When the brain is prepared to learn: Enhancing human learning using real-time fMRI

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ABSTRACT

The rate of learning or memory formation varies over time for any individual, partly due to moment-to-moment fluctuation of brain state. Functional neuroimaging has revealed the neural correlates of learning and memory, but here we asked if neuroimaging can causally enhance human learning by detection of brain states that reveal when a person is prepared or not prepared to learn. The parahippocampal cortex (PHC) is essential for memory formation for scenes. Here, activation in PHC was monitored in real-time, and scene presentations were triggered when participants entered "good" or "bad" brain states for learning of novel scenes. Subsequent recognition memory was more accurate for scenes presented in "good" than "bad" brain states. These findings show that neuroimaging can identify in real-time brain states that enhance or depress learning and memory formation, and knowledge about such brain states may be useful for accelerating education and training. Further, the use of functional neuroimaging as a causal, rather than correlative, tool to study the human brain may open new insights into the neural basis of human cognition.

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Introduction

The rate of learning or memory formation varies over time for any given individual, partly due to moment-to-moment fluctuation of brain state (Boly et al., 2007; Fernandez et al., 1999; Gilden et al., 1995). Varying levels of alertness, attention, and motivation likely contribute to fluctuating brain states for learning. Blood oxygenated level dependent (BOLD) signal levels in specific brain regions can be used to measure such brain state fluctuation. Although little is known about the relationship between fluctuating brain states and successful memory formation, there is ample evidence about neural systems that underlie successful learning. Humans and other mammalian species depend upon the integrity of a medial temporal lobe (MTL) system that is essential for declarative or explicit memory for events and facts (Cohen and Squire, 1980; Corkin, 2002; Graf and Schacter, 1985; Scoville and Milner, 1957; Squire, 1992). Within the MTL, there is considerable evidence that the parahippocampal cortex (PHC) is essential for successful memory formation for scenes. Patients with lesions in the PHC cannot learn new spatial environments (e.g., Epstein et al., 2001), and in healthy people there is greater PHC activation for scenes that are later remembered than for scenes that

are later forgotten (Brewer et al., 1998; Gabrieli et al., 1997; Stern et al., 1996). PHC activation is also associated with successful memory formation for words (e.g., Wagner et al., 1998). The important role of PHC in learning scenes may be related to its specialization for scenes in high-level vision — a functional region within PHC has been termed the "parahippocampal place area" or PPA because it responds maximally to scenes relative to other visual categories such as faces and objects (Epstein and Kanwisher, 1998).

There is also evidence that the brain state occurring *prior* to stimulus presentation (in contrast to the above-reviewed studies of stimulus-evoked activation that occurs in response to a stimulus) influences memory formation for that stimulus. Pre-stimulus evoked response potentials (ERPs) correlated with memory for words (Otten et al., 2006). Within the MTL, pre-stimulus sustained entorhinal activation correlated with successful memory for words (Fernandez et al., 1999), and pre-stimulus PPA activation correlated with successful memory for scenes (Turk-Browne et al., 2006).

Knowledge of brain states that correlate with learning creates the opportunity to enhance learning itself. In animal conditioning, hippocampal theta activity (2–8 Hz oscillatory field potentials) predicts behavioral learning rate (Berry et al., 1978; Berry and Swain, 1989; Seager et al., 2002). Triggering learning trials on the basis of hippocampal theta activity enhanced learning in eyeblink conditioning in rabbits (Asaka et al., 2005; Griffin et al., 2004; Seager et al., 2002). Thus, an invasive measure of brain state could be used to enhance learning in animals by having learning occur during an optimal brain state.

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Here, we asked whether human learning and memory could be increased or decreased by identifying, on a moment-to-moment basis, whether a person was in a good or bad brain state for learning scenes, and triggering presentation of each to-be-learned scene by the presence of a good or bad brain state. In Experiment 1, we examined whether such brain states that were good or bad for learning scenes could be identified in the PPA. In Experiment 2, we examined whether such brain states in the PPA, detected by real-time functional magnetic resonance imaging (fMRI) on a moment-moment basis, could be used to trigger scene presentation with the hypothesis that scenes triggered by good brain states would be better remembered than scenes triggered by bad brain states. Such a finding would offer evidence of the ability to monitor on-line whether a person is optimally prepared to learn, and the ability to use fMRI to causally enhance human learning in the sense that the real-time fMRI-measured brain state caused the scene presentation.

Experiment 1: identification of a brain state of preparedness to learn

The goal of Experiment 1 was to define the kind of BOLD signal of brain state that we could use to control learning in Experiment 2. Further, the location of that signal had to be a region that could be defined a priori in each individual, namely a PPA region (typical subsequent memory studies define memory-related regions a posteriori on the basis of memory outcomes).

Methods

Participants

Twenty right-handed participants (mean age = 27.1 years; 9 males, 11 females) with normal or corrected-to-normal vision participated (three participants were excluded because of excessive movement during scanning; one participant was excluded because of poor behavioral performance). Participants were paid, and gave written informed consent approved by the MIT Committee on Human Subjects.

Task materials and procedure

Participants were told that a recognition test would follow study of scenes during scanning. Participants viewed 250 color photographs of indoor and outdoor scenes, presented one at a time for 3 s, followed by a fixation cross for 9 s. For each trial, they were instructed to determine whether they thought that they would remember or forget the presented scene later, and to respond by pressing one of two buttons. Participants had up to 12 s (3 s of stimulus duration plus 9 s of fixation) to respond. Presentation of stimuli was randomized for all participants, and divided into 5 successive sessions. About 10 min after the scanned study phase, participants were administered on a computer a recognition memory test outside of the scanner consisting of 500 randomly presented scenes – 250 old (studied) and 250 new (unstudied foils) – with equal numbers of indoor and outdoor scenes in the studied and unstudied sets. Participants responded using a 4-button confidence scale ranging from old to new.

Image acquisition

Functional images were acquired using MRI at 3T with a 32-channel phased-array head coil with online motion correction enabled (Thesen et al., 2000) gradient-echo, echo-planar imaging pulse sequence (MAGNETOM TIM Trio, Siemens Healthcare, Erlangen, Germany). Pulse sequence parameters were: TR = 2 s, bandwidth = 2298 Hz/pixel, flip angle = 90°, matrix size = 64×64, field of view = 200×200 mm^2, number of slices = 32, slice thickness = 3.5 mm and slice gap = 10%.

Statistical analyses

All participants' imaging data were preprocessed (realigned, normalized and smoothed) and analyzed in SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). To investigate pre-stimulus BOLD signals and their correlation with successful learning, we performed a two-step subject-specific modeling analyses. First, each subject's trials were grouped into three experimental conditions 'remembered' ('hit'), 'know' ('weak hit'), and 'forgotten' ('strong' and 'weak misses' combined). The conditions were modeled using general linear modeling (GLM) with finite impulse responses (FIR) of order 6 as basis functions to derive subject-specific empirical hemodynamic response functions for each experimental condition. The second model for each subject included 2 s (1TR) pre-stimulus conditions (i.e., 'pre-stimulus hit', 'pre-stimulus weak hit', and 'pre-stimulus miss') in addition to 3 experimental conditions. For this GLM, a FIR of order 1 was used as a basis function for pre-stimulus conditions, and the derived empirical HRF's were used as basis functions for experimental conditions. This modeling approach accounted for the BOLD signals associated with the onset and subsequent encoding of scenes presented. A high-pass filter of 50 s was applied to the data.

To minimize the influence of guessing on analyses, we considered remembered scenes as only old scenes rated high-confident old and forgotten scenes as any old scene rated as either high-confident or low-confident new. Pre-stimulus activation levels for subsequently remembered (high-confident hits) and forgotten (misses) scenes were compared in individual participants. We used a PPA probability mask created from an independent set of fMRI data collected during a functional localizer for PPA for conducting an ROI analysis where the PPA was defined by greater activation for scenes than faces and objects.

Results

Recognition performance is reported in Table 1. Pre-stimulus activation in left PPA was significantly lower for remembered scenes than forgotten scenes ($t_{19} = 2.21$, $p = 0.04$ two-tailed) (Fig. 1).

A prior report of a positive correlation between pre-stimulus PPA activation and subsequent memory noted that pre-stimulus PPA activation predicted subsequent memory when no filter was applied, but did not predict subsequent memory using a 128 s period cutoff (Turk-Browne et al., 2006). Because stimuli are categorized a posteriori on the basis of memory outcome, the selection of a high-pass filter is somewhat arbitrary. Data were reanalyzed with no high-pass

Table 1
Average results (N = 20) from recognition memory test in Experiment 1.

	Mean (%)	Standard deviation (%)
Studied scenes		
Hits (total)	61.3	13.3
High-confident	40.1	14.2
Low-confident	21.1	11.8
Misses (total)	38.7	13.3
High-confident	22.9	11.0
Low-confident	15.9	16.6
Foils		
Correct rejections (total)	74.4	17.9
High-confident	36.8	22.4
Low-confident	37.6	20.2
False alarms (total)	25.6	17.9
High-confident	10.2	16.0
Low-confident	15.4	10.1
No responses	0.6	0.9

Old scenes (250 items) were categorized as either Hits or Misses with high or low confidence ratings, and foils (250 items) were categorized as correct rejections or false alarms with high or low confidence ratings.
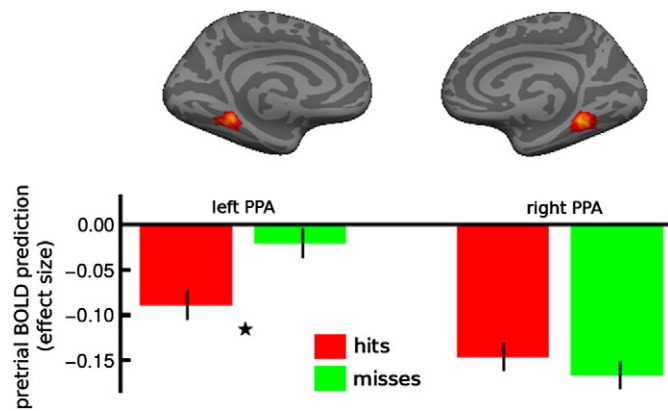
Fig. 1. Pre-stimulus activation level in parahippocampal place area (PPA) predicts learning of scenes in Experiment 1. Pre-stimulus activation levels in PPA were measured in effect sizes (i.e., estimated parameter values of the general linear model) and plotted in arbitrary units on the Y axis for subsequently remembered (hits) and forgotten (misses) scenes in bilateral PPA in Experiment 1. Left PPA BOLD signal 2 s (1 repetition time) prior to stimulus onset for remembered scenes is significantly lower than signal associated with forgotten scenes (*: p<0.05). Error bars represent 95% confidence intervals for within-subjects design (Cousineau, 2005).

filtering or with a longer (100 s) high-pass filter. Without high-pass filtering, there was no significant PPA activation difference between remembered and forgotten scenes. With the 100 s filter, the left PPA showed a marginally significant reduction in activation for remembered relative to forgotten scenes ($t_{19} = 1.97$, p = 0.06 two-tailed). Again, there was not a reliable difference in right PPA activation. In general, fMRI studies use a high-pass filter to reduce low-frequency noise, but it is of interest that these findings are sensitive to the choice of the high-pass filtering.

Discussion

The finding that lower pre-stimulus activation in the PPA correlated with subsequent memory for that stimulus is similar but opposite in direction from a previous study that reported a positive correlation between pre-stimulus PPA activation and subsequent memory for scenes (Turk-Browne et al., 2006). The difference in direction may be related to differences in inter-stimulus intervals (9 s in the present study to minimize overlap of hemodynamic responses between a stimulus-evoked trial and the subsequent pre-stimulus period vs. 2–6 s in the prior study) or the use of subject- and condition-specific empirical hemodynamic response functions (HRFs) in the present study to discount residual activation from the prior stimulus versus a canonical HRF in the prior study. Further, as noted previously (Turk-Browne et al., 2006), the selection of a high-pass filter value influences these findings.

Although the activation difference for subsequently remembered and forgotten scenes was significant only in the left PPA in Experiment 1, we used both left and right PPAs as ROIs in Experiment 2 because most studies examining memory for scenes have reported bilateral PHC activations associated with successful memory formation (Brewer et al., 1998; Ofen et al., 2007; Stern et al., 1996; Turk-Browne et al., 2006).

Experiment 2: controlling human learning via real-time monitoring of brain state

Methods

Participants

Sixteen right-handed participants (mean age = 21.5 years; 9 males, 7 females; all different participants from Experiment 1) with normal or corrected-to-normal vision participated.

Task materials and procedure

The real-time design required longer inter-stimulus periods than Experiment 1, so we could only present 40 to 80 study scenes in Experiment 2 relative to 250 study scenes in Experiment 1. To compensate for the reduced number of scenes, we shortened the stimulus duration to 1 s, and conducted the recognition test two hours post-scan so as to yield enough remembered and forgotten items for fMRI analyses. The imaging session consisted of two phases — (1) individual delineation of functional PPA and reference ROIs, and (2) the use of those ROIs to measure brain state and trigger scene presentation.

ROI definitions. Participant-specific bilateral PPAs were defined using a functional PPA localizer in which participants viewed a series of color images of indoor and outdoor scenes, objects, and faces in a block-design and responded with a button press whenever an item repeated. Each experimental block was 16 s in duration and consisted of 20 trials. There were 3 repeated images in each block and each kind of block repeated 3 times over the scan. Within each trial, an image was displayed on the screen for 500 ms followed by 300 ms of fixation. Four 16 s long fixation blocks were also included in the localizer, resulting in a scan that was just over 4 min with 128 measurements acquired. After image reconstruction and online motion correction, incoming images were stored to disk on a dedicated fMRI data analysis computer using a custom data sender via intranet communication. Once all images were acquired, an fMRI analysis was done using the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl/) while the participant was in the scanner. The PPAs were located by a cluster of voxels more active for scenes than faces and objects (Epstein et al., 1999).

A general linear model (GLM) design matrix was constructed based on the stimulus schedule of the functional localizer with canonical hemodynamic response functions to each of the scenes, objects and faces conditions and their temporal derivatives as bases. A GLM fit was performed and the parameter estimates were then transformed into statistical images representing activation in experimental conditions. The PPAs were identified by voxels with statistically significantly higher activation levels during indoor and outdoor scenes relative to faces and objects.

Bilateral PPA ROIs were defined by thresholding the scenes versus faces and objects statistics volume until bilateral clusters in the assumed region of PPA were clearly delineated from the rest of PHC and became similar in size and shape to the PPA ROI probability mask used in Experiment 1. All voxels that survived this thresholding were included in the PPA ROI. We then performed a dilation operation by 5 voxels on the PPA ROI to slightly expand the ROI so as to anticipate potential movement in the upcoming scan.

The group average PPA was computed off-line to depict the average location of the ROIs across participants. This was done by using spatial normalization with SPM5 to compute transformation matrix for spatially warping mean functional image to MNI space, and then applying the resulting transformation to individual participant's PPA ROIs. The PPA ROIs in MNI space were then averaged across participants to form a group average of PPA ROIs (Fig. 2).

The difference between PPA and reference ROIs was used as the signal to be monitored in real time. Participant-specific reference ROIs were created so that any changes in the PPA ROI reflected specific ROI fluctuations in BOLD signal, rather than broader, non-specific changes due to physiological noise or movement. Reference ROIs were constructed by taking the participant's whole-brain mask and subtracting regions that were active during all experimental conditions of scenes, faces, and objects (vs. fixation; threshold T = 0.1) as well as the dilated PPA ROI.

Measuring brain states and triggering stimulus presentation using rtfMRI. In the same scan session, participants passively viewed a fixation cross during scans while brain state was continuously monitored by
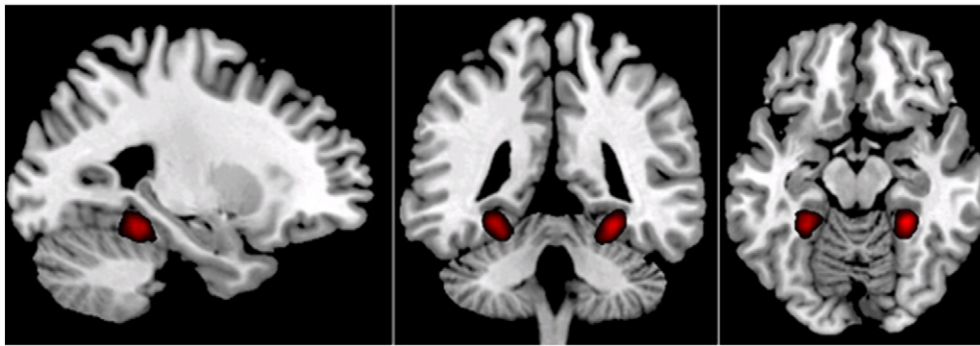
Fig. 2. Group average of PPA ROIs used for defining brain states in Experiment 2. All individual PPA masks were spatially normalized, and averaged to create a probabilistic map of PPA ROIs. Here, p>0.2 was used as a threshold to depict group average of PPA ROIs.

computing BOLD signal fluctuations within the PPA and reference ROIs. Incoming images were analyzed to estimate neural activation levels using a novel real-time fMRI method (Hinds et al., 2011).

Incoming EPI volumes were sent from the scanner via TCP/IP connection to an external analysis computer immediately after image reconstruction and motion-correction (Thesen et al., 2000), processed voxel-wise to estimate activation, and finally voxels within each ROI were combined. At each timepoint, an incremental GLM fit to each voxel's timeseries was updated. The model design included bases to account for zeroth and first order temporal trends, as well as bases to account for the activation evoked by item presentation. The contribution of each of these nuisance signals was removed from the measured signal, leaving contributions from neural sources and noise. The result was converted to units of standard deviation (SD) from baseline using the estimated timeseries variance given by the GLM. The activation level within each ROI was computed as the median SD across all the voxels in the ROI.

A brain state was defined as the difference between the PPA and the reference ROI, with a "good" brain state defined as PPA activation being less than the reference ROI activation by a participant-specific threshold and a "bad" brain state defined as the PPA activation being greater than the reference ROI by the same threshold (thresholds were participant-specific so as to obtain a similar number of trials per participant). Whenever the absolute value of the difference between the PPA and reference ROI activation exceeded a predefined SD threshold, i.e. whenever participants enter their "good" or "band" brain state, a study trial was triggered and one scene was presented on the screen for 1 s (Fig. 3). To prevent activation evoked by item presentation from corrupting future fluctuation estimates, an event centered at the trigger TR (2 s) was convolved with a canonical hemodynamic response function and added to the design matrix as a nuisance basis. No triggers were possible for 24 s following a trial. The participant-specific threshold was determined by manually adapting the threshold after each functional run (from the initial threshold of 1 SD) so there were approximately 10 triggers per each functional run. Trial trigger thresholds were determined at the outset of each run and held constant in that run. If there were too few trials triggered in a run, the threshold was adjusted prior to the next run so that enough trials would occur in the experiment to be support a contrast between remembered and forgotten scenes. Participant-specific thresholds ranged from 0.65 SD to 1 SD.

Participants were told that a recognition test would follow study of scenes during scanning. After a scene was presented, participants responded by pressing one of two buttons depending on whether the presented item was an indoor or an outdoor scene. No stimuli were repeated in the PPA localizer and rtfMRI encoding session. A minimum inter-trial interval of 24 s was required before the next trigger to ensure that the evoked response to the previous trial had returned to baseline. Each participant underwent between 5 and 7 brain-state triggering fMRI scans of 8 min, depending on how many good and bad

triggers were accumulated so that each participant had a minimum of 40 and a maximum of 80 trials.

About 2 h after the scanned study phase, participants were administered on a computer a recognition memory test outside of the scanner consisting of randomly presented studied scenes and foils. Unlike Experiment 1, participants were first asked if the test scene was 'old' or 'new', and when the response was 'old', then the participants were asked to rate their confidence using a 2-button scale.

Statistical analyses

Recognition accuracy was calculated as correct identification of old scenes (% hits) minus incorrect identification of new scenes (% false alarms) as old.

Results

Recognition performance for "good" and "bad" brain states is presented in Table 2. Participants were significantly more accurate for remembering scenes triggered by good brain states (Hits – False Alarms X = 22.3%, SD = 14.3%) than by bad brain states (Hits – False Alarms X = 15.5%, SD = 11.8%) (t_{15} = 2.78, p<0.014, two-tailed t-test) (Fig. 4). Hit rates in both brain states were significantly higher than false alarm rates (t_{15} = 6.23, p<0.001, two-tailed t-test). Memory improvements for scenes triggered by "good" relative to "bad" states were observed in 12 of 16 participants. The difference between good and bad brain states occurred for high-confident hits (t_{15} = 1.95, p<0.07, two-tailed t-test), with little difference for low-confident hits (t_{15} = 0.37, p = 0.71, two-tailed t-test).

We examined the consequence of using the difference between PPA and reference-ROI activations as triggers for scene presentation relative to only using the PPA activation values as triggers for scene presentation. Using PPA values only, there was still significantly better memory for scenes triggered by low than by high PPA activations (t_{15} = 3.34, p<0.005, two-tailed t-test).

Mean item positions across the good and bad brain states did not differ across participants (t_{15} = 0.08, p = 0.94, two-tailed). We also examined the distribution of good and bad brain states in a repeated measures ANOVA of brain state (good/bad) × run (Fig. 5), and also the distributions within runs (i.e., item positions within each run). The effects of state, run, and item positions within runs and their interactions were not significant (p's>0.79), suggesting that the differences in brain states were not related to factors such as primacy or recency effects or fatigue across the experiment.

Discussion

We identified a brain state in the PHG, specifically the PPA, that was associated with better or worse memory formation (Experiment 1), and
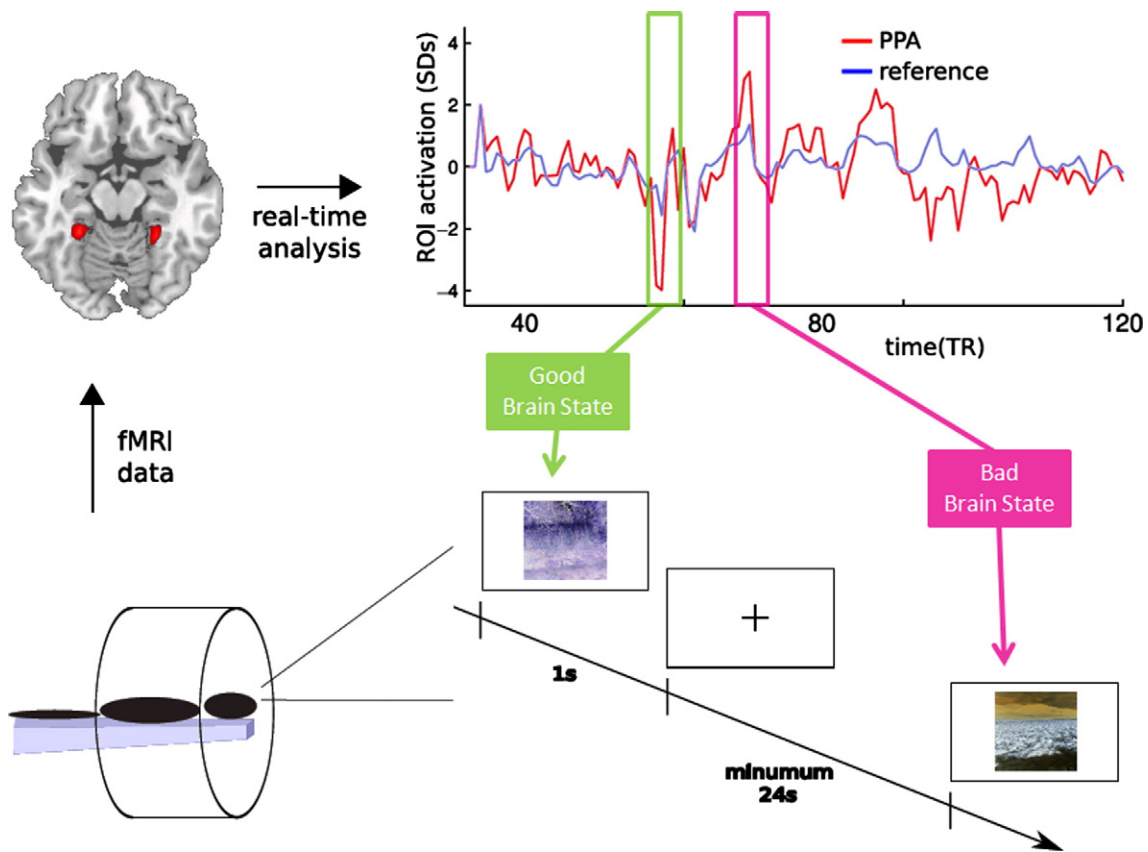
Fig. 3. The real-time fMRI system. A real-time fMRI system was used to monitor the brain signal in individual PPA ROIs. Individual's PPA regions were spatially normalized, and averaged to create a probabilistic map of PPA ROI across participants for this figure (regions in red are voxels that were in at least 30% of participants). Example from one participant plotted on the graph with PPA signal (red line) and the reference ROI signal (blue line). Whenever PPA ROI signal was less or more than reference ROI signal by an amount greater than the participant-specific threshold, a "good" or "bad" brain state trigger was issued to the stimulus presentation computer. When there was a "good" or "bad" trigger, a scene was presented for 1 s and participants were asked to label the scene as indoor or outdoor.

then used real-time fMRI to monitor that brain state and to present information to-be-learned in either a good or bad brain state for learning (Experiment 2). Real-time, dynamic measurement of brain state prior to stimulus presentation resulted in either increased or decreased learning depending upon whether the brain was in a good or bad state for learning. Indeed, successful formation for memories increased by over a third when the PPA was in a prepared-to-learn state. Thus, human brain preparedness to learn can be measured and used to control the rate of

learning or memory acquisition. There are, presently, no on-line behavioral measures of preparedness to learn that can be made prior to learning itself; brain measures may offer a unique window onto human preparedness to learn.

An unexpected finding was that decreased, rather than increased, pre-stimulus activation in the PPA predicted successful memory formation in both Experiments 1 and 2. This contrasts with the

Table 2
Average results (N = 16) from the recognition memory test for the good and bad brain states in Experiment 2.

	Mean (%)	Standard deviation (%)
Good brain state		
Hits (total)	48.8	16.6
High-confident	27.7	14.1
Low-confident	21.1	8.4
Misses	51.2	16.6
Bad brain state		
Hits (total)	41.9	15.8
High-confident	21.9	11.9
Low-confident	20.0	11.0
Misses	58.1	15.8
Foils		
False alarms (total)	26.5	11.3
High-confident	6.9	4.2
Low-confident	19.6	8.5
Correct rejections	73.5	11.3

Old scenes were categorized as either Hits or Misses, and further categorized with high or low confidence ratings. Foils were categorized as correct rejections (without confidence ratings) or false alarms with high or low confidence ratings.
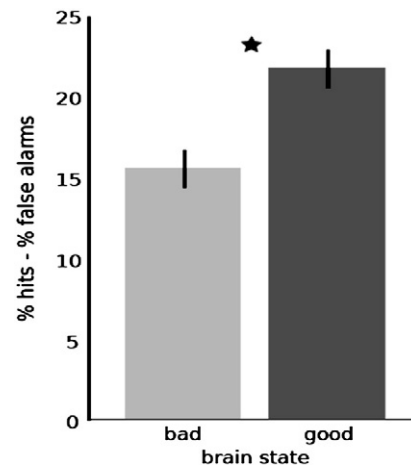

Fig. 4. Real-time measurement of brain state alters recognition performance. Participants were significantly more accurate for scenes in which presentation was triggered by a good brain state than a bad brain state. Error bars represent 95% confidence intervals for within-subjects design (Cousineau, 2005).
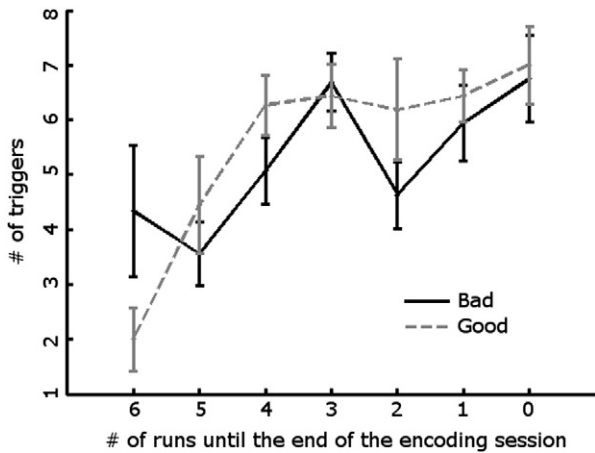
Fig. 5. Distribution of good and bad brain states across Experiment 2. Mean numbers of good and bad brain-state trials are plotted from beginning (Run 6) through the end (Run 0) of Experiment 2 for all 16 participants. Error bars represent standard errors computed over subjects for each run.

general finding that greater stimulus-evoked activation is associated with successful memory formation for scenes (e.g., Brewer et al., 1998; Gabrieli et al., 1997; Stern et al., 1996), and also with the prior observation that under different experimental circumstances greater pre-stimulus activation was associated with successful memory formation (Turk-Browne et al., 2006). The finding in this study that lower pre-stimulus PPA activation predicted superior learning appears convincing because it was not only replicated for the left PPA across Experiments 1 and 2, but also it was causal for superior memory formation in Experiment 2. It may be speculated that lower activation reflects a lack of processing activity in the PPA, and that more resources are available for memory encoding during such an ebb of PPA activity. Further studies will needed, however, to delineate the circumstances under which lesser or greater PPA activation is associated with superior memory formation for scenes.

One limitation of this study is that because ROIs were required to be defined during the same scan session as the real-time fMRI component of the study, the process of ROI delineation involved some observer-dependent decision making. Efforts were made to keep the number of voxels in ROI to be as consistent as possible across participants. Future studies will be needed to better automate ROI definition, but because the identical ROI was used within each participant to define good and bad brain states per subject, ROI definition did not bias the behavioral outcome. A second limitation was that because there was no neutral baseline, we cannot know whether the increased learning or decreased learning that occurred in good or bad brain states, respectively, reflect only gains, only losses, or both relative to baseline.

We measured brain state in a functional brain region, the PPA, specifically associated with learning scenes, and future studies can determine whether preparedness to learn can be measured in other brain regions associated with either other kinds of domain-specific knowledge (e.g., fusiform cortex for faces, amygdala for emotional material) or with domain-general learning (e.g., hippocampus). The use of a contrast between the PPA and a reference ROI was made to minimize the possibility that the PPA signal would reflect movement or broad physiological noise or broad arousal state of the brain. Domain-specific attentional or arousal mechanisms may be relevant, and future studies could manipulate attention and arousal to test this possibility. However, in a similar real-time triggering study involving reaction time to an unpredictable visual target (Hinds et al., submitted for publication), greater pre-stimulus activation in motor cortex (SMA) and lesser brain activation in default brain regions were found to be related to faster performance. These findings suggest that pre-stimulus measures of optimal brain states occur in neural systems that are associated with specific functions.

This study demonstrated that fMRI can not only identify the neural correlates of human behaviors, but also provide a kind of causal relation between brain activation and human behavior. Functional neuroimaging studies, including fMRI, are typically correlative in nature. In such studies, task conditions or materials are the independent variables used to drive variable kinds of behaviors, and the fMRI signal is the correlate of those behaviors. This correlative approach is fruitful in neuroscience, from single-cell animal neuro-physiology to human brain imaging, but causal methods are a valuable complement for the study of brain function. In the present study, the fMRI measure of PPA activation, relative to a reference ROI, was the independent variable that drove stimulus presentation, so the fMRI signal was the cause of behavior (good or bad learning). Thus, this study shows that fMRI can be used as a causal tool to study the functional organization of the human brain. Such causal activation, however, does not fully define a brain region as being causal or necessary for a behavior. For example, pre-stimulus fluctuations in the PPA may have correlated with brain functions in other brain regions that were causal for the memory formation.

Many fMRI studies have focused on impaired functions in neurological and psychiatric disease with the aim of understanding how impaired brain functions contribute to those diseases, but few, if any, fMRI studies have explored whether fMRI methods could enhance or optimize typical human abilities. The ability to identify when the brain is prepared to learn could, in theory, be useful for education and training. Either students could improve their ability to be prepared to learn, or teachers could recognize when students were prepared or not prepared to learn; in both cases learning would proceed more efficiently. Practical application of the newfound ability to identify brain preparedness to learn will require some sort of translation from fMRI to a method suitable for wider, practical use. How fMRI findings may be further optimized and translated into uses beyond a scanner is currently unknown, but these findings indicate that progress is possible in enhancing human learning by measuring brain states and using those measurements to guide effective learning.

Acknowledgment

References

Asaka, Y., Mauldin, K.N., Griffin, A.L., Seager, M.A., Shurell, E., Berry, S.D., 2005. Nonpharmacological amelioration of age-related learning deficits: the impact of hippocampal theta-triggered training. Proc. Natl. Acad. Sci. U. S. A. 102, 13284–13288.
Berry, S.D., Swain, R.A., 1989. Water deprivation optimizes hippocampal activity and facilitates nictitating membrane conditioning. Behav. Neurosci. 103, 71–76.
Berry, S.D., Rinaldi, P.C., Thompson, R.F., Verzeano, M., 1978. Analysis of temporal relations among units and slow waves in rabbit hippocampus. Brain Res. Bull. 3, 509–518.
Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., Phillips, C., Peigneux, P., Maquet, P., Laureys, S., 2007. Baseline brain activity fluctuations predict somatosensory perception in humans. Proc. Natl. Acad. Sci. U. S. A. 104, 12187–12192.
Brewer, J.B., Zhao, Z., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1998. Making memories: brain activity that predicts how well visual experience will be remembered. Science 281, 1185–1187.
Cohen, N.J., Squire, L.R., 1980. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science 210, 207–210.
Corkin, S., 2002. What's new with the amnesic patient H.M.? Nat. Rev. Neurosci. 3, 153–160.
Cousineau, D., 2005. Confidence intervals in within-subject designs: a simpler solution to Loftus and Masson's method. Tutorial in Quantitative Methods for Psychology, 1, pp. 42–45.
Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392, 598–601.
Epstein, R., Harris, A., Stanley, D., Kanwisher, N., 1999. The parahippocampal place area: recognition, navigation, or encoding? Neuron 23, 115–125.

Epstein, R., DeYoe, E., Press, D., Rosen, A., Kanwisher, N., 2001. Neuropsychological evidence for a topographical learning mechanism in parahippocampal cortex. Cogn. Neuropsychol. 18, 481–508.

Fernandez, G., Brewer, J.B., Zhao, Z., Glover, G.H., Gabrieli, J.D., 1999. Level of sustained entorhinal activity at study correlates with subsequent cued-recall performance: a functional magnetic resonance imaging study with high acquisition rate. Hippocampus 9, 35–44.

Gabrieli, J.D., Brewer, J.B., Desmond, J.E., Glover, G.H., 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 276, 264–266.

Gilden, D.L., Thornton, T., Mallon, M.W., 1995. 1/f noise in human cognition. Science 267, 1837–1839.

Graf, P., Schacter, D.L., 1985. Implicit and explicit memory for new associations in normal and amnesic subjects. J. Exp. Psychol. Learn. Mem. Cogn. 11, 501–518.

Griffin, A.L., Asaka, Y., Darling, R.D., Berry, S.D., 2004. Theta-contingent trial presentation accelerates learning rate and enhances hippocampal plasticity during trace eyeblink conditioning. Behav. Neurosci. 118, 403–411.

Hinds, O., Ghosh, S., Thompson, T.W., Yoo, J.J., Whitfield-Gabrieli, S., Triantafyllou, C., Gabrieli, J.D., 2011. Computing moment to moment BOLD activation for real-time neurofeedback. Neuroimage 54, 361–368.

Hinds, O., Thompson, T.W., Ghosh, S., Yoo, J.J., Whitfield-Gabrieli, S., Triantafyllou, C., Gabrieli, J.D., submitted for publication. Causal Roles of Default-Mode Network and Supplementary Motor Area in Human Vigilance: Evidence from Real-Time fMRI.

Ofen, N., Kao, Y.C., Sokol-Hessner, P., Kim, H., Whitfield-Gabrieli, S., Gabrieli, J.D., 2007. Development of the declarative memory system in the human brain. Nat. Neurosci. 10, 1198–1205.

Otten, L.J., Quayle, A.H., Akram, S., Ditewig, T.A., Rugg, M.D., 2006. Brain activity before an event predicts later recollection. Nat. Neurosci. 9, 489–491.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry 20, 11–21.

Seager, M.A., Johnson, L.D., Chabot, E.S., Asaka, Y., Berry, S.D., 2002. Oscillatory brain states and learning: impact of hippocampal theta-contingent training. Proc. Natl. Acad. Sci. U. S. A. 99, 1616–1620.

Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol. Rev. 99, 195–231.

Stern, C.E., Corkin, S., Gonzalez, R.G., Guimaraes, A.R., Baker, J.R., Jennings, P.J., Carr, C.A., Sugiura, R.M., Vedantham, V., Rosen, B.R., 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc. Natl. Acad. Sci. U. S. A. 93, 8660–8665.

Thesen, S., Heid, O., Mueller, E., Schad, L.R., 2000. Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. Magn. Reson. Med. 44, 457–465.

Turk-Browne, N.B., Yi, D.J., Chun, M.M., 2006. Linking implicit and explicit memory: common encoding factors and shared representations. Neuron 49, 917–927.

Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B.R., Buckner, R.L., 1998. Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. Science 281, 1188–1191.