Emotion
2012, Vol. 12, No. 1, 58–68

1528-3542/12/$12.00 DOI: 10.1037/a0026517

Human Anterior and Posterior Hippocampus Respond Distinctly to State and Trait Anxiety

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We examined whether anterior and posterior hippocampal subregions in humans show distinct relationships to state and trait anxiety. In rodents, the ventral (but not dorsal) hippocampus is critically involved in contextual anxiety, whereas dorsal hippocampus is affected by chronic stress and genetically bred trait anxiety. These studies suggest that state forms of anxiety may be more associated with anterior (ventral in rodents) hippocampus, whereas trait forms of anxiety maybe more associated with posterior (dorsal in rodents) hippocampus. Participants were placed under alternating blocks of threat of shock and safety conditions while performing a secondary task, and state and trait anxiety measures were obtained. Using subject-specific anatomically defined masks, we found that state anxiety was related to activity in anterior but not posterior hippocampus, whereas trait anxiety showed the opposite pattern. Additionally, a psychophysiological connectivity analysis showed that activity in anterior hippocampus was more strongly related to activity in ventromedial prefrontal cortex under threat than under safety conditions, significantly more so than activity in posterior hippocampus was. Hence, anterior hippocampus shows a distinct moment-to-moment connectivity profile with other neural regions during threat relative to posterior hippocampus. The findings provide several lines of evidence for functional differentiation of anterior and posterior hippocampal involvement across state and trait components of anxiety in humans.

Keywords: anxiety, hippocampus, fMRI

Supplemental materials: http://dx.doi.org/10.1037/a0026517.supp

Studies conducted primarily in rodents have suggested that along the longitudinal axis, the dorsal and ventral portions of the hippocampus should be considered distinct regions with distinct functions (Bannerman et al., 2004; Fanselow & Dong, 2010; Moser & Moser, 1998; Swanson & Cowan, 1977). However, less is known about whether analogous divisions are apparent along the longitudinal axis in humans (i.e., anteriorly and posteriorly). One possibility is that such subdivisions within the human hippocampus are simply not there. Alternatively, it may be the case that they are present, though the principles that elucidate the functional differentiation in humans are still in question (Schacter & Wagner, 1999; Small et al., 2001; Stark, 2007; Strange, Fletcher, Henson, Friston, & Dolan, 1999). To investigate these issues further, we drew on neuroanatomical findings from the animal literature, which indicate that the hippocampus has functionally distinct subregions (Moser & Moser, 1998), and connected them with psychological theory in human studies, which suggest that anxiety is composed of both state and trait forms (Spielberger, 1972; Spielberger, Gorsuch, & Lushene, 1970), to derive and test hypotheses about how activity in anterior and posterior hippocampus may relate to anxiety in humans.

Functional Subdivisions of Hippocampus in Nonhuman Animals

In rodents, the dorsal and ventral subdivisions of the hippocampus are distinct structurally and functionally (Bannerman et al., 2004; Fanselow & Dong, 2010; Moser & Moser, 1998; Swanson & Cowan, 1977). Ventral hippocampal lesions result in decreased anxious behavior in ethological settings without impairing performance on memory tasks (Bannerman et al., 2004; Moser, Moser, Forrest, & Andersen, 1995), suggesting a specific role in anxious emotion (Bannerman et al., 2004). Consistent with this, ventral

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This research has been supported by the James S. McDonnell Foundation 21st Century Science Program and National Science Foundation Grant BCS-0223843 awarded to Russell Poldrack, National Institutes of Health infrastructure support Grant R24 AT002681R24 awarded to the Psychophysiology and Pain Assessment Core, and a UCLA departmental dissertation research award and McGuigan/Oderberg Dissertation Fellowship awarded to Ajay Satpute. We also thank Karin Foerde and Naomi Kenner for help with stimuli and Alexa Zabat-Fran, Jessica Warman, Sherry Wang, and Ember Destefani for assistance in data collection.

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hippocampus shows a pattern of connectivity with cortical and subcortical areas typically involved in affect and affect regulation, including the amygdala, hypothalamus, and ventromedial prefrontal cortex (Moser & Moser, 1998; Thierry, Gioanni, & Dégénétais, 2000). This connectivity pattern is further mirrored in patterns of gene expression (Dong, Swanson, & Chen, 2009). By comparison, lesion (Moser et al., 1995; Moser, Moser, & Andersen, 1993), connectivity (Moser & Moser, 1998), and gene expression (Dong et al., 2009) studies all suggest that the dorsal hippocampus plays a more specific role in mnemonic processes (Moser & Moser, 1998; Fanselow, 2000).

Although this work suggests a fair degree of independence between the anxiety-related functions of ventral hippocampus from the memory-related functions of dorsal hippocampus (Bannerman et al., 2004; Fanselow & Dong, 2010; Moser & Moser, 1998), several anomalous findings make this theoretical formulation difficult to fully accept. In particular, the dorsal hippocampus is not immune to anxiety-related effects. Chronic stress results in reduced dorsal hippocampal neurons (e.g., Sapolsky, Krey, & McEwen, 1985), and rodents genetically bred for high trait anxiety show reduced cell proliferation in dorsal hippocampus (Uchida et al., 2008). Hence, though studies in rodents clearly implicate the hippocampus in anxiety, what specific roles these hippocampal subregions may play in anxiety remains unclear.

State and Trait Anxiety and Hippocampal Subdivisions

Drawing on theory and research in human studies of anxiety may provide some new avenues from which to explore these functional dissociations in the hippocampus. A central theoretical position in this research is that anxiety can be divided into state and trait components (Spielberger, 1972; Spielberger et al., 1970). State anxiety refers to the subjective experience of apprehension that occurs in response to transiently or acutely threatening events. For instance, state anxiety can be elicited by everyday situations such as having to take an exam or going to the dentist or in laboratory situations by threat of shock or social evaluation (Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Reiman, Fusselman, Fox, & Raichle, 1989). In contrast, trait anxiety refers to stable individual differences in the proneness to experience anxiety across various contexts and events (Spielberger, 1972; Spielberger et al., 1970). In humans, trait anxiety has been associated with both stressful life experiences and genetic similarity as measured in studies with monozygotic and dizygotic twins (Lau, Eley, & Stevenson, 2006; Legrand, McGue, & Iacono, 1999; Sarason, Johnson, & Siegel, 1978). Trait anxiety is believed to exert its influence through conscious or unconscious perceptual biases in interpreting the environment to be more or less threatening (e.g., Broadbent & Broadbent, 1988; Chan & Lovibond, 1996; Mogg, Bradley, & Hallowell, 1994).

Intriguingly, the factors that relate each subregion of hippocampus in rodents to anxiety are fairly distinct and map on to state and trait anxiety. Lesions to ventral hippocampus particularly influence anxiety-related behaviors in ethological settings in which anxiety is produced by transient, situation-dependent contexts. In comparison, anxiety-related influences on dorsal hippocampus in rodents involve chronic stress and anxious disposition, which parallel trait anxiety in humans. As such, we suggest that functional activity in the anterior hippocampus (ventral in rodents) may relate more to state anxiety and functional activity in the posterior hippocampus (dorsal in rodents) may relate more to trait anxiety.

The Present Experiment

To explore this hypothesis, 22 participants engaged in a functional magnetic resonance imaging (fMRI) experiment in which we examined the association between hippocampal activation to threat with subjective levels of state anxiety and trait anxiety. Alternating blocks of threat, safety, and a separate baseline block were presented. During the threat and safety blocks, participants engaged in a classification-learning task, which was included to address separate research questions that are in preparation for a different manuscript. Although the classification-learning task is more commonly associated with the basal ganglia than with the hippocampus (Knowlton, Squire, & Gluck, 1994), in our analyses, we included behavioral performance measures as covariates to control for learning performance. As such, the present paradigm allows for an examination of whether associations observed between state and trait anxiety and the hippocampal activity are independent of the relationships of hippocampal activity to classification learning.

To examine neural regions associated with threat, we contrasted periods of threat with periods of safety. However, the threat manipulation alone is not necessarily indicative of the subjective experience of anxiety (see Barrett, 2006, for a discussion of this issue). Indeed, participants can vary considerably in how they respond to threat of shock manipulations, with some showing much anxiety and others showing little anxiety and even finding the manipulation humorous, and these varying emotional responses to the manipulation have been associated with distinct physiological reactions to threat (Rhudy & Meagher, 2003). Hence, to further examine the relationship of hippocampal activity to the subjective experience of state anxiety and to trait anxiety, we correlated activity in anterior and posterior hippocampus to threat versus baseline with self-reported state anxiety to threat and to trait anxiety measures.

We hypothesized that state anxiety would show greater correlations with activity in anterior hippocampus and trait anxiety with activity in posterior hippocampus across subjects. To further examine the differentiation between anterior and posterior hippocampus on a within-subject moment-to-moment basis, we examined the functional connectivity of these regions with other brain areas during the threat periods relative to safety periods (i.e., psychophysiological interaction [PPI] analysis; Friston et al., 1997). For this analysis, we were particularly interested in connectivity with the ventromedial prefrontal cortex, because this region has a selective connection to anterior hippocampus and has been shown to be functionally associated with anterior hippocampus in representing threat contexts (cf. ventral hippocampus in rodents; Adhikari, Topiwala, & Gordon, 2010). On the basis of the notion that state anxiety is contextually bound but trait anxiety is less contextually specific, we hypothesized that if anterior hippocampus is associated with state anxiety, then moment-to-moment activity in anterior hippocampus would be more strongly correlated with other brain regions including the ventromedial prefrontal cortex during

the threat periods than during safety periods, whereas posterior hippocampus would be less likely to show such PPI effects.

Method

Participants

Participants (N = 22; 11 women; age range [19, 37]) were recruited from fliers, classroom announcements, and from the UCLA Department of Psychology subject pool. Participants were screened for being right-handed, having no prior history of psychological or neurological illness, not taking any psychoactive medications, not claustrophobic, and for MRI safety. They were compensated $25 for participation. For two participants, behavioral data for the classification task were missing because of computer failure, and for one participant, one run of fMRI data was terminated early by accident. Data from these participants are included where analyses permit. Participants gave informed consent prior to commencing the experiment.

Apparatus

Stimuli were presented over scanner-compatible goggles, responses were collected from a two-response button box, and foam pads were placed around participants' heads to minimize head motion. Shocks consisting of a 2-s pulse were delivered to the inside of the upper forearm using a Digitimer stimulation unit with scanner compatible electrodes (BIOPAC EL508 radiotranslucent electrodes). Shock level was calibrated separately for each subject to a level of 7 on a 10-point psychologically defined scale (1 = *not painful* at all, 10 = *severely painful*) prior to scans being collected.

Task

To induce anxiety, participants were placed under alternating blocks of threat of shock and safety (no threat of shock) conditions (see online supplementary figure; http://www.10.1037/a0026517). In between blocks, a separate visuomotor baseline block was presented after each threat or safe block. Hence, there was a total of six threat blocks and six safe blocks, each lasting 68 s, and 12 baseline blocks, each lasting 16 s. Prior to each block, an instruction cue appeared for 12 s, indicating whether the next block corresponded to a stimulation block, in which they were instructed that a shock may or may not be given; a safe block, in which they would not receive a shock; or a safe baseline that indicated they would not receive a shock and also that they would perform the visuomotor baseline task. Because the focus of the threat manipulation is on the anxiety produced by the threat and not the delivery of shock itself, only one shock was delivered to participants during the course of the experiment. The shock was delivered at the end of the last threat block rather than in the middle or beginning so as to avoid confounding neural activity related to experiencing anxiety with neural activity related to experiencing pain.

During the threat and safe blocks, participants performed two separate but identical learning tasks known as the "Weather Prediction Task" (WPT; Knowlton et al., 1994). The tasks were separate in that participants were shown completely different cues in the threat condition compared with the safe condition, but that were identical in that the learning structures were the same in both conditions. Participants were presented with abstract cues (circular, multicolored kaleidoscope images) that were probabilistically related to one of two outcomes (*sunny* or *rainy* weather in a fictitious city). Across subjects, each cue type was rotated across experimental conditions and which other cues it was paired with in those conditions so as to counterbalance them. On each trial, participants were presented with one of these images, made a prediction of the outcome by button press, and then received feedback. In each trial, a cue was displayed for 3.5 s during which participants indicated sunny or rainy by button press within the first 2.5 s, followed by feedback consisting of the word *rainy* or *sunny* displayed above the cue for the remaining 1 s. The display then cleared to a fixation cross for an intertrial interval (ITI) of 0.5 s. Trials were randomly organized within blocks with the constraint so that the same cue would never follow itself within three trials. For the visuomotor baseline task, a separate abstract cue was presented with the instruction "Press Left" above it, and participants simply pressed the left button. These trials also lasted for 3.5 s and had a 0.5-s fixation cross ITI. A total of 102 learning trials were presented in each condition and 48 visuomotor baseline trials.

Procedure

Participants were told they would complete two learning tasks: one under threat of shock and the other under neutral conditions. For the threat of shock instructions, participants were told that they would receive one to three shocks during the course of the experiment and that each successive shock would be slightly more painful than the preceding shock. They were also informed that because there were several stimulation blocks, it would be unlikely they would be shocked on most of them. This was done to ensure that subjects' base rate expectations were not too high, which may have led them to suspect that the threat of shock was a deception and not genuine. They completed a brief practice version of the task. Participants were then placed in the scanner, shock-intensity was calibrated (see the Apparatus subsection), and they completed the experimental task.

Afterward, participants were given a 12-min break during which they were asked to watch a nature video ("Winged Migration") on the computer, and diffusion tensor imaging [DTI] and structural scans were obtained. A probe of learning in the WPT was administered afterward, the description and analysis of which is in preparation for a separate manuscript. Participants were removed from the scanner and then completed a questionnaire packet assessing emotional states and personality attributes. The following were of interest here: (a) for each condition, the belief that they would get shocked [*not at all*: 0–6: Definitely] to make sure they believed the manipulation, (b) self-reported emotional responses during the threat and safety periods measured on a seven-point Likert scales [*not at all*: 0–6: Very] for the emotions (happy, anxious, aroused, angry, and bored), and (c) a trait anxiety scale (State-Trait Anxiety Inventory [STAI]-trait; Spielberger et al., 1970). For state anxiety, we used the self-reported state anxiety to threat. Similar measures for state anxiety to an experimentally manipulated context of threat have been used in other studies (e.g., Dalton, Kalin, Grist, & Davidson, 2005; Simpson, Drevets,

Snyder, Gusnard, & Raichle, 2001). For trait anxiety, we used the STAI-trait scale. We did not collect STAI-state measures.

Scanning Protocol

MRI data were collected on a 3-Tesla Siemens Allegra scanner. Structural scans consisted of a whole-brain, matched-bandwidth, high-resolution image (gradient-echo planar imaging [EPI[pulse sequence, repetition time [TR] = 5 s, echo time [TE] = 33 ms, field of view [FOV] = 200 mm, matrix size = [128, 128, 34], slice thickness = 4 mm, interleaved acquisition, collected at an oblique-axial orientation), and a whole-brain high-resolution magnetization-prepared rapid gradient-echo (MP-RAGE; gradient-echo EPI pulse sequence, TR = 2300 ms, TE = 2.1 ms, FOV = 256 mm, matrix size = [192, 192, 360], slice thickness = 1 mm, ascending acquisition, collected across the sagittal plane). FMRI acquisition used a gradient-echo EPI pulse sequence (TR = 2000 ms, TE = 30 ms, FOV = 200 mm, matrix size = [64, 64, 34], slice thickness = 4 mm, interleaved acquisition, collected in the same oblique-axial orientation as the matched-bandwidth image). Slices were positioned to obtain whole-brain coverage. The acquisition length was 217 TRs for each of the three learning runs and 302 TRs for the test run. Two diffusion tensor imaging scans were also collected (4 min each) as standard protocol.

Statistical Analysis

For behavioral data in the classification-learning task, mean reaction times (RTs) and percentage correct were calculated. A correct response was defined as making the most optimal choice across trials.

Imaging data were preprocessed in FMRIB Software Library (FSL) 4.0, and statistical analyses were conducted using a combination of FSL and NeuroElf (www.neuroelf.com). Whole-brain analyses were performed primarily to ensure that the threat of shock manipulation had an influence that was similar to prior investigations. Functional images were motion corrected and brain extracted. Images were then smoothed (8 mm full width at half maximum) and normalized to MNI-152space during preprocessing. Parameters for normalization into a standard space were obtained by multiplying the transformation matrices across a three-step process in which the functional images were registered to the high-resolution matched-bandwidth image (6 degrees of freedom [DOF] affine transformation), the high-resolution matched-bandwidth image was registered to the MP-RAGE (6 DOF affine transformation), and the MP-RAGE was registered to the MNI152 template (12 DOF affine transformation). A generalized linear model was fitted to the data consisting of separate regressors for the threat blocks, the safe blocks, the instruction cues, and the delivery of shock. The visuomotor baseline task was not explicitly modeled and thereby served as the baseline in the generalized linear model. Regressors were modeled as blocks and were convolved with a standard hemodynamic response function. Significant clusters were defined by using the Monte Carlo simulation as implemented by the AlphaSim algorithm implemented in NeuroElf. Clusters surpassing $p < .05$ (whole-brain corrected) were considered significant, and local maxima are reported.

Analysis Procedures for Anterior and Posterior Hippocampal Regions of Interest

Region of interest (ROI) masks. To specifically examine the contributions of hippocampus, anatomically defined masks for the hippocampus were generated using FSL FIRST (see online supplementary figures), an automated segmentation program. Masks for each subject were generated based on subject-level anatomy rather than group-normalized data for greater precision (Stark, 2007). To prevent overlap between the anterior hippocampus and amygdala, masks were generated for the amygdala using the same procedures, and only voxels that showed no overlap were included in the hippocampal masks (the maximum number of overlapping voxels was three, and the majority showed no overlap in the masks). To segregate anterior and posterior hippocampus, masks were separated by volume into anterior and posterior thirds (see online supplementary figures). Thirds were used to ensure less blurring between these regions and to be more consistent with emerging data on hippocampal subdivisions (Fanselow & Dong, 2010).

ROI analyses. Our goal was to examine functional activity in anterior and posterior hippocampal ROIs with as little blurring of functional activity between these regions as possible. To do so, functional images were motion corrected and brain extracted, but not smoothed. The same regression model as for the hippocampal ROI analyses was applied to the data. Percentage signal change values were calculated for each voxel and then averaged within masks. This method allows for estimates of effect size (magnitude) to be computed without bias (Kriegeskorte, Simmons, & Bellgowan, 2009).

To examine how subjective reports of state anxiety and trait anxiety were associated with activity in hippocampal ROIs, we extracted activity in these ROIs from the threat-versus-baseline comparison and correlated this activity with state and trait measures of anxiety using SPSS software. To ensure that the results were not driven by outliers, we used the following procedure for outlier correction. Regressions were performed, Cook's *D* values were obtained, and values that were 3 *SD*s from the mean were excluded. These steps were repeated until no more outliers remained in the analysis. Then, if the presence of the outliers influenced the significance of the test statistic, it was removed from the analysis. If not, it remained in the analyses. Across several analyses, the same participant recurred as an outlier and hence was removed from all analyses. Otherwise, no other outliers were found that also influenced the significance of the test statistics obtained.

PPI analyses. Whole-brain PPI analyses were conducted in order to investigate whether activity in anterior and posterior hippocampal ROIs show distinct patterns of moment-to-moment correlations with other regions of the brain. Seed activity for these analyses was obtained by averaging the neural activity within single-subject hippocampal ROI masks (i.e., activity was extracted for anterior and posterior hippocampal ROIs in each hemisphere separately). To perform the PPIs, first-level models were constructed that included the following main regressors: (a) task on (threat and safe) versus visuomotor baseline, (b) threat versus safe, (c) temporally filtered activity across the time course from either the left or the right anterior hippocampal seed region, (d) temporally filtered activity from the time course of the posterior hip-

pocampal seed region ipsilateral to the anterior hippocampal seed region, (e) the interaction of activity from the anterior hippocampal seed region with the threat versus safe regressor (anterior hippocampal PPI), and (f) the interaction of activity from the posterior hippocampal seed region with the threat versus safe regressor (posterior hippocampal PPI). To examine which regions show a difference in PPI effect for the anterior hippocampus in comparison to the posterior hippocampus, we compared the parameter estimates for (e) and (f). Instruction cues for the conditions and shock delivery were also modeled as controls. Separate models were constructed for each hemisphere. Significant clusters were obtained using the same approach as for the whole-brain analyses indicated above.

Although this analysis indicates which regions show significant differences in PPI connectivity in anterior versus posterior hippocampal ROIs (or vice versa), it does not indicate whether this is because anterior hippocampus shows a significantly positive PPI effect or because posterior hippocampus shows a significantly negative PPI effect. To determine the direction, we examined the (e) for the anterior hippocampal PPI and (f) for the posterior hippocampal PPI, separately. Importantly, these analyses control for activity in the alternate ROI, such that significant findings for the anterior hippocampal PPI alone are controlling for findings in the posterior hippocampal ROI and vice versa. We then used an inclusion mask to see whether regions that responded to the difference in PPIs between anterior and posterior hippocampus overlapped with regions showing a significant PPI effect in anterior hippocampus alone or posterior hippocampus alone.

To ensure that the PPI analyses were not due to unmodeled task effects (for a discussion, see http://www.fmrib.ox.ac.uk/Members/joreilly/ppi-issues/), the residuals from a model of task effects (not including the seed) were submitted to a principal components analysis and obtained components were visually inspected. No additional unmodeled task-related effects appeared in this analysis with respect to the hippocampus and ventromedial prefrontal cortex.

Results

State and Trait Anxiety Measures

Participants believed they would be shocked during the threat period ($M = 4.09$, $SD = 1.41$; one-sample $t(21) = 13.6$, $p < .001$), but no one believed they would be shocked during the safety period ($M = 0$, $SD = 0$). They also reported greater state anxiety ($M = 3.41$, $SD = .96$) and arousal ($M = 2.18$, $SD = 1.59$) during the threat period than during the safety period ($M = 1.14$, $SD = 1.08$; $M = .95$, $SD = 1.21$, for anxiety and arousal, respectively) (differences in anxiety, $t(21) = 7.67$, $p < .001$, Cohen's $d = 1.64$; differences in arousal, $t(21) = 4.29$, $p < .001$, Cohen's $d = 0.95$). Measures of self-reported state anxiety to threat and trait anxiety in both the behavioral pilot and the present study were not significantly correlated with each other (behavioral pilot: $r = -.13$, $p > .4$; imaging sample: $r = -.17$, $p > .4$), suggesting they may account for distinct variability (Spielberger, Gorusch, & Lushene, 1972; Spielberger & Vagg, 1984).

Effect of Threat of Shock on Neural Activity

Whole-brain analysis confirmed activation to threat versus safety that was found in prior threat of pain studies, including activation in the cingulate and anterior insula (see supplementary table and figure). Focusing in on hippocampal ROIs, the overall main effect of threat versus safety conditions on hippocampal activity were not significant (left anterior: $t(21) = -.94$, $p = .40$; right anterior: $t(21) = .07$, $p = .96$; left posterior: $t(21) = .51$, $p = .61$; right posterior: $t(21) = -.24$, $p = .81$).

State and Trait Anxiety Correlate With Activity in Anterior and Posterior Hippocampus

To examine the association between state and trait anxiety and activity in anterior and posterior hippocampal ROIs, neural activity in hippocampal ROIs was extracted for the comparison of threat versus baseline and correlated with anxiety measures. Functional activity in anatomically defined hippocampal ROIs showed significant relationships to self-reported state and trait anxiety (see Figure 1). Anterior hippocampal activity to threat showed positive correlations with self-reported state anxiety to threat (left anterior hippocampus: $r = .60$, $p = .004$; right anterior hippocampus: $r = .58$, $p = .006$), but bilateral posterior hippocampus did not (left posterior hippocampus: $r = .16$, $p = .48$; right posterior hippocampus: $r = .065$, $p = .78$). Conversely, bilateral posterior hippocampal activity to threat showed positive correlations with trait anxiety (left posterior hippocampus: $r = .46$, $p = .034$; right posterior hippocampus: $r = .44$, $p = .047$), but bilateral anterior hippocampus did not (left anterior hippocampus: $r = .05$, $p = .83$; right anterior hippocampus: $r = .27$, $p = .24$). These results suggest that anterior and posterior hippocampus respond distinctly to state and trait anxiety.

We further examined the specificity of these associations by performing multiple regression analyses. A regression analysis controlling for trait anxiety had no impact on the obtained relationship of state anxiety to anterior hippocampal activity (left anterior hippocampus: *semipartial* $r = .62$; right anterior hippocampus: *semipartial* $r = .64$); controlling for state anxiety had no impact on the observed relationship of trait anxiety to posterior hippocampal activity (left posterior hippocampus: *semipartial* $r = .5$; right posterior hippocampus: *semipartial* $r = .46$). Similarly, controlling for activity in ipsilateral anterior or posterior hippocampal activity had little or no effect on the observed relationships. That is, the relationship between state anxiety (as a dependent variable) and activity in anterior hippocampus (as an independent variable) was uninfluenced when activity in ipsilateral posterior hippocampus was included in the model (left anterior hippocampus: *semipartial* $r = .58$; right anterior hippocampus: *semipartial* $r = .60$). The relationship between trait anxiety (as the dependent variable) and activity in posterior hippocampus (as an independent variable) was uninfluenced when including activity in ipsilateral anterior hippocampus in the model (left posterior hippocampus: *semipartial* $r = .46$), though this relationship to right posterior hippocampus decreased slightly (*semipartial* $r = .36$). The interaction between state and trait anxiety did not correlate with activity in anterior or posterior hippocampal ROIs (all $ps > .15$). Finally, we examined whether self-reported anxiety under the safety period and trait anxiety correlated with activity in hip-

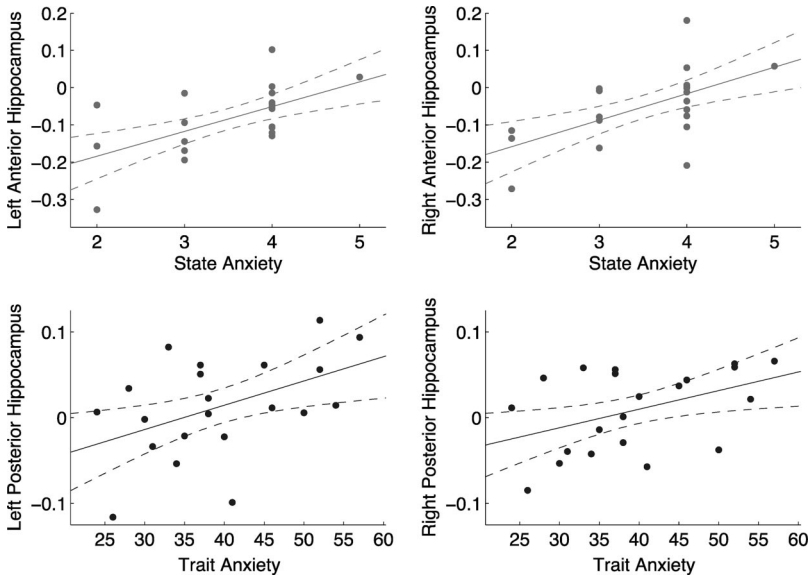

Figure 1. State and trait anxiety correlate with anterior and posterior hippocampal activity to threat. The two plots above (light grey circles) show that activity in anterior hippocampus to threat was positively correlated with self-reported state anxiety to the threat manipulation (left anterior hippocampus: $r = .60$, $p = .004$; right anterior hippocampus: $r = .58$, $p = .006$), whereas the two plots below (dark grey circles) show that activity in posterior hippocampus to threat was positively correlated with trait anxiety (left posterior hippocampus: $r = .46$, $p = .034$; right posterior hippocampus: $r = .44$, $p = .047$). Also pictured are the least-squares lines and 90% confidence bands.

pocampal ROIs to safety versus baseline. No significant effects were observed (all ps $> .1$).

Overall, these results suggest that state and trait anxiety are associated with anterior and posterior hippocampal activity within a context of threat. To further examine whether activity in hippocampus was specific to anxiety, we examined whether activity in hippocampal ROIs correlated with other self-report measures of emotion (Happy, Angry, Bored, and Aroused), but no significant correlates were found (all ps $> .1$, see online supplementary table).

Selective PPI Connectivity of Anterior (but Not Posterior) Hippocampus to Ventromedial Prefrontal Cortex

Next, we examined whether the moment-to-moment activity anterior hippocampus showed different functional connectivity patterns during threat than during safety with other brain regions (i.e., a PPI analysis; Friston et al., 1997) and whether such moment-to-moment activity could further distinguish anterior hippocampus from posterior hippocampus (i.e., a difference in PPI analyses in anterior and posterior hippocampi). Left anterior hippocampus showed significantly greater PPI connectivity (threat greater than safety) than left posterior hippocampus in anterior cingulate cortex (approximate Brodmann's Area ~BA 24/32) through ventromedial prefrontal cortex (~BA 10). To examine whether this interaction was due to a positive effect in left anterior hippocampus or a negative effect in left posterior hippocampus, PPI analyses were conducted for each region separately (see Supplementary Table for coordinates). This showed that significant activations in the difference between left anterior and left posterior hippocampal PPI analyses were driven by a greater PPI effect with left anterior hippocampus rather than by a negative PPI effect with left posterior hippocampus (Figure 2, light blue clusters indicate the overlap between the left anterior hippocampal PPI alone with the difference between left anterior and left posterior PPIs). No significant effects were found with the left posterior hippocampal PPI alone. Also, a direct comparison of PPIs from right anterior and posterior hippocampus showed no significant results.

Amygdala Activity and Anxiety

Though not the primary focus of this study, we conducted similar anatomically defined ROI analyses involving the amygdala. The main effect of threat versus safety on amygdala activity was not significant, left: $t(20) = 0.86$, $p = .4$; right: $t(20) = -1.58$, $p = .13$. However,like anterior hippocampus, amygdala was related to self-reported state anxiety during threat versus baseline, left: $r = .51$, $p = .02$; right: $r = .52$, $p = .016$, and was not significantly related to trait anxiety during threat, left: $r = .32$, $p = .15$; right: $r = .20$, $p = .39$. The interaction of state and trait anxiety was not associated with activity in amygdala (both ps $> .2$). Overall, this suggests that self-reported anxiety during threat was also related to heightened emotional arousal as indexed by amygdala.

Classification Task Performance

Behavioral piloting was conducted in a larger sample ($n = 42$) to ensure equivalent behavioral performance over time and even distributions of correct responses across trial types. Results from

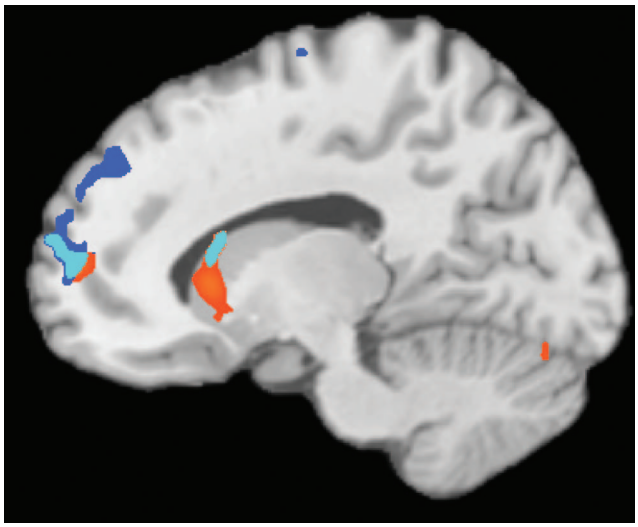

Figure 2. Neural regions showing greater functional connectivity during the threat versus safety period (PPI) with anterior hippocampus over posterior hippocampus. Activity in left anterior hippocampus is distinct from activity in left posterior hippocampus with regard to their connectivity profiles to other brain regions. The red blobs indicate the areas that showed greater moment-to-moment connectivity with left anterior hippocampal activity during threat versus safety periods (i.e., PPI connectivity) in comparison to the same PPI for left posterior hippocampal activity. To determine whether these regions were responding to a significant increase in PPI connectivity with anterior hippocampus or a significant decrease in PPI connectivity with posterior hippocampus, PPI analyses were performed for hippocampal ROIs separately. The blue blobs show regions that have greater PPI connectivity with the left anterior hippocampus alone. No regions showed significant PPI connectivity with left posterior hippocampus. In light blue is the overlap between the difference in hippocampal PPIs and the PPI for left anterior hippocampus alone, indicating that these regions are primarily driven an increase in PPI connectivity with left anterior hippocampus beyond contributions of left posterior hippocampus. Reported analyses are whole-brain corrected at the cluster level ($p < .05$). To help visualize the intersection (light blue blobs) more clearly, the blobs for the two contrasts (red and dark blue) were thresholded at a slightly more liberal value to see the surrounds. Image slice is shown at ($x = -14$).

this pilot showed roughly equivalent overall memory performance across threat and no threat conditions, Fs(1, 41) = .02, 1.40, ps > .2, for error rates and RTs, respectively. This was also the case in the present imaging sample, Fs(1, 19) = 1.28, .41, ps > .2, for error rates and RTs, respectively.

In the study design, participants were performing a classification-learning task during the threat-of-shock period and not during the baseline period. As such, it is possible that the correlations we observed with hippocampal ROIs and state and trait anxiety measures are mediated by learning performance (e.g., that participants with greater anxiety may have better performance on the learning task, which thereby leads to increased correlations with hippocampal activity). To ensure that the results were not a function of performance in the learning task, we included behavioral performance on the classification-learning task as a covariate. Behavioral performance was not associated with state anxiety, $r = .26$, $p = .29$; trait anxiety, $r = .12$, $p = .64$; or the interaction between state and trait anxiety, $r = .19$, $p = .46$, and also not to activity in hippocampal ROIs (all ps > .25). Moreover, controlling for behavioral performance using multiple regression analyses had no effect on the significance of the associations between anxiety measures and activity in hippocampal ROIs. Hence, classification learning does not account for the correlations obtained here.

Discussion

On the basis of theory and research in human studies of anxiety, which indicate that anxiety is composed of state and trait components (Spielberger, 1972; Spielberger et al., 1970), and behavioral and neural findings in studies of anxiety in rodents, which suggest that distinct subdivisions of the hippocampus are associated with contextual threats (Bannerman et al., 2004) and long-term stressors (e.g., Sapolsky et al., 1985; Uchida et al., 2008), we hypothesized that anterior and posterior hippocampal subregions in humans would be distinctly associated with state and trait forms of anxiety. To adequately address this question, we used targeted analytic techniques to separate activity in anterior hippocampus from posterior hippocampus (and from amygdala), by taking into account each participant's unique neuroanatomy. By doing so, we found that anterior hippocampal activity was uniquely associated with state anxiety, whereas posterior hippocampal activity was uniquely associated with trait anxiety. Furthermore, we found in a PPI analysis that during the threat period relative to the safety period, anterior hippocampal activity was more strongly correlated with several other prefrontal regions on a moment-to-moment basis than was posterior hippocampal activity. Such selective connectivity with prefrontal cortex suggests that anterior hippocampus is more involved in representing or responding to short-term contextual threats (in this case threat of uncertain shock) than is posterior hippocampus.

During the experiment, participants simultaneously completed a classification-learning task. Completing this task could be thought to interact with these results. Contrary to this notion, we found that performance on this task was not related to state or trait anxiety or to activity in hippocampal ROIs. Moreover, controlling for behavioral performance had no impact on the relationship between anxiety and activity in hippocampal ROIs. Hence, the results are unlikely to be accounted for by behavioral performance on the classification-learning task. Supporting this interpretation, a prior study in which participants completed a sequence learning task while under threat and safety conditions also found no interactive neural effects between the threat manipulation and activation during the behavioral task (Chua, Krams, Toni, & Passingham, 1999).

Broadly, these results support current themes in research on the hippocampus. First, research in nonhuman animals has suggested that the hippocampus is associated with anxiety, independently of its contribution to memory (Bannerman et al., 2004; Fanselow & Dong, 2010; Moser & Moser, 1998). The present results support this view by showing that activity in hippocampus is also associated with measures of anxiety in humans. A second theme is that the hippocampus displays distinct functionality along its longitudinal axis (Fanselow & Dong, 2010; Moser & Moser, 1998; Small et al., 2001). Here, we also observed dissociations between activity in anterior and posterior hippocampal ROIs, further supporting the fractioning of the hippocampus into subsections in humans. Fi-

nally, our results also promote a novel take on how hippocampal subregions may be involved in anxiety, as we discuss below.

The Anterior Hippocampus and State Anxiety

Along with the present findings, the involvement of anterior hippocampus in state anxiety is supported by several distinct lines of research in nonhuman animals. Behaviorally, lesions to anterior hippocampus produce anxiolytic effects across several behavioral tests for anxiety (Bannerman et al., 2004). Neurally, the anterior hippocampus shows a connectivity pattern to other neural regions that typically respond to threat, including its involvement in the HPA axis (Jacobson & Sapolsky, 1991), the amygdala (Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000), and ventromedial prefrontal cortex (Moser & Moser, 1998): all structures that have been centrally implicated in neural regions underlying anxiety (Rauch, Shin, & Wright, 2003). Similarly, it also shows a pattern of gene expression that mirrors that of the amygdala and hypothalamus (Dong et al., 2009).

We also found that anterior hippocampus shows selective PPI connectivity with prefrontal cortical regions above and beyond any contribution of posterior hippocampal connectivity with prefrontal regions. Such selective connectivity during a short-term period of threat supports the role of anterior hippocampus in state anxiety. Although the animal literature had previously demonstrated a structural connection between these regions (Moser & Moser, 1998; Thierry et al., 2000), these results extend the animal literature by showing that the connection is particularly operative under anxiety-provoking circumstances. Taken together, these findings support the hypothesis that state anxiety is related to activity in anterior hippocampus. They also support a reemerging viewpoint that the hippocampus may not be a mnemonic structure exclusively (Fanselow & Dong, 2010).

Despite these findings stemming from the animal studies, a handful of neuroimaging studies conducted in humans and using threat of pain paradigms have shown mixed results. Several have shown no association of the hippocampus to threat (Chua, Krams, Toni, & Passingham, 1999; Dalton et al., 2005; Hsieh, Stone-Elander, & Ingvar, 1999; Jensen, McIntosh, & Crawley, 2003; Porro, Baraldi, Pagnoni, & Serafini, 2002; Reiman et al., 1989; Simpson et al., 2001), at least one an overall decrease in activity to threat (Butler, Pan, Tuescher, & Engelien, 2007), and still others studying contextual fear conditioning showing increases in hippocampal activity (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Hasler et al., 2007; also see Ploghaus et al., 2000, for an expectancy violation model). Some of this inconsistency may be attributed to differences in the experimental paradigms used, such as the number of painful stimulations delivered and the demand placed on the subjects to internally maintain the threat context themselves or not.

However, beyond these factors, the present study raises three critical points on why such discrepancies are apparent between studies conducted in humans and those conducted in nonhuman animals. One is that the levels of pain used in human research are likely to be far milder than those used in animal research. Indeed, studies in rodents have shown that just a few tail shocks under restraint are capable of producing long-lasting PTSD-like symptoms in rodents (Rau, DeCola, & Fanselow, 2005). A second, related point is that threat of pain manipulations and the subjective emotional experience of anxiety are not necessarily synonymous with each other (see Barrett, 2006, for a discussion of this issue). Indeed, there are several individual differences in how people respond emotionally to the threat of shock, with some even finding the experience to be amusing (Rhudy & Meagher, 2003). In the present study, we found that hippocampal activity was particularly related to anxiety, but not to an overall effect of the threat manipulation. A final point, is that activity in anterior and posterior hippocampal subregions, as well as other medial temporal lobe structures, is likely to be blurred together when using whole-brain analysis approaches (Stark, 2007). The techniques used in the present study illustrate that these regions in fact contribute different sources of variability to anxiety—sources that could be adulterated when using standardized whole-brain analysis approaches. Future neuroimaging studies of anxiety may benefit from considering more targeted neuroanatomical analyses alongside subjective reports of anxious experience in examining the relationship of the hippocampus to anxiety.

The Posterior Hippocampus and Trait Anxiety

Although much attention has been given to the role of the anterior hippocampus in anxiety, far less attention has been paid to the involvement of posterior hippocampus in anxiety. In part, this may be because lesions to posterior hippocampus (or dorsal hippocampus in rodents) do not appear to influence anxiety-like behavior in rodents (Bannerman et al., 2004) and because the connectivity pattern and genetic expression of posterior hippocampus is not as associated with other emotion-related regions (Fanselow & Dong, 2010; Moser & Moser, 1998; Pitkänen et al., 2000). For these reasons, it has been argued that the posterior hippocampus is not as strongly involved in anxiety.

Contrary to this picture, however, other studies have shown that posterior hippocampal structure is influenced by chronic stress and through the genetic breeding of anxiety in rodents (Sapolsky et al., 1985; Uchida et al., 2008). In humans, these more longer term manipulations have been associated with increased levels of trait anxiety (Lau et al., 2006; Legrand et al., 1999; Sarason, Johnson, & Siegel, 1978). We observed that posterior hippocampal activity correlated with trait anxiety measures, which coincides with these results. This set of findings suggests that the posterior hippocampus is not immune to the influence of anxiety, but also that the kind of anxiety it is associated with is distinct from the state or more contextual bound forms of anxiety.

Indeed, the distinction between state and trait anxiety may help clarify some of these more puzzling inconsistencies. Speculatively, we suggest that posterior hippocampus may play an important role in mediating trait anxiety. One perspective on trait anxiety is that it is mediated by information-processing biases in attending to and interpreting events in the environment so as to appraise them as more threatening. In line with this notion, posterior hippocampus shows greater connectivity with posterior cortical regions (Fanselow & Dong, 2010), which may be involved in forming an initial perception or appraisal of one's environment. Such an initial appraisal may rely on the posterior hippocampus to access contexts that were similar, which ultimately may shape the way attention is directed to the environment and modulate the threat value placed on the context.

Implications for the Study of State and Trait Anxiety

The distinction between state and trait anxiety has been central to research in anxiety. It has lead to an abundance of novel research findings and research paradigms in both behavioral (Zeidner, 1998) and neural (e.g., Bishop, Jenkins, & Lawrence, 2007; Etkin et al., 2004) studies. However, since its inception, the underlying nature of the division between state and trait anxiety, particularly with regard whether state and trait anxiety reflect distinct components, has been unclear. Our results show that state and trait anxiety map onto distinct neural regions, which supports the division of anxiety into distinct components. These results coincide with recent behavioral (Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010) and neural (Bishop et al., 2007; Denkova et al., 2010) findings, which show dissociations between these two components of anxiety.

Our results further compliment the conceptual formulation of these components (Spielberger, 1972; Spielberger et al., 1970; Spielberger & Vagg, 1984). State anxiety is considered to reflect to the subjective feelings of apprehension experienced in response to a short-term stressor. We found that the subjective experience of anxiety during a period of short-term threat was associated with anterior hippocampal activity, which itself is associated with a network of regions involved in producing and regulating emotional responses, including the hypothalamic–pituitary–adrenal (HPA) axis and the ventromedial prefrontal cortex. Trait anxiety is considered to reflect enduring cognitive and perceptual biases in perceiving events to be more or less threatening to begin with. We found that trait anxiety was related to activity in the posterior hippocampus, which has a stronger connectivity profile with posterior cortical regions (Fanselow & Dong, 2010) and may underlie cognitive or perceptual biases in perceiving a stimulus or context to be more threatening. Ultimately, the results support the division of anxiety into distinct functional component reflecting state and trait anxiety and suggest that distinct networks may underlie their functionality.

A secondary consideration is the interaction between state and trait anxiety. As shown in several studies typically involving naturally varying state and trait anxiety, these components often, but not always, interact (Mathews, 1990; Williams, Mathews, & MacLeod, 1996). In the present study, we found no evidence for such interactions within anterior or posterior hippocampus or amygdala. However, the experiment was also designed to maximize the differences between state and trait anxiety by manipulating state anxiety using threat of shock. Intriguingly, other studies using similar procedures commonly do not find or report interactions between measures of state anxiety to the threat manipulation and trait measures of anxiety, and additionally, most do not show correlations between state and trait anxiety measures (e.g., Dalton et al., 2005; Grillon, Ameli, Foot, & Davis, 1993; Ochsner et al., 2006; Simpson et al., 2001). In contrast, studies that do observe state and trait interactions frequently do so by capitalizing on naturally varying state and trait anxiety in the subject population rather than inducing state anxiety using an experimental manipulation (Zeidner, 1998, for a review). This methodological difference may account for why interactive effects are not as commonly found in studies that experimentally manipulate state anxiety using threat of pain.

Conclusions and Future Directions

A central question of future interest is how the involvement of hippocampus in anxiety integrates with its well-established role in memory. Integration of anxiety and memory has been addressed previously (e.g., Gray & McNaughton, 2000), though not necessarily with specific reference to hippocampal subdivisions. To account for this, new models based on research in nonhuman animals have proposed a relatively strict division of the hippocampus into subregions that subserve mnemonic functions and others that subserve affective functions. Extending such models to humans, an increasing number of fMRI studies have also suggested that anterior and posterior hippocampal subregions may implement distinct functions, but do not support a strict separation of hippocampus into divisions that relate to anxiety and memory exclusively. Indeed, our study suggests that both anterior and posterior divisions are associated with anxiety, but different forms of anxiety. Similarly, numerous human neuroimaging studies have found that both regions are associated with mnemonic processes, though the kinds of mnemonic processes that engage each subregion may also be distinct (e.g., Schacter & Wagner, 1999). Future studies aimed at uncovering how the hippocampus integrates processes related to both anxiety and memory along its longitudinal axis may help to resolve these findings.

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Received January 5, 2011
Revision received October 25, 2011
Accepted October 27, 2011 ■