Synergistic Neural Circuits for Novelty and Goal-Directed Behavior

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Abstract

The ability to adapt in a dynamic world relies on detecting, learning, and responding to environmental changes. The detection of novelty serves as a critical indicator of such changes, prompting mechanisms to detect and respond to goal-relevant information. However, neural regions that support novelty detection and learning (hippocampus), salience detection (dopaminergic midbrain [VTA]), and executive function (prefrontal cortex [PFC]) have yet to be described as a sequential process that unfolds over time. Using functional magnetic resonance imaging (fMRI) we explored interactions between the hippocampus, VTA, and PFC in humans performing a novelty-imbued target-detection task. Hippocampal novelty activation predicted subsequent goal-directed VTA activity, enhancing readiness to detect goal-relevant information. Concurrently, goal-directed PFC activation modulated VTA target activation, refining focus on behaviorally significant cues. These circuits function both synergistically and independently, promoting subsequent hippocampal activity. This work provides new insights into how distributed circuits coordinate to optimize adaptive behavior.

Keywords: hippocampus, PFC, VTA, novelty, reward, dopamine, fMRI, MRI

Introduction

The ability to adapt to our dynamic world requires individuals to detect and learn from changes in its surroundings. For instance, encountering a detour sign on your daily commute can trigger learning signals to navigate a new route. This novelty signal would also indicate an increased likelihood of encountering additional important information—such as unexpected roadblocks, new directional signs, or a temporary stop sign. Furthermore, it would be adaptive to enhance plasticity and learn from this salient information, as you may have to take this new route for the following weeks. Thus, as you drive through this unfamiliar route for the first time, your brain needs to heighten its attention to and memory for goal-relevant information. While human and animal research has separately characterized circuits for novelty detection, target detection, and motivated learning, open questions remain about how these circuits interact to promote salience detection and subsequent learning for goal-relevant information. Here, we test a model by which regions that support learning, salience detection, and executive function– hippocampus, ventral tegmental area (VTA), and dorsolateral prefrontal cortex (dlPFC), respectively–work in concert over time to prime the hippocampus to respond to goal-relevant information.

Research in rodents has highlighted several circuits that are critical for translating novelty signals into goal-directed salience detection and learning. In their 'hippocampal-VTA loop' framework, Lisman and Grace (2005) propose a two-phase circuit: during the downward arc, novelty signals promote goal-directed behavior, while during the upward arc, plasticity for salient information is enhanced (Figure 1). Specifically, during the downward arc, the hippocampus detects environmental novelty (Bast, 2007; Kafkas & Montaldi, 2018; Kaplan et al., 2014; Knight, 1996), which in turn enhances tonic dopamine signalling in the VTA (Floresco et al., 2001, 2003; Legault & Wise, 2001). These tonic VTA signals are elevated for an extended

period of time, priming the VTA to amplify any other incoming signals (Goto & Grace, 2007; Grace et al., 2007; Lodge & Grace, 2006a). Upon encountering a subsequent goal-relevant cue, the dlPFC–which is known to detect goal-relevant information (Friedman & Robbins, 2022a; Menon & D'Esposito, 2022; Miller & Cohen, 2001; Thompson-Schill et al., 2005)–can stimulate phasic signalling in the VTA (Ballard et al., 2011; Carr & Sesack, 2000; Gariano & Groves, 1988; Murase et al., 1993). Phasic VTA signals, characterized by fast bursts of firing, mediate reward-related behaviors, including the refinement of goal-relevant responses and memory formation (Adamantidis et al., 2011; Schultz, 2010, 2019; Stuber et al., 2008; Totah et al., 2013; Wanat et al., 2009).

Then during the upward arc, the synergistic engagement of the VTA by the hippocampus and dlPFC releases dopamine into the hippocampus, enhancing plasticity and subsequent memory formation (Bethus et al., 2010; Davis et al., 2004; Frey & Morris, 1998; Gasbarri, Verney, et al., 1994; Redondo & Morris, 2011; Straube et al., 2003). This last arm of the circuit dovetails with a larger literature showing VTA projections to the hippocampus enhances hippocampal sensitivity to and plasticity for new information, thus supporting long-term memory (Li et al., 2003; Lisman et al., 2011; Lisman & Grace, 2005; Murty & Adcock, 2014).

Much of this circuit has been explored in rodents via tracing (Carr & Sesack, 2000; Gasbarri, Packard, et al., 1994; Gasbarri, Verney, et al., 1994; Swanson, 1982), lesion studies (Gasbarri et al., 1996; S. P. Kelley & Mittleman, 1999; Lipska et al., 1992; Schmelzeis & Mittleman, 1996), and pharmacological manipulations (Floresco et al., 2001; Legault & Wise, 2001; Lodge & Grace, 2006a, 2008), which has limited the ability to understand the dynamics of this system in real-time. Human neuroimaging has characterized this circuit piecemeal during awake behavior, including novelty-evoked hippocampal signals predicting VTA tonic signalling

(Murty et al., 2017), dlPFC interactions with phasic VTA signaling during goal-relevant behaviors (Ballard et al., 2011; Murty et al., 2017), and VTA interactions with the hippocampus during goal-relevant encoding (Miendlarzewska et al., 2016; Shohamy & Adcock, 2010). However, research has yet to investigate the downward and upward arc in tandem, precluding the ability to understand how and when these dynamics emerge across different levels of novelty and salience detection. To gain a more comprehensive understanding of this system necessitates characterizing whole-brain activity during a task where novelty is dissociated from subsequent goal-relevant responses.

The current study investigates hippocampus, VTA, and dlPFC dynamics in humans during novelty using fMRI. Although fMRI cannot directly measure dopaminergic signals, it affords the ability to examine multiple brain regions in awake humans during dynamic task performance. In line with the proposed downward arc of the hippocampal-VTA loop, we hypothesized that preceding hippocampus novelty activation will dynamically predict upcoming goal-directed VTA activation. Furthermore, we predicted that goal-directed behavior would engage the PFC and be associated with increased VTA activation. In line with the upward arc of the loop, we hypothesized that simultaneous engagement of hippocampus-VTA-mediated novelty and PFC-VTA-mediated goal-directed circuits would predict hippocampus engagement to goal-relevant information.

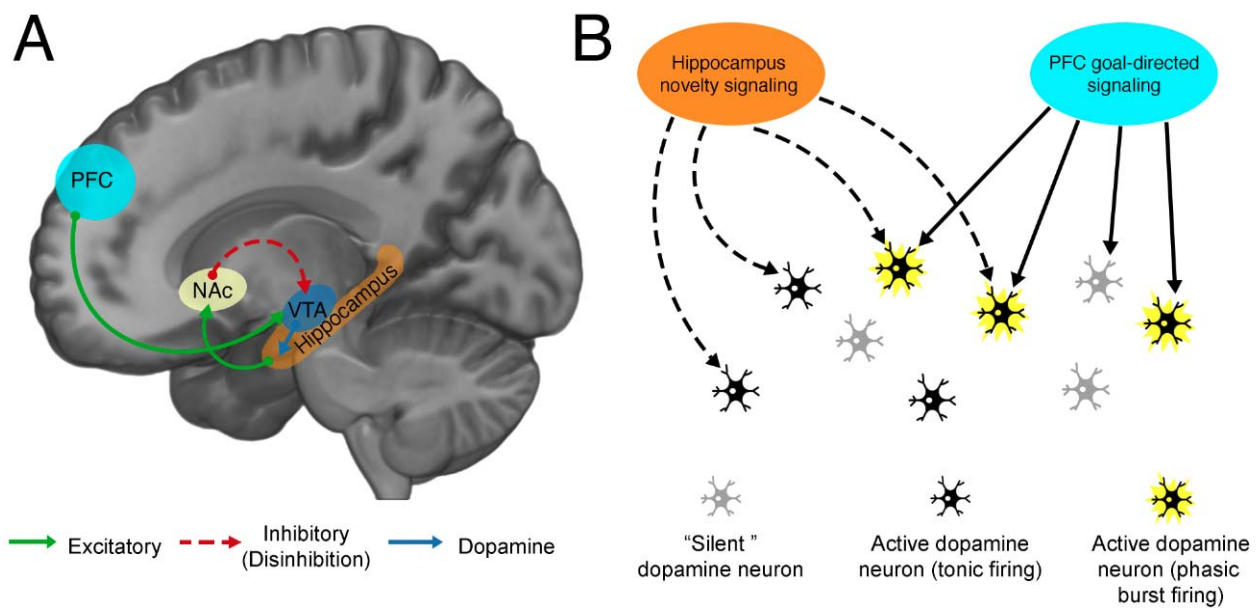

Figure 1: Afferent circuits modulating ventral tegmental area (VTA) activity. (A) The VTA is modulated by distinct afferent systems, the anterior hippocampus and prefrontal cortex (PFC). The anterior hippocampus modulates VTA activity via a polysynaptic circuit through the limbic striatum (i.e. nucleus accumbens [NAc]). The anterior hippocampus has an excitatory connection with the NAc, which forms a disinhibitory circuit with the VTA (via inhibition of the ventral pallidum, not pictured). The VTA has direct dopaminergic projections back to the hippocampus, influencing its function. The PFC has excitatory projections to the VTA. (B) VTA dopamine neuron activity states are modulated by the hippocampus and PFC. A substantial number of VTA dopamine neurons are not spontaneously firing (i.e. under tonic inhibition, "silent"). Hippocampal novelty signals release silent dopamine neurons from tonic inhibition, resulting in active spiking activity (i.e. tonic firing). In this way, hippocampal novelty signals control the baseline firing state of VTA dopamine neurons. In contrast, phasic burst firing, considered to be the behaviorally relevant activity of dopamine neurons, is modulated by the PFC. However, only neurons that are in a spontaneously active (tonic) state can elicit phasic burst firing. In this way, hippocampal novelty signaling and PFC goal-directed signaling synergistically modulate VTA dopamine neuron activity.

Method

Participants

Participants were recruited for this experiment as healthy control subjects in a larger study examining psychosis risk. The final sample with usable task data and structural scans included 77 healthy, right-handed participants. Informed consent was obtained from each participant in a manner approved by Temple University's Institutional Review Board.

Procedure

The protocol and materials used in this experiment were based on previously published work (Murty et al., 2013, 2017). In brief, the task involved two phases: a familiarization phase and a novelty exposure phase (Figure 2). Before scanning, participants 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 with these 80 stimuli.

Approximately 20 minutes later, participants entered the MRI scanner for the novelty exposure phase. During this phase participants viewed a sequence of outdoor scene images, including novel images that had never been seen before, as well as the familiar images seen previously during the familiarization phase (Figure 2). 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.

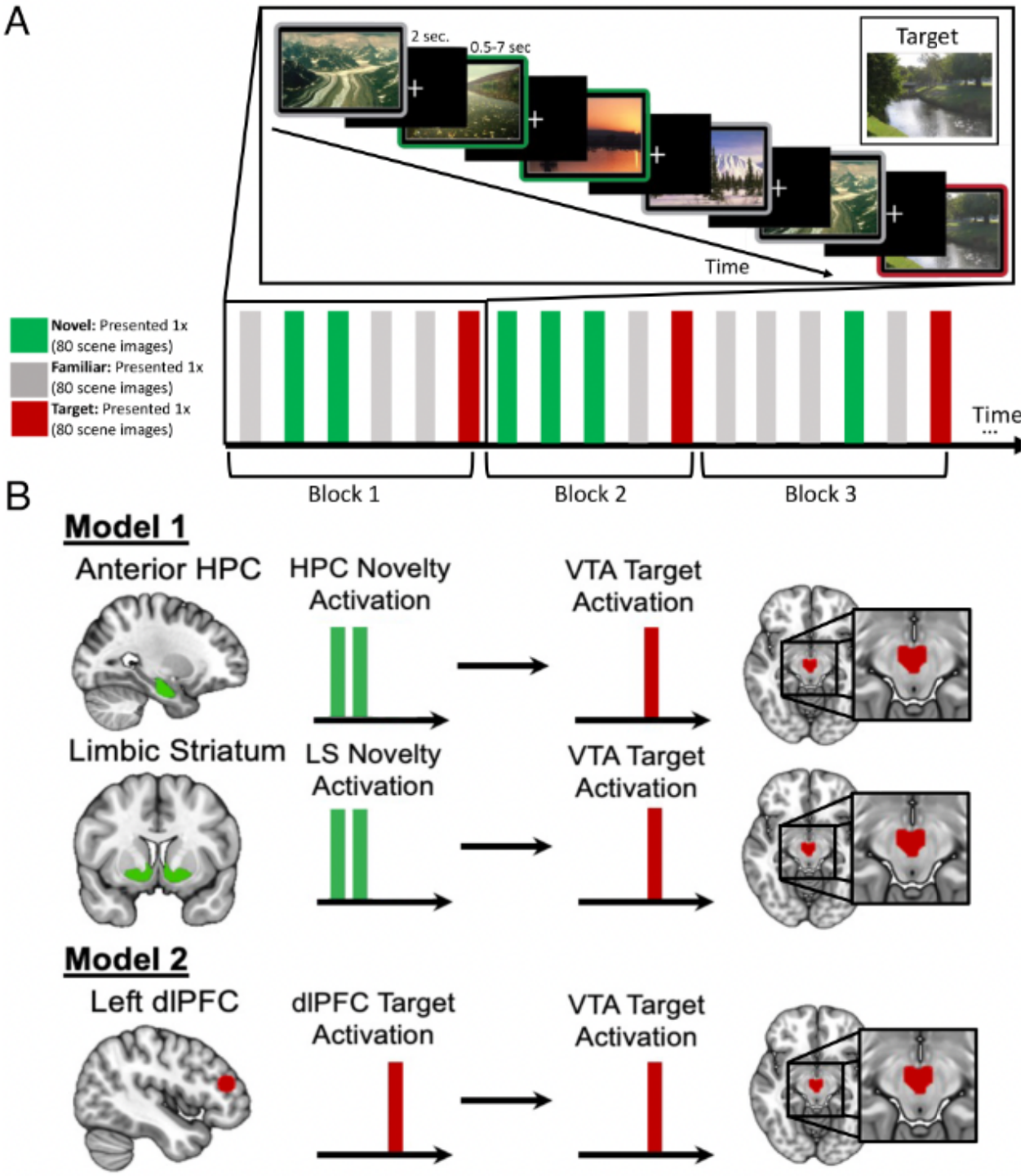

Figure 2: Experimental paradigm and fMRI model. (A) During the fMRI scan, participants performed a target detection task, pressing a button for a specific target image while incidentally viewing 80 familiar scenes (previously seen in the familiarization task) and 80 new scenes. (B) Forward-prediction fMRI models. Activation during novel and target trials was extracted on a segment-by-segment (block) basis. Linear mixed effect models were implemented

to predict target VTA activation from preceding hippocampal (HPC) novelty and limbic striatum novelty activation (Model 1) or concurrent dlPFC target activation (Model 2).

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 ms, voxel size = 2.38 x 2.38 x 2.5 mm, MB factor: 2). In addition, a high-resolution T1-weighted anatomical scan (MPRAGE sequence, voxel size = 0.9 mm isotropic) was acquired to aid in functional image coregistration.

DICOMs were converted to NIFTI format using dcm2niix (X. Li et al., 2016) and organized according to the Brain Imaging Data Structure (BIDS; (Gorgolewski et al., 2016)) using HeuDiConv (https://github.com/nipy/heudiconv). All fMRI preprocessing was performed using the established fMRIPrep pipeline (Esteban et al., 2019). The details below were adapted from the fMRIPrep preprocessing pipeline, with extraneous details omitted for clarity.

The T1w image was corrected for intensity non-uniformity (INU) using N4BiasFieldCorrection from ANTs (v2.2.0) (Tustison et al., 2010) and served as the T1w-reference throughout the workflow. Skull-stripping was performed on the T1w-reference using a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), with OASIS30ANTs as the target template (Avants et al., 2008). Brain tissue segmentation of cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) was performed on the brain-extracted T1w image using FAST (FSL 5.0.9) (Zhang et al., 2001). Volume-based spatial normalization to the MNI152NLin2009cAsym standard space was achieved through nonlinear registration with antsRegistration (ANTs v2.2.0), using brain-extracted versions of both the T1w reference and the T1w template.

For each subject, the following preprocessing steps were performed. First, a reference volume and its skull-stripped version were generated using a custom methodology in fMRIPrep. Head-motion parameters (transformation matrices and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using MCFLIRT (FSL 5.0.9) (Jenkinson et al., 2002). Slice-time correction was applied to the BOLD runs using 3dTshift from AFNI (Cox, 1996; Cox & Hyde, 1997). Based on the estimated susceptibility distortion, a corrected EPI reference was calculated to achieve more accurate co-registration with the anatomical reference. The BOLD reference was co-registered to the T1w reference using FLIRT (FSL 5.0.9) (Jenkinson & Smith, 2001) with the boundary-based registration cost function (Greve & Fischl, 2009). Co-registration was configured with nine degrees of freedom to account for any distortions remaining in the BOLD reference. The BOLD time-series (including slice-timing correction when applied) were resampled into their original native space by applying a single composite transformation to correct for head motion and susceptibility distortions. These resampled BOLD time-series are referred to as preprocessed BOLD in native space. The BOLD time-series were also resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space.

Automatic identification of motion artifacts using ICA-AROMA (Pruim et al., 2015) was performed on the preprocessed BOLD time-series in MNI space after removal of non-steady-state volumes and spatial smoothing with an isotropic Gaussian kernel of 6 mm full-width half-maximum (FWHM). AROMA motion components were included as regressors in subsequent analyses. Additional confounding time-series were calculated based on the preprocessed BOLD data, including framewise displacement (FD) and three regional signals (CSF, WM, and GM). FD was computed using the relative root mean square displacement between affines (Jenkinson

et al., 2002). The three global signals were extracted from the CSF, WM, and whole-brain masks. Notably, FD was not used for “scrubbing” (Power et al., 2012, 2014). All resampling operations were performed in a single interpolation step by composing all pertinent transformations (e.g., head-motion transform matrices, susceptibility distortion corrections when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964).

Region of Interest (ROI) Definition

Anatomical hippocampal ROIs were defined using the Harvard Oxford Subcortical Probabilistic Atlas, thresholded at 50%, and was divided into anterior and posterior based on the last slice in which the uncus was visible (y = -21 on the MNI template, (Poppenk et al., 2013). The VTA ROI was defined based on a probabilistic atlas, thresholded at 50% (Murty et al., 2014). This atlas was developed by averaging 50 hand-drawn ROIs based on previous methods utilizing anatomical landmarks in the midbrain, which allowed for the separation of the substantia nigra and VTA (Ballard et al., 2011; Naidich et al., 2009). The limbic (ventral) striatum (encompassing the nucleus accumbens) ROI was defined using a connectivity-based segmentation atlas with subdivisions for sensorimotor, executive, and limbic regions (Tziortzi et al., 2014). These striatal subdivisions also likely reflect separable functional pathways from midbrain dopaminergic regions (Elliott, D’Ardenne, Mukherjee, et al., 2022; Elliott, D’Ardenne, Murty, et al., 2022). Additionally, the homogeneity of dopamine release measured with positron emission tomography (PET) in response to the administration of amphetamine is significantly higher within these connectivity-based subdivisions of the striatum compared with within-anatomic subdivisions (i.e., putamen, caudate, and nucleus accumbens). Next, the ROIs

(hippocampus, VTA, and limbic striatum) were resampled to fit the dimensions of each of the functional dataset using AFNI's 3dResample (Cox, 1996).

fMRI Data Analysis

Detailed procedures and analysis methods for the fMRI data were employed to ensure rigorous and reproducible results. fMRI data were analyzed using AFNI version 24.0.06.

Univariate Analysis During Novelty Exposure Task

To measure BOLD response during the novelty exposure phase of the task, we computed a GLM with regressors for each condition (novel, familiar, target) for each block (40 of each). A block was defined as the trials preceding a target (Figure 2). Individual events were convolved with a double-gamma hemodynamic response (HDR) function. Noise-related measures were also added as additional nuisance regressors. 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 resulting contrasts were registered to standard MNI space, from which we then extracted the b parameters from each condition, (e.g., novel, familiar, target greater than baseline) for each block, for each participant. We examined univariate responses across our ROIs of interest, in the hippocampus, VTA, and limbic striatum, and dlPFC regions.

Statistical Analysis

Afferent Circuits Modulating Target VTA Activation.

We next ran a series of analyses to predict target VTA activation. First, we examined whether preceding activation during novelty trials in the anterior hippocampus and limbic striatum predicted activation during the subsequent target trial in the VTA. Given the

polysynaptic nature of the hippocampus-VTA circuit, the limbic striatum was included to examine if the activation was driven by the hippocampus instead of the intermediate striatal region. Next, we examined whether concurrent dlPFC target activation was associated with VTA target activation within a block. We implemented generalized linear mixed effects models for these analyses. These models were implemented using the lme4 package in R (lmer; R v 4.2.1), using a model comparison approach. In our first model we examined if the independent variable of ROI (anterior hippocampus novelty activation and limbic striatum novelty activation, within-subjects variables) improved the fit of a base model which included only participant ID (between-subjects variable) using an omnibus chi-squared test. In our second model we examined if the independent variable of ROI (dlPFC target activation, within-subjects variable) improved the fit of a base model which included only participant ID (between-subjects variable) using an omnibus chi-squared test. Model fit comparisons were described using AIC and BIC. All models were computed on a trial-wise level and included ‘subject’ as a random effect to account for within-subjects variation in the data. Likelihood ratio tests were conducted using the `anova()` function to determine whether the full model provided a significantly better fit than the baseline model.

To examine the specificity of the effect of preceding novelty and concurrent target trial activation on VTA target activation, we conducted permutation tests by shuffling trial labels, generating a null distribution of model coefficients across 1,000 permutations. This approach allowed us to test whether observed relationships between hippocampal and dlPFC activations with VTA target responses exceeded chance levels. Following each permutation, we recalculated model parameters and compared the resulting distributions to our observed data. These analyses

ensured that the predictive effects were not due to random associations but instead reflected reliable temporal dependencies.

Independence of Hippocampal Novelty and Goal-directed PFC Circuits

To investigate whether hippocampus novelty activation and target dlPFC activation independently modulates VTA activity we employed a linear mixed-effects model using the `lmer` function from the `lmerTest` package. Our analysis involved a full model that included both predictors, with a random intercept for participant ID to account for individual variability. To ensure that the predictors did not exhibit multicollinearity, we calculated Variance Inflation Factors (VIFs). VIF values close to 1 indicated that multicollinearity was not a concern.
To confirm that each predictor contributed uniquely to the model, we compared the full model with two reduced models, each excluding one predictor at a time. The first reduced model excluded hippocampal novelty signaling, and the second excluded target dlPFC signaling. Model fit comparisons were described using AIC and BIC. Likelihood ratio tests were conducted using the `anova()` function to determine whether the full model provided a significantly better fit compared to the reduced models.

Hippocampal Long-axis Specificity

Animal models predict that ventral (anterior in humans) hippocampal novelty signals modulate the VTA. Thus, we tested whether anterior versus posterior hippocampal novelty signals predicted subsequent VTA activation using linear mixed effects models and a model comparison approach. To test if posterior hippocampal signals predicted subsequent VTA target activation, in our first model we examined if the independent variable of ROI (posterior hippocampus novelty activation, within-subjects variable) improved the fit of a base model which included participant ID (between-subjects variable) using an omnibus chi-squared test. To

test if the posterior hippocampus better predicted VTA target activation than the anterior hippocampus we next examined if the independent variable of ROI (posterior hippocampus novelty activation, within-subjects variable) improved the fit of a base model which included participant ID (between-subjects variable) and anterior hippocampus novelty activation (within-subjects variable) using an omnibus chi-squared test. Model fit comparisons were described using AIC and BIC. All models were computed on a trial-wise level and included 'participant ID' as a random effect to account for within-subjects variation in the data. Likelihood ratio tests were conducted using the `anova()` function to determine whether the full model provided a significantly better fit compared to the reduced models.

Specific versus Relative Novelty

We next examined whether preceding hippocampal novelty activation predicting target VTA activation is specific to activation during the novel images only (specific novelty) or is sustained throughout the preceding block (relative novelty). We tested these hypotheses using linear mixed effects models and a model comparison approach. In our models we examined if the independent variable of ROI (hippocampal response to familiar scenes only [relative novelty], within-subjects variable) improved the fit of a base model which included participant ID (between-subjects variable) and hippocampal response to novel scenes only (specific novelty, within-subjects variable) using an omnibus chi-squared test. Model fit comparisons were described using AIC and BIC. All models were computed on a trial-wise level and included 'participant ID' as a random effect to account for within-subjects variation in the data. Likelihood ratio tests were conducted using the `anova()` function to determine whether the full model provided a significantly better fit than the baseline model.

Afferent Circuit Modulation of Hippocampus Sensitivity

To investigate how hippocampal and prefrontal modulation of the VTA (i.e., the downward arc) contribute to subsequent hippocampal sensitivity during target trials (i.e., the upward arc), we implemented a path analysis using the lavaan package (Rosseel, 2012) with our time-lagged fMRI model. Regression coefficients were estimated using maximum likelihood, and mediation effects were calculated with the product-of-coefficients approach. Standard errors (SEs) and 95% confidence intervals (CIs) were estimated via bootstrapping (1,000 samples), which is robust to non-normality, increases power, and minimizes imprecision due to small sample sizes (Kelley, 2005). Global model fit was assessed using the comparative fit index (CFI) and root mean square error of approximation (RMSEA), with benchmarks of CFI > 0.90 and RMSEA ≤ 0.07 indicating good fit (Kline, 2015; Steiger, 2007). Pathways were considered significant if the 95% CI did not include zero. All coefficients are presented as standardized (β) values to allow comparison of effect magnitudes within and across models. Standardized path coefficients were used as path effect sizes (Nieminen et al., 2013).

Results

Hippocampal Novelty Activation Predicts Target VTA Activation

To test whether hippocampal novelty signals affect subsequent goal-relevant phasic VTA responses, we investigated whether activation in the hippocampus during novel trials predicted subsequent event-evoked responses in VTA during target trials. Confirming our predictions, we found that adding hippocampal novelty activation as a predictor significantly improved model fit for predicting target VTA activation (AIC and BIC without hippocampal novelty activation: -1981.0, -1964.4; AIC and BIC with hippocampal novelty activation: -1987.1, -1964.9; model comparison: $\chi^2[1] = 8.06$, $p < 0.01$, Figure 3A). Given the polysynaptic nature of the hippocampal circuit through the limbic striatum, we next ran a model that included limbic

striatum activation. The model comparison showed that including the limbic striatum did not significantly improve model fit compared to including only hippocampal novelty activation (AIC and BIC without limbic striatum activation: -1987.1, -1964.9; AIC and BIC with limbic striatum activation: -1986.8, -1959.1; model comparison: $\chi^2[1] = 1.75$, $p = 0.186$).

We next tested whether hippocampal novelty responses predicting target VTA activity were temporally specific (i.e., the preceding novelty trials) by implementing a permutation test in which we shuffled the trial labels, generating a distribution of model coefficients (t-values) across 1,000 permutations. The confidence interval (CI) of the t-values for the model coefficients ranged from -1.61 to 2.44, indicating that the observed effects did not significantly deviate from those expected by chance at the 95% confidence level. This permutation test indicated that the effect of novelty on target VTA activation was specific to the preceding novelty trials from the same block (Figure 4A).

dlPFC Target Activation Predicting VTA Target Activation

To test whether dlPFC target signals affect phasic VTA responses, we investigated whether activation in the dlPFC predicted phasic VTA responses during goal-directed behavior (target trials). Including dlPFC target activation in the model significantly improved fit over the baseline model (AIC and BIC without dlPFC target activation: -3240.4, -3222.3; AIC and BIC with dlPFC target activation: -3268.8, -3244.7; model comparison: $\chi^2[1] = 30.44$, $p < 0.001$, Figure 3B).

We next tested whether these effects were temporally specific by implementing a permutation test in which we shuffled the trial labels, generating a distribution of model coefficients (t-values) across 1,000 permutations. The confidence interval (CI) of the t-values for the model coefficients ranged from -1.79 to 2.19, indicating that the observed effects did not

significantly deviate from those expected by chance at the 95% confidence level, indicating that the effect of target dlPFC activation on target VTA activation was specific to the target trials from the same block (Figure 4B). In accordance with the rodent literature, these results indicate that phasic dlPFC target activation predicts phasic VTA target activation.

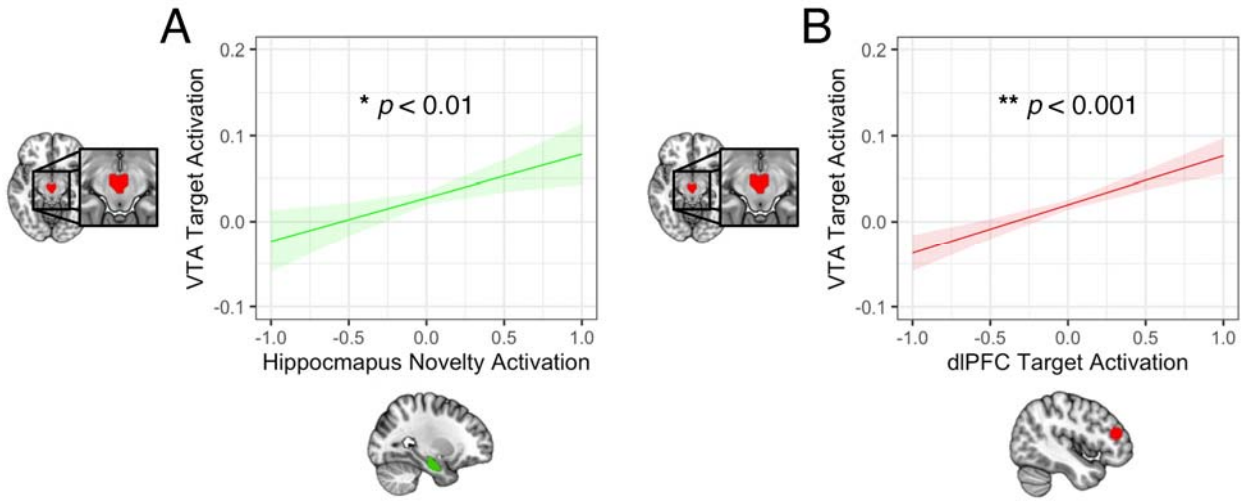

Figure 3: Estimated marginal effects from the linear mixed effects models. (A) Predicted values of VTA target activation as a function of hippocampus novelty activation, averaged over the random intercepts for subjects. The solid line represents the fixed effect estimate, and the shaded area indicates the 95% confidence interval. **(**B) Predicted values of VTA target activation as a function of dlPFC target activation, averaged over the random intercepts for subjects. The solid line represents the fixed effect estimate, and the shaded area indicates the 95% confidence interval.

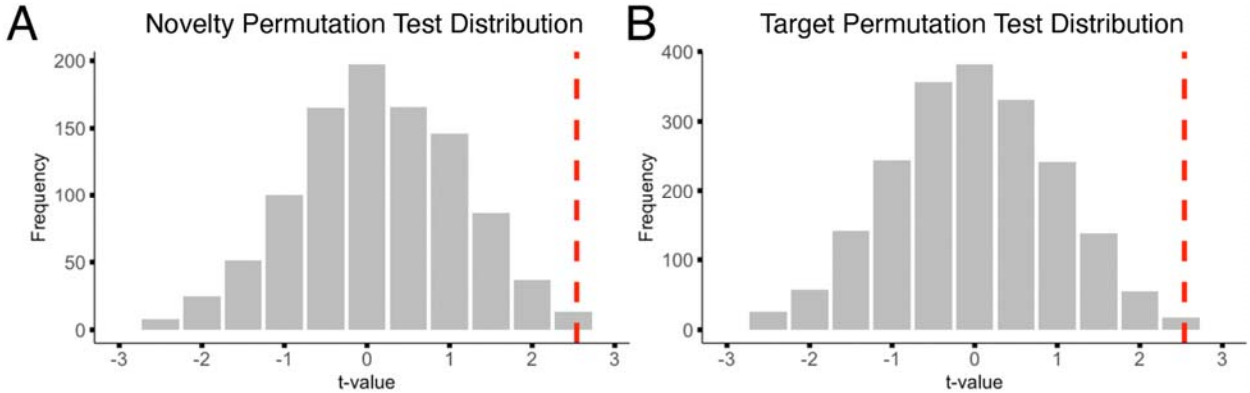

Figure 4: Permutation distributions. (A) Distribution of t-values from shuffling the trial labels of hippocampal novelty trials predicting target VTA trials. **(**B) Distribution of t-values from shuffling the trial labels of dlPFC target trials predicting target VTA trials. Dashed red line represents the observed t-value of the predictor from the model.

Independence of Hippocampal Novelty and Goal-directed PFC Circuits

We next investigated whether hippocampus novelty activation and target dlPFC activation independently influences goal-directed phasic VTA responses. We fit a full model that included both hippocampal novelty activation and target dlPFC activation as fixed effects, while accounting for individual variability with a random intercept for participant ID. Variance Inflation Factors (VIFs) were calculated to check for multicollinearity between predictors. Both VIF values were approximately 1 (Hippocampal Novelty: 1.002, dlPFC Target: 1.002), indicating that multicollinearity was not a concern. Examining the fixed effects in the full model, both predictors were statistically significant. Hippocampal novelty activation was a significant positive predictor of VTA activation, $t(1864) = 2.61$, $p < 0.01$, and target dlPFC activation showed a robust positive association, $t(1865) = 5.51$, $p < 0.001$.

Likelihood ratio tests revealed that removing hippocampal novelty activation significantly worsened the model fit, $\chi^2(1) = 6.82$, $p < 0.01$, suggesting that hippocampal novelty activation contributes uniquely to VTA engagement. Similarly, removing target dlPFC activation resulted in a significant reduction in model fit, $\chi^2(1) = 30.12$, $p < 0.001$, indicating that target dlPFC activation also independently predicts VTA engagement. These results support the hypothesis that hippocampal novelty and goal-directed PFC circuits independently contribute to VTA engagement.

Hippocampal Long-Axis Specificity

Rodent research suggests that these effects would be specific to ventral regions of the hippocampus akin to the anterior hippocampus in humans (Fanselow & Dong, 2010; Poppenk et al., 2013; Strange et al., 2014). Therefore, we examined whether the observed effects were specific to the anterior hippocampus. We first tested whether including posterior hippocampal novelty activation would improve model fit compared to a baseline model. Interestingly, we

found that including posterior hippocampal activation in the model significantly improved fit over the baseline model (AIC without posterior hippocampal novelty activation: -1981.0; AIC with posterior hippocampal novelty activation: -1985.1; BIC without posterior hippocampal novelty activation: -1964.4; BIC with posterior hippocampal novelty activation: -1963.0; model comparison: $\chi^2[1] = 6.12$, $p = 0.013$). However, the results were mixed, as the AIC values favored the model with posterior hippocampal activation, while the BIC values suggested a less clear improvement, indicating a trade-off between model fit and complexity. The model examining anterior versus posterior hippocampal activation showed that adding posterior hippocampal novelty activation did not significantly improve model fit for predicting target VTA activation compared to anterior hippocampal activation (AIC without posterior hippocampal activation: -1987.1; AIC with posterior hippocampal activation: -1986.2; BIC without posterior hippocampal activation: -1964.9; BIC with posterior hippocampal activation: -1958.5; model comparison: $\chi^2[1] = 1.11$, $p = 0.293$). The results provide some evidence of a role for posterior hippocampus novelty singling in modulating VTA engagement, although there is greater support for a specific role for the anterior hippocampus in modulating VTA responses following novelty exposure.

Specific versus Relative Novelty

There are two ways to conceptually quantify novelty. A more specific definition may define novelty exclusively to scenes that have never been seen before, while a more relative definition may incorporate all scenes which gradually vary in their novelty signal. In this later case a familiar stimulus could still maintain a moderated novelty response which could still engage hippocampal activity. We tested whether the novelty benefit was specific to novel scenes in the preceding block (specific novelty) or a sustained signal through the block (relative

novelty). To address this, we compared two models: the first model included hippocampal activation in response to novel scenes only (specific novelty), while the second model incorporated hippocampal activation in response to both novel and familiar scenes (relative novelty). Our analysis showed that the model including both novel and familiar scenes—capturing the relative novelty effect—significantly improved the prediction of subsequent VTA activation compared to the specific novelty model (AIC with specific novelty: -1609.1; AIC with relative novelty: -1616.4; BIC with specific novelty: -1587.8; BIC with relative novelty: -1589.7; model comparison: $\chi^2[1] = 9.25$, $p = 0.002$). These findings suggest that a sustained novelty signal, encompassing both novel and familiar scene activations, is more critical for modulating downstream VTA engagement than a response limited to specific novel stimuli.

Afferent Circuit Modulation of Hippocampus Sensitivity

Rodent models hypothesize that hippocampal novelty signals upregulate VTA engagement. Critically, the VTA has a dopaminergic projection back to the VTA, increasing its sensitivity. In this way, novelty can prime hippocampal plasticity via VTA neuromodulatory signaling. We hypothesized that hippocampal novelty activation would predict subsequent hippocampal activation to target scenes. However, this should be mediated by the respective circuits investigated here, the hippocampal novelty circuit (hippocampus - VTA - hippocampus) and the dlPFC goal-directed circuit (dlPFC - VTA - hippocampus). We tested this using a path analysis (serial mediation model). Figure 4 depicts the effects of the paths linking hippocampal novelty activation to each mediator and hippocampal target activation, Table 1 reports the statistics. We found a significant total effect (path f, $\beta = 0.163$, 95% CI = 0.117 - 0.210, $p < 0.01$), suggesting that increased hippocampal novelty activation predicts subsequent hippocampal target activation (Figure 4). Path analyses revealed that both the hippocampus-VTA

novelty circuit (d*c, hippocampal novelty - VTA target - hippocampal target) and the dlPFC-VTA goal-directed circuit (b*c, dlPFC target- VTA target - hippocampal target) significantly mediated hippocampal sensitivity to subsequent targets (CFI = 1.00; RMSEA = 0.00). After controlling for these afferent circuits, the direct effect of hippocampal novelty activation on hippocampal target activation was still significant (f', β = 0.143, 95% CI = 0.100 - 0.188, $p < 0.01$).The model R^2 for hippocampal target activation was 0.121, indicating that afferent circuit pathways accounted for a significant portion of variance in hippocampal activation. Other indirect effects were not significant. Statistics for the other direct and indirect effects are reported in Supplemental Table 1.

Table 1. Direct and indirect effects of hippocampal (HPC) novelty activation on subsequent HPC target activation

Outcome	**β**	**BootSE**	**BootLLCI**	**BootULCI**
Direct Effect				
HPC Novelty – HPC Target	0.143***	0.023	0.100	0.188
HPC Novelty Circuit				
HPC Novelty – VTA Target – HPC Target	0.012*	0.005	0.002	0.021
dlPFC Goal-Directed Circuit				
dlPFC Target – VTA target	0.018*	0.004	0.011	0.026

*

Other Indirect Effects				
HPC Novelty – dlPFC Target – VTA Target – HPC Target	0.001	0.001	0.000	0.003
HPC Novelty – dlPFC Target – VTA Target – HPC Target	0.007	0.004	-0.001	0.015

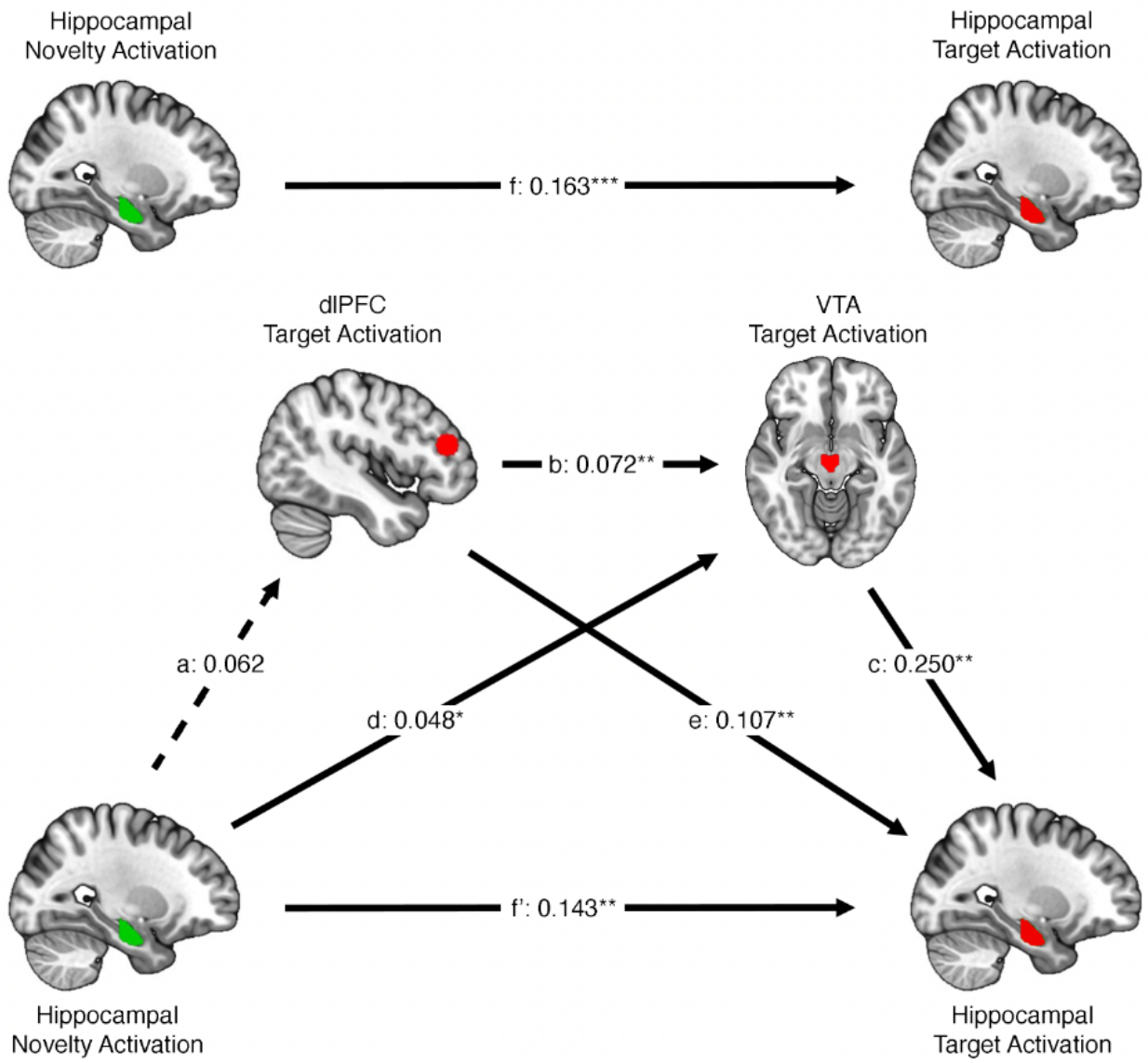

Figure 4: Path analysis of afferent circuits modulating hippocampal plasticity. * Denotes $p < 0.05$, ** $p < 0.01$.

Discussion

Adaptive behavior requires an organism to detect and learn from changes in the environment. Novelty detection plays a crucial role in this process, acting as a signal for meaningful changes in the environment and triggering adaptive responses to goal-relevant information. However, open questions remain about how the brain translates these novelty

signals to promote salience detection and subsequent learning that facilitate responses to goal-relevant information. Rodent research suggests that novelty can promote a positive feedback loop, wherein hippocampal novelty circuits can prime hippocampal responses to goal-relevant stimuli via engaging hippocampal-VTA and PFC-VTA circuits (Grace et al., 2007; Legault & Wise, 2001; Lisman et al., 2011; Lisman & Grace, 2005; Lodge & Grace, 2008). However, although rodent research provides circuit level specificity, how these circuits interact during sustained motivational states (i.e. novelty) and transient salience detection remain opaque. In the current study, we implemented a combination of advanced fMRI analysis techniques and path analysis to characterize the unique contributions of hippocampal novelty and PFC goal-directed circuits modulating VTA activation and their subsequent effect on hippocampal engagement. We found that hippocampal novelty signals and PFC goal-directed signals dynamically and synergistically predicted subsequent VTA engagement. Additionally, these circuits independently mediated subsequent hippocampal activation. These findings provide critical insights into afferent circuits modulating mesolimbic signals in humans and their downstream effect on hippocampal plasticity during goal-directed behavior.

Afferent Modulation of VTA Engagement

Previous animal research has provided circuit-level framework for understanding how novelty signals affect mesolimbic engagement. Our findings dovetail prior work in animal models that describe the hippocampal-VTA loop as a crucial circuit for novelty-driven VTA engagement. Here, we found that preceding anterior hippocampal novelty signals enhance subsequent VTA engagement during goal-directed target detection. Permutation analyses showed that this effect was specific to hippocampal novelty activation during the preceding trials within a block. Additionally, we observed that this effect was driven by hippocampal novelty signaling

and not limbic striatum (nucleus accumbens) signaling. This result supports the notion that the anterior hippocampus plays a specialized role in detecting novelty and priming the VTA, consistent with the polysynaptic circuitry observed in non-human animals (Legault & Wise, 2001; Otmakhova et al., 2013). This homology reinforces the importance of hippocampal-VTA interactions in modulating motivational processes in dynamic environments.

Previous studies have highlighted the influential role of the prefrontal cortex (PFC) in modulating motivated behavior through mesolimbic engagement, particularly through the modulation of phasic VTA activity. Specifically, the PFC has been shown to detect goal-relevant stimuli (Blumenfeld & Ranganath, 2007; Menon & D'Esposito, 2022; Miller & Cohen, 2001) and is implicated in attention and executive functions (Benchenane et al., 2011; Friedman & Robbins, 2022b; Paneri & Gregoriou, 2017; Rossi et al., 2009; Zanto et al., 2011) and motivated behavior (Cohen et al., 2014; Jimura et al., 2010; Murty & Adcock, 2014). Likewise, tasks that disrupt attention and executive function have been shown to impair motivated behavior (Elliott & Brewer, 2019). Furthermore, the PFC has been shown to stimulate the VTA (Ballard et al., 2011; Murty et al., 2017), thereby potentially enhancing hippocampal sensitivity to new information (Murty & Adcock, 2014). Our finding aligns with the established role of the PFC in modulating attention and executive function to prioritize goal-relevant information.

Hippocampal and PFC Circuits Prime Hippocampal Sensitivity

Animal studies have demonstrated that dopaminergic neuromodulation is crucial for synaptic plasticity in the hippocampus (Frey et al., 1993; Frey & Morris, 1998; Huang & Kandel, 1995), increasing hippocampal sensitivity (Hammad & Wagner, 2006; Swant et al., 2008) and stabilizing hippocampal representations (Martig & Mizumori, 2011; Nguyen et al., 2014; Retailleau & Morris, 2018; Tran et al., 2008; Werlen & Jones, 2015). Studies in humans have

shown that increased motivational demands improve memory encoding, and that this is mediated by engagement of the VTA and hippocampus (Adcock et al., 2006; Elliott, Blais, et al., 2020; Elliott, McClure, et al., 2020; Gruber et al., 2016; Knowlton & Castel, 2022; Shigemune et al., 2014; Wittmann et al., 2007a, 2007b). Our combined use of traditional fMRI and path analysis methods allowed us to test aspects of the hippocampal-VTA-PFC network that have not been detailed in previous models, including the Lisman and Grace model. Importantly, our study provides empirical evidence for the timing and mechanistic interplay between these circuits. Specifically, we showed that the hippocampus and dlPFC independently influence VTA activity, but their effects converge to enhance hippocampal sensitivity to goal-relevant information.

These findings suggest a form of synergistic coincidence detection, where the temporal and mechanistic coordination of these signals is critical for optimal VTA modulation. Importantly, our results highlight that while the hippocampal and PFC inputs to the VTA function independently, they ultimately converge to modulate downstream hippocampal processing, as shown by our path analysis. This finding comports with rodent literature that has shown combined activation of the hippocampal novelty pathway and PFC pathways significantly amplifies both VTA neuron population activity and burst firing (Grace et al., 2007; Lodge & Grace, 2006a). This suggests that the synchronous activity of distinct afferent inputs to the VTA synergistically upregulates the VTA, which in turn primes the hippocampus, promoting hippocampal plasticity.

Hippocampal Long-Axis Specificity

Rodent models specify that the hippocampal novelty signal is specifically driven by the ventral hippocampus. It is also hypothesized in humans that the hippocampus is structurally and functionally heterogeneous along the anterior-posterior (long) axis. Indeed, human research has

shown preferential structural (Elliott et al., 2024) and functional connectivity between the anterior hippocampus and the VTA (Cowan et al., 2021; Kahn & Shohamy, 2013). By demonstrating that anterior hippocampal novelty signals, rather than posterior, are critical for modulating VTA activity, our data add granularity to the understanding of hippocampal long-axis specificity in humans.

Specific versus Relative Novelty

We found that hippocampal activation was sustained throughout the preceding block, and not specific to trial-wise novel scene activation. This finding aligns with the observation from rodent studies that the neuromodulatory influence of novelty on synaptic plasticity extends beyond the initial period of exploration. Specifically, research has shown that rats exploring a novel spatial environment experience a temporally extended reduction in the threshold for long-term potentiation (LTP) induction in the hippocampal CA1 region, persisting 15 to 30 minutes after the novelty experience (Li et al., 2003; Straube et al., 2003). This enhancement in LTP can be blocked by D1/D5 receptor antagonists, suggesting that the novelty-facilitated increase in hippocampal synaptic plasticity is dopamine dependent (Davis et al., 2004). Our finding of sustained hippocampal activation across the block comports with these rodent results, as it suggests that novelty-induced neuromodulation could continue to enhance hippocampal plasticity even when familiar stimuli are encountered in the same context. This sustained activation may reflect an adaptive mechanism whereby the hippocampus maintains an elevated state of plasticity, enhancing learning and memory processes for familiar information presented within a novel context.

Limitations and Future Directions

Although our data establish the significance of the hippocampal and PFC circuits in VTA modulation, we acknowledge that this does not represent a complete mediation of the hippocampal target responses. There are several other afferent circuits implicated in VTA modulation, including the habenula (Christoph et al., 1986; Hennigan et al., 2015; Stamatakis & Stuber, 2012), medial prefrontal cortex (mPFC; Gao et al., 2007; Gariano & Groves, 1988; Parker et al., 2011; Sevensson & Tung, 1989; Takahashi et al., 2011), and pedunculopontine nucleus (Lodge & Grace, 2006b; Lokwan et al., 1999; Sesack & Carr, 2002; Yoo et al., 2017). Future studies should investigate these additional pathways to provide a more comprehensive understanding of how VTA activity is orchestrated by multiple neural inputs.

Recent research has also indicated a role for a locus coeruleus (LC) neuronal projection to the hippocampus in coding novelty and enhancing hippocampal plasticity (Takeuchi et al., 2016; Yamasaki & Takeuchi, 2017). It has been proposed that the LC-hippocampus pathway may specifically encode responses to distinct novelty, enhancing initial memory consolidation through heightened plasticity. This process relies on the corelease of dopamine and noradrenaline, promoting robust and vivid memory encoding for stimuli encountered in discrete, novel episodes (Duszkiewicz et al., 2019). In this way, an LC-hippocampus pathway may be better suited to encode novelty in a trial-specific manner. However, human research investigating LC-hippocampal projections and novelty coding is methodologically challenging and lacking.

Animal models of the hippocampal-VTA circuit posit that the hippocampus regulates VTA dopamine neurons. However, the VTA also contains glutamatergic and GABAergic cells. fMRI relies on an indirect measure of neuronal activity (i.e., the BOLD signal), and does not allow for the direct classification of cell type. BOLD signals in the VTA likely reflect the integrated activity of these neuronal subtypes, complicating the interpretation of whether

observed activity specifically reflects dopaminergic processes or the broader functional role of the VTA. As such, future studies combining BOLD imaging with complementary techniques (e.g., pharmacological manipulations) are needed to disentangle the contributions of different neurotransmitter and neuromodulatory systems to novelty-driven VTA-hippocampal interactions.

Although our findings demonstrate novelty-driven increases in hippocampal sensitivity, an important limitation is the absence of measures explicitly linking this neural activity to memory outcomes. While the observed hippocampal responses suggest potential for enhanced plasticity, it remains unclear whether these changes lead to measurable memory benefits. Without behavioral assessments, we cannot determine whether the novelty-driven hippocampal sensitivity observed in this study facilitates memory encoding or consolidation. To address this, future research should incorporate explicit memory testing alongside neural measures to directly evaluate the functional impact of novelty-driven VTA-hippocampal interactions. Such an approach would provide a more comprehensive understanding of the relationship between novelty, hippocampal activity, and memory, helping to bridge the gap between observed neural dynamics and their potential behavioral relevance.

Conclusions

Our study sheds light on the complex interplay between novelty and goal-directed circuits in the brain, emphasizing the independent yet convergent roles of the hippocampus and prefrontal cortex in modulating VTA activity, promoting hippocampal plasticity to support future adaptive responses. This study highlights the dynamic coordination of distributed neural circuits in optimizing adaptive behavior. These findings have broad implications for understanding how the brain prioritizes and processes information in dynamic environments, contributing to adaptive behavior and learning.

Conflicts of Interest

The authors declare no conflicts of interest.

Resource Availability

Lead Contact

Further information and requests for resources should be directed to the lead contact, Blake Elliott (Blake.Elliott@temple.edu).

Materials Availability

This study did not generate reagents

Data and Code Availability

The data and code that support the findings of this study are openly available at https://github.com/blelliott23/

Any additional information required to reanalyze the data reported in this work paper is available from the lead contact upon request.

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Supplemental Table 1. Direct and indirect effects of hippocampal (HPC) novelty activation on subsequent HPC target activation

Outcome	**β**	**BootSE**	**BootLLCI**	**BootULCI**
Novel HPC - Target dlPFC (a)	0.062	0.036	-0.008	0.135
Target dlPFC - Target VTA (b)	0.072	0.014	0.044	0.100
Target VTA - Target HPC (c)	0.250	0.026	0.200	0.300
Novel HPC - Target VTA (d)	0.048	0.019	0.010	0.085
Target dlPFC – Target HPC (e)	0.107	0.017	0.071	0.138
Novel HPC - Target HPC (f)	0.143	0.023	0.100	0.188
indirect_1 - a*b*c	0.001	0.001	-0.001	0.003
indirect_2 - a*e	0.007	0.004	-0.001	0.015
indirect_3 - d*c	0.012	0.005	0.002	0.021
indirect_4 - b*c	0.018	0.004	0.011	0.026
Total Effect - a*b*c+a*e+d*c+f	0.163	0.024	0.117	0.210
Total Indirect - b*c+e	0.125	0.018	0.089	0.158