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Amygdala and ventral tegmental area differentially interact with hippocampus and cortical medial temporal lobe during rest in humans

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Abstract

Neuromodulatory regions that detect salience, such as amygdala and ventral tegmental area (VTA), have distinct effects on memory. Yet, questions remain about how these modulatory regions target subregions across the hippocampus and medial temporal lobe (MTL) cortex. Here, we sought to characterize how VTA and amygdala subregions (i.e., basolateral amygdala and central-medial amygdala) interact with hippocampus head, body, and tail, as well as cortical MTL areas of perirhinal cortex and parahippocampal cortex in a task-free state. To quantify these interactions, we used high-resolution resting state fMRI and characterized pair-wise, partial correlations across regions-of-interest. We found that basolateral amygdala showed greater functional coupling with hippocampus head, hippocampus tail, and perirhinal cortex when compared to either VTA or central-medial amygdala. Furthermore, the VTA showed greater functional coupling with hippocampus tail when compared to central-medial amygdala. There were no significant differences in functional coupling with hippocampus body and parahippocampal cortex. These results support a framework by which neuromodulatory regions do not indiscriminately influence all MTL subregions equally, but rather bias information processing to discrete MTL targets. These findings provide a more specified model of the intrinsic properties of systems underlying MTL neuromodulation. This emphasizes the need to consider heterogeneity both across and within neuromodulatory systems to better understand affective memory.

KEYWORDS

amygdala, hippocampus, medial temporal lobe, neuromodulation, resting state fMRI, ventral tegmental area

1 | INTRODUCTION

A longstanding body of research describes how human affective experience at encoding improves memory (LaBar & Cabeza, 2006). However, memories are multi-dimensional, and different emotional states are known to modulate different aspects of episodic memory (Bowen, Kark, & Kensinger, 2018; Clewett & Murty, 2019). Behaviorally, reward motivation often facilitate relational memory, whereas threat and punishment often facilitate item-based memory and may even impair relational memory (Bennion, Ford, Murray, & Kensinger, 2013; Miendlarzewska, Bavelier, & Schwartz, 2016; Murty & Adcock, 2017; Yonelinas & Ritchey, 2015). To explain these results, Murty and Adcock (2017) proposed a model that distinct neuromodulatory regions centered on ventral tegmental area (VTA) and amygdala biases engagement of different medial temporal lobe (MTL) regions during encoding. This model posits that VTA activation supports relational memory by engaging the hippocampus, whereas amygdala activation supports item-based memory by engaging cortical MTL. Although

evidence for this model has accrued from emotional and motivational memory encoding paradigms, an open question remains as to whether these neuromodulatory biases in MTL engagement are intrinsic properties of these systems or if they only emerge in the context of affective experience. The current study investigated the functional connectivity of neuromodulatory regions, centered on the VTA and amygdala, with targets throughout the MTL using high-resolution resting state fMRI.

Different neuromodulatory regions involved in detecting salience and initiating motivated behaviors are known to have particular effects on MTL-dependent memory (Murty & Adcock, 2017; Yonelinas & Ritchey, 2015). During tasks of reward motivation, the VTA has been shown to facilitate hippocampal-dependent encoding, which in turn supports relational memory (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Miendlarzewska et al., 2016; Murty & Adcock, 2014; Wittmann et al., 2005). For example, Adcock et al. (2006) found that memory enhancements for neutral stimuli incentivized by reward were associated with greater interactions between VTA and hippocampus leading to better recollection. Conversely, during tasks of threat motivation, the amygdala, rather than the VTA, has been shown to facilitate cortical MTL-dependent encoding, which in turn supports item-based memory. For example, Murty, LaBar, and Adcock (2012) found that memory enhancements for neutral stimuli incentivized with avoidance of electrical shock were associated with functional interactions between the amygdala and parahippocampal cortex. Together, these studies provide neuroimaging evidence that the VTA and amygdala interact with different regions in the MTL during affective experiences.

It remains unknown, however, whether biases detailed above exist in the absence of motivational incentives or salient affective cues. One possibility is that although biases exist in these systems, they operate in an intrinsic organization, such that increases of activity in a given neuromodulatory region (i.e., the VTA) would result in increased engagement of a specific MTL target (i.e., the hippocampus) regardless of the affective context. Within this framework, the relationships between the VTA and amygdala with the MTL that are apparent during memory encoding should also exist in neutral contexts or during resting state without explicit task goals. An alternative explanation for the organization of neuromodulatory regions over the MTL are context specific and dependent on goal states, implying that only in affective or motivational states do these biases emerge. In this alternative framework, there may not exist an intrinsic organization of neuromodulatory regions over the MTL apparent during neutral contexts or during rest.

Another open question in neuromodulation regards the characterization of the amygdala's targets across the MTL during memory encoding. Although prior work has shown that amygdala engagement can impair hippocampal-dependent encoding (Bennion et al., 2013; Murty & Adcock, 2017; Yonelinas & Ritchey, 2015), some emotional memory research has shown amygdala-related enhancements in hippocampal engagement during encoding (Cahill & McGaugh, 1998; LaBar & Cabeza, 2006; Murty, Ritchey, Adcock, & LaBar, 2011; Tyng, Amin, Saad, & Malik, 2017). One reason why there may be a discrepancy across the affective memory literature is that often within human neuroimaging the amygdala is treated as a unified structure. However, animal work has characterized the amygdala as a collection of subregions, including basolateral amygdala (BLA) and central-medial amygdala (CeM), each with different functional properties (Goosens & Maren, 2001; Moscarello & Maren, 2018). For example, the BLA is known for active avoidance of threat, whereas CeM is known for freezing response to threat. As such, engagement of these subregions will produce different behavioral profiles in animals and may correspond with different encoding strategies in humans, culminating in downstream consequences on human memory. Delineating the functional connectivity of the BLA and CeM with the hippocampus and cortical MTL may help begin to resolve conflicting findings across the human neuroimaging literature and impact how the amygdala should be characterized within emotional memory research.

The current study investigated how neuromodulatory regions centered on the VTA and amygdala interact with the hippocampus (head, body, tail) as well as the cortical MTL (perirhinal cortex, parahippocampal cortex) using resting state fMRI. Analyses were focused on characterizing functional coupling of the VTA and amygdala with discrete MTL targets in the absence of motivational incentives or affective cues by using resting state fMRI. Using resting state fMRI allowed us to resolve whether previously demonstrated connectivity patterns shown during affective memory encoding generalize to task-free states. Furthermore, we used high-resolution fMRI, which allowed us to resolve anatomical differences between the BLA and CeM subregions of the amygdala, which would be predicted by the animal literature. Our results show that the patterns of connectivity of these neuromodulatory regions during rest partially align with those identified during affective memory tasks, but important differences emerge when considering discrete sub-circuits.

2 | METHODS

2.1 | Participants

High-resolution fMRI data (1.5 mm isotropic) were collected from 22 English-speaking young adults, who reported no history of neurological and or psychiatric disorders (N = 22, 13 female, age range: 18–32 years). Data were collected as part of a previously-published dataset on emotional memory encoding (Ritchey, Wang, Yonelinas, & Ranganath, 2019); this prior report did not include the resting state analyses described here. The data collected were approved by the Institutional Review Board at the University of California, Davis, and all participants provided written informed consent prior to the experiment.

2.2 | Image acquisition

Structural and functional MRI data were collected on a Siemens Skyra 3T scanner using a 32-channel head coil. Details about data

acquisition parameters can be found in the prior report (Ritchey et al., 2019). In brief, a high-resolution T1-weighted structural image was acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (voxel size = 1.0 mm isotropic) and a high-resolution T2-weighted structural image was acquired using a turbo spin-echo sequence, oriented perpendicular to the longitudinal axis of the hippocampus (in-plane resolution = 0.45 mm^2; slice thickness = 1.9 mm). Functional images were acquired parallel to the longitudinal axis of the hippocampus using a multi-band gradient echo planar imaging (EPI) sequence (TR = 2010 ms; TE = 25 ms; flip angle = 79°; multi-band acceleration factor = 2; total axial slices = 52; in-plane resolution = 1.5 mm^2; slice thickness = 1.5 mm). The acquisition parameters result in coverage across the MTL and in the midbrain. Data were only used from the pre-encoding resting state scans before any emotional stimuli were viewed.

2.3 | Defining regions of interest

Analyses were focused on ROIs across neuromodulatory seeds of the BLA, CeM, and VTA (Figure 1) as well as targets across the hippocampus head, hippocampus body, hippocampus tail, perirhinal cortex, and parahippocampal cortex. Below, we detail methods for defining each of the ROIs. BLA and CeM were manually segmented on individual T2 images (Ritchey et al., 2019). VTA was defined using a probabilistic atlas, thresholded at 75% (Murty et al., 2014). This VTA probabilistic ROI was binarized and back-transformed into each individual's anatomical space. Hippocampus head, body, and tail were segmented with the Automatic Segmentation of Hippocampal Subfields (ASHS) software applied to individual T2 images, using the UPenn PMC atlas (Yushkevich et al., 2015) and corrected by hand when necessary. Perirhinal cortex and parahippocampal cortex ROIs were manually segmented on individual T2 images (Ritchey, Montchal, Yonelinas, & Ranganath, 2015). No voxel selection procedure beyond anatomical delineation was performed for any of our ROIs. All ROIs were visually inspected to ensure each aligned with participant's anatomical image. Table 1 displays the mean volume and standard deviation for each of ROIs as well as their temporal SNR. Visualization of each individual participant's ROIs can be found in the supplemental material.

2.4 | Preprocessing/denoising

Functional imaging data were realigned and the T2 high-resolution image was registered to the mean functional image using SPM8. We next ran a general linear model (GLM) on the resting state data to remove noise-related factors, including time series extracted from white matter and cerebral spinal fluid, six head-motion parameters, and the first derivatives of each of the six head-motion parameters. Furthermore, censored time points, characterized by greater than 0.3 mm in frame displacement or 1.5% global mean signal change using Artifact Detection Tools (ART), were also included in the GLM. After de-noising, the functional images were bandpass filtered at 0.01 Hz and 0.10 Hz using AFNI's 3dBandpass.

TABLE 1 Seed and MTL target ROI voxel volume summary

ROI	Mean	SD	tSNR[a]
BLA	3,940.14	22.75	173.22
CeM	885.59	13.91	63.65
VTA	1,040.82	9.43	110.42
PRC	6,666.68	39.86	167.26
PHC	6,570.77	29.60	221.95
HPC: Head	5,082.14	27.63	183.96
HPC: Body	4,838.14	18.98	254.86
HPC: Tail	692.46	18.12	38.21

[a]tSNR was performed on the mean time series extracted from the ROIs.

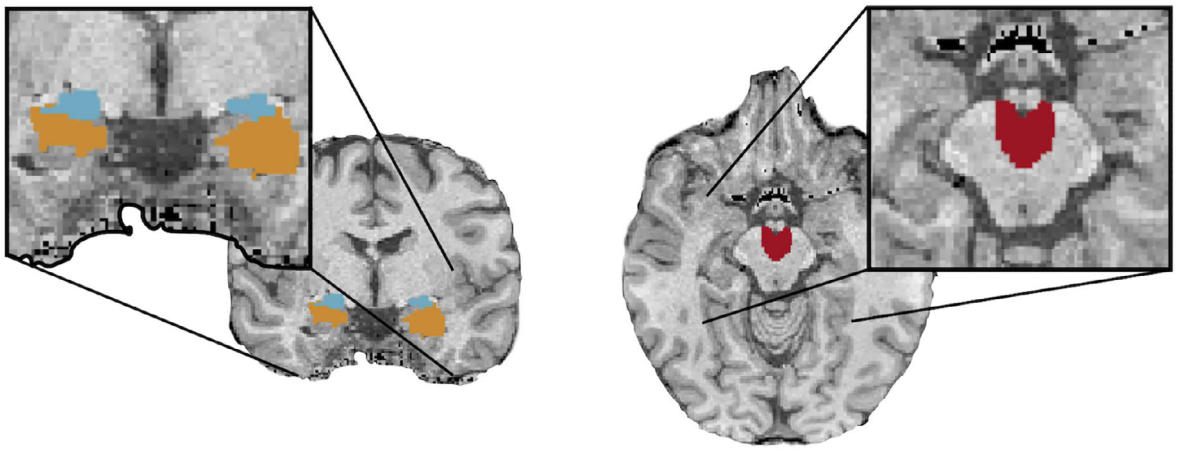

FIGURE 1 An individual participant's neuromodulatory ROIs. BLA (orange) and CeM (blue) left, and VTA (red) right

2.5 | Data analysis

We first resampled all of the preprocessed functional data and anatomical ROIs into 1.0 mm space. For each ROI, we then extracted the eigen variate of the weighted mean within the ROI using FSL's fslmeants. To account for shared variance across the neuromodulatory seeds, on the extracted time series, we calculated partial, pairwise correlations incorporating all three seeds and a single MTL target. By using a partial correlation, the variance across each of the neuromodulatory seeds was controlled when calculating the correlation values. We then *z*-scored these values for all subsequent analyses. To control for correlations which may have been driven by the proximity between the seed regions and the target ROI, we conducted post-hoc analyses comparing connectivity for contralateral seed-target pairs (i.e., left VTA/BLA/CEM to right MTL targets).

Z-scored correlation values were analyzed at the group level using R software (R package version 3.4.1). To determine if connectivity with each MTL regions differed across neuromodulatory seeds, using a mixed-effects linear model (lmer the lme4 library), we first looked to see if the independent variable of neuromodulatory seed (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 BIC. If this chi-squared value was significant or trending, paired *t*-tests were then performed as a post hoc analysis in each MTL region to compare functional coupling scores of neuromodulatory seeds. Significance was set at $p < 0.05$, and trends at $p < 0.10$.

3 | RESULTS

3.1 | Seed and target regions

Seed-regions within the BLA and CeM were hand drawn on individual participant anatomical images, whereas definitions of the VTA were derived from a probabilistic atlas thresholded at 75% overlap. In Table 2, we provide the mean correlation between each pair of seed regions. To account for this shared variance across seed ROIs, all presented analysis were performed using a partial regression approach that accounted for each seed region. Each target region was hand drawn on individual participant anatomical images, and correlations with target regions are detailed below. Visualization of each ROI and the functional MRI coverage for each participant is provided in the Supplemental Materials.

TABLE 2 Correlations between seed ROIs

Regions	Pearson's *r*	SD (*r*)
BLA-VTA	0.26	0.20
BLA-CEM	0.57	0.15
VTA-CEM	0.20	0.23

3.2 | Hippocampal functional coupling

In hippocampus head (Figure 2, top), adding neuromodulatory seed into the model significantly improved model fit (BIC w/o seed: 43.72; BIC w/ seed: 14.14; model comparison: $\chi^2[2] = 37.96$, $p < 0.001$). Post hoc paired *t*-tests revealed greater functional coupling of

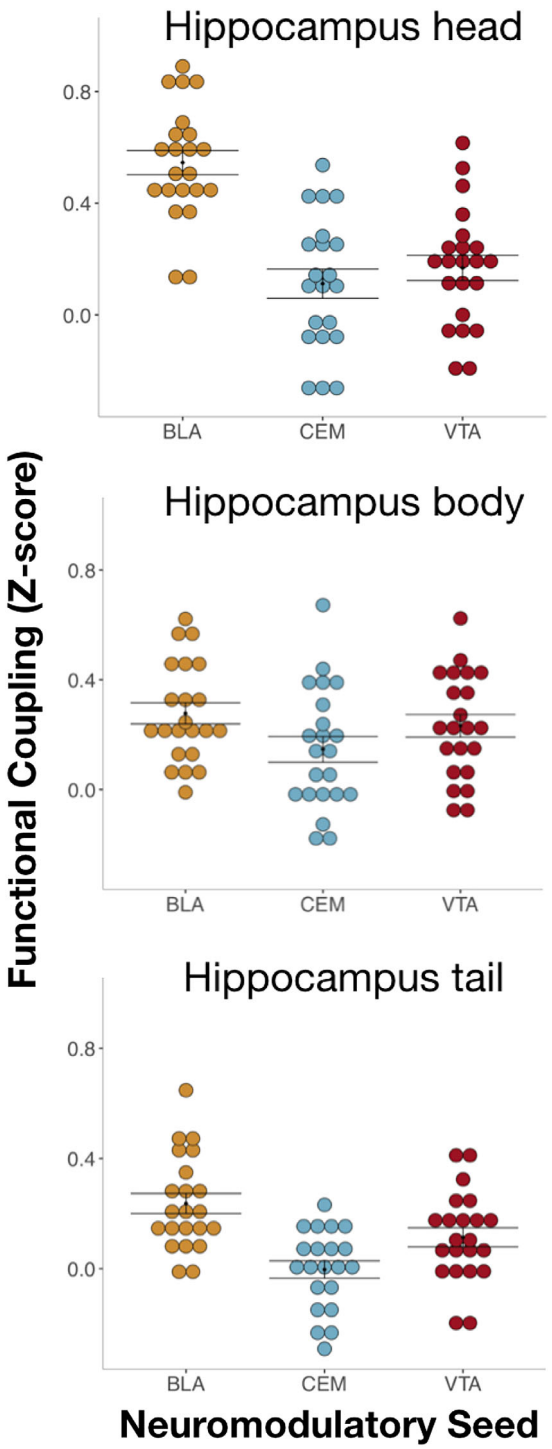

FIGURE 2 Functional coupling of hippocampal targets with the BLA, CEM, and VTA [Color figure can be viewed at wileyonlinelibrary.com]

hippocampus head with BLA compared to CeM (t[21] = 5.70, p < 0.001, d = 2.49) as well as with BLA compared to VTA (t[21] = 5.53, p < 0.001, d = 2.41). There were no significant differences between functional coupling of hippocampus head with CeM compared to VTA (p = 0.304).

In hippocampus body (Figure 2, middle), adding neuromodulatory seed improved model fit at the trend-level (BIC w/o seed: −7.96; BIC w/ seed: −11.38; model comparison: χ^2[2] = 4.96, p = 0.084). Post hoc paired t-tests revealed a trend toward greater functional coupling of hippocampus body with BLA compared to CeM (t[21] = 1.75, p = 0.094, d = 0.76). There were no significant differences between functional coupling of hippocampus body with BLA compared to VTA (p = 0.447), or CeM compared to VTA (p = 0.150).

In hippocampus tail (Figure 3, bottom), adding neuromodulatory seed into the model significantly improved model fit (BIC w/o seed: −18.24; BIC w/ seed: −33.20; model comparison: χ^2[2] = 23.34, p < 0.001). Post hoc paired t-tests revealed greater functional coupling of hippocampus tail with BLA compared to CeM (t[21] = 4.26, p < 0.001, d = 1.86), as well as with BLA compared to VTA (t[21] = 2.78, p = 0.011, d = 1.21). In addition, we found greater functional coupling of hippocampus tail with VTA compared to CeM (t[21] = 2.82, p = 0.010, d = 1.23).

All of the comparisons above showed the same pattern of results when performing analysis to control for the proximity of ROIs by estimating functional coupling between seed regions and targets in the contralateral hemisphere contralateral (Supplemental Materials), except the differences between the VTA compared to the CEM in the hippocampus tail was nonsignificant (p = 0.13).

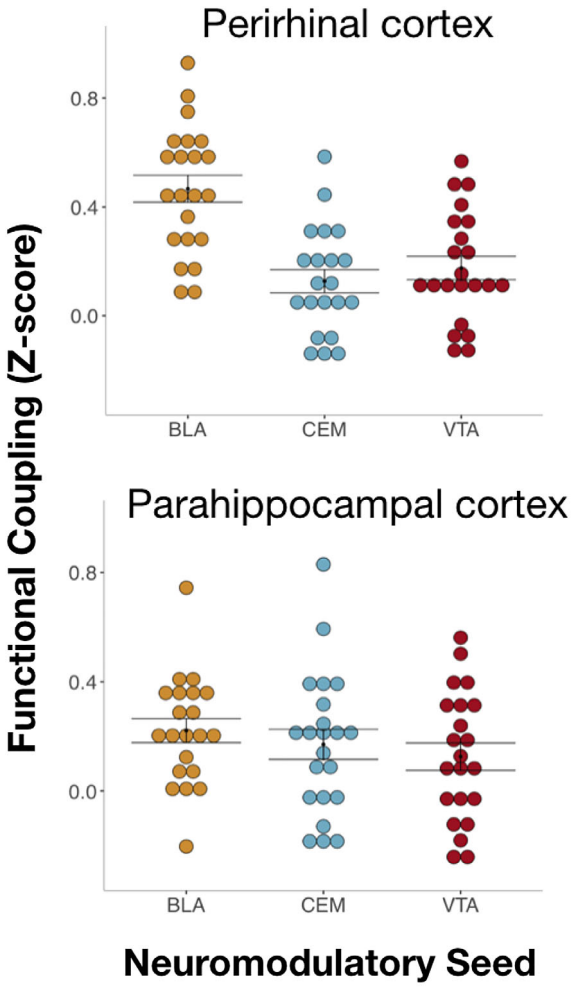

FIGURE 3 Functional coupling of cortical MTL targets with the BLA, CeM, and VTA [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Cortical MTL functional coupling

In perirhinal cortex, adding neuromodulatory seed into the model significantly improved model fit (BIC w/o seed: 24.73; BIC w/ seed: 4.63; model comparison: χ^2[2] = 28.49, p < 0.001). Post hoc paired t-tests revealed greater functional coupling of perirhinal cortex with BLA compared to CeM (t[21] = 4.36, p < 0.001, d = 1.90) as well as with BLA compared to VTA (t[21] = 4.53, p < 0.001, d = 1.98). There were no significant differences between functional coupling of perirhinal cortex with CeM compared to VTA (p = 0.309). In the parahippocampal cortex, adding neuromodulatory seed into the model did not result in a significantly improved model fit (BIC w/o seed: 11.97; BIC w/ seed: 19.48; model comparison: χ^2[2] = 0.87, p = 0.647). All of the comparisons above showed the same pattern of results when performing analysis to control for the proximity of ROIs by estimating functional coupling between seed regions and targets in the contralateral hemisphere contralateral (Supplemental Materials).

4 | DISCUSSION

Our results support a model by which different neuromodulatory regions uniquely biases information processing across discrete MTL targets during rest. We found that BLA had greater functional coupling than either CeM or VTA for both the hippocampus head and tail, as well BLA showed marginal increases when compared to CeM for the hippocampus body. Furthermore, VTA had significantly greater functional coupling than CeM for hippocampus tail. In cortical MTL, we found that BLA had greater functional coupling than both CeM and VTA in perirhinal cortex, whereas no significant differences were found in parahippocampal cortex across neuromodulatory regions. In general, our findings suggest that biases between neuromodulatory structures and the MTL exist during rest, which, in part, follows an organizational structure seen during emotional memory encoding. Notably, our results also support the importance of delineating the amygdala into subregions, as BLA and CeM showed distinct profiles of functional interactions with the MTL. Our results emphasize the need to consider the intrinsic properties of systems underlying MTL neuromodulation as well as heterogeneity both across and within neuromodulatory systems to better understand affective memory.

The theoretical model previously presented proposes that during human encoding the VTA, in contrast to the amygdala, biases memory

toward the hippocampus (Murty & Adcock, 2017). Here, we tested whether the same organizational schema exists during resting state, where participants did not have any specific task goals or explicit affective experiences. In general, we found the patterns were not consistent when examined during rest. Especially, for hippocampus head, body and tail, amygdala subregion BLA showed greater functional coupling compared to VTA. One reason these differences may develop is that biases in functional connectivity with the VTA and amygdala may emerge only during affective or motivational states. In line with this interpretation, prior work has shown that VTA interactions with both cortical and subcortical structures are more prominent in the context of motivationally relevant states when compared to resting state or an intrinsic baseline (Ballard et al., 2011; Murty et al., 2018). In the ensuing logic, VTA modulation over the hippocampus may emerge only in affective states that engage VTA, which has been previously been shown in the context of reward motivation (Adcock et al., 2006; Gruber, Watrous, Ekstrom, Ranganath, & Otten, 2013; Murty & Adcock, 2014; Wolosin, Zeithamova, & Preston, 2013), novelty (Wittmann, Daw, Seymour, & Dolan, 2008), and curiosity (Gruber, Gelman, & Ranganath, 2014). Further from a mnemonic perspective, this research compliments recent research showing that regions within motor and sensory cortex dynamically shift as a function of mnemonic state to better support long-term memory (Schedlbauer & Ekstrom, 2019).

Although, in general, our results did not show biases toward greater functional coupling with the VTA compared to amygdala in the hippocampus, we did see that VTA showed greater functional coupling with the hippocampus tail compared to amygdala subregion CEM. This outcome is consistent with the theoretical model previously presented that VTA drives hippocampal processing over the amygdala. Given this, the current results imply the theoretical model is only reliable when considering the CEM subregion. In models of human emotional memory (Bowen et al., 2018; Murty et al., 2011), amygdalar neuromodulation over the hippocampus has not been specified at the level of its component subregions. Interestingly, animal work has demonstrated the importance of delineating between BLA versus CeM when characterizing threat-related behavior. For example, the BLA is known to regulate active avoidance in responses to low threat, whereas the CeM is known to elicit startle and freezing response to high threat (Moscarello & Maren, 2018). The fact that different behavioral profiles are regulated by these discrete amygdalar regions is bolstered by the idea that CeM and BLA may also differentially influence hippocampal-dependent memory. In essence, our results suggest a model by which affective contexts that engage BLA may enhance hippocampal-dependent encoding, whereas those that engage CeM may impair hippocampal-dependent encoding.

Moving beyond hippocampal neuromodulation, recent empirical work has begun to describe how the amygdala may facilitate processing in cortical MTL rather than the hippocampus. Based on this work, multiple theoretical models have detailed a critical role for amygdala–perirhinal cortex interactions in driving emotional memory enhancement (Ritchey et al., 2019) as well as memory encoding under threat (Murty et al., 2012). In line with this framework, BLA showed significantly greater connectivity with the perirhinal cortex compared to VTA, supporting a strong engagement of this circuit during emotional memory encoding. However, we did not see a similar pattern of results when characterizing CeM interactions with perirhinal cortex or when characterizing the influence of any of the neuromodulatory regions over the parahippocampal cortex. Bearing in mind this finding, our results could support that biases of the perirhinal cortex by the amygdala are limited to engagement of BLA rather than CeM, thus stressing the importance of delineating these two subregions. An alternative possibility is that we only characterized the difference across these subregions during resting state, and there could also be interactions between CeM and perirhinal cortex in threat-related contexts which evoke behaviors such as freezing or startle. Again, deliberating between these interpretations of the data warrant studies with a focus on the unique contributions of BLA and CeM during memory encoding in threatening contexts.

The current results broaden an understanding of how amygdala and VTA influence engagement of the MTL. By studying systems during resting state, we were able to identify sub-circuits that appear in the absence of an affective state or explicit goal orientation. Furthermore, our data emphasizes the advantage of using high-resolution neuroimaging to characterize these circuits. We found that characterizing the amygdala as a unitary structure was insufficient to fully explain its interactions with the MTL, and it was necessary to fractionate the amygdala into subregions to reveal different patterns of functional connectivity. This type of precision will be necessary to better understand the nature of amygdala interactions with the MTL. Last, this path of inquiry may also help decipher conflicting literature of amygdalar engagement either enhancing or impairing hippocampal function in the context of emotional memory.

Collectively, we conclude that the contextual state of an individual is essential when characterizing neuromodulatory influences. As exemplified by the BLA-MTL circuit biases which were prominent during rest, suggesting that this circuit may have wide-spread influences across diverse contexts. However, for other circuits, as with our findings of VTA-MTL and CeM-MTL, neuromodulatory influences were limited to certain MTL targets, suggesting that these circuits are specific to motivationally relevant targets. Finally, our results emphasize the need for more imaging research using high-resolution imaging to characterize these circuits. The current study made use of neuroimaging data at a resolution which allowed us to delineate between amygdalar sub-regions, from which differential connectivity patterns were shown to arise. Although we cannot directly assay the contents of thoughts, goals, and emotions during resting state, which then follows that if resting state lies along a continuum of other human affective states our results indicate nonlinearities across emotional memory circuits as we traverse these diverse states. This supports the idea that resting state may not be a theorized baseline signal or static intrinsic activity and requires careful consideration when used in comparison to an experimental manipulation (Morcom & Fletcher, 2007). Future research will endeavor to understand not only how but when neuromodulation occurs, which will provide a deeper perception of momentary affective experience being incorporated into our larger

models of the world. This in turn could help with the abstract question of why neuromodulation is crucial for human memory.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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