Behavioral/Cognitive

VTA and Anterior Hippocampus Target Dissociable Neocortical Networks for Post-Novelty Enhancements

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The detection of novelty indicates changes in the environment and the need to update existing representations. In response to novelty, interactions across the VTA-hippocampal circuit support experience-dependent plasticity in the hippocampus. While theories have broadly suggested plasticity-related changes are also instantiated in the cortex, research has also shown evidence for functional heterogeneity in cortical networks. It therefore remains unclear how the hippocampal-VTA circuit engages cortical networks, and whether novelty targets specific cortical regions or diffuse, large-scale cortical networks. To adjudicate the role of the VTA and hippocampus in cortical network plasticity, we used fMRI to compare resting-state functional coupling before and following exposure to novel scene images in human subjects of both sexes. Functional coupling between right anterior hippocampus and VTA was enhanced following novelty exposure. However, we also found evidence for a double dissociation, with anterior hippocampus and VTA showing distinct patterns of post-novelty functional coupling enhancements, targeting task-relevant regions versus large-scale networks, respectively. Further, significant correlations between these networks and the novelty-related plasticity in the anterior hippocampal-VTA functional network suggest that the central hippocampal-VTA network may facilitate the interactions with the cortex. These findings support an extended model of novelty-induced plasticity, in which novelty elicits plasticity-related changes in both local and global cortical networks.

Key words: **cortex; fMRI; functional coupling; hippocampus; novelty; VTA**

Significance Statement

Novelty detection is critical for adaptive behavior, signaling the need to update existing representations. By engaging the bidirectional hippocampal-VTA circuit, novelty has been shown to induce plasticity-related changes in the hippocampus. However, it remains an open question how novelty targets such plasticity-related changes in cortical networks. We show that anterior hippocampus and VTA target cortical networks at different spatial scales, with respective enhancements in post-novelty functional coupling with a task-relevant cortical region and a large-scale memory network. The results presented here support an extended model of novelty-related plasticity, in which engaging the anterior hippocampal-VTA circuit through novelty exposure propagates cortical plasticity through hippocampal and VTA functional pathways at distinct scales, targeting specific or diffuse cortical networks.

Introduction

Novelty indicates that existing memories need to be updated with new information. The brain has specialized systems to process novelty, resulting in plasticity-related changes that facilitate the retention of new memories (Ranganath and Rainer, 2003; Lisman and Grace, 2005; Shohamy and Adcock, 2010). Prior work has focused on how circuits centered on the hippocampus and VTA contribute to novelty-related plasticity, yet open questions remain about how novelty restructures cortical networks.

The VTA-hippocampal circuit is critical for novelty processing. The hippocampus has been shown to detect novelty (Knight, 1996; Tulving et al., 1996; Strange et al., 1999; Ranganath and Rainer, 2003; Axmacher et al., 2010; Shohamy and Adcock, 2010; Kafkas and Montaldi, 2018), and in response, signals to the VTA to stimulate the release of dopamine (Lisman and Grace, 2005), which enhances hippocampal plasticity (Huang and Kandel, 1995; Li et al., 2003; Lisman and Grace, 2005; Moncada and Viola, 2007; Rossato et al., 2009; Bethus et al., 2010; Shohamy and Adcock, 2010). VTA-hippocampal interactions are therefore critical in selectively strengthening synapses representing novel information, facilitating its retention. However, less attention has

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focused on how engagement of this circuit promotes experience-dependent plasticity in cortical networks in humans.

The neocortex plays a critical role in the persistent representation of memories. Theories suggest that, while the hippocampus rapidly encodes new information, the cortex has a slower learning rate, gradually extracting central information through the repeated reactivation, or replay, of the hippocampal trace (Wilson and McNaughton, 1994; McClelland et al., 1995; Girardeau and Zugaro, 2011; Joo and Frank, 2018). As a result, the cortex represents this information more abstractly, facilitating its incorporation into existing long-term memory without interference (McClelland et al., 1995; Moscovitch et al., 2016). As dopaminergic activity during novelty exposure has been shown to influence subsequent replay (McNamara et al., 2014), it follows that hippocampal-cortical interactions also induce plasticity in the cortex to update and retain representations of novel information (Squire and Zola-Morgan, 1991; Wang and Morris, 2010; Moscovitch et al., 2016). However, research has yet to consider which cortical networks the VTA-hippocampal circuit targets for such plasticity-related changes.

Theories predicated on hippocampal-cortical interactions tend to treat cortex as one homogeneous structure. In contrast, research has shown that replay is coordinated between the hippocampus and specific neocortical regions (Ji and Wilson, 2007; Lansink et al., 2009; Peyrache et al., 2009; Wierzynski et al., 2009) and provided evidence for functional differences across cortical networks, such as the posterior medial and anterior temporal (PMAT) network specialized for memory-related processes (Ranganath and Ritchey, 2012; Ritchey et al., 2015; Barnett et al., 2020). It thus remains unclear how effects of novelty would map onto such functional heterogeneity in cortical network organization. One possibility is that novelty facilitates plasticity-related changes in networks with relatively specific cortical targets, affecting only regions specialized for processing the novel content presented during a specific task. Alternatively, plasticity could be elicited across a widespread network of cortical regions that may not directly respond novel task-relevant features, but that are specialized for memory-guided behavior. Evidence for both possibilities exist, albeit through different pathways: reports have shown experience-dependent enhancements in functional coupling specifically between hippocampus and task-relevant cortical regions (Tambini et al., 2010; Vilberg and Davachi, 2013; Schlichting and Preston, 2014; Murty et al., 2017b; Collins and Dickerson, 2019), whereas VTA dopaminergic signaling has widespread projections across regions beyond the hippocampus (Shohamy and Adcock, 2010; Murty and Dickerson, 2016).

The current study interrogated how the hippocampus and VTA restructure network dynamics for plasticity-related changes following novelty exposure. Using fMRI, we compared functional coupling during resting-state scans before, and following, exposure to novel scene images. We report a double dissociation in the scale of novelty-related functional coupling enhancements for right anterior hippocampus and VTA with a task-relevant cortical region and large-scale memory-related PMAT network, respectively. The findings support a model by which engaging the hippocampal-VTA circuit through novelty exposure propagates changes in cortical networks at different scales of distribution.

Materials and Methods

Participants

Participants were recruited for this experiment as control subjects in a larger study examining psychosis risk. The final sample with usable data on the novelty task and pre- and post-task resting-state scans yielded 37 participants of both sexes included in all analyses. Informed consent was obtained from each participant in a manner approved by Temple University's Institutional Review Board.

Figure 1. Experiment design. In the first phase of the experiment, participants were familiarized with scene images during a continuous recognition task. In the scanner, participants first underwent a baseline resting-state scan (pre-novelty rest), followed by the novelty-exposure phase, in which novel scene images were presented intermixed with the familiar images while participants completed a target detection task. Immediately following this task, participants completed a second, post-novelty, resting-state scan.

Table 1. Coordinates for PMAT ROIs[a]

Region	Abbreviation	MNI coordinates (*x*, *y*, *z*)
PM network		
1 Right thalamus	RPTHAL4	22, −30, 6
2 Left medial occipital cortex	LMOCC1	−2, −78, −2
3 Left occipital pole	LOCCP1	−16, −96, 22
4 Right occipital	ROCC2	16, −98, 20
5 Right precuneus	RPREC3	18, −68, 24
6 Right medial occipital cortex	RMOCC3	14, −72, 8
7 Right occipital pole	ROCCP2	14, −88, 4
8 Left PhC	LPHC1	−14, −50, −6
9 Right PhC	RPHC2	18, −46, −4
10 Left precuneus cortex	LPREC1	−14, −60, 18
11 Right medial occipital cortex	RMOCC2	6, −58, 14
12 Left occipital cortex	LOCC1	−38, −82, 28
13 Right angular gyrus	RANG2	52, −48, 28
14 Left precuneus	LPREC5	−2, −60, 34
15 Left retrosplenial cortex	LRSC1	−8, −50, 14
16 Left precuneus	LPREC2	−12, −50, 40
17 Right retrosplenial cortex	RRSC2	8, −46, 16
18 Right precuneus	RPREC4	18, −52, 36
AT network		
19 Left dorsolateral prefrontal cortex	LDLPFC1	−24, 60, 24
20 Left medial prefrontal cortex	LMPFC	−2, 60, 34
21 Right dorsolateral prefrontal cortex	RDLPFC2	18, 58, 24
22 Left temporal pole	LTPC1	−44, 4, −42
23 Right middle temporal gyrus	RPMTG2	54, −2, −32
24 Left orbitofrontal cortex	LOFC2	−6, 16, −22
25 Right orbitofrontal cortex	ROFC3	24, 12, −24
26 Right temporal pole	RTPC2	38, 20, −40
27 Left orbitofrontal cortex	LOFC1	−16, 24, −20
28 Left middle temporal gyrus	LPMTG1	−64, −36, −10
29 Right anterior inferior temporal gyrus	RAITG2	64, −14, −28
30 Right frontal pole	RFPC2	38, 60, −10
31 Right fusiform cortex	RFUS2	40, −18, −28
32 Right perirhinal cortex	RPRC	30, −12, −36
33 Left fusiform cortex	LFUS1	−42, −14, −30
34 Right orbitofrontal cortex	ROFC4	8 , 22, −20

[a]The coordinates for the PMAT ROIs were adapted from Ritchey et al. (2014) and used as central points to generate 5 mm spherical kernels.

Procedures

The protocol and materials used here were based on previously published work (Murty et al., 2013, 2017a). In brief, the task involved two phases: a familiarization and a novelty exposure phase (Fig. 1). Participants first completed the familiarization phase in which 120 outdoor scene images were shown one at a time while participants completed a continuous recognition task; 80 of the scene images were repeated 6 times ("familiar") while 40 were presented just once (foils), with the repetition aimed at familiarizing participants to these 80 stimuli. Approximately 20 min later,

participants entered the MRI scanner for the novelty exposure phase, in which they viewed a sequence of outdoor scene images, which included novel images that had never been seen before, as well as the familiar images (seen previously during the familiarization phase). In the novelty exposure phase, participants completed a target detection task in which they were instructed to press a button every time a specific outdoor scene image ("target") was presented. The target scene image was repeated 40 times, intermixed with the 80 novel scene images and 80 "familiar" scene images. All trials were presented in a randomized order.

Critically, and where the current experiment diverges from prior published work using this protocol, all participants completed resting-state scans before and following the target detection task in the fMRI scanner, a design used previously to compare experience-dependent changes in resting-state functional coupling (Tambini et al., 2010; Tompary et al., 2015; Murty et al., 2017b). Resting-state sessions lasted 5.8 min, and participants were instructed to keep their eyes open and look at the fixation cross on the screen.

MRI data acquisition and preprocessing

Scanning was completed on a 3T Siemens Magnetom Prisma scanner. Functional imaging data were collected using a multiband EPI pulse sequence (TR = 1.73 s, TE = 25, voxel size = 2.38 × 2.38 × 2.5 mm, MB factor: 2). In addition, a high-resolution T1-weighted anatomic scan (MPRAGE sequence, voxel size = 0.9 mm isotropic) was acquired to aid in functional image coregistration.

All fMRI preprocessing was performed using the FSL (version 6.0.3) fMRI Expert Analysis Tool version 6 (FSL: http://fsl.fmrib.ox.ac.uk/fsl/). Functional images were skull stripped with the Brain Extraction Tool, high-pass filtered (60 s cutoff), spatially smoothed with a 5 mm FWHM kernel, intensity normalized, and MCFLIRT was applied for motion correction. Functional data were registered to the high-resolution anatomic scans with FSL's FLIRT tool (Linear with BBR), then to standard MNI space using FNIRT's nonlinear registration (12 DOF, 10 mm warp resolution). Additionally, noise-related measures were computed for average signal in CSF and white matter masks (generated using FSL's FAST segmentation tool), time points of excessive head motion (identified using FSL's motion outliers tool), as well as the six head motion parameters and their first derivatives. The same preprocessing pipeline was conducted for the rest and task scans.

ROI definition

Anatomical hippocampal ROIs were defined using the Harvard Oxford Subcortical Pro-babilistic Atlas, thresholded at 50%, and in MATLAB, divided lengthwise into equal segments delineating the anterior, mid, and posterior thirds using custom code. The VTA ROI was defined based on a probabilistic atlas, thresholded at 75% (Murty et al., 2014). Additional ROIs were defined based on coordinates reported in prior work using the exact same task; for the parahippocampal cortex (PhC) ROI, we used the coordinates for a region in left PhC previously shown to be sensitive to novelty exposure (Murty et al., 2013) (MNI coordinates: −28, −54, −14). The ROIs in the PMAT network were based on coordinates reported in a previous publication defining these two networks (Ritchey et al., 2014), although we excluded the hippocampal ROIs included in the PMAT network as we were interested in dynamics between hippocampus and VTA with these regions. The PMAT network describes regions in the posterior medial (PM) and anterior temporal (AT) networks (Ranganath and Ritchey, 2012; Ritchey et al., 2015; Inhoff and Ranganath, 2017). The full list of PMAT ROIs is included in Table 1. All ROIs generated from coordinates were defined using a spherical 5 mm kernel.

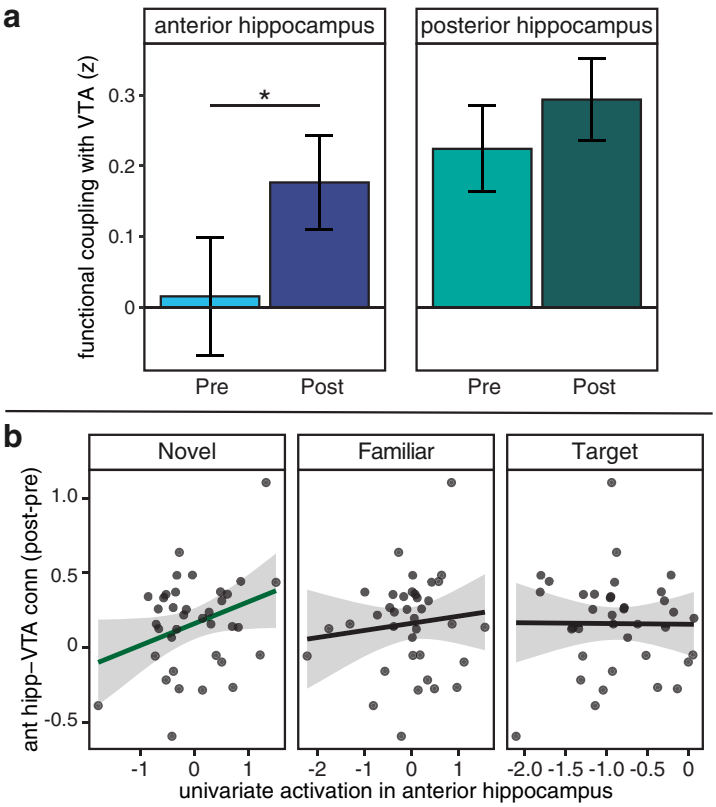

Figure 2. Changes in resting-state functional coupling between right hippocampus and VTA. ***a***, Right anterior hippocampal-VTA functional coupling is significantly greater during the post-task rest scan (dark blue) compared with the pre-task baseline (light blue), whereas posterior hippocampal-VTA functional coupling did not significantly change following novelty exposure. Error bars indicate SEM. ***b***, The change in right anterior hippocampal-VTA functional coupling (post-task minus pre-task) marginally correlates with univariate activation in right anterior hippocampus during novel task trials, but not familiar or target trials during the task. All plots: Black dots represent individual participants. Gray ribbon represents 95% CIs.

fMRI data analysis

Functional coupling analysis. To compute resting-state functional coupling measures, we first calculated GLMs for the pre- and post-novelty exposure resting-state runs, which only included noise regressors. The data were then registered to standard MNI space and bandpass filtered between 0.01 and 0.1. For both runs, we then extracted the average time course from each ROI. We measured functional coupling as the correlation between the time courses between ROIs. Functional coupling between pairs of ROIs was calculated as the correlation between each ROI's time course (e.g., for anterior hippocampus and VTA, or anterior hippocampus with PhC), whereas the functional coupling with the PMAT network ROIs was calculated by taking the average of each pairwise correlation between the seed region (anterior hippocampus or VTA) with each ROI in the PMAT network. We calculated both the coupling with the combined PMAT network, as well as the coupling with the respective PM and AT regions. Fisher's r to z transformations were applied to all pairwise correlation measures before averaging and further statistical analyses were computed.

Univariate analyses during novelty-exposure task. To measure BOLD response during the novelty exposure phase of the task, we computed a GLM with three regressors for the trials of the novel, familiar, and target conditions. Following on our prior work (Murty et al., 2013),

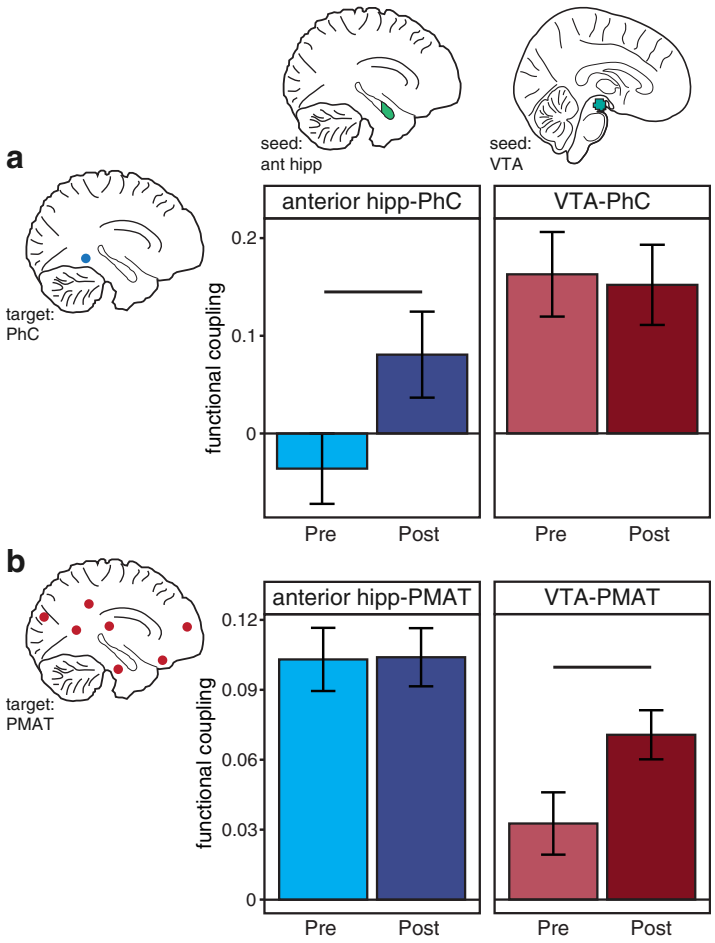

Figure 3. Dissociation in novelty-related plasticity in functional coupling of anterior hippocampus and VTA with cortical network targets. ***a***, Comparing changes in anterior hippocampal (left) and VTA (right) functional coupling with the task-relevant PhC region following novelty exposure yielded a significant Seed × Session interaction effect, driven by a significant post-task enhancement only for anterior hippocampal-PhC functional coupling, with no significant change in VTA-PhC functional coupling between the pre- and post-task scans. Error bars indicate SEM. ***b***, In contrast, VTA-PMAT functional coupling showed a post-novelty enhancement compared with pre-task baseline, but there was no significant change in anterior hippocampal-PMAT functional coupling, driving the significant Seed × Session interaction effect.

this GLM also included three regressors measuring the habituation for each trial type, calculated as a linear decrease across the trial presentations. Noise-related measures (see above) were also added as additional nuisance regressors. The resulting contrasts were registered to standard MNI space, from which we then extracted the β parameters from each contrast of interest (e.g., novel, familiar, target greater than baseline). We examined univariate responses across our ROIs of interest, in the hippocampus, VTA, PhC, and PMAT regions, the latter of which we calculated as the average univariate activation in all of the regions in the network. In addition to overall BOLD activation in these ROIs, one of our central questions with the univariate analyses was to examine whether novelty-evoked univariate activation correlated with the change in functional coupling from pre- to post-novelty exposure.

Statistical analysis

All reported statistical analyses are two-tailed, and $p < 0.05$ was considered significant for all tests. Repeated-measures ANOVAs were performed and followed up with paired sample t tests where applicable. Statistics were performed with R version 3.5.1, RStudio (RStudio, version 0.99.903) and MATLAB (The MathWorks) using both built-in and custom functions. Bonferroni correction was applied to the four tests used to assess change in hippocampal-VTA functional coupling calculated for long-axis region and hemisphere using p.adjust in R.

Results

Changes in hippocampal-VTA functional connectivity

The circuit between the hippocampus and VTA is critical in novelty processing, from the detection of novelty to the subsequent dopaminergic-based enhancements in LTP in the hippocampus (Lisman and Grace, 2005; Shohamy and Adcock, 2010). As such, we predicted that functional coupling between the hippocampus and VTA would be enhanced following the novelty exposure session. We expected to see this relationship particularly between VTA and anterior, rather than posterior, hippocampus as the former has more often been implicated in novelty processing (Strange et al., 1999; Poppenk et al., 2013; Kafkas and Montaldi, 2018). We additionally particularly focused on right hippocampus, as prior work using this paradigm found a peak in novelty-related activation in this region (Murty et al., 2013). Pre- and post-task measures of functional coupling between anterior and posterior hippocampus with VTA were separately calculated (see Materials and Methods).

As seen in Figure 2*a*, the functional coupling between right anterior hippocampus and VTA was significantly greater during the post-task compared with pre-task session ($t_{(36)} = -3.07$, $p = 0.004$; Bonferroni-corrected $p = 0.016$). However, as predicted, right posterior hippocampal-VTA functional coupling did not significantly differ across resting-state scans ($t_{(36)} = -1.34$, $p = 0.19$, corrected $p = 0.75$). Left anterior and posterior hippocampal functional coupling with VTA did not show significant changes across sessions (left anterior, $t_{(36)} = -1.69$, $p = 0.1$, corrected $p = 0.39$; left posterior $t_{(36)} = -1.66$, $p = 0.11$, corrected $p = 0.42$). Together, these results illustrate that functional coupling between anterior hippocampus and VTA seems to be sensitive to novelty-related plasticity enhancements.

The hippocampal-VTA loop is thought to rely on the hippocampus' role as a novelty detector. It is therefore expected that the enhancement in anterior hippocampal-VTA functional coupling would be related to the responsiveness of the anterior hippocampus to novelty, measured as BOLD signal during novel trials in the novelty-exposure task (see Materials and Methods). Indeed, the change in right anterior hippocampal-VTA functional coupling, calculated as the difference between functional coupling during the post- and pre-task exposure rest sessions, marginally correlated with the univariate activation in right anterior hippocampus during novel trials ($r = 0.32$, $p = 0.056$; Fig. 2*b*). Though a marginal correlation, no subject in this analysis was identified as a statistical outlier, as defined using Mahalanobis distance and a χ^2 cut off with an α of 0.001. This relationship with univariate activation in anterior hippocampus during novel trials is consistent with prior work suggesting that the circuit between the hippocampus and VTA is activated via

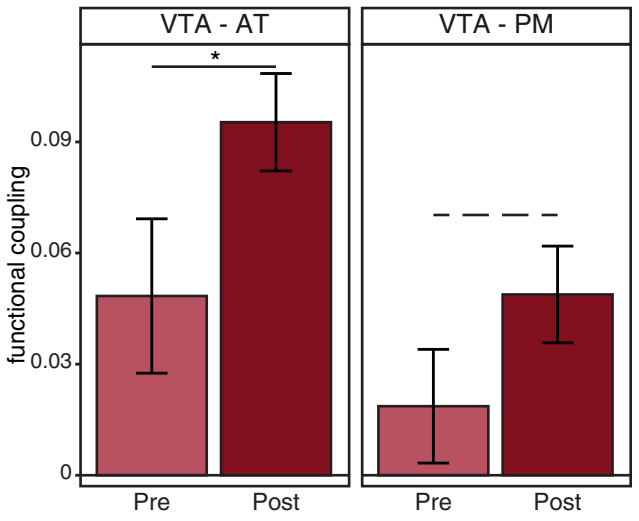

Figure 4. Change in functional coupling between VTA and AT and PM cortical networks. VTA showed significant post-task enhancements in functional coupling with the regions of the AT network (left). While only marginally significant, VTA-PM functional coupling showed a similar pattern (right), suggesting that the VTA targets a relatively diffuse set of memory-related regions for plasticity-related changes. Error bars indicate SEM.

the anterior hippocampus' role as a novelty detector (Lisman and Grace, 2005). There was not a significant correlation between changes in right anterior hippocampal-VTA coupling and anterior hippocampal univariate activation during familiar trials ($r = 0.11$, $p = 0.51$), or target trials ($r = -0.009$, $p = 0.96$; Fig. 2*b*).

Together, these results confirm the importance of interactions between the hippocampus and VTA in novelty processing, providing evidence that plasticity-related changes in the hippocampal-VTA circuit are related to the response to the exposure to novelty in the hippocampus.

Dissociation in hippocampal and VTA plasticity-related cortical targets

The main goal of this experiment was to query the scale by which novelty-related plasticity changes restructure downstream cortical network dynamics. In particular, we were interested in adjudicating whether the hippocampal-VTA circuit targets specific task-relevant sensory cortical regions or has diffuse targets across a network of cortical regions involved in memory-related processes. We therefore examined changes in functional coupling between right anterior hippocampus and VTA with the task-relevant PhC, a region known to process scene images and scene novelty (Davachi, 2006; Howard et al., 2011; Murty et al., 2013), compared with the large-scale PMAT network, which consists of regions in the PM and AT networks and is functionally specialized for functions, such as episodic and contextual memory and processing the motivational relevance of stimuli (Ranganath and Ritchey, 2012; Ritchey et al., 2015). We reasoned that, because the widespread set of regions in the PMAT network are related to memory-related processes, but not necessarily directly engaged in processing novelty of task-relevant information, examining changes in functional coupling with the hippocampus and VTA would provide insight about how novelty-related plasticity is induced across downstream targets in memory-related networks.

A 2(Seed: ant hipp, VTA) × 2(Network: PMAT, PhC) × 2 (Session: Pre, Post) repeated-measures ANOVA yielded a significant Seed × Network × Session interaction effect ($F_{(1,36)} = 9.08$, $p = 0.005$), indicating a dissociation in the experience-dependent changes in functional coupling between anterior hippocampus and VTA depending on the target cortical network. This analysis also resulted in a significant Seed × Network interaction ($F_{(1,36)} = 12.68$, $p = 0.001$), and a marginal main effect of Session ($F_{(1,36)} = 3.96$, $p = 0.054$).

To unpack the significant interaction effect, we conducted follow-up 2(Seed: ant hipp, VTA) × 2(Session: Pre, Post) repeated-measures ANOVAs for each network target, PhC and PMAT, separately. For PhC, the ANOVA resulted in a main effect of Seed region ($F_{(1,36)} = 5.55$, $p = 0.024$), and a significant Seed × Session interaction ($F_{(1,36)} = 6.21$, $p = 0.017$). As shown in Figure 3*a*, follow-up *t* tests revealed that this significant interaction effect was driven by a post-encoding enhancement in anterior hippocampal-PhC functional coupling ($t_{(36)} = -2.67$, $p = 0.01$), with no significant change in VTA-PhC functional coupling ($t_{(36)} = 0.28$, $p = 0.78$).

Likewise, a 2(Seed) × 2(Session) repeated-measures ANOVA on the functional coupling between anterior hippocampus and VTA with the PMAT network resulted in a significant Seed × Session ($F_{(1,36)} = 4.3$, $p = 0.045$) interaction effect, as well as significant main effects of Seed ($F_{(1,36)} = 11.85$, $p = 0.001$) and Session ($F_{(1,36)} = 5.46$, $p = 0.025$). However, in contrast to the results with PhC, follow-up *t* tests demonstrated that this interaction was driven by a significant post-task change in functional coupling between VTA and PMAT regions ($t_{(36)} = -3.89$, $p = 0.0004$), with no significant difference in anterior hippocampal-PMAT functional coupling ($t_{(36)} = -0.07$, $p = 0.95$; Fig. 3*b*). Therefore, while only anterior hippocampus showed significant changes in functional coupling with PhC, only the VTA showed changes in functional coupling with the PMAT regions.

Since regions of the AT network in particular have been implicated in processing affective, salient information (Ranganath and Ritchey, 2012; Ritchey et al., 2015), we next separately examined coupling with the PM and AT networks. As seen in Figure 4, VTA-AT functional coupling showed a significant post-task enhancement ($t_{(36)} = -2.8$, $p = 0.008$), whereas the change in VTA-PM functional coupling was only marginally significant ($t_{(36)} = -1.95$, $p = 0.059$). However, as a 2(PMAT network) × 2 (Session) repeated-measures ANOVA did not yield a significant PMAT network × Session interaction ($F_{(1,36)} = 0.43$, $p = 0.52$), we continue to collapse across the PMAT networks for all further analyses.

To further visualize how widespread the VTA's post-task functional coupling enhancements are with all regions in the PMAT network, we plotted the difference in post-novelty – pre-novelty coupling measures between VTA and all regions in the PM and AT networks. As Figure 5*a* illustrates, the majority of regions have positive change scores, indicating greater post-task functional coupling with VTA compared with the pre-task measure. In contrast, the visualization of the change in functional coupling between anterior hippocampus with all regions of the PMAT network shows a much more variable pattern, with only few regions showing positive change scores (Fig. 5*b*). This visualization thus confirms the consistency with which VTA diffusely targets cortical regions in these networks for novelty-related plasticity benefits.

Together, these results reveal a double dissociation in the cortical networks that anterior hippocampus and VTA target for plasticity-related changes following a task involving

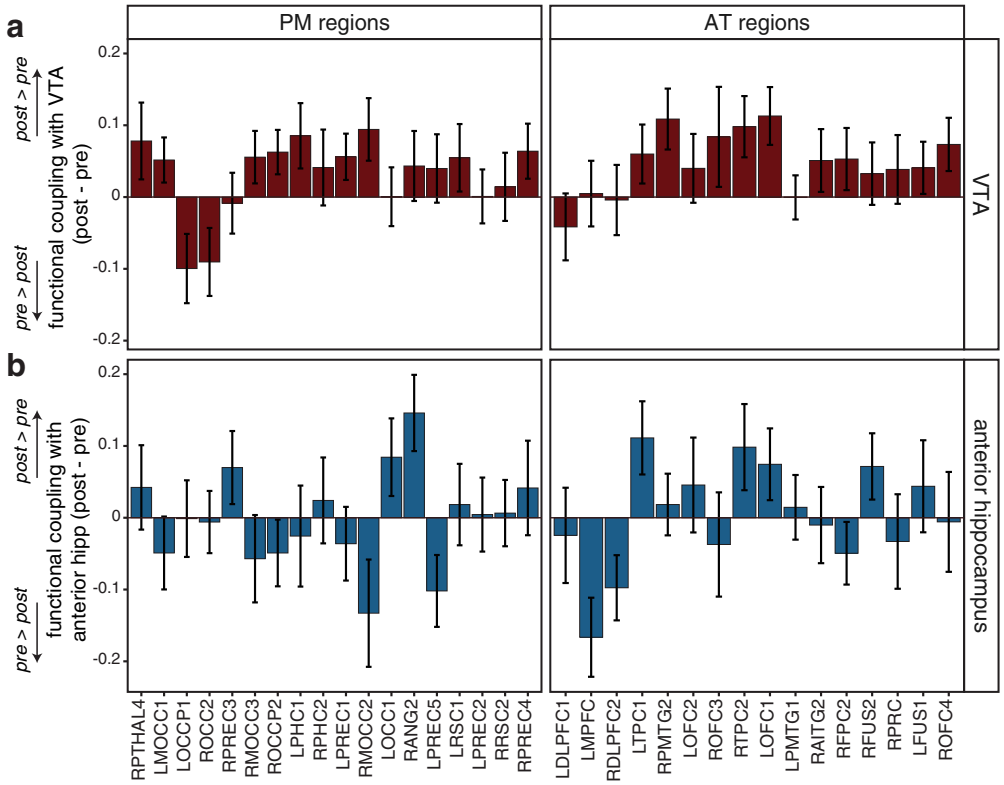

Figure 5. Pairwise change in functional coupling between PMAT regions with VTA and anterior hippocampus. ***a***, Visualizing the change in functional coupling following novelty exposure (post-/pre-task) between VTA and all regions included in the PMAT networks illustrates the widespread nature of these effects. The majority of regions show positive difference scores, indicating greater post-task functional coupling with VTA compared with the pre-task measure. ***b***, In contrast, in the bottom two graphs, the visualization of the post-/pre-task change in functional coupling between anterior hippocampus with all regions included in the PMAT networks shows a variable pattern of effects. Unlike with VTA, only a few regions show positive values, confirming that anterior hippocampus does not seem to target widespread regions for novelty-related functional coupling enhancements. These graphs were used only for visualization purposes, and no statistical tests were calculated on these values.

exposure to novelty, with significant post-encoding enhancements only between anterior hippocampus and the task-relevant PhC and VTA and the diffuse regions in the PMAT network.

Modulation of plasticity-related changes

To build on these results, we interrogated whether the respective changes in anterior hippocampal and VTA functional coupling with the cortical target networks are related to the post-task change in anterior hippocampal-VTA coupling. Since this latter circuit is central to the detection of novelty and release of dopamine that facilitates plasticity-related changes, we hypothesized that the magnitude of the post-task enhancement of anterior hippocampal-VTA functional coupling may modulate the extent of the significant plasticity-related changes between each regions and cortical networks.

We calculated change scores for the functional coupling measures (post-novelty – pre-novelty exposure) and examined the correlation between right anterior hippocampal-VTA functional coupling change with the respective changes in right anterior hippocampal and VTA coupling with the diffuse and specific cortical target networks. As shown in Figure 6*a*, the change in anterior hippocampal-VTA functional coupling positively correlated with both the change in anterior hippocampal-PhC functional coupling ($r = 0.44$, $p = 0.006$) and VTA-PMAT functional coupling ($r = 0.43$, $p = 0.008$), the networks that selectively showed significant post-task enhancements. In contrast, the post-task change in anterior hippocampal-VTA coupling did not significantly correlate with the changes in functional coupling in the networks that did not show significant post-task enhancements, the VTA-PhC network ($r = 0.08$, $p = 0.65$), or anterior hippocampal-PMAT network ($r = 0.09$, $p = 0.61$), suggesting specificity in this cross-network relationship (Fig. 6*b*). Moreover, the correlation between the changes in anterior hippocampal-PhC and VTA-PMAT functional coupling was not statistically significant ($r = 0.18$, $p = 0.29$), suggesting that the significant correlation with the hippocampal-VTA dynamics is not purely driven by individual subjects with greater change scores. Instead, together, these results suggest that novelty-related changes in the anterior hippocampal-VTA network may play a particular role in modulating pathways of cortical network plasticity, between anterior hippocampus and VTA with their respective cortical network target regions.

Univariate response to novelty across ROIs

The main aim of this study was to adjudicate how engaging the hippocampal-VTA circuit results in downstream plasticity-related changes in cortical networks. However, by considering the response of these ROIs during the target detection novelty exposure task, we can better examine how sensitivity across these ROIs varies during novelty processing, and understand changes in coupling between these regions following novelty exposure. Thus, we characterized differences in univariate BOLD signal during the novel, familiar, and target trials (see Materials and Methods).

Our main interest was to investigate novelty responses in the anterior hippocampus and PhC ROIs, both regions thought to be part of the novelty responsive network (Hawco and Lepage, 2014; Kafkas and Montaldi, 2014, 2018). As shown in Figure 7, in right anterior hippocampus, univariate activation was significantly lower during target trials compared with both the novel ($t_{(36)}$ = 7.30, $p < 0.0001$) and familiar trials ($t_{(36)} = 7.05$, $p < 0.0001$). However, somewhat surprisingly, univariate activation during novel and familiar trials did not significantly differ ($t_{(36)} = 0.36$, $p = 0.72$). This pattern of results may be consistent with the anterior hippocampus being sensitive to relative novelty (i.e., how new the stimulus is compared with its local environment), as novel and familiar stimuli are trial-unique while the target scene stimulus was repeated 40× (Kafkas and Montaldi, 2018). In contrast, in the left parahippocampal region, univariate responses to the novel, familiar, and target trials showed a graded pattern. Univariate activation during novel trials was significantly greater than familiar trials ($t_{(36)} = 3.16$, $p = 0.003$), and both novel and familiar trials evoked greater univariate responses compared with target trials (novel vs target: $t_{(36)} = 9.97$, $p < 0.0001$; familiar vs target: $t_{(36)} = 7.71$, $p < 0.0001$). These results are consistent with the PhC being sensitive to absolute novelty (i.e., how new the stimulus is in general), and supports task relevance of the PhC, tracking the novelty of the presented scene stimuli.

For completeness, we also examined univariate activation in the VTA and PMAT regions. In the VTA, we did not find a significant difference between novel and familiar trials ($t_{(36)} = 0.72$, $p = 0.47$); however, univariate activation was significantly greater for target trials compared with both novel ($t_{(36)} = -4.13$, $p = 0.0002$) and familiar trials ($t_{(36)} = -3.72$, $p = 0.0007$). These results are in line with the goal relevance of target trials in the target-detection task (see Materials and Methods), and consistent with prior work suggesting that the VTA does not show event-evoked novelty responses (Murty et al., 2013, 2017a). Finally, the average univariate activation in the PMAT network regions showed a pattern similar to the anterior hippocampus, with greater activation in novel and familiar trials compared with target trials (novel vs target: $t_{(36)} = 5.64$, $p < 0.0001$; familiar vs target: $t_{(36)} = 6.27$, $p < 0.0001$), but no significant difference between the novel and familiar trials ($t_{(36)} = -0.56$, $p = 0.58$). Together, these findings suggest all of the *a priori* ROIs examined here were engaged by our task, albeit in different ways perhaps consistent with functional specifications.

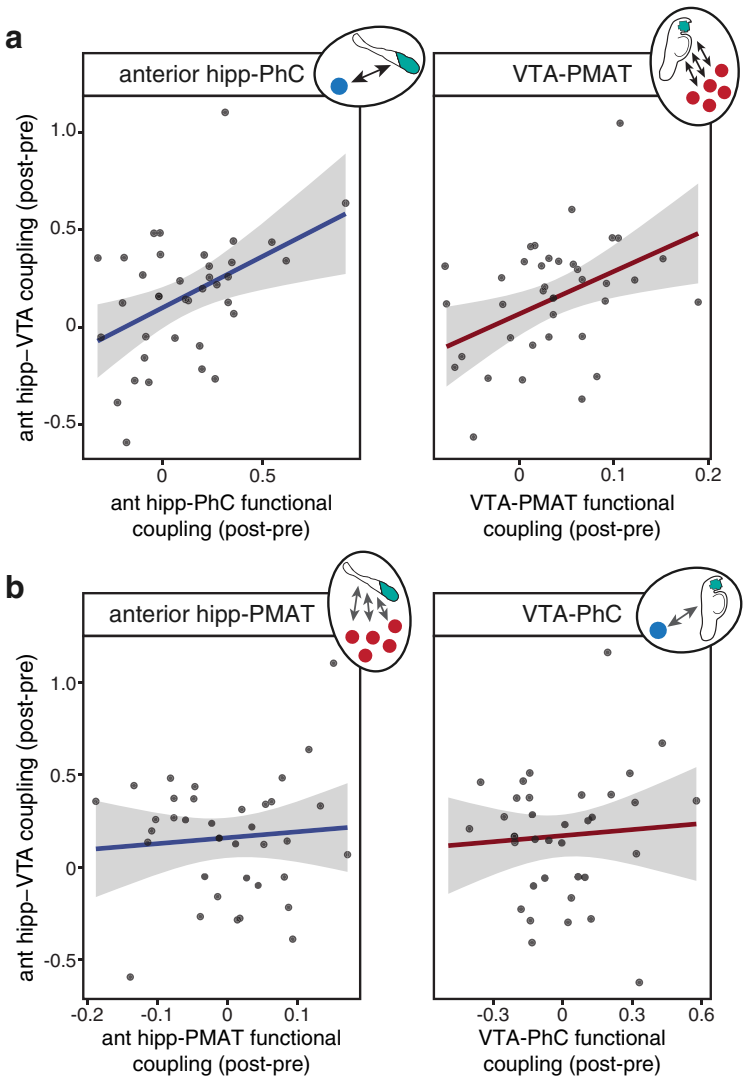

Figure 6. Relationship between anterior hippocampal-VTA functional coupling and coupling changes in cortical networks. ***a***, The change in right anterior hippocampal-VTA functional coupling (post- minus pre-task) positively correlates with the changes in functional coupling between both right anterior hippocampal-PhC (left) and VTA-PMAT networks (right), suggesting that the extent of novelty-related enhancements in the central anterior hippocampal-VTA circuit is related to the changes between anterior hippocampus and VTA and their respective cortical target networks. ***b***, In contrast, the change in anterior hippocampal-VTA functional coupling did not significantly correlate with the change in either anterior hippocampal-PMAT functional coupling (left) or VTA-PhC functional coupling (right). These networks did not show experience-dependent coupling enhancements, suggesting that these results may be in line with the scale of cortical networks targeted by the anterior hippocampus and VTA. All plots: Black dots represent individual participants. Gray ribbon represents 95% CIs.

Discussion

Together, these results provide new evidence that a task involving novelty exposure engages cross-regional interactions at distinct scales. Comparing resting-state functional coupling measured before and after novelty exposure yielded findings that expand current understanding about novelty's effects on network-level experience-dependent plasticity. First, right anterior hippocampal-VTA functional coupling showed experience-dependent enhancements, and this change marginally correlated with anterior hippocampal univariate activation during novel trials. Most critically, there was a double dissociation in the cortical regions targeted for plasticity-related changes, with right anterior hippocampus showing experience-dependent increases in functional coupling with task-relevant PhC, but not with the large-scale PMAT memory

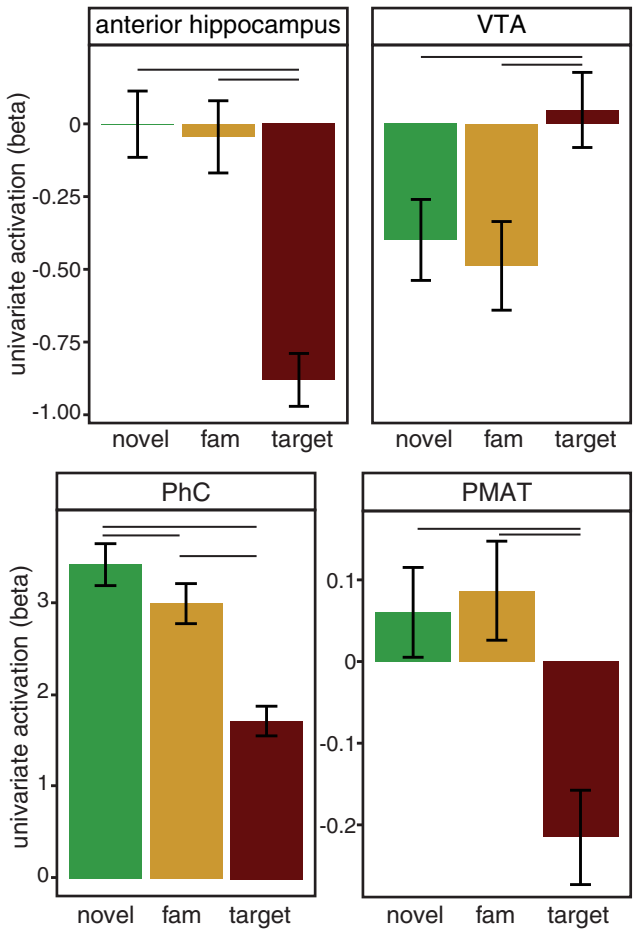

Figure 7. Univariate activation in ROIs. BOLD signal was differentially modulated during novel, familiar, and target trials depending on the ROI. In right anterior hippocampus, PhC, and PMAT regions, univariate activation during novel and familiar trials was significantly greater than target trials. However, univariate activation in VTA was greater during target trials than novel or familiar trials. Only PhC showed significantly greater univariate activation during novel trials than familiar trials, consistent with the sensitivity of this region to novelty. Error bars indicate SEM.

network, whereas VTA showed post-novelty functional coupling enhancements with the PMAT network, but not PhC. These findings provide support for a new model of novelty-induced plasticity, in which novelty elicits plasticity-related changes in both local and global cortical networks.

The hippocampus, particularly anterior hippocampus, is sensitive to novelty detection (Knight, 1996; Tulving et al., 1996; Strange et al., 1999; Ranganath and Rainer, 2003; Axmacher et al., 2010; Shohamy and Adcock, 2010; Poppenk et al., 2013; Kafkas and Montaldi, 2018), perhaps because of its underlying circuitry which facilitates comparisons between sensory inputs and predictions generated from prior experience (Hasselmo and Schnell, 1994; Lisman and Grace, 2005; Kumaran and Maguire, 2006, 2007a,b; Duncan et al., 2012). It is thought that the hippocampus responds to novelty by signaling the VTA to release dopamine, which projects back to the hippocampus to enhance LTP, selectively strengthening synapses coding novel information (Lisman and Grace, 2005). Evidence supporting this model includes reports of dopamine-related enhancements in hippocampal LTP (Huang and Kandel, 1995; Li et al., 2003; Lisman and Grace, 2005; Moncada and Viola, 2007; Rossato et al., 2009; Bethus et al., 2010; Shohamy and Adcock, 2010), and increased hippocampal and VTA coactivation and functional coupling during novelty exposure (Schott et al., 2004; Kafkas and Montaldi, 2015; Murty et al., 2017a). Here, we demonstrate that functional coupling between anterior hippocampus and VTA is enhanced following exposure to novelty, indicative of increases in shared information processing between these regions. Further, this change in coupling was marginally related to anterior hippocampal univariate activation during novel trials, consistent with the hippocampal novelty response facilitating this cross-regional signaling.

How does post-encoding facilitation of the VTA-hippocampal circuit lead to downstream changes in cortical network plasticity? Dopamine can influence replay in the hippocampus during reward motivation (McNamara et al., 2014), such that engaging the VTA-hippocampal circuit may also bias novelty-related plasticity in cortical networks. Our results suggest that, rather than a unified role, engaging the VTA-hippocampal circuit facilitates cortical network plasticity through pathways with distinct resolutions: the anterior hippocampus targets local, task-relevant cortical regions, whereas VTA has more global effects, targeting large-scale networks.

The VTA-hippocampal circuit seems to modulate the plasticity-related changes in these networks. Post-novelty enhancements for both anterior hippocampal-PhC and VTA-PMAT networks positively correlated with the change in anterior hippocampal-VTA functional coupling. Individual subjects with overall greater coupling values did not drive this effect, as the correlation between anterior hippocampal-PhC and VTA-PMAT coupling was not significant, suggesting a particular role of the VTA-hippocampal circuit. This relationship was also specific to the networks influenced by novelty exposure: VTA-hippocampal coupling did not significantly correlate with hippocampal-PhC or VTA-PMAT coupling changes. Novelty-related enhancements in the VTA-hippocampal circuit may facilitate plasticity-related changes across cortical networks, respectively, targeted by the hippocampus and VTA.

The current findings raise the possibility that engaging the anterior hippocampal and VTA pathways have distinct consequences. In prior work, experience-dependent changes in functional coupling with task-relevant cortical regions are related to superior subsequent memory for task content (Tambini et al., 2010; Vilberg and Davachi, 2013; Tompary et al., 2015; Murty et al., 2017b; Collins and Dickerson, 2019). The hippocampus may target task-relevant regions to stabilize sensory aspects of novel information, facilitating later memory retrieval. Thus, distributing information processing between the hippocampus and task-relevant regions novelty could promote the retention of event-specific information.

In contrast, research has implicated the VTA in more diffuse outcomes, with dopaminergic projections from the VTA modulating synaptic plasticity (Jay, 2003; Seamans and Yang, 2004), and influencing the stability of information processing across large-scale cortical networks (Shafiei et al., 2019). Post-novelty enhancements in VTA-PMAT functional coupling may reflect more general effects on behavioral processes, consistent with dopamine's widespread role in functions, including memory, decision-making, and motor actions (Jay, 2003; Shohamy and Adcock, 2010). There was some indication of a stronger post-novelty coupling enhancement between VTA and the AT network, implicated in processing affective mnemonic content and object recognition (Ranganath and Ritchey, 2012; Ritchey et al., 2015), consistent with novelty signaling motivationally relevant changes in the environment and facilitating plasticity-related

changes to update existing internal models and coordinate behavioral responses. While the current experiment did not index behavioral outcomes, future work should explore the behavioral contributions of the differential scales of hippocampal and VTA network targets.

Novelty is known to have a broad impact on learning, memory, and cognition by not only facilitating plasticity, but also supporting higher-order heuristics and schemas (Krebs et al., 2009; van Kesteren et al., 2012). Yet, it remained unclear how a single behavioral state could facilitate plasticity in a way that fosters memory for event-specific details while also contributing to higher-order cognition. Our findings illustrate a more complex mechanism for how novelty influences neural networks to support this diversity in behaviors. We can therefore integrate our findings and existing literature into an extended model (Fig. 8). In this model, as in prior work and the Lisman and Grace (2005) model, the hippocampus and VTA form a central, bidirectional circuit that responds to novelty in the environment by stimulating dopaminergic release. In addition to enhancing hippocampal LTP, engaging the hippocampal-VTA circuit also modulates plasticity in downstream local and global cortical networks, respectively, targeted by the anterior hippocampus and VTA. Such experience-dependent coupling enhancements between hippocampus and task-relevant sensory cortex may facilitate specific memory reactivation, whereas VTA coupling with large-scale memory networks may impact information processing across widespread regions. As a result, novel information could be used to update existing models of the world.

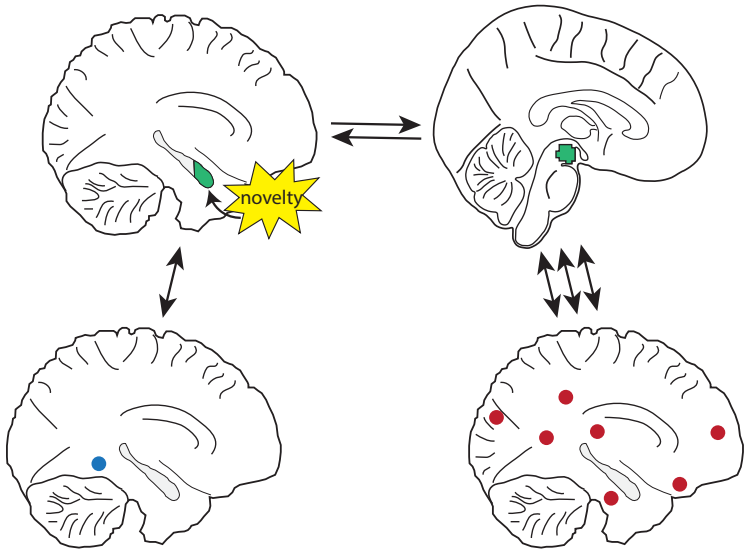

Figure 8. Schematic model illustrating plasticity-related network changes resulting from novelty exposure. In this model integrating the current results with prior literature, the anterior hippocampus and VTA form a bidirectional circuit (top row) in which the hippocampus responds to novelty in the environment and activates the VTA to release dopamine, in turn enhancing hippocampal LTP. Engaging the VTA-hippocampal circuit also facilitates plasticity-dependent changes in cortical networks, with each region influencing the cortex at distinct scales: anterior hippocampus targets task-relevant sensory regions (bottom left) while VTA targets large-scale memory networks (bottom right). Plasticity-related changes in these local and global networks may contribute to the diverse behavioral outcomes evoked by novelty exposure, including specific memory reactivation and information processing across diffuse regions, respectively. Together, this expanded model illustrates how novelty influences neural networks, shedding light on the differential contributions of the anterior hippocampus and VTA in propagating cortical network plasticity.

The present work also raises questions for future research. First, somewhat surprisingly compared with prior work (Strange et al., 1999; Poppenk et al., 2013; Kafkas and Montaldi, 2018), in our study novel trials did not evoke greater univariate activation than familiar trials in anterior hippocampus, although both were greater than target trials. This may reflect a relative rather than absolute novelty response; in our experiment, novel and familiar scene images were each shown once during the novelty-exposure session, while the target image was repeated 40 times. When only considering local task context, novel and familiar trials are comparatively more novel than the repeated target trials. In contrast, the PhC results are consistent with absolute novelty, with novel trials eliciting greater activation than familiar and target trials. This interpretation dovetails well with Kafkas and Montaldi's (2018) hypothesis that anterior hippocampus only engages the mesolimbic dopamine system in response to contextual, or relative, novelty. However, more research is needed to unpack how distinct novelty types affect downstream plasticity. Further, reports suggest a broader "novelty network," including early visual cortex and ventral visual stream regions, may facilitate hippocampal novelty responses (Hawco and Lepage, 2014; Kafkas and Montaldi, 2014, 2018), yet the role of these regions, if any, in facilitating plasticity-related processes is unclear. Future work will need to investigate how this broader network engages the hippocampal-VTA circuit, and whether regions in the network contribute to distinct novelty signal types.

Our design compared functional coupling during pre- and post-task rest scans, a method used to characterize experience-dependent network changes (Tambini et al., 2010; Tompary et al., 2015; Murty et al., 2017b). While there is always some environmental novelty that cannot be controlled, this design is well suited to isolate task-related coupling changes, and control for potential confounds from exposure to novelty outside of the task. For example, novelty responses from extra-experimental events (e.g., scanner environment) or the familiarization phase would be incorporated into the baseline coupling measure and could not drive the observed coupling enhancements. However, with this design, we cannot conclude whether novel trials alone produced the results as the task also includes familiar and target trials. Indeed, as discussed, novelty responses may represent the relative task context. Using a between-subjects manipulation in future work could parse each trial type's contributions. Further, future work could test whether similar network plasticity is seen in other domains, such as reward, which also engages the hippocampal-VTA circuit to facilitate long-term adaptive memories (Cowan et al., 2021). Finally, resting-state scans prevent the direct assessment of participants' internal states, which could differ between the two scans (e.g., from fatigue, scanner acclimation). Although it is unlikely such differences would cause the observed pattern of results, future work could probe thought content during rest.

Together, this work sheds light on the diverse effects of novelty on functional networks, broadening our understanding of how novelty engages, and restructures, network dynamics across the brain and opening critical questions for future research.

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