma design, enrolling individuals before exposure to the trauma; therefore, causal inferences should be made with caution. A previous study found a specific effect of the volume of the anterior hippocampus in nonexposure treatments (16). Therefore, future studies should further investigate whether certain subregions of the hippocampus are driving the findings reported here and whether the pattern of results differs between exposure and nonexposure treatments.

The findings shed light on the potential mechanism underlying the better prognosis for individuals with larger pretreatment hippocampal volume in the treatment of PTSD and point to the role that an increase in hippocampal volume during treatment may play in driving better outcomes. The findings suggest a potential merit of classical theories of treatment personalization, such as the theory of capitalizing on strengths (50,51), in the field of neuroscience. Specifically, those individuals who may be most able to benefit from an increase in hippocampal volume are those who have a larger volume even before the start of treatment, suggesting that the "rich get richer" phenomenon may be at play regarding hippocampal volume. This raises potential hypotheses about the different capabilities of individuals to benefit from curative processes such as neurogenesis. Elucidating neural biomarkers predictive of therapeutic outcome for subgroups of individuals with PTSD, in this case individuals with larger hippocampal volume, may assist in identifying clinical targets for treatment selection and improve treatments for this subgroup of individuals (53). The finding that the main results were replicated despite the many differences between the two studies further supports the validity and generalizability of the findings and their robustness for replication.

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