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Anterior hippocampal volume predicts affect-focused psychotherapy outcome

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Abstract

Background. The hippocampus plays an important role in psychopathology and treatment outcome. While posterior hippocampus (PH) may be crucial for the learning process that exposure-based treatments require, affect-focused treatments might preferentially engage anterior hippocampus (AH). Previous studies have distinguished the different functions of these hippocampal sub-regions in memory, learning, and emotional processes, but not in treatment outcome. Examining two independent clinical trials, we hypothesized that anterior hippocampal volume would predict outcome of affect-focused treatment outcome [Interpersonal Psychotherapy (IPT); Panic-Focused Psychodynamic Psychotherapy (PFPP)], whereas posterior hippocampal volume would predict exposure-based treatment outcome [Prolonged Exposure (PE); Cognitive Behavioral Therapy (CBT); Applied Relaxation Training (ART)].

Methods. Thirty-five patients with posttraumatic stress disorder (PTSD) and 24 with panic disorder (PD) underwent structural magnetic resonance imaging (MRI) before randomization to affect-focused (IPT for PTSD; PFPP for PD) or exposure-based treatments (PE for PTSD; CBT or ART for PD). AH and PH volume were regressed with clinical outcome changes.

Results. Baseline whole hippocampal volume did not predict post-treatment clinical severity scores in any treatment. For affect-focused treatments, but not exposure-based treatments, anterior hippocampal volume predicted clinical improvement. Smaller AH correlated with greater affect-focused treatment improvement. Posterior hippocampal volume did not predict treatment outcome.

Conclusions. This is the first study to explore associations between hippocampal volume sub-regions and treatment outcome in PTSD and PD. Convergent results suggest that affect-focused treatment may influence the clinical outcome through the 'limbic' AH, whereas exposure-based treatments do not. These preliminary, theory-congruent, therapeutic findings require replication in a larger clinical trial.

Introduction

Posttraumatic stress disorder (PTSD) and panic disorder (PD) are highly prevalent, debilitating psychiatric disorders (Kessler *et al*., 1995; Kessler *et al*., 2005*a*, 2005*b*; Neria *et al*., 2008, 2011; Management of PTSD Work Group, 2017). Although phenomenologically distinct, these two clinical syndromes overlap in symptoms and psychological features. Clinical similarities include frequent panic attacks, high baseline anxiety levels, deficits in emotional regulation, and avoidance of distressing stimuli (North *et al*., 2009). Therapeutic approaches to PTSD and PD also share core features, with two broad treatment types having different treatment foci. While exposure-based treatments expose patients to their anxiety-provoking triggers, affect-focused treatments ask patients to focus on their emotions as they emerge, identify them and their consequences, and discuss them openly with their therapist. Elucidating neural biomarkers predictive of therapeutic outcome in these two different treatment types might assist in identifying clinical targets for treatment selection and improving existing treatments (Patel *et al*., 2012).

The hippocampus is considered to play an important role in psychopathology through its involvement in memory functions (Brohawn *et al*., 2010) and fear-related learning processes (Corcoran *et al*., 2005; Quirk and Mueller, 2008). Indeed, research has shown hippocampal abnormalities in both PTSD (Stein *et al*., 1997; Driessen *et al*., 2000; Vythilingam, 2002) and PD (Bandelow *et al*., 2016; 2017), implicating smaller overall hippocampal volume (O'Doherty *et al*., 2015; Rubin *et al*., 2016), diminished hippocampal activity (Etkin and

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Wager, 2007), and altered connectivity (Lazarov *et al.*, 2017). Recently, we reported a clinical trial of PTSD associating smaller overall hippocampal volume with poorer treatment response following Prolonged Exposure (PE), an exposure-based treatment (Rubin *et al.*, 2016).

Although most clinical research investigating the hippocampus has studied it as a unitary structure, functionally discrete hippocampal sub-regions along its longitudinal axis have increasingly been recognized based on gene expression and anatomical connectivity (Fanselow and Dong, 2010; Chen and Etkin, 2013; Zarei *et al.*, 2013). Research has shown functional differences between anterior and posterior hippocampus (AH and PH), indicating the primary involvement of PH in spatial and episodic memory and cognitive functions. The more 'limbic' anterior region appears primarily involved in emotion and affect (Fanselow and Dong, 2010; Small *et al.*, 2011; Poppenk *et al.*, 2013), and closely linked to emotional behavior (Fanselow and Dong, 2010; Zeidman and Maguire, 2016). Despite this increased attention, treatment-focused research addressing the different roles of these sub-regions is lacking (Chen and Etkin, 2013; Lazarov *et al.*, 2017). Better understanding the neural abnormalities of these sub-regions and their association with treatment outcome is thus vital in identifying potential novel treatment targets (Patel *et al.*, 2012).

We sought to explore hippocampus sub-region correlates of psychotherapy outcome in two patient samples (PTSD, PD) that underwent pre-treatment structural magnetic resonance imaging (MRI) scans as part of two large randomized controlled trials (Markowitz *et al.*, 2015; Milrod *et al.*, 2016). The first sample, comprising 35 unmedicated patients with chronic PTSD, was randomized to 14-week treatment with PE, Interpersonal Psychotherapy (IPT), or Relaxation Therapy (RT). The second sample, comprising 24 patients with PD, was randomized to a 12-week treatment of Cognitive Behavioral Therapy (CBT), Panic-Focused Psychodynamic Psychotherapy (PFPP), or Applied Relaxation Training (ART). As IPT and PFPP both focus on affect and emotions affecting relationships in the patient's present life (Markowitz *et al.*, 2009, 2015; Milrod *et al.*, 2016), outcome of these affect-focused treatments might correlate with baseline anterior hippocampal volume, as it is known to process abstract emotional aspects of memory and learning (Bannerman *et al.*, 2003, 2014; Fanselow and Dong, 2010; Abdallah *et al.*, 2017; Zeidman and Maguire, 2016). Conversely, for PE, CBT, and ART, all exposure-based treatments, therapeutic outcome might correlate with posterior hippocampal volume, as this sub-region influences spatial and episodic memory and cognitive functions, closely related to specific details of events, rehearsed in imaginal exposure (Doeller *et al.*, 2008; Kaplan *et al.*, 2014). As RT lacked an affect or exposure focus, it was omitted from present analyses.

Based on our prior finding associating greater whole hippocampal volume with PE efficacy in PTSD (Rubin *et al.*, 2016), and lack of prior research associating hippocampal sub-region with treatment outcome, we suspected an association with larger hippocampal sub-region volume. That is, the larger posterior hippocampal volume might predict increased exposure-based therapeutic response, while larger anterior hippocampal volume might predict increased affect-based therapeutic response. In sum, this study aimed to explore potential correlations of baseline anterior and posterior hippocampal volume with clinical symptom change following different treatments (Markowitz *et al.*, 2015, 2017; Milrod *et al.*, 2016).

Methods

PTSD sample

The study enrolled patients between April 2008 and November 2012 at the New York State Psychiatric Institute (Markowitz *et al.*, 2015). Of the 35 patients undergoing pretreatment structural MRI scans, 11 patients received PE, 14 IPT, and 10 RT (the last, as noted, were excluded from present analyses). Following initial phone screen, eligible individuals signed informed consent for an extended intake evaluation interview to ascertain a primary diagnosis of PTSD and exclusion criteria. Independent evaluators (Ph.D. level) established current and lifetime diagnoses using the Clinician-Administered PTSD Scale (CAPS; Weathers *et al.*, 2001) and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID-DSM-IV; First *et al.*, 1995; Markowitz *et al.*, 2015). Eligible patients signed IRB-approved treatment study consent, were randomly assigned to PE or IPT in 1:1 ratio, stratified by major depressive disorder (MDD) defined by a SCID diagnosis of MDD and score $\geqslant$20 on the 24-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). The IPT and PE groups did not differ statistically in age, sex, education, or baseline CAPS scores.

Treatments

PE (Foa and Rothbaum, 1998) comprised ten weekly 90-min sessions delivered (900 min) over 14 weeks. PE helps the patient reconstruct a coherent trauma narrative, presents a rationale for facing feared trauma reminders, helps the patient to construct a fear hierarchy, and uses repeated imaginal and *in vivo* exposures to help patients habituate to traumatic memories and potentially extinguish them. *IPT* for PTSD (Markowitz, 2016) comprised 14 weekly 50-min sessions (700 min). Unlike PE, IPT focuses not on past trauma but on its current interpersonal sequelae, on patient numbness to affect, and on using affect as a guide to handling daily interpersonal encounters. IPT seeks to help patients determine who they can trust, build social skills and social support, and re-establish a sense of mastery of the environment.

Patients

Patients were 18–65 years old, with a primary DSM-IV diagnosis of PTSD and CAPS score $\geqslant$50 (i.e. reflecting at least moderately severe PTSD; Blake *et al.*, 1995). Exclusion criteria were present or past psychotic disorders, bipolar disorder, unstable medical conditions, substance dependence, active suicidal ideation; antisocial, schizotypal, borderline, or schizoid personality disorder; prior non-response to $\geqslant$8 weeks of a PE or IPT; and concurrent outside psychotherapy or pharmacotherapy.

Measures

Treatment-blinded independent evaluators used established assessments. PTSD symptom severity was assessed using the CAPS, considered the canonical observer instrument for DSM-IV PTSD symptom severity. It has established validity (Weathers *et al.*, 2001) with good internal consistency (Cronbach's $\alpha = 0.87$) and interrater reliability for all three clusters (intrusion, hyperarousal, and avoidance subscales; r values >0.92). Treatment response was defined *a priori* as >30% improvement from baseline in CAPS score, and remission as final CAPS score <20 (Weathers *et al.*,

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2001). Depressive symptom severity was assessed by HAM-D (Hamilton, 1960), the most widely used observer-rated measure. Study independent evaluators showed excellent interrater reliability on the CAPS (Shrout-Fleiss intraclass reliability coefficient = 0.93) and Ham-D (0.89) (Markowitz *et al.*, 2015).

PD sample

The study enrolled patients between September 2006 and March 2012 at Weill Cornell Medical College (WCMC) and University of Pennsylvania (Penn). Twenty-four patients underwent pre-treatment structural MRI scans: nine patients received CBT, 11 PFPP, and four ART. Individuals eligible after telephone screen signed informed consent for an intake interview to determine DSM-IV PD as a primary diagnosis and to assess exclusion criteria. Independent evaluators (M.A.'s) established current and lifetime diagnoses using the Anxiety Disorders Interview Schedule (ADIS-IV; DiNardo and Brown, 1995). PD severity was assessed using the 7-item Panic Disorder Severity Scale (PDSS; Shear *et al.*, 1997). Eligible patients signed IRB-approved informed consent and were randomly assigned to CBT, PFPP, or ART in a 2:2:1 ratio using within-site stratification of depression and agoraphobia. The CBT, PDPP, and ART groups did not differ statistically in age, sex, education, or baseline PDSS scores.

Treatments

CBT followed a version of the Panic Control Therapy protocol (Barlow and Craske, 2006), modified to fit the 24-session/45 min twice-weekly study format. CBT involved education about anxiety and panic, identification and correction of maladaptive thoughts about anxiety and panic, training in slow, diaphragmatic breathing, and in session exposure to bodily sensations designed to mimic those experienced during panic (interoceptive exposure). *In vivo* exposure homework assignments were introduced at Session 17 for patients with significant agoraphobic avoidance. Session 24 covered review and relapse prevention. *PFPP* (Milrod *et al.*, 1997) was divided into three phases: Treatment of Acute Panic, Treatment of Panic Vulnerability, and Termination. Treatment strategy assumes that panic symptoms have psychological unconscious meanings that need uncovering to achieve relief. Elucidating the meaning of symptoms involves viewing them in a more complex fashion, a process that improves Reflective Functioning (Fonagy and Target, 1997). To this end, therapy explores circumstances and feelings surrounding panic onset, personal meanings of panic symptoms, and feelings and content of panic episodes. *ART* followed Cerny's ART manual (Cerny *et al.*, unpublished) modified to a twice-weekly, 24-session format. Progressive muscle relaxation training focuses attention onto muscle groups, tensing the muscle group for 5–10 s, attending to the sensations of tension, relaxing the muscle group, attending to the difference between the sensations of tension and relaxation, and suggests deepening relaxation. ART involved no cognitive restructuring or interoceptive exposure, but an *in vivo* exposure component applied the learned relaxation skills to anxiety-provoking circumstances such as riding the subway.

Patients

Patients were 18–70 years old, with a primary DSM-IV diagnosis of PD. Exclusion criteria comprised psychotic disorders, bipolar disorder, unstable medical conditions, substance dependence, and acute suicidality.

Measures

The study employed established assessments collected by treatment-blinded independent evaluators. The Anxiety Disorders Interview Schedule Lifetime Version for DSM-IV (ADIS-IV-L; DiNardo and Brown, 1995) is a structured interview designed to assess current episodes of anxiety disorders and to permit differential diagnosis among DSM-IV anxiety disorders. The 7-item PDSS, the primary dependent variable, provides a diagnosis-based, composite, global rating of PD severity. Treatment response was defined *a priori* as ⩾40% improvement from baseline PDSS total score (Shear *et al.*, 1997; Barlow *et al.*, 2000). PDSS has acceptable psychometric properties (Shear *et al.*, 1997) and internal consistency (Cronbach's $\alpha = 0.65$). Study independent evaluators showed excellent PDSS interrater reliability [Intraclass Correlation Coefficient (ICC) = 0.95].

Both samples (PTSD, PD)

Imaging study exclusion criteria comprised ferromagnetic implants (e.g. pacemaker); metal braces or retainers; irremovable transdermal medication patches; history of concussion, seizure disorder, or other neurological illness; claustrophobia; and a positive pregnancy test.

Three patients with PTSD dropped out (one IPT, two PE), leaving 22 (13 IPT, nine PE) patients who completed the study protocol and provided endpoint CAPS scores. Three patients with PD dropped out (one PFPP, one CBT, one ART), leaving 24 (11 PFPP, nine CBT, four ART) patients who completed the study protocol and provided endpoint PDSS scores.

MRI Data Acquisition

Imaging for both samples as performed on the same GE Sigma 3 T whole body scanner (Milwaukee, WI) using a GE single channel quadrature head coil for both transmitting and receiving radio frequency signal. Head positioning in the magnet was standardized using the canthomeatal line. A T1-weighted sagittal localizing image was used to position axial functional images parallel to the anterior commissure-posterior commissure line. High-resolution anatomical MRI brain scans were acquired using a T1-weighted 3D spoiled gradient echo pulse sequence (TR = 6.1 ms, TE = 2.4 ms, matrix = 256 × 256, 170 slices, thickness = 1 mm, FA 11°).

Data analysis

Regional gray matter volume (GMV) was assessed with whole brain voxel-based morphometry (VBM) using SPM12 (http://www.fil.ion.ucl.ac.uk/spm Welcome Trust Centre for Neuroimaging, London, UK), implemented in Matlab R2016a (MathWorks). Briefly, images were first segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using the unified segmentation procedure (Ashburner and Friston, 2005). The segmented images were then spatially normalized using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007). These fully normalized images were resliced with trilinear interpolation to a final voxel size of $1.5 \times 1.5 \times 1.5$ mm^3. An additional 'modulation' step multiplied each spatially normalized gray matter

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Table 1. Demographic table for PTSD sample

	PE			IPT			
	N	Mean	S.D.	*N*	Mean	S.D.	*p*
Age	9	38.80	10.90	13	42.20	10.76	0.302
Gender (M)	4	–	–	5	–	–	0.778
Education	9	15.40	2.20	13	15.50	1.80	0.908
CAPS baseline	9	64.66	14.64	13	70.60	15.20	0.73
HAMD baseline	9	16.66	5.61	11	19.50	7.99	0.46
MDD	2	–	–	8	–	–	
Sexual trauma	1	–	–	5	–	–	
Race		–	–		–	–	0.383
White	6	–	–	12	–	–	
Black	1	–	–	0	–	–	
Asian	1	–	–	1	–	–	
Other	0	–	–	0	–	–	

image by its relative volume before and after normalization, ensuring the preservation of the total amount of gray matter in each voxel. Finally, the optimally processed gray matter images were smoothed with an isotropic Gaussian kernel (full-width half-maximum = 8 mm) to ensure a normal distribution of the data as required by subsequent statistical parametric tests. The total volume of the gray matter, white matter, and CSF was determined, and total intracranial volume (TIV) was calculated from the sum of the volume of the gray matter, white matter, and CSF and used as a covariate in the statistical analysis.

The hippocampus was divided along the anterior-posterior axis into three equal sections ($y = -10$ to -21 mm, $y = -21$ to -32 mm, and $y = -32$ to -43 mm) as in prior research (Chen and Etkin, 2013; Lazarov, *et al.*, 2017). Only AH and PH were included in statistical analyses.

Statistical analysis

Statistical analyses employed SPSS 24 software (SPSS Inc. Chicago, IL, USA). Within each diagnostic group (PTSD, PD), independent-sample *t* tests were used to compare treatment groups on baseline clinical symptoms, age, and years of education. χ^2 tests were used to analyze differences in sex and race.

To test our hypotheses that anterior and posterior hippocampal GMV would predict treatment outcome, we conducted linear regression analyses separately in each diagnostic group (PTSD, PD) and within each treatment group, with pre-to-post-clinical score changes (CAPS or PDSS) as the dependent variable, and whole hippocampus and AH and PH as predictors, adjusted for TIV, age, and sex. Such adjustments are standard in the field and in our previous neuroimaging research (e.g. Rubin *et al.*, 2016). We tested the differences of the coefficients from these regression analyses using the *Z*-test: $Z = (b1 - b2)/(\sqrt{SEb_1^2 + SEb_2^2})$. To explore whether the ratio or difference between hippocampus sub-regions influenced in the results, we conducted linear regression analyses with CAPS or PDSS (pre/post) score reduction as the dependent variable, dividing and subtracting, as separate analysis, the GMV of AH *v.* PH (PH/AH and PH-AH) as independent variables, adjusted for TIV, age, and sex.

Results

Table 1 and 2 present demographics of both imaging samples, indicating no significant differences among the treatment groups.

PTSD sample results

Seven (54%) IPT completers ($n = 13$) and 5 (55%) PE completers ($n = 9$) met treatment response criteria (>30% CAPS improvement) at week 14 (Markowitz *et al.*, 2015).

Linear regression analysis found that baseline whole hippocampus GMV was not associated with CAPS changes in either PTSD treatment group (IPT: $t = -0.74$, $p = 0.48$; PE: $t = 0.02$, $p = 0.98$). For IPT, but not PE, regression analyses found that baseline AH GMV predicted symptom changes measured by CAPS reduction (IPT: $t = -3.619$, $p = 0.009$; PE: $t = 0.533$, $p = 0.631$), adjusting for PH, TIV, age, and sex. This finding does not appear to be a power effect driven due to the smaller PE sample size, as the amount of variance explained by all independent variables (AH, PH, sex, age, TIV) was robust in both treatment groups (IPT: $r^2 = 0.831$, $f^2 = 4.92$; PE: $r^2 = 0.90$, $f^2 = 9.0$). The direction of the association indicated that *smaller pre-treatment anterior hippocampal volume was associated with larger CAPS improvement in IPT*. In effect, a 0.01 decrease in AH GMV was associated with a greater final CAPS improvement of 15.9 points, a clinically meaningful difference (Weathers *et al.*, 2001). For PE and IPT, CAPS reduction was not associated with baseline posterior hippocampal volume (IPT: $t = 2.071$, $p = 0.077$; PE: $t = 0.347$, $p = 0.752$).

Further analyses testing the difference of the coefficients among the treatment groups revealed significantly different AH regression weights between IPT and PE ($Z = 3.00$, $p = 0.0027$). The PH showed equivalent regression weights between IPT and PE ($Z = 1.56$, $p = 0.11$). In *post hoc* analyses, subtracting or dividing anterior from posterior hippocampal volume yielded no significant findings for any treatment.

To ensure that outlier scores did not explain the association of IPT outcome with anterior hippocampal GMV, we removed the one patient with scores >2 standard deviations from the mean and reran the analyses, which were unchanged: baseline AH

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Table 2. Demographic table for PD sample

	ART			CBT			PFPP			
	N	Mean	S.D.	*N*	Mean	S.D.	*N*	Mean	S.D.	*p**
Age	4	34.25	13.18	9	36.33	16.51	11	41.90	16.16	0.103
Gender (M)	0	–	–	3	–	–	1	–	–	0.84
Education	4	5.25	2.06	9	4.44	1.42	10	5.00	1.77	0.99
PDSS baseline	4	15.25	3.10	9	13.00	4.50	11	12.73	3.40	0.537
PDSS post	4	5.75	3.30	9	4.30	2.96	11	5.36	2.46	0.6
Race		–	–		–	–		–	–	0.11
White	3	–	–	4	–	–	9	–	–	
Black	1	–	–	5	–	–	1	–	–	
Asian	0	–	–	0	–	–	0	–	–	
Other	0	–	–	0	–	–	1	–	–	

*p value is between the affect-focused treatment (PFPP) and exposure-based treatment (ART, CBT)

volume still predicted IPT CAPS changes ($p = 0.003$, $t = -4.836$), adjusting for TIV, age, and sex.

PD sample results

Eight (73%) of the 11 PFPP completers met treatment response criteria (⩾40% PDSS improvement) at week 12; for CBT ($n = 9$) and ART ($n = 4$), response rates were 100% and 75%, respectively.

Linear regression analysis found baseline whole hippocampus GMV was not associated with PDSS changes in any of the PD treatment groups (PFPP: $t = -0.70$, $p = 0.52$; CBT and ART: $t = 0.01$, $p = 0.98$). For PFPP, but not the other treatments (CBT or ART), regression analyses indicated baseline AH GMV predicted symptom changes measured by PDSS reduction (PFPP: $t = -5.95$, $p = 0.01$; CBT and ART: $t = -1.399$, $p = 0.221$), adjusting for PH, TIV, age. and sex. This finding did not appear to be a power effect driven due to smaller treatment (CBT or ART) sample sizes, as the variance explained by all independent variables was again robust in all treatment groups (PFPP: $r^2 = 0.941$, $f^2 = 15.67$; CBT and ART: $r^2 = 0.61$, $f^2 = 1.56$). The direction of the association indicated that *smaller baseline anterior hippocampal volume was associated with greater PDSS improvement in PFPP.* In effect, a 0.01 decrease in anterior hippocampus GMV was associated with a greater final PDSS improvement of 3.47 points, a clinically meaningful difference. Baseline posterior hippocampal volume was not significantly associated with any treatment (PFPP: $t = -0.948$, $p = 0.413$; CBT and ART: $t = -0.186$, $p = 0.86$).

Analyses testing coefficient differences between affect-focused treatment (PFPP) and exposure-based treatments (CBT and ART) revealed significantly different AH regression weights ($Z = 2.286$, $p = 0.01$). The PH showed equivalent regression weights between affect-focused and exposure-based treatments.

In *post hoc* analyses, subtracting or dividing anterior from posterior hippocampal volume yielded no significant findings for any treatments.

Discussion

Our main finding suggests that hippocampal sub-regions might differentially predict affect-focused, but not exposure-based, treatment outcomes among patients with PTSD and PD. Whereas whole hippocampal volume did not predict treatment outcome, baseline anterior hippocampal volume significantly predicted therapeutic outcomes for IPT and PFPP, two affect-focused interventions. No comparable significant relationship emerged for posterior hippocampal volume.

IPT and PFPP do not involve exposure-based techniques (Markowitz *et al.*, 2009, 2015; Busch *et al.*, 2012; Markowitz, 2016; Milrod *et al.*, 2016) but instead focus on aiding patients to identify different emotions and relate them to emotionally charged aspects of their lives. Thus, affect-focused treatments involve an emotional aspect of memory that may engage AH (Zeidman and Maguire, 2016; Abdallah *et al.*, 2017). Based on our previous findings with a PE trial in PTSD (Rubin *et al.*, 2016), we had originally anticipated that greater anterior hippocampal volume might predict better affect-focused treatment outcome; surprisingly, an opposite pattern emerged. A potential *post hoc* interpretation of this finding is that smaller baseline AH indicates neural deficits characterizing patients for whom affect-based treatment (IPT in PTSD, or PFPP in PD) may be particularly efficacious. Thus, reduced AH volume might represent a potential treatment target. This neuroanatomical finding could further suggest that, following treatment, anterior hippocampal volume might increase, through neurogenesis, or show greater density, reflecting greater functional connectivity to other brain areas (cf., Ismaylova *et al.*, 2018). This hypothesis would accord with the affect-focused treatments' aim of improving clinical symptoms such as affective numbing, which could rely on AH engagement. Moreover, the AH may play a crucial role in recalling and imagining emotionally charged decision making, needed in emotionally charged settings or relationships, which affect-focus treatments emphasize and target, such as when using role-playing exercises in IPT (Zeidman and Maguire, 2016), or in transference interpretation in dynamic therapy (Busch *et al.*, 2012). Accordingly, anterior hippocampal volume could potentially serve as a biomarker for treatment selection.

Our complementary hypothesis, that baseline posterior hippocampal volume would predict PE outcome, was not confirmed. The lack of a significant finding may reflect inadequate statistical power across three varying treatments (PE $n = 9$; CBT = 9; ART = 4), i.e. a Type II statistical error. Finally, we found no relationship between sub-regional (AH-PH) volume ratio and treatment outcome,

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suggesting that these results are specific to each hippocampal region. These findings, that different hippocampal regions might predict efficacy of differing domains of psychotherapy is an unprecedented finding, albeit clearly requiring more research to test this hypothesis.

This study has several limitations. Small sample sizes present the risk of false positive and negative findings. Although our sample sizes are small, the variance explained by the independent variables is robust in all treatment groups. Despite the small sample size for each treatment group, we decided not to pool patient into two separate 'treatment-type' groups (viz., exposure-based and affect-focused) as patients carried different diagnoses (PTSD and PD). Pooling them, while increasing sample size, would have created noisier, more heterogeneous samples, obscuring potential results. Thus, the present study demands replication with larger samples, which might allow pooling across psychopathologies. Future studies employing larger patient samples could also conduct similar, but within diagnostic group, analyses, adding functional fMRI and post-treatment follow-up imaging to determine whether affect-focused psychotherapies normalize the anterior hippocampal volume deficit observed here. Despite these caveats, the present study raises the intriguing possibility that anterior hippocampal volume might constitute a biomarker for affect-focus treatments' response in PTSD and PD.

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References

Abdallah CG, Wrocklage KM, Averill CL, Akiki T, Schweinsburg B, Roy A, Martini B, Southwick SM, Krystal JH and Scott JC (2017) Anterior hippocampal dysconnectivity in posttraumatic stress disorder: a dimensional and multimodal approach. *Translational Psychiatry* **7**, e1045.

Ashburner J (2007) A fast diffeomorphic image registration algorithm. *Neuroimage* **38**, 95–113.

Ashburner J and Friston KJ (2005) Unified segmentation. *Neuroimage* **26**, 839–851.

Bandelow B, Baldwin D, Abelli M, Altamura C, Dell'Osso B, Domschke K, Fineberg NA, Grünblatt E, Jarema M, Maron E, Nutt D, Pini S, Vaghi MM, Wichniak A, Zai G and Riederer P (2016) Biological markers for anxiety disorders, OCD and PTSD - a consensus statement. Part I: Neuroimaging and genetics. *World Journal of Biological Psychiatry* **17**, 321–365.

Bandelow B, Baldwin D, Abelli M, Bolea-Alamanac B, Bourin M, Chamberlain SR, Cinosi E, Davies S, Domschke K, Fineberg N, Grünblatt E, Jarema M, Kim YK, Maron E, Masdrakis V, Mikova O, Nutt D, Pallanti S, Pini S, Ströhle A, Thibaut F, Vaghi MM, Won E, Wedekind D, Wichniak A, Woolley J, Zwanzger P and Riederer P (2017) Biological markers for anxiety disorders, OCD and PTSD: A consensus statement. Part II: Neurochemistry, neurophysiology and neurocognition. *World Journal of Biological Psychiatry* **18**, 162–214.

Bannerman DM, Grubb M, Deacon RM, Yee BK, Feldon J and Rawlins JN (2003) Ventral hippocampal lesions affect anxiety but not spatial learning. *Behavioural Brain Research* **139**, 197–213.

Bannerman DM, Sprengel R, Sanderson DJ, McHugh SB, Rawlins JN, Monyer H and Seeburg PH (2014) Hippocampal synaptic plasticity, spatial memory and anxiety. *Nature Reviews Neuroscience* **15**, 181–192.

Barlow DH and Craske MG (2006) *Mastery of Your Anxiety and Panic*, 4th Edn. New York: Oxford.

Barlow DH, Gorman JM, Shear MK and Woods SW (2000) Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *Journal of the American Medical Association* **283**, 2529–2536.

Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS and Keane TM (1995) The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress* **8**, 75–90.

Brohawn KH, Offringa R, Pfaff DL, Hughes KC and Shin LM (2010) The neural correlates of emotional memory in posttraumatic stress disorder. *Biological Psychiatry* **68**, 1023–1030.

Busch F, Milrod B, Singer M and Aronson A (2012) *Panic Focused Psychodynamic Psychotherapy: Extended Range: Psychodynamic Psychotherapy for Anxiety Disorders: A Transdiagnostic Treatment Manual*. New York: Taylor & Francis.

Cerny JA, Klosko J and Barlow DH (1985) *Anxiety treatment project: combined relaxation and cognitive therapy treatment manual*. Unpublished manuscript, the phobia and anxiety disorders clinic. New York, Albany: State University of New York.

Chen AC and Etkin A (2013) Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. *Neuropsychopharmacology* **38**, 1889–1898.

Corcoran KA, Desmond TJ, Frey KA and Maren S (2005) Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. *Journal of Neuroscience* **25**, 8978–8987.

DiNardo PA and Brown TA (1995) *Anxiety Disorders Interview Schedule For DSM-IV: Current Version (ADIS-IV)*. New York: Graywinds.

Doeller CF, King JA and Burgess N (2008) Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Sciences of the USA* **105**, 5915–5920.

Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, Osterheider M and Petersen D (2000) Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry* **57**, 1115–1122.

Etkin A and Wager TD (2007) Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry* **164**, 1476–1488.

Fanselow MS and Dong HW (2010) Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* **65**, 7–19.

First MB, Spitzer RL, Gibbon M and Williams JB (1995) Structured Clinical Interview for DSM-IV Axis I Disorders -- Patient edition (SCID-I/P, Version 2.0). New York: New York State Psychiatric Institute, Biometrics Research Department.

Foa EB and Rothbaum BO (1998) *Treating the Trauma of Rape: Cognitive-Behavioral Therapy for PTSD*. New York: Guilford.

Fonagy P and Target M (1997) Attachment and reflective function: their role in self-organization. *Developmental Psychopathology* **9**, 679–700.

Hamilton M (1960) A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**, 56–62.

Ismaylova E, Di Sante J, Gouin JP, Pomares FB, Vitaro F, Tremblay RE and Booij L (2018) Associations between daily mood states and brain gray matter volume, resting-state functional connectivity and task-based activity in healthy adults. *Frontiers in Human Neuroscience* **12**, 168.

Kaplan R, Horner AJ, Bandettini PA, Doeller CF and Burgess N (2014) Human hippocampal processing of environmental novelty during spatial navigation. *Hippocampus* **24**, 740–750.

Kessler RC, Sonnega A, Bromet E, Hughes M and Nelson CB (1995) Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry* **52**, 1048–1060.

https://doi.org/10.1017/S0033291719000187 Published online by Cambridge University Press

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR and Walters EE (2005*a*) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Kessler RC, Chiu WT, Demler O and Walters EE (2005*b*) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 617–627.

Lazarov A, Zhu X, Suarez-Jimenez B, Rutherford BR and Neria Y (2017) Resting-state functional connectivity of anterior and posterior hippocampus in posttraumatic stress disorder. *Journal of Psychiatric Research* **94**, 15–22.

Management of Posttraumatic Stress Disorder Work Group (2017) VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version 3.0–2017. Available at https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf (Accessed 13 May 2018).

Markowitz JC (2016) *IPT for PTSD: Interpersonal Psychotherapy for Posttraumatic Stress Disorder*. New York: Oxford University Press.

Markowitz JC, Milrod B, Bleiberg KL and Marshall RD (2009) Interpersonal factors in understanding and treating posttraumatic stress disorder. *Journal of Psychiatric Practice* **15**, 133–140.

Markowitz JC, Petkova E, Neria Y, Van Meter P, Zhao Y, Hembree E, Lovell K, Biyanova T and Marshall RD (2015) Is exposure necessary? A randomized clinical trial of interpersonal psychotherapy for PTSD. *American Journal of Psychiatry* **172**, 430–440.

Markowitz JC, Neria Y, Lovell K, Van Meter PE and Petkova E (2017) History of sexual trauma moderates psychotherapy outcome for posttraumatic stress disorder. *Depression and Anxiety* **34**, 692–700.

Milrod B, Busch F, Cooper A and Shapiro T (1997) *Manual of Panic-Focused Psychodynamic Psychotherapy*. Washington, DC: American Psychiatric Association Press.

Milrod B, Chambless DL, Gallop R, Busch FN, Schwalberg M, McCarthy KS, Gross C, Sharpless BA, Leon AC and Barber JP (2016) Psychotherapies for panic disorder: a tale of two sites. *Journal of Clinical Psychiatry* **77**, 927–935.

Neria Y, Nandi A and Galea S (2008) Post-traumatic stress disorder following disasters: a systematic review. *Psychological Medicine* **38**, 467–480.

Neria Y, DiGrande L and Adams BG (2011) Posttraumatic stress disorder following the September 11, 2001, terrorist attacks: a review of the literature among highly exposed populations. *American Psychologist* **66**, 429–446.

North CS, Suris AM, Davis M and Smith RP (2009) Toward validation of the diagnosis of posttraumatic stress disorder. *American Journal of Psychiatry* **166**, 34–41.

O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR and Lagopoulos J (2015) A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Research* **232**, 1–33.

Patel R, Spreng NR, Shin LM and Girard TA (2012) Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews* **36**, 2130–2142.

Poppenk J, Evensmoen HR, Moscovitch M and Nadel L (2013) Long-axis specialization of the human hippocampus. *Trends in Cognitive Science* **17**, 230–240.

Quirk GJ and Mueller D (2008) Neural mechanisms of extinction learning and retrieval. *Neuropsychopharmacology* **33**, 56–72.

Rubin M, Shvil E, Papini S, Chhetry BT, Helpman L, Markowitz JC, Mann JJ and Neria Y (2016) Greater hippocampal volume is associated with PTSD treatment response. *Psychiatry Research* **252**, 36–39.

Shear MK, Brown TA, Barlow DH, Money R, Sholomskas DE, Woods SW, Gorman JM and Papp LA (1997) Multicenter collaborative panic disorder severity scale. *American Journal of Psychiatry* **154**, 1571–1575.

Small SA, Schobel SA, Buxton RB, Witter MP and Barnes CA (2011) A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nature Reviews Neuroscience* **2011**, 585–601.

Stein MB, Koverola C, Hanna C, Torchia MG and McClarty B (1997) Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine* **27**, 951–959.

Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, Brummer M, Staib L, Vermetten E, Charney DS, Nemeroff CB and Bremner JD (2002) Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry* **159**, 2072–2080.

Weathers FW, Keane TM and Davidson JRT (2001) Clinician-Administered PTSD Scale: a review of the first ten years of research. *Depression and Anxiety* **13**, 132–156.

Zarei M, Beckmann CF, Binnewijzend MA, Schoonheim MM, Oghabian MA, Sanz-Arigita EJ, Scheltens P, Matthews PM and Barkhof F (2013) Functional segmentation of the hippocampus in the healthy human brain and in Alzheimer's disease. *Neuroimage* **66**, 28–35.

Zeidman P and Maguire EA (2016) Anterior hippocampus: the anatomy of perception, imagination, and episodic memory. *Nature Reviews Neuroscience* **17**, 173–182.

https://doi.org/10.1017/S0033291719000187 Published online by Cambridge University Press