Title

In vivo structural connectivity of the reward system along the hippocampal long axis

Journal

Hippocampus, 34(7)

ISSN

1050-9631

Authors

Elliott, Blake L

Mohyee, Raana A

Ballard, Ian C

et al.

Publication Date

2024-07-01

DOI

10.1002/hipo.23608

In Vivo Structural Connectivity of the Reward System Along the Hippocampal Long-Axis

Blake L. Elliott[1]

Raana A. Mohyee[1]

Ian C. Ballard[2]

Ingrid R. Olson[1]

Lauren M. Ellman[1]

Vishnu P. Murty[1]

1. Department of Psychology and Neuroscience, Temple University, Philadelphia, PA, USA
2. Department of Psychology, University of California, Riverside, Riverside, CA, USA,

Correspondence: Blake L. Elliott; Blake.Elliott@temple.edu

Abstract

Recent work has identified a critical role for the hippocampus in reward-sensitive behaviors, including motivated memory, reinforcement learning, and decision-making. Animal histology and human functional neuroimaging have shown that brain regions involved in reward processing and motivation are more interconnected with the ventral/anterior hippocampus. However, direct evidence examining gradients of structural connectivity between reward regions and the hippocampus in humans is lacking. The present study used diffusion MRI and probabilistic tractography to quantify the structural connectivity of the hippocampus with key reward processing regions in vivo. Using a large sample of subjects (N=628) from the human connectome dMRI data release, we found that connectivity profiles with the hippocampus varied widely between different regions of the reward circuit. While the dopaminergic midbrain (VTA) showed stronger connectivity with the anterior versus posterior hippocampus, the vmPFC showed stronger connectivity with the posterior hippocampus. The limbic (ventral) striatum demonstrated a more homogeneous connectivity profile along the hippocampal long-axis. This is the first study to generate a probabilistic atlas of the hippocampal structural connectivity with reward-related networks, which is essential to investigating how these circuits contribute to normative adaptive behavior and maladaptive behaviors in psychiatric illness. These findings describe nuanced structural connectivity that sets the foundation to better understand how the hippocampus influences reward-guided behavior in humans.

Keywords: hippocampus, anatomy, episodic memory, reward, dopamine, DTI, MRI

Introduction

The hippocampus is a deep brain structure associated with episodic memory and spatial navigation (Burgess et al., 2002; Scoville & Milner, 1957; Squire, 1992; Lisman et al., 2017; Moser et al., 2008; O'Keefe & Nadel, 1978). However, the hippocampus is also functionally involved in a variety of adaptive behaviors including future planning (Buckner, 2010; Mullaly & Maguire, 2014; Stachenfeld et al., 2017; Benoit et al., 2011), reward-learning (Wirth et al., 2009; Devenport et al., 1981; Holscher et al., 2003; Ploghaus, et al. 2000; Ballard et al., 2019), novelty coding (Whittman et al., 2007; Bunzeck & Düzel, 2006; Kumaran & Maguire, 2007) and value-based decision-making (Palombo et al., 2015; Tang et al., 2021; Shadlen & Shohamy, 2016; Shohamy & Daw, 2015; Bunzeck et al., 2010; Wimmer & Shohamy, 2012). Its role in adaptive behavior has been mirrored in studies showing hippocampal alterations in maladaptive behaviors associated with reward processing, such as anhedonia and depression (Lodge & Grace, 2008; 2011; Grace, 2016; Lee et al., 2012; Zackova et al., 2021). While the focus of this prior work has been centered on the hippocampus, evidence suggests it subserves these adaptive behaviors through structural and functional connectivity with brain regions guiding motivation. Non-human animal histology has shown that brain regions involved in reward processing and motivation, including the ventromedial prefrontal cortex (vmPFC), limbic (ventral) striatum (encompassing the nucleus accumbens), and ventral tegmental area (VTA), are interconnected with the hippocampus (Lisman & Grace, 2005; Haber & Knutson, 2010; Poppenk et al., 2013). However, evidence for this structural connectivity in humans is lacking, leaving open questions about whether these circuits show profiles homologous to those seen in rodents and non-human primates. Here, we characterized structural connectivity of reward-related regions across the long-axis of the hippocampus in humans using diffusion MRI.

Motivation is a crucial factor driving learning and goal-directed behavior. Motivation is mediated by engaging a network of brain regions (Haber & Knutson, 2010), centered on the ventral tegmental area (VTA), limbic striatum, and medial prefrontal cortex (mPFC), particularly its more ventral portions (e.g., ventromedial prefrontal cortex, vmPFC), suggesting that they are prime targets to investigate in the context of hippocampal structural connectivity. The VTA consist of dopamine neurons that send reward prediction error signals (along with other heterogenous signals, Matsumoto & Hikosaka, 2009; Bromberg-Martin et al., 2010; Lammel et al., 2014; Ljungberg et al., 1992) to the striatum and other brain regions. The limbic striatum is critical for associative learning and motivation (Mogenson et al., 1980; Yang et al, 2018; Schultz et al., 1997). The vmPFC supports reward learning and decision-making by representing abstracted reward or affective value and providing predictions about future outcomes (Rolls, 2019; Rudebeck & Murray 2014; Wilson et al. 2014). Critically, research in animals has shown the hippocampus to have direct and/or indirect connectivity to each of these regions (Kelley et al., 1982; Groenewegen et al., 1987; Scofield et al., 2016; Cavada et al., 2000; Fanselow & Dong, 2010; Gasbarri et al., 1991; Gasbarri et al., 1996; Swanson et al., 1982).

Connectivity with the hippocampus is not homogenous, but rather the dorsal and ventral hippocampus –which corresponds with the posterior and anterior hippocampus in humans, respectively– have distinct patterns of connectivity with other brain regions, which may underlie their functional differences. Specifically, the dorsal/posterior hippocampus is more strongly connected with parietal and retrosplenial cortices, reflecting its role in navigation, reinstatement, and retrieval (Moser & Moser, 1998; Sherril et al., 2013; Whitlock et al., 2008; Kim, 2015; Sheldon & Levine, 2016). The ventral/anterior hippocampus is more connected with the amygdala, striatum, hypothalamus, midbrain, and medial prefrontal regions (Fanselow & Dong,

2010; Strange et al., 2014; Lisman & Grace, 2005), reflecting its role in affective processing, emotion regulation, and emotional memory (LeDoux, 1993; Mather, 2007; Phelps, 2004; Zhu et al., 2019). These structural differences have functional consequences, as evidenced by studies showing that dorsal hippocampal structure is correlated with spatial memory performance, whereas ventral hippocampal structure is correlated with affective processing (e.g. emotion regulation and novelty detection; Bannerman et al., 2003; Bannerman et al., 2004; Nadel, 1968; Woollett & Maguire, 2011; Van Rooij et al., 2015; Willard et al., 2009; Richardson et al., 2004; Snytte et al., 2022; Moser & Moser, 1998; Kafkas & Montaldi, 2018; Cowan et al., 2021). These patterns of connectivity suggest that the flexibility of different adaptive behaviors may result in differential connectivity of reward regions along the hippocampal long axis, however, how reward regions preferentially target the hippocampus has yet to be dissected in humans.

Although tracer studies (Swanson et al., 1992, Gasbarri et al., 1994) and functional imaging (Kahn & Shohamy, 2013) in humans have begun to classify the organization of the HPC long-axis, in-vivo structural connectivity in humans is lacking. Here, we leveraged a large diffusion weighted imaging (DWI) dataset collected as part of the Human Connectome Project and utilized probabilistic tractography to segment the hippocampus according to its connectivity to regions associated with motivation and adaptive behavior, including the VTA, limbic striatum, and vmPFC. Further, we generated a probabilistic atlas of the hippocampus reflecting how connectivity with reward regions vary across its long-axis to bolster research on hippocampal contributions to adaptive behavior. Delineating the structural connectivity of the hippocampal long-axis with reward regions in humans is crucial for interpreting human neuroimaging findings and translating findings from animal research, as well as understanding the role of these regions in adaptive and maladaptive behaviors.

Method

Participants

The study sample comprised participants enrolled in the Human Connectome Project (HCP; https://www.humanconnectome.org). Data were obtained from the WU-Minn HPC Consortium S900 Release; participants from whom T1-weighted and diffusion-weighted MRI scans were acquired, and for whom complete structural metrics generated using the HCP FreeSurfer pipeline, were included in this study (WU-Minn HCP Consortium, 2015). Our goal was to have at least 500 usable participants. BEDPOSTX was successful with 664 participants. Of those, 36 failed probabilistic tractography. Altogether, 628 participants were included in the final analyses. We determined this to be an acceptable sample size and proceeded with our analysis pipeline on these participants. Participant demographics (age, biological sex assigned at birth, race, and ethnicity) can be found in Table 1.

MRI Acquisition, Preprocessing, and Analysis

HCP data acquisition and preprocessing pipeline procedures are detailed here: (Van Essen et al., 2013, Van Essen et al., 2012, Barch et al., 2013, Glasser et al., 2013). We utilized the minimally preprocessed diffusion MRI (dMRI) data that were provided by the HCP S900 release. The dMRI data had gone through EPI distortion, eddy current, and motion correction, gradient nonlinearity correction, and registration of the mean b0 volume to a native T1 volume. In addition to the HCP minimally pre-processed pipeline, we processed the dMRI data with FSL's BEDPOSTX (Behrens et al., 2007) to model white matter fiber orientations and crossing fibers.

Structural connectivity analysis

Tractography

The diffusion-weighted data were processed using FSL FDT toolbox version 6.0.6.5 (Smith et al., 2004; www.fmrib.ox.ac.uk/fsl). Measures of tract strength were calculated using probabilistic tractography with a partial volume model (Behrens et al., 2003), allowing for up to 2 fiber directions in each voxel (Behrens et al., 2007). Fiber tracking was conducted in parallel for each voxel within a predefined seed mask (bilateral hippocampus). We used 5,000 samples per voxel, a curvature threshold of 0.2, and a step length of 0.5 mm. Tractography analyses were conducted in each subject's native anatomical space and the results registered to Montreal Neurological Institute (MNI) space by providing transformation parameters estimated via a 2-step procedure. First, the fractional anisotropy (FA image) was registered to each subject's high-resolution T1-weighted image using FSL's linear image registration tool with six degrees of freedom and a mutual information cost function (FLIRT; Jenkinson et al., 2002). Next, the T1-weighted image was nonlinearly registered to the $2 \times 2 \times 2$ mm^3 nonlinear MNI template with FSL's non-linear image registration tool (FNIRT). Finally, the transformation parameters obtained from these two steps were concatenated to yield the mapping from the DWI to MNI space. Tractography was performed separately for the left and right hippocampus, and possible tracts were restricted to the hemisphere of origin using an exclusion mask of the contralateral hemisphere.

Segmentation

To assess connectivity of the hippocampus with reward-related regions, we used four masks, defined *a priori*. Following previous diffusion tractography segmentations of the thalamus (Behrens et al., 2003; Johansen-Berg et al., 2005) and striatum (Tziortzi et al., 2014) the target regions of interest were chosen based on their anatomical characteristics. It's important to note that these anatomical regions naturally differ in size. This size variation could potentially

influence general observations, but it's more relevant for analyzing individual differences in tract-strength rather than creating distinct within-subject parcellations. Our primary focus centers on exploring interactions along the longitudinal axis of the hippocampus. In this context, any potential effects related to the size of these regions of interest are unrelated.

The seed masks (hippocampus) were defined using the Harvard-Oxford subcortical atlas integrated within FSL (Figure 1). The target area of the limbic (ventral) striatum was defined using a connectivity-based segmentation atlas with subdivisions for sensorimotor, executive, and limbic regions (Tziortzi et al., 2014). The vmPFC masks were defined from Bhanji et al. (2019). This mask is an inclusive vmPFC/OFC mask that includes the whole area of prefrontal cortex that is both ventral ($z < 0$ in standardized coordinate space) and medial (i.e., superior and inferior medial gyri, anterior cingulate gyrus, gyrus rectus, medial orbital gyrus, and the adjacent sulci). The functional relevance of this mask was investigated using the Neurosynth meta-analytic engine and topic-based mapping (Yarkoni et al., 2011; Poldrack et al., 2012). Bhanji et al. discovered that vmPFC activation was significantly associated with social, emotion, and decision-making functions (2019). The seed ROI for the VTA was defined using a probabilistic atlas of human SN/VTA (Murty et al., 2014). We used a 50% probability threshold. The MNI space target masks were normalized to each participant's native space using the inverse of the spatial normalization parameters. To tailor the ROIs to individual anatomy, we masked the ROIs with individually segmented gray matter (GM) images generated from freesurfer.

Projections from the hippocampus to the vmPFC, limbic striatum, and VTA were estimated following standard procedures, such that seed-based classification maps were first thresholded so that only voxels with at least 10 tracts terminating in one of the target regions were kept (Cohen et al., 2009; Forstmann et al., 2012, van den Bos et al., 2014). Next, the voxel

values were converted into proportions of the number of tracts reaching the target mask from one voxel, divided by the number of tracts generated from that voxel (maximum 5,000).

Hippocampus Topology

To assess the topology of connectivity of reward regions along the hippocampal long-axis, each subject's value map was divided into head, body, and tail regions (Duvernoy et al., 1998). Notably, the head represents more ventral/anterior portions whereas the tail represents more dorsal/posterior portions. We used the mean of these value maps as the measure hippocampal connectivity across its long axis with the VTA, limbic striatum, and vmPFC. Differences in the topology of hippocampus connectivity along the long-axis were investigated using a repeated measures Analysis of Variance (ANOVA) with the following within-subject factors: reward region (vmPFC, limbic striatum, VTA), hippocampal long-axis region (head, body, tail) and hemisphere (left, right). We tested for differences between specific reward regions and long-axis regions using pairwise comparisons with Bonferroni correction. The anova_test function (with type III sum of squares) in R (version 4.1.2) was used for the ANOVA and the t.test function in R was used for the pairwise comparisons.

The head, body, and tail of the hippocampus were defined in the MNI 152 T1-weighted image (Fonov et al., 2009; Fonov et al., 2011; Figure 2) using the anatomical benchmarks outlined by the Hippocampal Subfields Group for the European Joint Programme for Neurodegenerative Disease Research (JPND; Olsen et al., 2019). The hippocampal head comprises the region between (and including) the anterior most slice (in the coronal view) in which the hippocampus appears and the posterior most slice in which the uncus is visible. The hippocampal body consists of the region between the hippocampal head and the last slice in which the lamina quadrigemina (colliculi) are visible in the posterior brain stem. The

hippocampal tail comprises the region between the posterior-most slice of the body and the posterior-most slice in which the hippocampal formation is visible. Hippocampus topology was assessed using the mean tract density for each region (head, body, tail) separately for each hemisphere (Figure 3).

Hippocampus Connectivity Atlas

To further investigate hippocampal long-axis topology we created two group-averaged probabilistic atlases, one that allows for overlap of voxels at the individual participant level and a "hard" segmentation that does not allow for overlap. To generate the probabilistic hippocampus connectivity atlas (allowing for overlap), we created group-averaged maps with increased levels of thresholding. Following standard procedures (Tziortzi et al., 2014; Elliott et al., 2022a) we thresholded each individual's ROIs to the vmPFC, VTA, and limbic striatum at 50 streamlines per voxel for each hemisphere. Once each individuals' ROIs were thresholded, they were binarized and averaged together to create a group-averaged atlas. The resulting atlases (HPC-Limbic Striatum, HPC-vmPFC, HPC-VTA) are publicly available at https://github.com/blelliott23/HCP-Hippocampus-Reward-Diffusion-Segmentation.

The previous method allows for voxels to overlap between each ROI (as long as the voxel met the minimum number of streamlines to that ROI). An additional "hard" segmentation was conducted following standard procedures (Johansen-Berg et al., 2005; Tziortzi et al., 2014). This segmentation precludes individual voxels from overlapping within a single subject (Figure 4). To generate this "hard" segmentation, ROIs for each individual were thresholded at 10 streamlines. Next, each voxel was calculated as a proportion of the total number of streamlines from that voxel to reach any target. Each voxel was then assigned to the target region that had the highest probability of connection. These ROIs were then binarized and averaged together to

create a group-averaged atlas (Figure 5). The resulting atlas (HPC-Limbic Striatum, HPC-vmPFC, HPC-VTA) are publicly available at https://github.com/blelliott23/HCP-Hippocampus-Reward-Diffusion-Segmentation.

Results

Hippocampus topology

Hippocampus connectivity to each reward region is summarized in Figure 3. A 3x3x2 repeated measures ANOVA with Greenhouse-Geisser corrections was conducted to investigate whether hippocampal connectivity (tract density) varied among reward regions (vmPFC, limbic striatum, VTA), long-axis region (Head, Body, Tail), and hemisphere (Left, Right), as well as their interactions. The tractography values were tested for normality using the Shapiro-Wilk test statistic. Of the 18 connectivity values (head, body, and tail for each target ROI for each hemisphere) 10 failed the Shapiro-Wilk test. However, given the large sample size, even slight deviations from normality will be significant. Additionally, the ANOVA test has been shown to be quite robust to deviations in normality at larger samples sizes (> 30; Ghasemi & Zahediasl, 2012; Blanca Mena et al., 2017). Given inspection of the distributions of the data (figure 3), Q-Q plots and the large sample size in the current study, we deemed implementation of the ANOVA to be appropriate.

Main Effect of Reward region: There was a significant main effect of reward region, $F(1.80, 1126.78) = 923.29$, $p < .001$, $\eta p2 = .596$, indicating that tract density differed significantly across the three reward regions (vmPFC, limbic striatum, and VTA). Post-hoc analyses with Bonferroni correction revealed that tract density for the vmPFC ($M = 0.41$, $SD = 0.12$) was significantly higher than the limbic striatum ($M = 0.38$, $SD = 0.09$, $p < .001$) and the VTA ($M = 0.21$, $SD =$

0.11, $p < .001$). Tract density for the limbic striatum was significantly lower than the vmPFC, but higher than the VTA ($p < .001$).

Long-axis region: There was a significant main effect of hippocampal long-axis region ($F(1.60, 1004.25) = 7.83$, $p < .001$, $\eta p2 = .012$) indicating that tract density differed significantly across the three long-axis regions (head, body, and tail). Post-hoc analyses with Bonferroni correction revealed that tract density for the head region ($M = 0.33$, $SD = 0.10$, $p < .001$) was significantly higher than the body ($M = 0.33$, $SD = 0.14$, $p < .001$, mean difference = $3.19e^{-5}$) but not significantly different from the tail ($M = 0.33$, $SD = 0.17$, N.S., mean difference = $5.76e^{-7}$). Tract density for the body was significantly lower than the head and the tail (mean difference = $3.25e^{-5}$ $p = .001$).

Hemisphere: There was a small, but significant main effect of hemisphere, $F(1, 627) = 19.02$, $p <. 001$, $\eta p2 = .029$. Tract density was relatively greater in the left compared to the right hemisphere ($M = 0.33$, $SD = 0.14$ vs. $M = 0.33$, $SD = 0.13$, $p < .001$, mean difference = $2.85e^{-5}$).

Interactions:

Reward region x hippocampal long-axis region x hemisphere: There was a significant interaction between reward region (vmPFC, limbic striatum, VTA) hippocampal long-axis region (head, body, tail), and hemisphere (left,right), $F(2.82, 1768.80) = 31.50$, $p < .001$, $\eta p2 = .048$. Although we did not have a priori hypotheses about interactions with hemispheres, for completeness they are fully investigated here.

Reward region x hippocampal long-axis region: There was a significant interaction between reward region (vmPFC, limbic striatum, VTA) and hippocampal long-axis region (head, body, tail), $F(2.42, 1515.94) = 2475.38$, $p < .001$, $\eta p2 = .798$, indicating that tract density to each

reward region differed across the three long-axis regions. Post-hoc analyses with Bonferroni correction revealed that the VTA connectivity with the head of the hippocampus (M = 0.31, SD = 0.10) was significantly higher than the body (M = 0.18, SD = 0.08, $p < .001$) and the tail region (M = 0.14, SD = 0.06, $p < .001$). Tract density from the body was significantly higher than the tail ($p < .001$). The results suggest that in humans, the hippocampus has graded connectivity with the VTA, with the strongest connectivity from the anterior (head) region of the hippocampus.

Post-hoc analyses of hippocampal long-axis connectivity with the vmPFC revealed that the head of the hippocampus (M = 0.33, SD = 0.10) was significantly lower than the body (M = 0.41, SD = 0.12, $p < .001$) and the tail region (M = 0.47, SD = 0.11, $p < .001$). Tract density from the body was significantly lower than the tail ($p < .001$). The results suggest that in humans, the hippocampus has graded connectivity with the vmPFC, with the strongest connectivity from the posterior (tail) region of the hippocampus.

Post-hoc analyses of hippocampal long-axis connectivity with the limbic striatum revealed that the head of the hippocampus (M = 0.36, SD = 0.09) was significantly lower than the body (M = 0.40, SD = 0.09, $p < .001$) and the tail region (M = 0.39, SD = 0.01, $p < .001$). Tract density from the body was significantly higher than the tail ($p < .001$). The results suggest that in humans, the hippocampus has a distributed connectivity profile with the limbic striatum, with a slight preference for the strongest connectivity from the body of the hippocampus.

Reward region x hemisphere: There was a significant interaction between reward region (vmPFC, limbic striatum, VTA) and hemisphere (left, right), $F(1.79, 1119.43) = 24.01$, $p < .001$, $\eta p2 = .037$, indicating that tract density to each reward region differed across hemispheres. Post-hoc analyses with Bonferroni correction revealed that the VTA connectivity in the left

hemisphere (M = 0.21, SD = 0.11) was not significantly different from the right (M = 0.21, SD = 0.11, N.S.). Post-hoc analyses of vmPFC connectivity revealed that the left hemisphere (M = 0.41, SD = 0.13) was significantly higher than the right (M = 0.39, SD = 0.11, $p < .001$). Post-hoc analyses of limbic striatum connectivity revealed that the left hemisphere (M = 0.37, SD = 0.10) was significantly lower than the right (M = 0.39, SD = 0.10, $p < .001$).

Hippocampal long-axis region x hemisphere: There was a significant interaction between hippocampal long-axis region (head, body, tail) and hemisphere (left, right), $F(1.78, 1118.94) = 12.33$, $p < .001$, $\eta p2 = .019$. However, post-hoc analyses with Bonferroni correction revealed that the hippocampal head connectivity in the left hemisphere (M = 0.33, SD = 0.10) was not significantly different from the right (M = 0.33, SD = 0.09, N.S.). Post-hoc analyses of hippocampal body connectivity revealed that the left hemisphere (M = 0.33, SD = 0.14) was not significantly different from the right (M = 0.33, SD = 0.14, N.S.). Post-hoc analyses of hippocampal tail connectivity revealed that the left hemisphere (M = 0.33, SD = 0.17) was not significantly different from the right (M = 0.33, SD = 0.16, N.S.).

Discussion

This is the first study, to our knowledge, to delineate the structural connectivity of the hippocampal long-axis with key nodes across the reward circuit using diffusion MRI and probabilistic tractography in humans. We found that the hippocampus has a distinct connectivity profile across the long axis to each reward region examined. The dopaminergic midbrain (VTA) displayed the strongest connectivity to the anterior hippocampus. The vmPFC displayed stronger connectivity to the posterior hippocampus. Finally, the limbic striatum was more distributed along the hippocampal long-axis, with a slight preference for the body of the hippocampus. We

compiled these connectivity profiles to generate a publicly available, probabilistic atlas of the hippocampus centered on structural connectivity with reward-related networks to support future neuroimaging studies characterizing hippocampal involvement in adaptive behaviors.

Although research in non-human animals has progressed in characterizing hippocampal-reward circuits, studies in humans are scarce, limiting our ability to translate findings from animal studies when considering hippocampal contributions to adaptive behavior. In this study, we probed hippocampal connectivity with three reward ROIs: The VTA, vmPFC, and limbic (ventral) striatum. We selected these regions based on known non-human primate anatomy, and a human meta-analyses of functional neuroimaging studies using the terms "reward" and "subjective value" using two separate methods (an automated tool Neurosynth, Figure 6; and a researcher generated approach, Batra et al. 2013; Yarkoni et al., 2011; Poldrack et al., 2012). To our knowledge, our study is the first to characterize hippocampal long-axis connectivity to these regions. A recent study (Dalton et al., 2022) investigated cortico-hippocampal structural connectivity in humans using diffusion-weighted imaging and tractography. However, we restricted our investigation to be specifically to the regions critical for reward-related functions (including novelty). With regard to the long-axis, the authors found preferential connections between specific areas within temporopolar and inferolateral temporal cortices had strongest connectivity with the head/body of the HPC while medial parietal and occipital cortical areas had a connectivity bias with the tail. However, this study was limited to investigations of cortical regions and did not take into account subcortical areas such as the striatum and VTA. While we have provided the foundation for understanding the relationship between reward regions and the hippocampus here, it will be important in the future to extend these efforts to other nuclei and circuits that are involved in reward processing (Haber & Knutson, 2010).

The VTA forms a bi-directional circuit with the hippocampus which invigorates adaptive behavior in response to reward and novelty, as well as prioritizing memory for these events (Lisman et al., 2011; Rutishauser, 2019; Legault & Wise, 1999; Legault & Wise, 2001; Lodge & Grace, 2006), which is critical for behaviors such as reward memory and decision-making (Adcock et al, 2006, Elliott et al., 2020a; Elliott et al., 2020b; Shohamy & Adcock, 2010; Shohamy & Daw, 2015). Our results revealed that connectivity with the VTA was localized predominantly in the anterior hippocampus, which is consistent with rodent studies showing that VTA dopamine neurons predominantly innervate the ventral hippocampus (Gasbarri 1994a, 1994b; Oades & Halliday, 1987; Swanson, 1982; Verney et al., 1985).

These VTA results are also in line with human fMRI studies (Krebs et al., 2011; Adcock et al., 2006; Murty et al., 2017). Prior work using human neuroimaging has shown VTA and anterior hippocampus activation to novelty (Poppenk et al., 2013; Cowan et al., 2021; Kafkas & Montaldi, 2018; Kumaran & Maguire, 2006; Strange & Dolan, 2001; Poppenk et al., 2008). Additionally, human fMRI has demonstrated VTA-HPC connectivity to be critical for reward-motivated memory encoding (Adcock et al., 2006; Wittmann et al., 2005; Shigemune et al., 2014; Wolosin et al., 2012; Gruber et al., 2016), with studies showing a bias towards engagement of anterior hippocampus. Further, previous research has found structural connectivity between the VTA and HPC to be positively correlated with individual differences in reward-motivated memory performance (Elliott et al., 2022b). Our findings integrate these two lines of research by providing a putative mechanism for functional biases towards the anterior hippocampus during motivated memory based on its structural connectivity, which supports future studies using multi-modal imaging approaches to understand function-structure relationships.

The HPC and vmPFC have been implicated in adaptive behaviors including reward-learning, motivation, decision-making, and episodic memory. In non-human primates HPC-vmPFC connectivity has been associated with prospection (Rolls 2019; Rudebeck & Murray 2014). The vmPFC represents abstracted reward or affective values and provides predictions about future outcomes (Rolls 2021; Rudebeck & Murray 2014; Mainen & Kepecs, 2009; Kable & Glimscher, 2009; Klein-Flugge et al., 2022). Previous research has shown that HPC-vmPFC connectivity is crucial for more adaptive forms of episodic memory, including remote autobiographical memory, schematic representations, and inference (Gilboa & Marlatte, 2017; McCormick et al., 2018; Schlichting & Preston, 2015). Notably, these functions have been hypothesized to rely primarily on anterior HPC-vmPFC activity (Abela & Chudasama, 2013; Schumacher et al, 2016; Viard 2011; Monk et al., 2021), which is consistent with structural connectivity we found between the most anterior portions of the HPC and vmPFC (figure 5), but is surprising given the robust connectivity we found with the posterior portions of the HPC (discussed below). In fact, HPC-vmPFC connectivity from the head of HPC was greater than HPC-VTA connectivity from the head, $t(627) = 3.81$, $p < .001$, Cohen's $d = 0.15$. (Figure 3). This could be a potentially important area where dopaminergic reward signals from the VTA integrate with signals from the vmPFC to support adaptive behaviors. This finding could be meaningful in terms of localizing function within the anterior HPC. However, as noted previously, the target regions of interest were chosen based on their anatomical characteristics, and thus naturally differ in size. This size variation could potentially influence general observations (but it's more relevant for analyzing individual differences in tract-strength rather than creating distinct within-subject parcellations). Our primary focus was on exploring interactions along the longitudinal axis of the hippocampus. In this context, any potential effects

related to the size of these regions of interest are unrelated, but main effects should be interpreted with caution. However, the potential of diffusion results being biased by ROI size or distance is likely less of a contributing factor than anatomical specificity/connectivity, as previous studies (Dalton et al., 2022) have shown minimal connectivity between large areas of the PFC and anterior HPC.

The current study found robust connectivity from the tail of the HPC (i.e., posterior HPC) with the vmPFC. A recent study by Dalton and colleagues (2022) also investigated connectivity of the HPC long-axis with the cortex using diffusion imaging. Despite well documented functional connectivity between the HPC and vmPFC (Li et al., 2015; Adnan et al., 2016; Barnett et al., 2021; Monk et al., 2021) the authors found very weak structural connectivity between the anterior HPC and vmPFC, consistent with the results observed here. Additionally, a study by Rosen and Halgren (2022) found that long-range connections between the hippocampus and functionally associated frontal cortical areas may involve fewer than 10 axons per square millimeter. The authors concluded that the density of axons between brain regions that are spatially distant yet functionally connected may be significantly lower than previously believed. It could be that the growing body of evidence of distinct HPC-vmPFC structural and functional connectivity are driven by sparse direct connections (possibly from the most anterior portion of the hippocampus, observed here, which may be occluded when using the entire HPC head as an ROI) or by indirect connectivity. The vmPFC has been shown to have both direct connectivity with the HPC and indirect connectivity via the cingulate cortex (pregenual anterior cingulate and memory-related posterior parts of the posterior cingulate cortex, Rolls et al., 2023a, 2023b). Our vmPFC mask from Bhanji et al. (2019) employed in the current also includes the ventral region of the anterior cingulate cortex (figure 1). The use of this broader mask could have led to the

increased connectivity with the HPC tail (possibly via the cingulate cortex). This is an exciting area for future research and stresses the importance of in-vivo structural connectivity dissections in humans. Future studies using more fine-grained dissection techniques with additional waypoints are needed to explore this hypothesis.

This raises important questions about the role of the posterior hippocampus in adaptive behaviors. The vmPFC facilitates the transmission of affective (reward/emotion) information to the hippocampus, enhancing episodic memory formation and retrieval by incorporating affective values into memory processes. Moreover, this connectivity also plays a crucial role in navigation, where the affective input from the vmPFC to the HPC guides goal-oriented navigation (Rolls, 2022). One possible interpretation of this finding is partially explained by the posterior medial (PM) and anterior temporal (AT) framework (PMAT; Ritchey et al., 2015). The PMAT framework delineates two major cortical systems: the posterior medial (PM) and anterior temporal (AT) systems, both interconnected, with the HPC and vmPFC serving as integration hubs. PM is implicated in processes like episodic memory, spatial and temporal processing, scene perception, and social cognition, while AT is involved in recognition and associative memory, affective processing, semantic processing, and object perception. These processes are also thought to be segregated along the HPC long-axis, with the AT network primarily targeting the anterior HPC, and PM network with the posterior HPC. Our findings suggest that more attention should be paid to how types of representations stored in the posterior hippocampus, both spatial and non-spatial, contribute to adaptive behavior.

Regarding the limbic striatum, we found a relatively more homogenous connectivity profile across the hippocampal long axis. Animal work has shown that the hippocampus has strong efferent projections to the nucleus accumbens, via the ventral subiculum (Legault & Wise,

2001, Blaha et al., 1997; Taepavarapruk et al., 2000; Floresco et al., 2001; Floresco et al., 2003), which is known to regulate reward behavior (LeGates et al,. 2018), as well as stimulate reward seeking behavior in previously rewarded contexts. In line with these functions, rewards increase synchronization between HPC and limbic striatum neurons (Tabuchi et al., 2000), which have been shown to be critical for drugs of abuse (Sjulson, et al., 2018). The limbic striatum is also necessary to relay hippocampal signals to DA neurons (Lisman & Grace, 2005), which dovetails with human neuroimaging showing that HPC- limbic striatum connectivity is associated with reward motivation and associative learning (Ballard et al., 2019; Shigemune et al., 2014) as well as interactions between feedback learning and episodic memory (Davidow et al., 2016). Additionally, resting state fMRI in humans has shown maximal correlation between the limbic striatum and the body of the HPC (Kahn & Shohamy, 2013), consistent with our results. Given our structural connectivity results, we predict that limbic striatum -hippocampal signaling may be implicated in a wide range of behaviors given that it has diffuse projections across the hippocampus.

Previous animal studies have found connectivity with the limbic striatum from both the dorsal and ventral hippocampus (Groenewegen et al., 1996; Naber & Witter, 1998; Swanson & Kohler, 1986; Fanselow et al., 2010). However, it is thought that a gradient exists both structurally and functionally with the limbic striatum along the hippocampal long-axis, such that more anterior regions innervate the medial limbic striatum (shell) and are involved in more affective behaviors (Strange et al., 2014). In line with animal studies, our results found distributed and relatively homogenous limbic striatum connectivity along the HPC long-axis. Although not investigated in the current study, it is possible that our results would differ should specific regions of the limbic striatum (i.e. core and shell) be considered. Another exciting

structure to examine is the fornix, which is known to provide connections to the limbic striatum with the long-axis of the hippocampus. In line with our results, the fornix is distributed along the entire hippocampal long-axis, and has been shown to be intimately involved with both motivated behavior and the generation of hedonic responses (Trouche et al., 2019).

Prior work, outside the domain of reward, has shown that the hippocampus is anatomically and functionally distinct along its long-axis (ventral-dorsal in rodents, anterior-posterior in primates) both in its internal structure as well as its broader network connectivity. Within the hippocampus, the anterior and posterior hippocampus have distinct proportions of subfields (lower proportion of DG in anterior HPC than in posterior HPC, and a higher proportion of CA1–3 in anterior HPC than in posterior HPC, which may reflect differences in neurogenesis) as well as distinct cytoarchitecture and genetic domains (Fanselow & Dong, 2010; Dong et al., 2009; Thompson et al., 2008). Regarding network connectivity, in non-human primates, the posterior hippocampus has stronger connectivity with the retrosplenial cortex, area TE in the inferior temporal lobe, and anterior cingulate cortices (Insausti & Muñoz, 2001; Cenquizca & Swanson, 2007; Risold et al., 1997; Van Groen & Wyss, 2003), as well as the rostrolateral limbic striatum and rostral caudoputamen (Groenewegen et al., 1996; Naber & Witter, 1998; Swanson & Kohler, 1986). In contrast, non-human primate research indicates that the anterior hippocampus has stronger connectivity with the amygdala, hypothalamus, and medial (shell) of the limbic striatum, VTA, Insula, and vmPFC (Poppenk et al., 2013). Critically, our findings could support a model in which different reward regions may engage discrete parts of the hippocampus to propagate downstream neural signals to distinct subcortical and cortical networks in service of adaptive behavior.

It has been shown that in vivo fiber tracking can be prone to errors (Maier-Hein et al., 2017; Daducci et al., 2014; Côté et al., 2013). Post-mortem studies are much more precise for resolving anatomical connections, but come with their own limitations. The in vivo diffusion imaging approach in the current study addresses the inherent limitations of post-mortem studies, such as small sample sizes. Our study, conducted in a large population, not only provides a robust foundation for human anatomical research but also sets the stage for subsequent high-resolution post-mortem investigations. Future post-mortem studies will be invaluable for dissecting the precise nature of the connectivity identified here.

Another limitation of the current study is the lack of predefined waypoints and a priori tract considerations. However, previous research, both in humans and animals, has not definitively determined the waypoints for the connections under investigation, particularly given the complex bidirectional relationships among these regions. For instance, when examining VTA projections to the anterior hippocampus, researchers have identified direct HPC-VTA connectivity, indirect HPC-nucleus accumbens-VTA connectivity, and indirect HPC-nucleus accumbens-ventral pallidum-VTA connectivity (Lisman & Grace, 2005, Haber, 2016). The intricacies of HPC-PFC connectivity add further complexity, involving both direct and indirect pathways through the cingulate cortex, thalamus, nucleus accumbens, VTA, and basolateral amygdala, among others (Li et al., 2015; Rolls et al., 2023a; Rolls et al., 2023b). Additionally, many of these pathways have been delineated in animal models, which poses further empirical questions due to the vast evolutionary distance between humans. Because of the potential for false negatives with specific waypoints, a data-driven approach was deemed most appropriate for our parcellation, although we acknowledge the possibility of errant paths in the analysis. This approach aimed to avoid subjectivity and potential bias introduced by specifying predefined

regions, which could be influenced by prior knowledge or assumptions about anatomical pathways derived from animal histology which may or may not exist to the same extent in humans. While our focus was on parcellating the hippocampus based on anatomical connectivity rather than recreating each specific tract, future research should carefully dissect the proposed pathways with known anatomical waypoints.

Previous studies have shown significant HPC-vmPFC , HPC- VTA, and HPC-limbic striatum functional connectivity (Li et al., 2015; Cowan et al., 2021, Krebs et al., 2011, Murty et al., 2017, Tompary et al., 2015; Wolosin et al., 2012; Adnan et al., 2016; Barnett et al., 2021; Monk et al., 2021). Investigations of functional connectivity to these regions along the hippocampal long-axis have found preferential connectivity from the anterior hippocampus (head and anterior body) with the vmPFC, VTA, and limbic striatum (Kahn & Shohamy, 2013; Barnett et al., 2021). The results of the current study support these findings while also diverging and providing specificity. While we observed significant structural connectivity with the whole HPC (head, body, and tail) with all regions, vmPFC connectivity was strongest with the tail, and limbic striatum connectivity was relatively homogenous with a slight preference for the body. Previous studies have shown strong functional relationships for neural regions that are not directly connected or indirectly connected (Honey et al., 2008). For example, the current study comports with recent findings demonstrating weak structural connectivity between the anterior HPC and vmpFC, despite well described functional connectivity, setting the stage for investigations of indirect regions that may mediate this relationship (described previously). The current study provides important converging evidence for the unique structural HPC connectivity that can have substantial implications on the interpretation of observed functional activations.

Our findings of distinct connectivity amongst the hippocampus and reward regions set the foundation to begin investigating how individual differences in structural connectivity may differentially relate to individual differences in adaptive behavior. Another direction for future research is to investigate the functional significance of the heterogeneity in hippocampal connectivity profiles observed in this study by either examining brain-behavior relationships in large-scale studies or by conducting studies that simultaneously collect neuroimaging and DTI data. The available tasks in the Human Connectome Database lack elements such as memory manipulation, consideration of prior knowledge, contextual shifts, or novelty that would sufficiently activate the hippocampal-reward circuits we are interested in exploring. Thus, structure-function correlations of this parcellation remain an interesting area for future research. Finally, the probabilistic atlas generated in this study could be a valuable tool for guiding future research on the role of the hippocampus in psychopathology, particularly in conjunction with other neuroimaging techniques such as functional MRI and positron emission tomography (PET) in clinical populations. The hippocampus is disrupted in a variety of mental disorders , such as psychotic disorders (Lodge & Grace, 2011), posttraumatic stress disorder (Shin et al., 2006; van Rooij et al., 2015; Tanriverdi et al., 2022) and depression (Belujon & Grace, 2017; Grace, 2016), and is sensitive to environmental perturbations, such as childhood trauma and stress (Vythilingam et al., 2002; Kim & Diamond, 2002; Lupien & Lepage, 2001). In addition, childhood trauma and stress have been linked to anhedonia (lower reward functioning) in those at risk for psychosis (O'Brien et al., 2023), which highlights the clinical relevance to mapping out hippocampal contributions to reward circuitry.

The current study provides a foundation for future investigations into the anatomical and functional implications of the hippocampus and reward-related regions using more tailored

regions of interest based on the underlying anatomical connectivity. This will enhance our understanding of the neural circuitry underlying adaptive behaviors and contribute to the development of novel therapeutic interventions for psychopathologies associated with reward processing (e.g. amotivation and anhedonia). The present study advances our knowledge of the structural connectivity of the HPC in humans, characterizing long-axis regions with distinct connectivity to reward-related regions.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available via the Human Connectome project at https://www.humanconnectome.org. The resulting hippocampus-reward region connectivity atlases are openly available at https://github.com/blelliott23/HCP-Hippocampus-Reward-Diffusion-Segmentation.

References

Abela, A. R., & Chudasama, Y. (2013). Dissociable contributions of the ventral hippocampus and orbitofrontal cortex to decision-making with a delayed or uncertain outcome. European Journal of Neuroscience, 37(4), 640-647.

Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. (2006). Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron, 50(3), 507-517.

Adnan, A., Barnett, A., Moayedi, M., McCormick, C., Cohn, M., & McAndrews, M. P. (2016). Distinct hippocampal functional networks revealed by tractography-based parcellation. Brain Structure and Function, 221, 2999-3012.

Ballard, I. C., Wagner, A. D., & McClure, S. M. (2019). Hippocampal pattern separation supports reinforcement learning. Nature communications, 10(1), 1-12.

Bannerman, D. M., Grubb, M., Deacon, R. M. J., Yee, B. K., Feldon, J., & Rawlins, J. N. P. (2003). Ventral hippocampal lesions affect anxiety but not spatial learning. Behavioural brain research, 139(1-2), 197-213.

Bannerman, D. M., Rawlins, J. N. P., McHugh, S. B., Deacon, R. M. J., Yee, B. K., Bast, T., ... & Feldon, J. (2004). Regional dissociations within the hippocampus—memory and anxiety. Neuroscience & biobehavioral reviews, 28(3), 273-283.

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., ... & Van Essen, D. C. (2013). Function in the human connectome: task-fMRI and individual differences in behavior. Neuroimage, 80, 169-189.

Barnett, A. J., Reilly, W., Dimsdale-Zucker, H. R., Mizrak, E., Reagh, Z., & Ranganath, C. (2021). Intrinsic connectivity reveals functionally distinct cortico-hippocampal networks in the human brain. PLoS biology, 19(6), e3001275.

Bartra, O., McGuire, J. T., & Kable, J. W. (2013). The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. Neuroimage, 76, 412-427.

Behrens, T. E., Berg, H. J., Jbabdi, S., Rushworth, M. F., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain?. neuroimage, 34(1), 144-155.

Behrens, T. E., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A. M., Boulby, P. A., ... & Matthews, P. M. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nature neuroscience, 6(7), 750-757.

Belujon, P., & Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. International Journal of Neuropsychopharmacology, 20(12), 1036-1046.

Benoit, R. G., Gilbert, S. J., & Burgess, P. W. (2011). A neural mechanism mediating the impact of episodic prospection on farsighted decisions. Journal of Neuroscience, 31(18), 6771-6779.

Bhanji, J., Smith, D. V., & Delgado, M. (2019). A brief anatomical sketch of human ventromedial prefrontal cortex.

Blaha, C. D., Yang, C. R., Floresco, S. B., Barr, A. M., & Phillips, A. G. (1997). Stimulation of the ventral subiculum of the hippocampus evokes glutamate receptor-mediated changes in dopamine efflux in the rat nucleus accumbens. European Journal of Neuroscience, 9(5), 902-911.

Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. Neuron, 68(5), 815-834.

Buckner, R. L. (2010). The role of the hippocampus in prediction and imagination. Annual review of psychology, 61, 27-48.

Bunzeck, N., & Düzel, E. (2006). Absolute coding of stimulus novelty in the human substantia nigra/VTA. Neuron, 51(3), 369-379.

Bunzeck, N., Dayan, P., Dolan, R. J., & Duzel, E. (2010). A common mechanism for adaptive scaling of reward and novelty. Human brain mapping, 31(9), 1380-1394.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. Neuron, 35(4), 625-641.

Cavada, C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suárez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cerebral cortex, 10(3), 220-242.

Cenquizca, L. A., & Swanson, L. W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. Brain research reviews, 56(1), 1-26.

Cohen, M.X., Schoene-Bake, J.C., Elger, C.E., Weber ,B. (2009). Connectivity-based segregationofthehumanstriatumpredictspersonalitycharacteristics. NatNeurosci12:32–34.

Côté, M. A., Girard, G., Boré, A., Garyfallidis, E., Houde, J. C., & Descoteaux, M. (2013). Tractometer: towards validation of tractography pipelines. Medical image analysis, 17(7), 844-857.

Cowan, E. T., Fain, M., O'Shea, I., Ellman, L. M., & Murty, V. P. (2021). VTA and anterior hippocampus target dissociable neocortical networks for post-novelty enhancements. Journal of Neuroscience, 41(38), 8040-8050.

Daducci, A., Canales-Rodrı, E. J., Descoteaux, M., Garyfallidis, E., Gur, Y., Lin, Y. C., ... & Thiran, J. P. (2013). Quantitative comparison of reconstruction methods for intra-voxel fiber recovery from diffusion MRI. IEEE transactions on medical imaging, 33(2), 384-399.

Davidow, J. Y., Foerde, K., Galván, A., & Shohamy, D. (2016). An upside to reward sensitivity: the hippocampus supports enhanced reinforcement learning in adolescence. Neuron, 92(1), 93-99.

Devenport LD, Devenport JA, Holloway FA. (1981): Reward-induced stereotypy: Modulation by the hippocampus. Science 212: 1288–1289.

Dickerson, K. C., & Delgado, M. R. (2015). Contributions of the hippocampus to feedback learning. Cognitive, Affective, & Behavioral Neuroscience, 15, 861-877.

Dong, H.W., Swanson, L.W., Chen, L., Fanselow, M.S., and Toga, A.W. (2009). Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1. Proc. Natl. Acad .Sci. USA 106, 11794–11799.

Duvernoy, H. M. (1998). The Human Hippocampus. Springer. https://doi.org/10.1007/978-3-662-03628-0

Elliott, B. L., Blais, C., McClure, S. M., & Brewer, G. A. (2020a). Neural correlates underlying the effect of reward value on recognition memory. NeuroImage, 206, 116296.

Elliott, B. L., D'Ardenne, K., Murty, V. P., Brewer, G. A., & McClure, S. M. (2022b). Midbrain–Hippocampus Structural Connectivity Selectively Predicts Motivated Memory Encoding. Journal of Neuroscience, 42(50), 9426-9434.

Elliott, B. L., D'Ardenne, K., Mukherjee, P., Schweitzer, J. B., & McClure, S. M. (2022a). Limbic and executive meso-and nigrostriatal tracts predict impulsivity differences in attention-deficit/hyperactivity disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 7(4), 415-423.

Elliott, B. L., McClure, S. M., & Brewer, G. A. (2020b). Individual differences in value-directed remembering. Cognition, 201, 104275.

Fanselow, M. S., & Dong, H. W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures?. Neuron, 65(1), 7-19.

Floresco, S. B., Blaha, C. D., Yang, C. R., & Phillips, A. G. (2001). Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: cellular mechanisms of input selection. Journal of Neuroscience, 21(8), 2851-2860.

Floresco, S. B., West, A. R., Ash, B., Moore, H., & Grace, A. A. (2003). Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nature neuroscience, 6(9), 968-973.

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. NeuroImage, 54(1), 313–327. https://doi.org/10.1016/j.neuroimage.2010.07.033

Fonov, V., Evans, A., McKinstry, R., Almli, C., & Collins, D. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. NeuroImage, 47, S102. https://doi.org/10.1016/S1053-8119(09)70884-5

Forstmann, B. U., Keuken, M. C., Jahfari, S., Bazin, P. L., Neumann, J., Schäfer, A., ... & Turner, R. (2012). Cortico-subthalamic white matter tract strength predicts interindividual efficacy in stopping a motor response. Neuroimage, 60(1), 370-375.

Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., ... & Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. American Journal of Psychiatry, 162(7), 1256-1265.

GASBARRI, A.; PACKARD, M. G.; CAMPANA, E. and PACITTI, C.(l994a) Anterograde and retrograde tracing of projections from the ventral tegmental area to the hippocampal formation in the rat. Brain Res. Bull 2: 445-452.

GASBARRI, A.; VERNEY, C.; INNOCENZI, R.; CAMPANA, E. and PACITTI, C. (1994b) Mesolimbic dopaminergic neurons innervating the hippocampal formation in the rat: A combined retrograde tracing and immunohistochemical study. Brain Res. 668: 71-79.

Gasbarri,A.,Campana,E.,Pacitti,C.,Hajdu,F.,Tombol,T.:Organizationoftheprojectionsfrom theventraltegmentalareaoftsaitothehippocampalformationintherat.J.Hirnforsch.32(4), 429–437(1991)

Gasbarri,A.,Packard,M.,Sulli,A.,Pacitti,C.,Innocenzi,R.,Perciavalle,V.:Theprojectionsof theretrorubralfielda8tothehippocampalformationintherat.Exp.BrainRes.112(2),244–252 (1996)

Gilboa, A., & Marlatte, H. (2017). Neurobiology of schemas and schema-mediated memory. Trends in cognitive sciences, 21(8), 618-631.

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., ... & Wu-Minn HCP Consortium. (2013). The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage, 80, 105-124.

Grace, A. A. (2016). Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nature Reviews Neuroscience, 17(8), 524-532.

Groenewegen, H. J., Vermeulen-Van der Zee, E. T., Te Kortschot, A., & Witter, M. P. (1987). Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. Neuroscience, 23(1), 103-120.

Groenewegen, H. J., Wright, C. I., & Beijer, A. V. (1996). The nucleus accumbens: gateway for limbic structures to reach the motor system?. Progress in brain research, 107, 485-511.

Gruber, M. J., Ritchey, M., Wang, S. F., Doss, M. K., & Ranganath, C. (2016). Post-learning hippocampal dynamics promote preferential retention of rewarding events. Neuron, 89(5), 1110-1120.

Haber, S. N. (2016). Corticostriatal circuitry. Dialogues in clinical neuroscience, 18(1), 7-21.

Haber, S. N., & Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology, 35(1), 4-26.

Holscher C, Jacob W, Mallot HA. (2003): Reward modulates neuronal activity in the hippocampus of the rat. Behav Brain Res 142: 181–191.

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. Proceedings of the National Academy of Sciences, 106(6), 2035-2040.

Insausti, R., & Munoz, M. (2001). Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (Macaca fascicularis). European Journal of Neuroscience, 14(3), 435-451.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage, 17(2), 825-841.

Johansen-Berg, H., Behrens, T. E., Sillery, E., Ciccarelli, O., Thompson, A. J., Smith, S. M., & Matthews, P. M. (2005). Functional–anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. Cerebral cortex, 15(1), 31-39.

Kable, J. W., & Glimcher, P. W. (2009). The neurobiology of decision: consensus and controversy. Neuron, 63(6), 733-745.

Kafkas, A., & Montaldi, D. (2018). How do memory systems detect and respond to novelty?. Neuroscience letters, 680, 60-68.

Kahn, I., & Shohamy, D. (2013). Intrinsic connectivity between the hippocampus, nucleus accumbens, and ventral tegmental area in humans. Hippocampus, 23(3), 187-192.

Kelley, A. E., Domesick, V. B., & Nauta, W. J. H. (1982). The amygdalostriatal projection in the rat—an anatomical study by anterograde and retrograde tracing methods. Neuroscience, 7(3), 615-630.

Kim, H. (2015). Encoding and retrieval along the long axis of the hippocampus and their relationships with dorsal attention and default mode networks: the HERNET model. Hippocampus, 25(4), 500-510.

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. Nature Reviews Neuroscience, 3(6), 453-462.

Klein-Flügge, M. C., Jensen, D. E., Takagi, Y., Priestley, L., Verhagen, L., Smith, S. M., & Rushworth, M. F. (2022). Relationship between nuclei-specific amygdala connectivity and mental health dimensions in humans. Nature human behaviour, 6(12), 1705-1722.

Krebs, R.M. et al. (2011) Novelty increases the mesolimbic functional connectivity of the substantia nigra/ventral tegmental area (SN/VTA) during reward anticipation: evidence from high-resolution fMRI. Neuroimage 58, 647–655

Kumaran, D., & Maguire, E. A. (2006). An unexpected sequence of events: mismatch detection in the human hippocampus. PLoS biology, 4(12), e424.

Kumaran, D., & Maguire, E. A. (2007). Match–mismatch processes underlie human hippocampal responses to associative novelty. Journal of Neuroscience, 27(32), 8517-8524.

Lammel, S., Lim, B. K., & Malenka, R. C. (2014). Reward and aversion in a heterogeneous midbrain dopamine system. Neuropharmacology, 76, 351-359.

LeDoux, J. E. (1993). Emotional memory systems in the brain. Behavioural brain research, 58(1-2), 69-79.

Lee, J. S., Chun, J. W., Kang, J. I., Kang, D. I., Park, H. J., & Kim, J. J. (2012). Hippocampus and nucleus accumbens activity during neutral word recognition related to trait physical anhedonia in patients with schizophrenia: an fMRI study. Psychiatry Research: Neuroimaging, 203(1), 46-53.

LeGates, T. A., Kvarta, M. D., Tooley, J. R., Francis, T. C., Lobo, M. K., Creed, M. C., & Thompson, S. M. (2018). Reward behaviour is regulated by the strength of hippocampus–nucleus accumbens synapses. Nature, 564(7735), 258-262.

Legault, M., & Wise, R. A. (1999). Injections of N-methyl-D-aspartate into the ventral hippocampus increase extracellular dopamine in the ventral tegmental area and nucleus accumbens. Synapse, 31(4), 241-249.

Legault, M., & Wise, R. A. (2001). Novelty-evoked elevations of nucleus accumbens dopamine: dependence on impulse flow from the ventral subiculum and glutamatergic

neurotransmission in the ventral tegmental area. European Journal of Neuroscience, 13(4), 819-828.

Li, M., Long, C., & Yang, L. (2015). Hippocampal-prefrontal circuit and disrupted functional connectivity in psychiatric and neurodegenerative disorders. BioMed research international, 2015.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron, 46(5), 703-713.

Lisman, J., Buzsáki, G., Eichenbaum, H., Nadel, L., Ranganath, C., & Redish, A. D. (2017). Viewpoints: how the hippocampus contributes to memory, navigation and cognition. Nature neuroscience, 20(11), 1434-1447.

Lisman, J., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. Trends in neurosciences, 34(10), 536-547.

Ljungberg, T., Apicella, P., & Schultz, W. (1992). Responses of monkey dopamine neurons during learning of behavioral reactions. Journal of neurophysiology, 67(1), 145-163.

Lodge, D. J., & Grace, A. A. (2006). The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. Neuropsychopharmacology, 31(7), 1356-1361.

Lodge, D. J., & Grace, A. A. (2008). Hippocampal dysfunction and disruption of dopamine system regulation in an animal model of schizophrenia. Neurotoxicity research, 14, 97-104.

Lodge, D. J., & Grace, A. A. (2011). Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. Trends in pharmacological sciences, 32(9), 507-513.

Lupien, S. J., & Lepage, M. (2001). Stress, memory, and the hippocampus: can't live with it, can't live without it. Behavioural brain research, 127(1-2), 137-158.

Maier-Hein, K. H., Neher, P. F., Houde, J. C., Côté, M. A., Garyfallidis, E., Zhong, J., ... & Descoteaux, M. (2017). The challenge of mapping the human connectome based on diffusion tractography. Nature communications, 8(1), 1349.

Mainen, Z. F., & Kepecs, A. (2009). Neural representation of behavioral outcomes in the orbitofrontal cortex. Current opinion in neurobiology, 19(1), 84-91.

Mather, M. (2007). Emotional arousal and memory binding: An object-based framework. Perspectives on Psychological Science, 2(1), 33-52.

Matsumoto, M., & Hikosaka, O. (2009). Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature, 459(7248), 837-841.

McCormick, C., Ciaramelli, E., De Luca, F., & Maguire, E. A. (2018). Comparing and contrasting the cognitive effects of hippocampal and ventromedial prefrontal cortex damage: a review of human lesion studies. Neuroscience, 374, 295-318.

Mogenson, G. J., Jones, D. L., & Yim, C. Y. (1980). From motivation to action: functional interface between the limbic system and the motor system. Progress in neurobiology, 14(2-3), 69-97.

Monk, A. M., Dalton, M. A., Barnes, G. R., & Maguire, E. A. (2021). The role of hippocampal–ventromedial prefrontal cortex neural dynamics in building mental representations. Journal of cognitive neuroscience, 33(1), 89-103.

Moser, M. B., & Moser, E. I. (1998). Functional differentiation in the hippocampus. Hippocampus, 8(6), 608-619.Moser, E. I., Kropff, E., & Moser, M. B. (2008). Place cells, grid cells, and the brain's spatial representation system. Annu. Rev. Neurosci., 31, 69-89.

Murty, V. P., Shermohammed, M., Smith, D. V., Carter, R. M., Huettel, S. A., & Adcock, R. A. (2014). Resting state networks distinguish human ventral tegmental area from substantia nigra. Neuroimage, 100, 580-589.

Murty, V. P., Tompary, A., Adcock, R. A., & Davachi, L. (2017). Selectivity in postencoding connectivity with high-level visual cortex is associated with reward-motivated memory. Journal of Neuroscience, 37(3), 537-545.

Naber, P. A., & Witter, M. P. (1998). Subicular efferents are organized mostly as parallel projections: a double-labeling, retrograde-tracing study in the rat. Journal of comparative neurology, 393(3), 284-297.

Nadel, L. (1968). Dorsal and ventral hippocampal lesions and behavior. Physiology & Behavior, 3(6), 891-900.

O'Brien, K. J., Ered, A., Korenic, S. A., Olino, T. M., Schiffman, J., Mittal, V. A., & Ellman, L. M. (2023). Childhood trauma, perceived stress and anhedonia in individuals at clinical high risk for psychosis: multigroup mediation analysis. The British Journal of Psychiatry, 1-7.

O'Keefe J, Nadel L. 1978. The Hippocampus as a Cognitive Map. New York: Oxford University Press.

Oades, R. D., & Halliday, G. M. (1987). Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. Brain Research Reviews, 12(2), 117-165.

Olsen, R. K., Carr, V. A., Daugherty, A. M., La Joie, R., Amaral, R. S. C., Amunts, K., Augustinack, J. C., Bakker, A., Bender, A. R., Berron, D., Boccardi, M., Bocchetta, M., Burggren, A. C., Chakravarty, M. M., Chételat, G., de Flores, R., DeKraker, J., Ding, S.-L., Geerlings, M. I., … Wisse, L. E. M. (2019). Progress update from the hippocampal

subfields group. Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring, 11, 439–449. https://doi.org/10.1016/j.dadm.2019.04.001

Palombo, D. J., Keane, M. M., & Verfaellie, M. (2015). How does the hippocampus shape decisions?. Neurobiology of Learning and Memory, 125, 93-97.

Phelps, E. A. (2004). Human emotion and memory: interactions of the amygdala and hippocampal complex. Current opinion in neurobiology, 14(2), 198-202.

Ploghaus A, Tracey I, Clare S, Gati JS, Rawlins JN, Matthews PM. (2000): Learning about pain: The neural substrate of the prediction error for aversive events. Proc Natl Acad Sci U S A 97: 9281–9286.

Poldrack, R. A. et al. Discovering Relations Between Mind, Brain, and Mental Disorders Using Topic Mapping. PLoS Comput. Biol. 8, (2012).

Poppenk, J., Walia, G., McIntosh, A. R., Joanisse, M. F., Klein, D., & Köhler, S. (2008). Why is the meaning of a sentence better remembered than its form? An fMRI study on the role of novelty-encoding processes. Hippocampus, 18(9), 909-918.

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. Trends in cognitive sciences, 17(5), 230-240.Rolls ET (2019) The orbitofrontal cortex. Oxford University Press, Oxford

Richardson, M. P., Strange, B. A., & Dolan, R. J. (2004). Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nature neuroscience, 7(3), 278-285.

Risold, P. Y., & Swanson, L. W. (1997). Connections of the rat lateral septal complex. Brain research reviews, 24(2-3), 115-195.

Ritchey, M., Libby, L. A., & Ranganath, C. (2015). Cortico-hippocampal systems involved in memory and cognition: the PMAT framework. Progress in brain research, 219, 45-64.

Rolls ET (2021) Brain computations: what and how. Oxford University Press, Oxford. https://doi.org/10.1093/oso/9780198871 101.001.0001

Rolls ET, Xiang JZ. (2005): Reward-spatial view representations and learning in the primate hippocampus. J Neurosci 25:6167– 6174.

Rolls, E. T. (2019). The orbitofrontal cortex. Oxford University Press.

Rolls, E. T. (2022). The hippocampus, ventromedial prefrontal cortex, and episodic and semantic memory. Progress in Neurobiology, 102334.

Rolls, E. T., Deco, G., Huang, C. C., & Feng, J. (2023a). The human orbitofrontal cortex, vmPFC, and anterior cingulate cortex effective connectome: emotion, memory, and action. Cerebral cortex, 33(2), 330-356.

Rolls, E. T., Wirth, S., Deco, G., Huang, C. C., & Feng, J. (2023b). The human posterior cingulate, retrosplenial, and medial parietal cortex effective connectome, and implications for memory and navigation. Human Brain Mapping, 44(2), 629-655.

Rosen, B. Q., & Halgren, E. (2022). An estimation of the absolute number of axons indicates that human cortical areas are sparsely connected. PLoS Biology, 20(3), e3001575.

Rudebeck, P. H., & Murray, E. A. (2014). The orbitofrontal oracle: cortical mechanisms for the prediction and evaluation of specific behavioral outcomes. Neuron, 84(6), 1143-1156.

Rutishauser, U. (2019). Testing models of human declarative memory at the single-neuron level. Trends in cognitive sciences, 23(6), 510-524.

Schlichting, M. L., & Preston, A. R. (2015). Memory integration: neural mechanisms and implications for behavior. Current opinion in behavioral sciences, 1, 1-8.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. Science, 275(5306), 1593-1599.

Schumacher, A., Vlassov, E., & Ito, R. (2016). The ventral hippocampus, but not the dorsal hippocampus is critical for learned approach-avoidance decision making. Hippocampus, 26(4), 530-542.

Scofield, M. D., Heinsbroek, J. A., Gipson, C. D., Kupchik, Y. M., Spencer, S., Smith, A. C. W., ... & Kalivas, P. (2016). The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacological reviews, 68(3), 816-871.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. Journal of neurology, neurosurgery, and psychiatry, 20(1), 11.

Shadlen, M. N., & Shohamy, D. (2016). Decision making and sequential sampling from memory. Neuron, 90(5), 927-939.

Sheldon, S., & Levine, B. (2016). The role of the hippocampus in memory and mental construction. Annals of the New York Academy of Sciences, 1369(1), 76-92.

Sherrill, K. R., Erdem, U. M., Ross, R. S., Brown, T. I., Hasselmo, M. E., & Stern, C. E. (2013). Hippocampus and retrosplenial cortex combine path integration signals for successful navigation. Journal of Neuroscience, 33(49), 19304-19313.

Shigemune, Y., Tsukiura, T., Kambara, T., & Kawashima, R. (2014). Remembering with gains and losses: effects of monetary reward and punishment on successful encoding activation of source memories. Cerebral cortex, 24(5), 1319-1331.

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Annals of the New York Academy of Sciences, 1071(1), 67-79.

Shohamy, D., & Adcock, R. A. (2010). Dopamine and adaptive memory. Trends in cognitive sciences, 14(10), 464-472.

Shohamy, D., & Daw, N. D. (2015). Integrating memories to guide decisions. Current Opinion in Behavioral Sciences, 5, 85-90.

Sjulson, L., Peyrache, A., Cumpelik, A., Cassataro, D., & Buzsáki, G. (2018). Cocaine place conditioning strengthens location-specific hippocampal coupling to the nucleus accumbens. Neuron, 98(5), 926-934.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., ... & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage, 23, S208-S219.

Snytte, J., Fenerci, C., Rajagopal, S., Beaudoin, C., Hooper, K., Sheldon, S., ... & Rajah, M. N. (2022). Volume of the posterior hippocampus mediates age-related differences in spatial context memory and is correlated with increased activity in lateral frontal, parietal and occipital regions in healthy aging. NeuroImage, 254, 119164.

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

Stachenfeld, K. L., Botvinick, M. M., & Gershman, S. J. (2017). The hippocampus as a predictive map. Nature neuroscience, 20(11), 1643-1653.

Strange, B. A., & Dolan, R. J. (2001). Adaptive anterior hippocampal responses to oddball stimuli. Hippocampus, 11(6), 690-698.

Strange, B. A., Witter, M. P., Lein, E. S., & Moser, E. I. (2014). Functional organization of the hippocampal longitudinal axis. Nature Reviews Neuroscience, 15(10), 655-669.

Swanson, L. W. N. (1982). The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain research bulletin, 9(1-6), 321-353.

Swanson, L. W., & Kohler, C. (1986). Anatomical evidence for direct projections from the entorhinal area to the entire cortical mantle in the rat. Journal of Neuroscience, 6(10), 3010-3023.

Tabuchi, E. T., Mulder, A. B., & Wiener, S. I. (2000). Position and behavioral modulation of synchronization of hippocampal and accumbens neuronal discharges in freely moving rats. Hippocampus, 10(6), 717-728.

Taepavarapruk, P., Floresco, S. B., & Phillips, A. G. (2000). Hyperlocomotion and increased dopamine efflux in the rat nucleus accumbens evoked by electrical stimulation of the ventral subiculum: role of ionotropic glutamate and dopamine D 1 receptors. Psychopharmacology, 151, 242-251.

Tang, W., Shin, J. D., & Jadhav, S. P. (2021). Multiple time-scales of decision-making in the hippocampus and prefrontal cortex. Elife, 10, e66227.

Tanriverdi, B., Gregory, D. F., Olino, T. M., Ely, T. D., Harnett, N. G., van Rooij, S. J., ... & Murty, V. P. (2022). Hippocampal Threat Reactivity Interacts with Physiological Arousal to Predict PTSD Symptoms. Journal of Neuroscience, 42(34), 6593-6604.

Thompson, C.L., Pathak, S.D., Jeromin, A., Ng, L.L., MacPherson, C.R., Mortrud, M.T., Cusick, A., Riley, Z.L., Sunkin, S.M., Bernard, A., et al. (2008). Genomic anatomy of the hippocampus. Neuron 26, 1010–1021.

Tompary, A., Duncan, K., & Davachi, L. (2015). Consolidation of associative and item memory is related to post-encoding functional connectivity between the ventral tegmental area and different medial temporal lobe subregions during an unrelated task. Journal of Neuroscience, 35(19), 7326-7331.

Trouche, S., Koren, V., Doig, N. M., Ellender, T. J., El-Gaby, M., Lopes-dos-Santos, V., ... & Dupret, D. (2019). A hippocampus-accumbens tripartite neuronal motif guides appetitive memory in space. Cell, 176(6), 1393-1406.

Tziortzi, A. C., Haber, S. N., Searle, G. E., Tsoumpas, C., Long, C. J., Shotbolt, P., ... & Gunn, R. N. (2014). Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. Cerebral cortex, 24(5), 1165-1177.

van den Bos, W., Rodriguez, C. A., Schweitzer, J. B., & McClure, S. M. (2014). Connectivity strength of dissociable striatal tracts predict individual differences in temporal discounting. Journal of Neuroscience, 34(31), 10298-10310.

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E., Yacoub, E., Ugurbil, K., & Wu-Minn HCP Consortium. (2013). The WU-Minn human connectome project: an overview. Neuroimage, 80, 62-79.

Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T. E., Bucholz, R., ... & WU-Minn HCP Consortium. (2012). The Human Connectome Project: a data acquisition perspective. Neuroimage, 62(4), 2222-2231.

Van Groen, T., & Wyss, J. M. (2003). Connections of the retrosplenial granular b cortex in the rat. Journal of Comparative Neurology, 463(3), 249-263.

Van Rooij, S. J. H., Kennis, M., Sjouwerman, R., Van Den Heuvel, M. P., Kahn, R. S., & Geuze, E. (2015). Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. Psychological medicine, 45(13), 2737-2746.

Verney, C., Baulac, M., Berger, B., Alvarez, C., Vigny, A., & Helle, K. B. (1985). Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. Neuroscience, 14(4), 1039-1052.

Viard, A., Doeller, C. F., Hartley, T., Bird, C. M., & Burgess, N. (2011). Anterior hippocampus and goal-directed spatial decision making. Journal of Neuroscience, 31(12), 4613-4621.

Vythilingam, M., Heim, C., Newport, J., Miller, A. H., Anderson, E., Bronen, R., ... & Bremner, J. D. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. American Journal of Psychiatry, 159(12), 2072-2080.

Whitlock, J. R., Sutherland, R. J., Witter, M. P., Moser, M. B., & Moser, E. I. (2008). Navigating from hippocampus to parietal cortex. Proceedings of the National Academy of Sciences, 105(39), 14755-14762.

Willard, S. L., Friedman, D. P., Henkel, C. K., & Shively, C. A. (2009). Anterior hippocampal volume is reduced in behaviorally depressed female cynomolgus macaques. Psychoneuroendocrinology, 34(10), 1469-1475.

Wilson, R. C., Takahashi, Y. K., Schoenbaum, G., & Niv, Y. (2014). Orbitofrontal cortex as a cognitive map of task space. Neuron, 81(2), 267-279.

Wimmer, G. E., & Shohamy, D. (2012). Preference by association: how memory mechanisms in the hippocampus bias decisions. Science, 338(6104), 270-273.

Wirth S, Avsar E, Chiu CC, Sharma V, Smith AC, Brown E, Suzuki WA. (2009): Trial outcome and associative learning signals in the monkey hippocampus. Neuron 61: 930–940.

Wittmann, B. C., Bunzeck, N., Dolan, R. J., & Düzel, E. (2007). Anticipation of novelty recruits reward system and hippocampus while promoting recollection. Neuroimage, 38(1), 194-202.

Wittmann, B. C., Schott, B. H., Guderian, S., Frey, J. U., Heinze, H. J., & Düzel, E. (2005). Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron, 45(3), 459-467.

Wolosin, S. M., Zeithamova, D., & Preston, A. R. (2012). Reward modulation of hippocampal subfield activation during successful associative encoding and retrieval. Journal of cognitive neuroscience, 24(7), 1532-1547.

Woollett, K. and Maguire, E.A. (2011) Acquiring ‘the knowledge’ of London’s layout drives structural brain changes. Curr. Biol. 21, 21092114.

WU-Minn HCP Consortium. 2015. WU-Minn HCP 900 subjects release: reference manual, appendix I – protocol guidance and HCP session protocols, pp. 1–55.

Yang, H., de Jong, J. W., Tak, Y., Peck, J., Bateup, H. S., & Lammel, S. (2018). Nucleus accumbens subnuclei regulate motivated behavior via direct inhibition and disinhibition of VTA dopamine subpopulations. Neuron, 97(2), 434-449.

Yarkoni, T., Poldrack, R. & Nichols, T. Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods 8, 665–670 (2011).

Zackova, L., Jani, M., Brazdil, M., Nikolova, Y. S., & Marečková, K. (2021). Cognitive impairment and depression: meta-analysis of structural magnetic resonance imaging studies. NeuroImage: Clinical, 32, 102830.

Zhu, Y., Gao, H., Tong, L., Li, Z., Wang, L., Zhang, C., ... & Yan, B. (2019). Emotion regulation of hippocampus using real-time fMRI neurofeedback in healthy human. Frontiers in human neuroscience, 13, 242

Table 1. *Participant Demographics.*

Age (years) M (SD) [range]	28.7 (3.7) [22-36]
Sex % (n) Male	43.7 (275)
Ethnicity % (n) Hispanic	8.9 (56)
Unknown/Not Reported	1.0 (6)
Race % (n)	
American Indian/Alaska Native	.16 (1)
Asian/Pacific Islander	5.1 (32)
Black	14.5 (91)
White	75.5 (474)
More than one race	2.7 (17)
Unknown/Not Reported	2.1 (13)

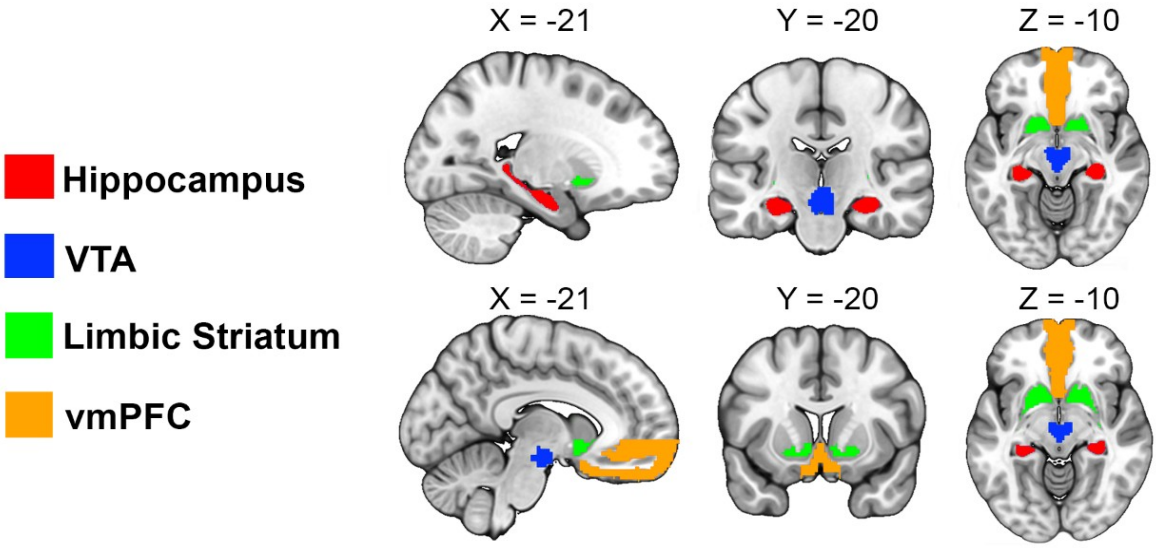

Figure 1: Seed and target regions for the probabilistic tractography analysis. The target region of the limbic striatum was functionally segmented based on projections from motor, executive, and limbic cortices (Tziortzi et al., 2014). The target region of the vmPFC was functionally correlated with meta-analyses of social, emotion, and economic valuation or decision-making (Bhanji et al., 2019). The target region of the midbrain was generated from VTA probabilistic atlas (Murty et al., 2014). The seed region of the hippocampus was generated from the Harvard-Oxford subcortical atlas (Frazier et al., 2005).

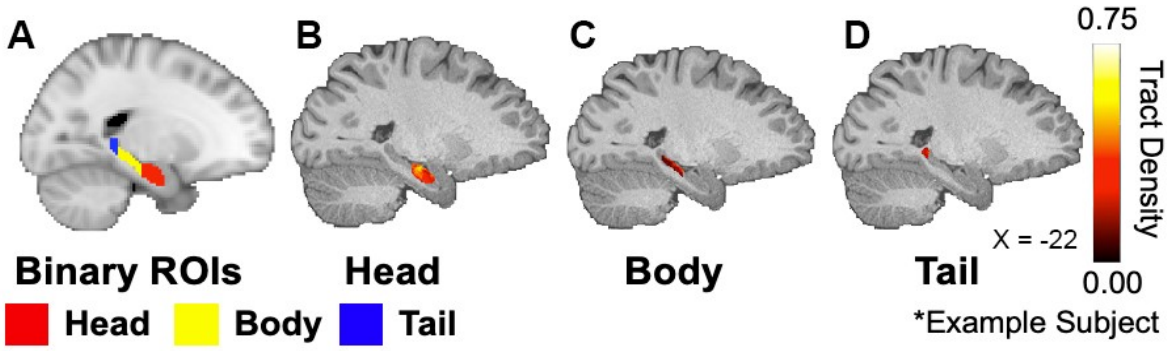

Figure 2: Within-subject tract density measure along the hippocampal long axis (head, body, and tail). A) Head, body and tail ROIs in MNI space. B) Voxel-wise tract density in the head of the hippocampus. C) Voxel-wise tract density in the body of the hippocampus. D) Voxel-wise tract density in the tail of the hippocampus. Mean voxel-wise tract density in each hippocampus ROI was computed for use in the ANOVA.

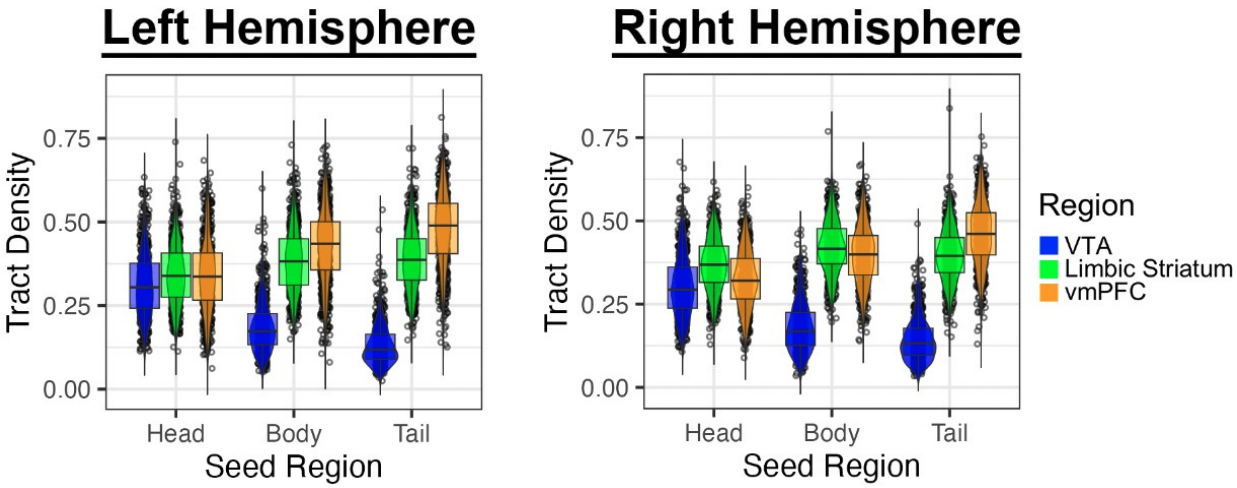

Figure 3: Within-subject mean tract density to each reward ROI along the hippocampal long axis (head, body, and tail) for each hemisphere. All main effects and interactions are statistically significant.

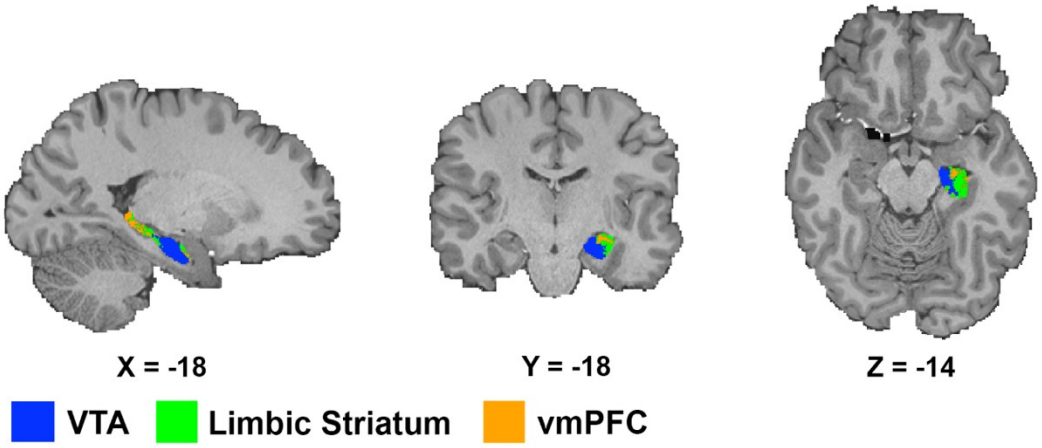

Figure 4: Hard segmentation on an example subject. The hippocampus was segmented by assigning each voxel to the ROI with which it had the highest connection probability (Johansen-Berg et al. 2005). After this "hard" segmentation, the areas in the hippocampus that associate with each target region were established.

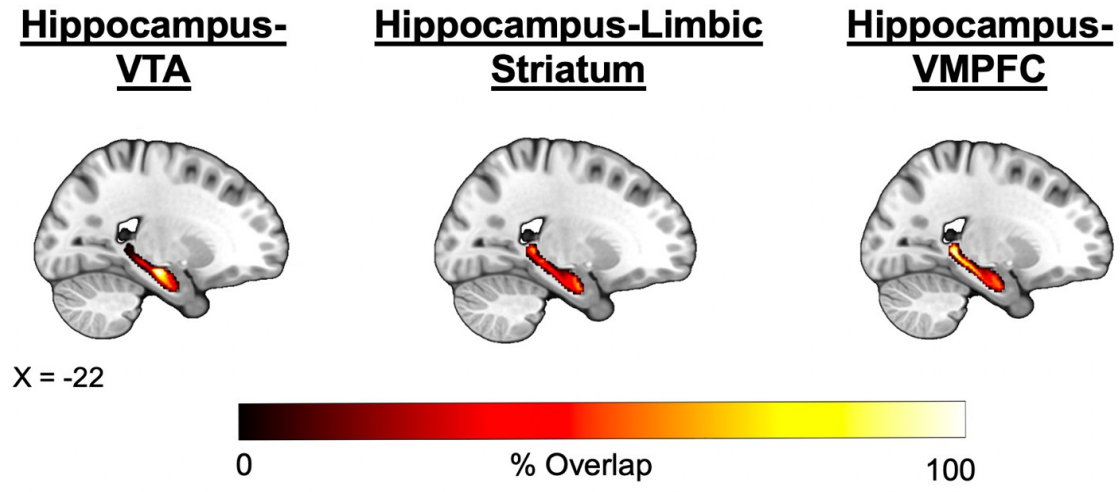

Figure 5: Hard segmentation group-averaged projections. Heat map represents the percent overlap of participants. A probabilistic atlas of the group-averaged projections is publicly available on Github.

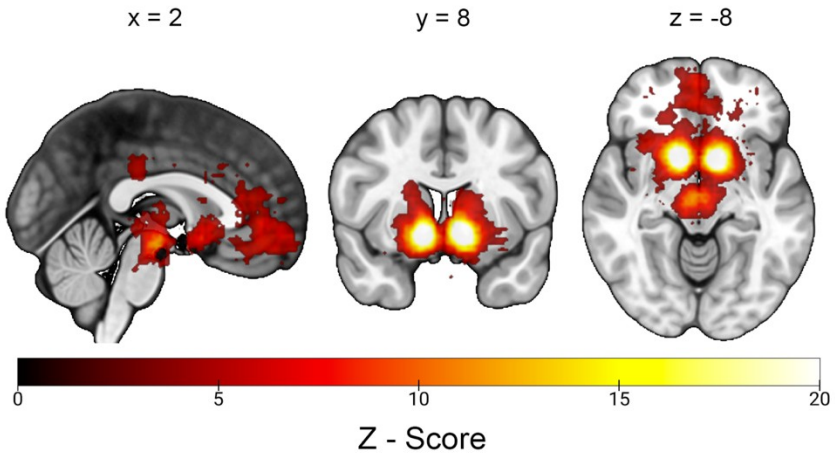

Figure 6: Neurosynth term-based meta-analysis conducted for the term "reward". The meta-analysis of 928 studies revealed large clusters centered on the VTA, ventral striatum, and vmPFC. The map can be examined at http://www.neurosynth.org/analyses/terms/reward.