The functional reach of the hippocampal memory system to the oculomotor system

Abbreviated title:
Stimulation of the Hippocampus Results in Oculomotor Responses

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Abstract

Visual exploration is influenced by what we remember. Amnesic cases, who have damage to the hippocampus (HC) and/or extended medial temporal lobe (MTL), show alterations in their gaze patterns relative to neurologically intact adults on tasks of memory. Recent work has revealed an extensive set of polysynaptic connections between the hippocampus and oculomotor system. However, little is known about how activation within the HC may impact the oculomotor system. In the present work, we conducted simulations of the functional interactions between the two systems by leveraging a computational modeling platform (The Virtual Brain; thevirtualbrain.org) with structural connectivity as defined through the CoCoMac database and tractography data from macaques. We examined how activity dissipated throughout the pre-identified polysynaptic pathways when subregions of the HC, and regions of the broader MTL, were stimulated. Stimulation of CA1, pre- and para-subiculum, and entorhinal, perirhinal, and parahippocampal cortices each resulted in observable responses in regions of the oculomotor system, including the frontal eye fields. Stimulation of the subiculum and CA3 did not culminate in responses in the frontal eye fields, and in such instances, activity was also not observed in parietal areas, posterior cingulate, and V4, suggesting that these regions may be important for transmitting information from the HC to regions within the oculomotor system. These findings provide novel evidence that activity originating within the HC and/or MTL may travel through specific nodes and pathways to influence the oculomotor system.

Significance Statement

No major account of oculomotor (eye movement) guidance considers the influence of the hippocampus and broader medial temporal lobe system, yet it is clear that information is exchanged between the two systems. Prior experience influences current viewing, and cases of amnesia due to compromised hippocampal/medial temporal lobe function show specific alterations in viewing behaviour. Using computational modeling, we show that stimulation of subregions of the hippocampus and regions of the medial temporal lobe results in observable responses in brain regions that are involved in the control of eye movements. These findings suggest that information from memory may be readily provided to the oculomotor system, and calls for a reconsideration of the neural circuitry involved in oculomotor guidance.

Introduction

It is now well established that information maintained in memory can influence ongoing active exploration of the visual environment (Hannula et al., 2010; Loftus & Mackworth, 1978). The influence of prior experience on current viewing has been shown in both humans and macaques; for instance, more viewing is directed to novel items compared to items that have been previously viewed (Fantz, 1964; Fagan, 1970; Zola et al., 2000; Whitehead et al., 2018), and more viewing is directed to areas of the visual world that have been altered from a prior viewing (Ryan et al., 2000; Smith, Hopkins, & Squire, 2006). Eyetracking has been used as a tool to probe the integrity of function in the hippocampus (HC) and regions of the broader medial temporal lobe (MTL), which are critical for the formation and use of memory representations (see Hannula et al., 2010, for review). Amnesic cases who have compromised HC and/or MTL show specific changes in their viewing behavior compared to healthy individuals (Ryan et al., 2000; Hannula et al., 2007; Warren et al., 2010; Olsen et al., 2015). Similar findings have been observed in older adults who have suspected HC/MTL compromise (Ryan et al., 2007), and certain viewing patterns have been shown to track with entorhinal cortex (ERC) volumes (Yeung et al., 2017).

Despite a wealth of evidence linking HC/MTL function to gaze patterns, research is just now beginning to outline the anatomical connections between the HC/MTL memory system and the oculomotor system. There are no known direct connections between hippocampal subfields and the oculomotor system, and current models of oculomotor control do not consider the influence of the HC/MTL memory system. However, recent evidence has identified an extensive set of polysynaptic pathways, spanning extrastriate, posterior parietal, and prefrontal regions, that serve to connect the oculomotor and memory systems and may mediate the exchange of information between them (Shen, Bezgin, Selvam, McIntosh & Ryan, 2016).

The relationship between oculomotor behavior and HC/MTL function is reciprocal: oculomotor behavior can influence neural responses in the HC/MTL, and neural responses in the HC/MTL predict ongoing visual exploration. In macaques, HC and ERC neurons are modulated by gaze fixations and saccades (Killian, Jutras, & Buffalo, 2012; Sobotka, Nowicka, & Ringo, 1997; also see Leonard et al., 2015; Hoffman et al., 2013). Complementary neuroimaging evidence in humans has shown that visual sampling (number of gaze fixations) is predictive of HC activity (Liu et al., 2017). In macaques and humans, damage to the HC/MTL results in altered visual exploration (Chau et al., 2011; Olsen et al., 2015) and HC responses in humans are predictive of subsequent gaze patterns that express memory retrieval (Hannula & Ranganath, 2009; Ryals et al., 2015). Such evidence collectively demonstrates that neural integrity and/or function within the HC/MTL is related to oculomotor *behavior.* However, it remains to be determined whether and how HC/MTL activity affects *neural activity* in the oculomotor system.

The goal of the present work was to leverage a computational modeling and neuroinformatics platform, The Virtual Brain (TVB; thevirtualbrain.org), to identify functionally relevant nodes and pathways from the HC/MTL that may culminate in responses in key regions within the oculomotor system that provide motoric (e.g., frontal

eye fields) and cognitive control (e.g., dorsolateral prefrontal cortex, anterior cingulate) of eye movements. Structural connectivity in the TVB model was defined through the CoCoMac database and using prior tractography data from macaques (Shen, Goulas, Gati, et al., 2015). Stimulation protocols were adapted from Spiegler, Hansen, Bernard, McIntosh, Jirsa (2016), in which TVB models were created to test how stimulation of distinct nodes resulted in the selective activation of distributed networks. Of particular interest was the observation that stimulation of the frontal eye field node elicited activity in a 'memory' network.

In the present work, subregions within the HC, as well as the ERC, perirhinal (areas 35 and 36), and parahippocampal (areas Tf and Th) cortices of the MTL, were each stimulated separately, and we examined how activity dissipated throughout the pre-identified anatomical pathways between the memory and oculomotor systems (Shen et al., 2016). Critically, we examined whether activity was ultimately observable in area 46 (dorsolateral prefrontal cortex; dlPFC), area 24 (anterior cingulate; ACC), and frontal eye fields (FEF) following HC/MTL stimulation. Responses of intermediary nodes were examined in cases where stimulation of a HC/MTL node did *not* culminate in observable responses in the oculomotor system, in an effort to highlight regions that may serve as a functional interface between the two systems.

Methods

A macaque network with 154 nodes (77 per hemisphere), as defined by the FV91 parcellation (Felleman & Van Essen 1991) from CoCoMac (cocomac.g-node.org) and a review of the extant literature, was used to define the structural connectivity. Self-connections were not included in the matrix. To find weightings between regions, we ran tractography on diffusion-weighted MR imaging data from 10 male adult macaque monkeys (9 *Macaca mulatta*, 1 *Macaca fascicularis*, age 5.8 ± 1.9 years), averaged the normalized number of streamlines across animals, and normalized the weights from 0 to 3 (Shen et al., 2015; Shen et al., in manuscript). Weights were normalized to 3 because when normalized to 1, simulated amplitudes would go over the activation threshold (see below) even without stimulation. For visualization on the F91 macaque surface, we used a triangulated cortex surface with 70078 nodes, with 34132 nodes in right side and 35946 nodes in the left. Simulations were performed using TheVirtualBrain software platform (thevirtualbrain.org). The dynamics of each node in the macaque network were given by the following generic 2-dimensional planar oscillator equation:

$$\begin{aligned}\dot{V}_i &= \tau(-fV_i^3 + eV_i^2 + gV_i + \alpha W_i + \xi \sum_{j=1}^{N} w_{ij} V_j(t - \Delta_{ij}) + \gamma I \\ \dot{W}_i &= \tau^{-1}(cV_i^2 + bV_i - \beta W_i + a)\end{aligned}$$

where the fast variable V represents mean subthreshold (local field potential) neural activity at node i, W is a slower timescale recovery variable; the differential time constants of V vs. W are controlled by the time scale separation parameter τ.
The global connectivity scaling factor ξ acts on all incoming connections to each node, which are also weighted individually by the connectivity weights matrix w (as described above). Exogenous stimulation currents of interest in the present study enter the system through the input variable I. Transmission between network nodes was retarded according to the conduction delays matrix $\Delta = L/v$, where L is a matrix of inter-regional tract lengths and v is axonal conduction velocity. As in Spiegler et al. (2016), cubic, quadratic, and linear coefficients for V and W were set such that the dynamics reduce to a classic Fitzhugh-Nagumo system. Additional model parameters are listed in Table 1.

Brain dynamics operate near criticality when at rest (Ghosh et al., 2008). When criticality is reached, the nodes will naturally oscillate with constant magnitude. Setting g to near criticality will make the node respond with a strong amplitude, and a longer lasting oscillation. If far from the critical point, the amplitude responses will be weak, slow, and fade quickly. If spreading within a chain, the excitation will decay quickly as it travels. Realistically, there will be re-entry points where the node is re-stimulated, making the excitation last longer and travel farther through the network (Spiegler et al., 2016). Following Spiegler et al. (2016), we tuned the model parameter such that the working point of each node was in a critical regime. The system of delay-differential equations shown above were solved numerically using a Heun Deterministic integration scheme, with step size dt=0.1 Simulations were run for 15000 ms, with stimulus onset starting at 10000ms to allow for settling of the initial transient resulting from randomly specified initial conditions. A repetitive, pulsed stimulation waveform was used, with a repetition period of 5000 and pulse duration of 100ms.

To create a more realistic model we stimulated V1 to find activation times of the following areas: V1, V2, V3, V4, middle temporal and medial superior temporal. We then compared the resulting activation times to available empirical data (Schmolensky et al., 1998) and adjusted ξ, g, v, and the stimulus weighting γ accordingly. Global coupling ξ was used and was set to 0.012 but values we tried ranged from 0.1 to 0.001. Axonal conduction velocities in the macaque brain are estimated to be in the range between 3-10 m/s (Girard, Hupé, Bullier, 2001; Caminiti et al., 2013). We therefore set conduction velocity v= to 8.2 m/s.

Stimulus weighting was set to gamma = 0.03; other values ranging from 0.01 to 0.1 were used in the testing process. The g parameter was set to -0.1 so it would be close to the critical point of 0. Parameters were varied to get biologically plausible activation times of V1 to the rest of the visual system. Activation times following V1 stimulation were aligned with what was observed in empirical data as presented in Schmolesky et al (1998), as shown in Table 2. Differences with empirical times (e.g., MST and FEF) may be due to the assumption used here of a single conduction velocity for all connections between nodes, and the fact that we do not consider the time a given region would take to process information before responses are generated throughout the broader network.

The same parameters were then used to stimulate the subregions of the hippocampus (CA3, CA1, subiculum, pre-subiculum, para-subiculum), enthorinal cortex (ERC), areas 35 and 36 of the perirhinal cortex (PRC), and areas Tf and Th of the parahippocampal cortex (PHC), to look for the activations of nodes whose pathways may serve to mediate the exchange of information between the memory and oculomotor systems (Shen et al., 2016). These nodes included areas V2, V4, 7a, granular insular cortex, anterior cingulate cortex , 46, 12, proisocortex, 5, 10, 11, orbitofrontal area 13, orbitofrontal area 14, 23, 25, 32,and 11. We further examined whether activation was observed in regions important for oculomotor guidance, including the dorsolateral prefrontal cortex (area 46), anterior cingulate cortex (area 24), and the frontal eye fields. To define our threshold for when nodes were considered active, we found the absolute maximum of each node during the period of 0-200ms before stimulation. We then examined when, following stimulation, activation of that node surpassed the baseline maximum, and considered this to be the activation time.

Results

HC Subregion Stimulation

Activation of the subiculum (S) resulted in observable responses throughout the rest of the HC/MTL (except for CA3). Responses were observed in orbitofrontal regions, which are intermediary between the HC and the oculomotor system, as well as in area 46 and 24, but no responses were observed in the FEF (Figure 1). Stimulation of CA3 resulted in largely similar activation patterns as stimulation to S, except that responses in each node were observed at consistently later times, and responses were not found in area 24 within the observed period. Stimulation of CA1 resulted in observable responses in all of the intermediary nodes, and ultimately within 46, 24, and FEF, in that order (Figure 2). Stimulation of CA1 resulted in relatively rapid responses that were observed in area 46 when compared to the timing of area 46 responses following stimulation of S or CA3. Stimulation of the pre-subiculum and para-subiculum resulted in similar patterns of observable responses to that of CA1 stimulation, however of all of the hippocampal subregions, stimulation of the pre-subiculum resulted in the earliest timing of responses observed in the three oculomotor regions of interest (46, 24, FEF). See Table 3 for all activation times.

MTL Stimulation

Stimulation of any of the broader regions within the MTL (ERC, 35, 36, Tf, Th) resulted in observable responses within each of the nodes, and within oculomotor regions 46, 24, and FEF. Stimulation of extra-hippocampal MTL regions resulted in faster responses in orbitofrontal regions compared to HC subregion stimulation. Stimulation of regions 35/36 and of Tf/Th also resulted in considerably earlier responses in 46, 24, and FEF, as well as in posterior parietal region 7a and regions V4 and V2 than what was observed with ER or HC subregion stimulation (with the exception of the pre-subiculum). Stimulation of the regions Tf/Th also resulted in relatively faster responses within the subregions of the HC compared to stimulation of ERC or perirhinal cortices. See Table 3 for all activation times.

Discussion

In the present work, we identified the relevant nodes by which information from the HC/MTL may be directed to regions within the oculomotor system. Although not considered in models of oculomotor control, the HC is nonetheless well connected anatomically to the oculomotor system through a set of polysynaptic pathways that span medial temporal, frontal, parietal, and visual cortices (Shen et al., 2016). As defined in the CoCoMac database, the ERC, PRC, and PHC cortices of the MTL are each directly connected to one or more regions within the oculomotor system, and the PRC and region Tf of the PHC are directly connected to the FEF. The TVB model used here to examine stimulation propagation of neural responses was based on the structural connectivity as defined in CoCoMac and supplemented by tractography data from macaques (Shen et al., 2015). Stimulation of regions within the HC/MTL resulted in observable responses in area 24 (ACC) and area 46 (dlPFC), which are important for the cognitive control of eye movements (Johnston & Everling, 2008). Stimulation of the presubiculum, parasubiculum, CA1, and each of the MTL regions, resulted in observable responses in the FEF, which plays a key role in the motor programming of eye movements (Hanes & Schall, 1996). Previous neuropsychological and neuroimaging findings have demonstrated a functional relationship between HC/MTL and oculomotor behavior (for review, see Hannula et al., 2010). The present work, in concert with these previous findings, suggests that information represented through the functions of the HC/MTL may directly influence ongoing neural activity of the oculomotor system, which is then manifested as changes in visual exploration behavior. The results here add to the growing call for a reconsideration of the neural regions that support oculomotor guidance (Shen et al., 2016), and for the examination of the influence of visual exploration behavior on memory function and neural responses in the HC/MTL (Liu et al., 2017; Voss et al., 2017).

Stimulation of the CA1 resulted in observable responses in the FEF, whereas stimulation of the CA3 did not. The lack of responses in the FEF following CA3 stimulation is perhaps not surprising, given that there are no known direct connections between the CA3 and the oculomotor regions investigated here; whereas direct connections have been observed from the CA1 to the ACC and DLPFC and were included in the present model. In prior anatomical studies with macaques, connections have not been observed from CA3 to the PRC or PHC (Aggleton, 2012), which would have otherwise provided an anatomical interface to regions of the oculomotor system. By contrast, there are considerable projections from the EC back to the CA3, and there are projections from the CA1 back to CA3 (and from CA3 back to the dentate gyrus) (for review, see Aggleton, 2012). This pattern of functional and anatomical interfaces between CA3 and CA1, and each with oculomotor regions, may align well with the purported representational functions of the CA1 and CA3 that have been discussed in the broader memory literature. The auto-associative network CA3 has been proposed to enable *pattern separation,* that supports the development of detailed representations that are distinct from others in memory (Yassa & Stark, 2011; Norman & O'Reilly, 2003). The projections from CA3 to CA1, and then from CA1 to beyond, are considered important for *pattern completion* in which information from the external world may be compared to existing memory

representations based on partial cue information, for the purpose of integration, or retrieval. Thus, information that is extracted from the visual world via gaze exploration may be bound across space and time via the auto-associative network of the CA3. Information represented by the CA3 would then likely only influence ongoing neural responses in the oculomotor system and gaze exploration behavior through its projections to, and subsequent cognitive operations within, CA1, as well as the broader MTL (Rolls, 2013).

The macaque literature shows that the subiculum has similar anatomical projections to those observed in the CA1 (Aggleton, 2012). In the model here, the subiculum is directly connected to the ACC and dlPFC, but not to the FEF. Although positioned as the main output of the hippocampus (O'Mara et al., 2001), stimulation of the subiculum did not result in observable responses within the oculomotor regions considered here. The subiculum is directly connected to the PRC, ERC, and PHC. In comparison to CA1, the tract lengths and weights are longer and weaker from the subiculum to each of these regions (Shen et al., 2015). A longer duration of stimulation, or multiple pulses of stimulation, in the subiculum, may have resulted in responses within the FEF, ACC, or dlPFC. Alternatively, stimulation of the subiculum may influence responses within regions of the broader oculomotor system that were not considered here. We did not include the subcortical routes by which the HC/MTL may interface, anatomically and functionally, with the oculomotor system, and the subiculum is the predominant source of HC projections to subcortical regions, including the thalamus and mammillary bodies (O'Mara, 2005; Saunders, Mishkin & Aggleton, 2005).

The subiculum, presubiculum, and parasubiculum mature earlier in the primate than other regions of the HC and the ERC, suggesting that these regions may subserve additional or different representational functions than the rest of the regions within the HC/MTL (Lavenex, Lavenex, & Amaral, 2004; Lavenex, Lavenex, 2013). Studies of selective subiculum lesions in rats using the Morris Water Maze showed a pattern of behavior distinct from rats that had selective lesions to the CA fields of the hippocampus (Morris et al., 1990): whereas HC-lesioned rats circled the edge of the platform in a stereotyped fashion, the subiculum-lesioned rats showed a random exploration of the pool. The findings suggested that whereas the HC forms a flexible representation of the spatial relations among cues in the environment, the subiculum may use such information to support the precise localization of, and directional heading towards, a target of interest (Morris et al., 1990; O'Mara 2005). To the best of our knowledge, complementary lesion studies have not been performed in primates; however, recordings of single neurons in primates have shown 'spatial view' cells in the CA1 that fire in response to where the monkey is looking in space, even when the view is obscured (Rolls & O'Mara, 1995), and head direction cells are evident within the presubiculum (Robertson et al., 1999), which align with the representational specificity suggested by the lesion work. Here, stimulation of the presubiculum resulted in rapid, observable responses within the FEF. Accurate target selection by the eyes may be supported by information regarding head direction, including information from the presubiculum, which culminates in the FEF.

Functional responses in the subicular complex, which includes the presubiculum and parasubiculum, have been routinely observed in human neuroimaging studies of scene perception, construction, and memory (Zeidman & Maguire, 2016), prompting the suggestion that the pre- and para-subiculum, due to its anatomical positioning as the primary target of information from the parieto-medial temporal pathway, may be preferentially positioned to represent scene layouts in a holistic fashion (Dalton & Maguire, 2017). Notably, however, the relative timing of the responses observed here following stimulation of pre- versus parasubiculum differed: stimulation of presubiculum resulted in considerably faster responses observed in the ACC, dlPFC, and FEF. The efferent targets of these regions in non-human primates are similar (Christiansen et al., 2016), and both regions are directly connected to dlPFC, and neither is directly connected to either the ACC or FEF, in our model here. However, in rats, the anatomy and connectivity of the parasubiculum has been shown to be uniquely different from that of surrounding regions (Tang et al., 2016). Cells within the parasubiculum of the rat have demonstrated grid, border, and head-direction responses (Tang et al., 2016; Boccara et al., 2010), and through its outputs that predominantly target the ERC, the parasubiculum may provide information that supports the grid cell mapping of the ERC (Tang et al., 2016; Peyrache, Schieferstein, Buzsaki, 2017). Based on these properties, Tang et al. (2016) suggested that the parasubiculum may function as a 'pointer' by providing online spatial information of the agent's location in space, rather than having a role in the long-term storage of spatial information. In this regard, the slower timing of activity from the parasubiculum to the FEF relative to stimulation of the presubiculum may reflect distinct, underlying functional specializations that support ongoing visual exploration. While the parasubiculum may note the overall spatial layout that slowly changes across time, the presubiculum may use this representation of spatial layout for precise targeting of visual objects that are selected for exploration through successive gaze fixations by the oculomotor system. However, these functional distinctions are speculative, and remain to be tested in non-human and human primates.

In contrast to the differential patterns of responses following stimulation of the subicular complex and CA fields, stimulation of each of the MTL cortices resulted in observable responses in each of the three oculomotor regions considered here. Areas 35/36 (and Tf) have direct connections to the FEF, and stimulation of these areas resulted in comparatively faster responses observed in the FEF than stimulation of other HC/MTL regions, aside from the presubiculum. The MTL cortices may serve as intermediary nodes that permit the (relatively rapid) transfer of information from HC subregions to the oculomotor system. Each region may provide unique representational content that influences ongoing visual exploration in a top-down manner.

Evidence from non-human primates, and neuropsychological and neuroimaging studies with humans, have been used in support of the idea that the PRC mediates lasting representations of complex conjunctions of features into distinct, coherent objects due to its position at the apex of the ventral visual processing stream (Graham, Barense & Lee, 2010; Erez, Cusack, Kendall & Barense, 2016). By contrast, damage to Tf/Th in macaques results in differentially greater memory impairments for object location as compared to the objects themselves, as well as impairments in memory for the flexible,

relational, configuration of objects (Alvarado & Bachevalier, 2005). Some neurons in the macaque PHC have receptive fields that map to locations of stimuli in the periphery of the gaze, and some PHC neurons respond to the position of the eyes (Sato & Nakamura, 2003). When combined with human neuroimaging studies that show PHC responses to the spatial and non-spatial (semantic) context of objects (Diana, Yonelinas, Ranganath, 2012), such findings suggest a role for the PHC in representing information regarding the broader spatial or cognitive context of the environment (Eichenbaum, Yonelinas, Ranganath, 2007).

The ERC, in primates and in humans, receives input through two functional pathways from PRC (to anterolateral ERC) and PHC (to posteromedial ERC) (Naber et al., 1997; Suzuki & Amaral, 1994, Maass et al., 2015), and in turn, project to distinct areas of the CA1, pre-, and para-subiculum (Witter, 2017; Caballero-Bleda & Witter, 1993). Research regarding the functional significance of the distinct regions of the ERC in human and non-human primates is just emerging; however, in primates, cells in posterior ERC code for saccade direction during visual exploration (Killian, Potter, Buffalo, 2015). Eyetracking research with older adults shows that volumes within the alERC significantly predicted viewing behavior that reflected processing of the spatial arrangement of an object's component features (Yeung et al., 2017). Such findings suggest that regions within the ERC may provide information regarding the spatial arrangement of features within an object and the relative positioning of objects in space. More broadly, ERC lesions in primates disrupt the relational organization of items in memory, including spatial and non-spatial (i.e., hierarchical) relations among objects (Buckmaster, Eichenbaum, Amaral, Suzuki & Rapp, 2004).

All together, prior literature suggests that the PRC may provide lasting information regarding the features of objects, the PHC may provide information regarding the surrounding (spatial or non-spatial) environment, and the ERC may provide information regarding the relative spatial arrangements of features within objects, and the relative spatial (and non-spatial) arrangements among objects within the environment. These MTL regions may collectively serve as the functional interface to communicate information maintained within lasting representations in order to accurately, and rapidly, prioritize gaze fixations to areas of interest in the visual world. Moreover, the HC/MTL regions may serve to continually bind and update information regarding the relative arrangements within and among objects across gaze fixations (Liu et al., 2017). In this manner, visual exploration can inform memory, and memory can influence oculomotor guidance, in a cyclical fashion.

Responses emanating from HC/MTL stimulation sites that ultimately resulted in observable responses in the ACC, dlPFC, and FEF traversed through multiple frontal, visual, and parietal nodes. This suggests that there may be multiple routes by which information maintained in memory may influence ongoing visual exploration. In the cases in which stimulation of a HC subregion (CA3 and subiculum) did *not* result in observable responses within one or more of the oculomotor regions examined here, responses were also not observed in parietal areas 5 and 7a, posterior cingulate area 23, and V4. Area 5 has been implicated in mapping visual and body-centered frames of

reference to support visually-guided reaching (Seelke et al., 2012). Cells in area 7a are responsive to eye position and saccades (Bremmer, Distler, Hoffman, 1997). Stimulation of area 7a results in saccadic eye movements (Shibutani, Sakata, Hyvarinen, 1984), and this region may have a role in representing spatial positions across multiple frames of reference (eye, body, head; Andersen, Essick, & Siegel, 1985; Snyder, Grieve, Brotchie & Andersen, 1998). The posterior cingulate has been identified as part of the human default mode network (Buckner, Andrews-Hanna, Schacter, 2008) that is active during internally directed cognitions, including recalling the past and imagining the future (Addis et al., 2007). The posterior cingulate is functionally correlated with the HC/MTL in macaques as well as in humans, suggestive of a homologous default mode network in primates (Vincent, Kahn, Van Essen & Buckner, 2010). Neurons in V4 of the macaque are known to integrate visual and oculomotor information, and V4 neurons show remapping of space towards that of a saccade target, thereby bridging the spatial representations pre- and post-saccade (Neupane, Guitton, Pack, 2016). All together, this may suggest that V4, parietal regions, and the posterior cingulate may be important functional interfaces by which internal representations from the HC/MTL are used to support the spatial mapping and planning of future eye movements.

The present findings, and the resulting interpretations given above, provides a set of predictions regarding the informational content and the functionally relevant nodes that transmit information in order to influence oculomotor guidance. These predictions can then be tested in in primates and in humans, with intracranial recordings or noninvasively with neuroimaging measures that consider the timing of neural responses and the phase coupling of neural oscillations across regions of interest. Note that while we have commented on the *relative* timing (faster/slower; earlier/later) of observable responses across stimulation sites, we do not wish to make claims regarding the *absolute* timing of any of the observed responses, as the simulations here may not be reflective of the specific timing of the systems. One reason for this is that the model used here assumes a single conduction velocity for each pairwise connection (and all local nodes have the same architecture), whereas in reality white matter fascicles contain axons with a range of calibers, and therefore a range or distribution of conduction velocities an associated delays. A second is that our simulations did not consider integration time; i.e. the amount of time it would take each region to process the relevant incoming information before passing it along as action potentials. In this sense, the stimulus-response characteristics studied here occur within a passive system.

Further questions raised by our findings include where and when distinct types of information from the HC/MTL are integrated to influence visual exploration, including saccade timing and the selection of targets that are prioritized for foveation. Multiple memory 'signals' are evident within patterns of gaze fixations, including memory for single stimuli (Althoff & Cohen, 1999; Smith & Squire, 2017) memory for the relative spatial relations within objects (Yeung et al., 2017), and memory for the relative spatial positions among objects (Ryan et al., 2000; Smith, Hopkins & Squire, 2006), and inter-object associations (Hannula et al., 2007). Dissociations in these memory signals can be observed within single gaze patterns in neuropsychological cases (Ryan et al., 2000; 2003). Alternatively, the functionally distinct representations that are supported by the

HC/MTL may not actually be integrated within the oculomotor system; rather, each may guide visual exploration at different moments, as time unfolds, as new information in the visual world is sampled, and as task demands are enacted and ultimately met.

A network analysis approach, such as the one used here, can be instrumental in revealing the broad dynamics by which behavior is governed. Evaluation of the functional dynamics, in the context of known anatomical interfaces, provides a more comprehensive understanding of how information may be exchanged between the memory and oculomotor systems, as well as the broader function of each system (Mišić, Goñi, Betzel, Sporns, & McIntosh, 2014; Vlachos, Aertsen, & Kumar, 2012). The present work reveals a number of functionally relevant nodes and pathways by which information from the HC/MTL may influence neural responses within the oculomotor system, and guide ongoing visual exploration. Neurophysiological recordings, alongside neuroimaging and neuropsychological studies, across species, provide important information regarding the representational content that is supported by distinct regions of the brain. However, the relative timing by which activity traverses within the broader network may speak to the functional relevance of such representational content in influencing broader aspects of behavior. Here, the patterns of observable responses, and the timing by which stimulation of distinct regions of the HC/MTL culminate in responses in regions within the oculomotor system, suggest that memory for objects may provide rapid guidance for gaze prioritization and selection, while memory for relative spatial positions in the environment may provide accurate targeting of objects for foveation. These findings call for a reconsideration of the neural architecture that supports oculomotor guidance, and suggest that the HC/MTL may provide important information to guide visual exploration across time.

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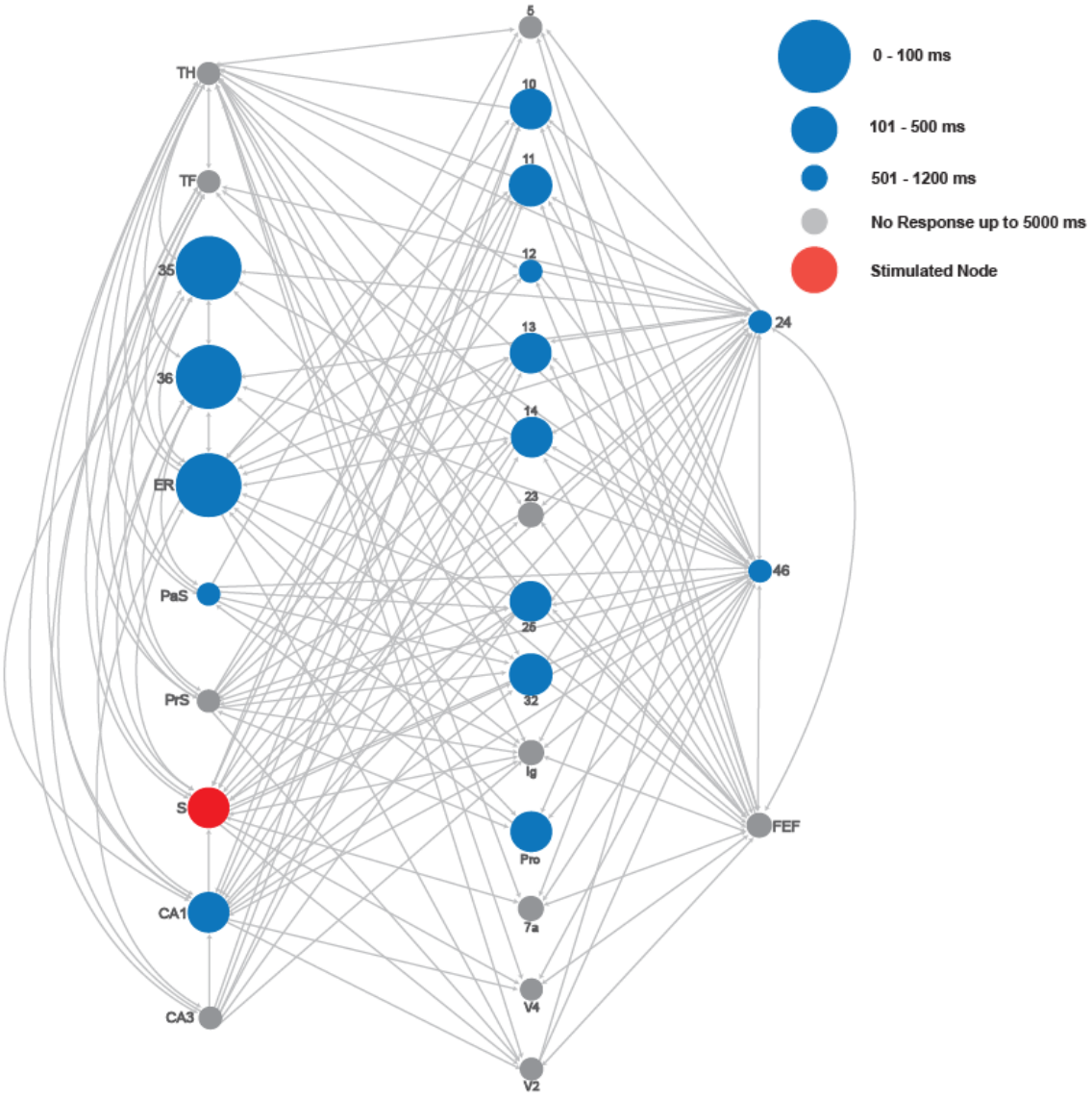
Legends

Figure 1. Stimulation of the subiculum (red circle) resulted in observable responses (blue circles) in multiple HC/MTL nodes, intermediary nodes, and areas 24 (ACC) and 46 (dlPFC), but not in the frontal eye fields (FEF). Size of the circles scale with elapsed time prior to an observed response. Grey circles note no observed response in the node. Grey lines denote direct connections between nodes.

Figure 2. Stimulation of the CA1 (red circle) resulted in observable responses (blue circles) in multiple HC/MTL nodes, intermediary nodes, and in regions governing oculomotor control, including the frontal eye fields (FEF). Size of the circles scale with elapsed time prior to an observed response. Grey lines denote direct connections between nodes.

Figure 1.


0 - 100 ms
101 - 500 ms
501 - 1200 ms
No Response up to 5000 ms
Stimulated Node
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CA1
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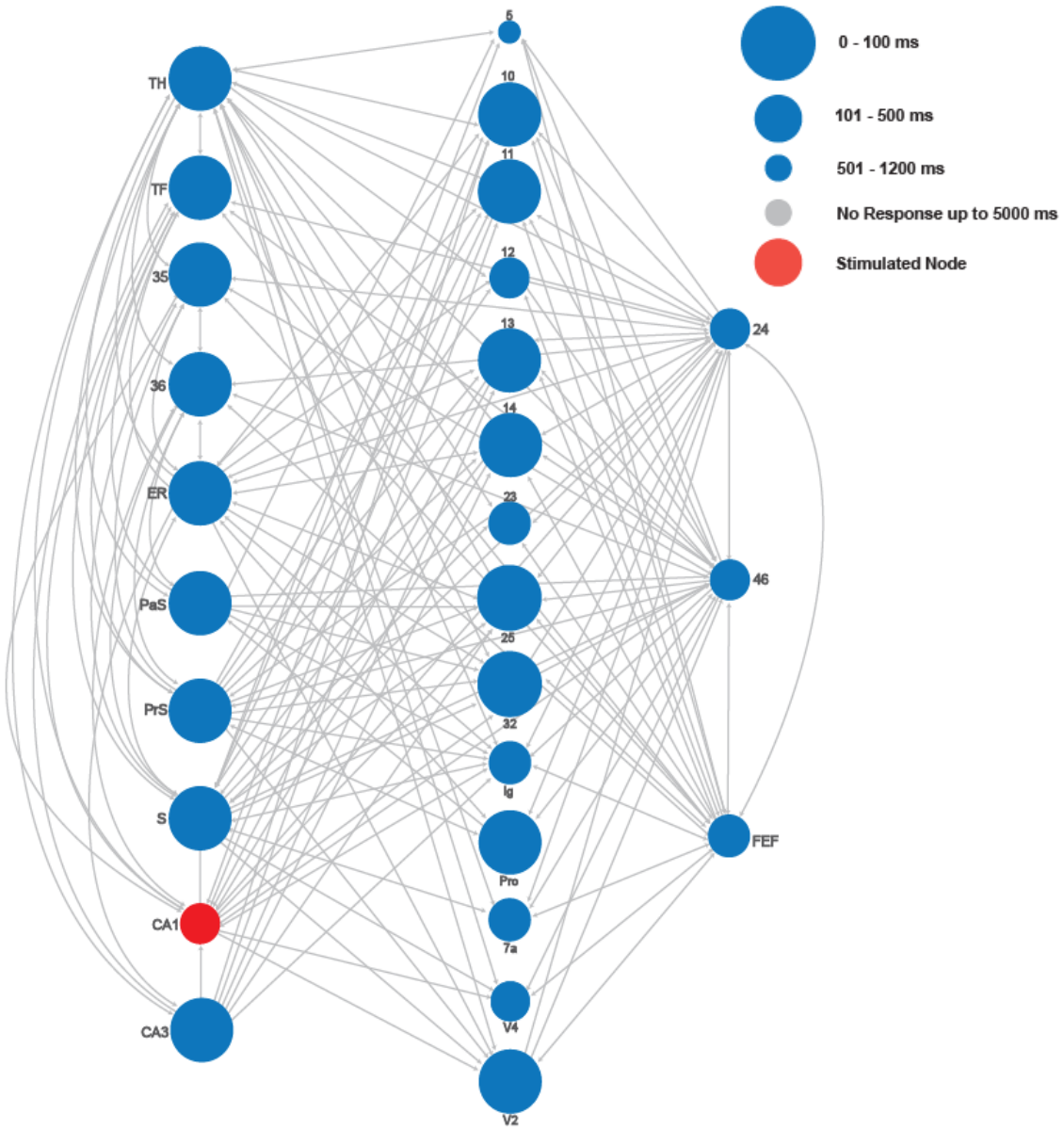
Ig
Pro
7a
V4
V2
24
46
FEF

Figure 2.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No Response up to 5000 ms
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Table 1. 2d oscillator model parameters used in simulation based of the model used by Spiegler et al. (2016).

Parameter	Value	Description
d	0.07674	Temporal scale factor
τ	1	Time-scale hierarchy parameter
f	1	Coefficient for fast variable cubic self-feedback term
e	0	Coefficient for fast variable quadratic self-feedback term
g	-0.1	Coefficient of fast variable linear self-feedback term
α	1	Coefficient for linear input term from slow to fast variable
γ	1	Additional scaling parameter for fast variable constant input I and long-range inputs
c	0	Coefficient for quadratic input term from fast variable to slow variable
b	-12.3038	Coefficient for linear input term from fast variable to slow variable
β	0	Coefficient for slow variable linear self-feedback term
a	0	Slow variable constant input term
I	0	Fast variable constant input term

Table 2. V1 stimulation and resulting activation times. Conduction velocity was set at 8.2 m/s and global coupling was set at 0.01196.

Empirical Values	**Mean ± STD response latencies relative to V1 (ms)** (Schmolesky et al, 1998)	**Activation time (ms)**
V1	0	0
V2	16 ±21.1	4
V3	6 ±10.7	4
V4	38 ±23.4	8
MT	6 ±10.7	9
MST	8 ±16.1	37 (lateral)
		47 (dorsal)
FEF	9 ±13	99

Table 3. Activation times (ms) in left hemisphere following stimulation of hippocampal subfields and medial temporal lobe regions. S= subiculum, PrS = pre-subiculum, PaS=para-subiculum; ERC = enthorinal cortex; 35/36 = perirhinal cortex; Tf/Th = parahippocampal cortex. *0* = stimulation onset; N/A = no response observed.

		Stimulated Node									
		CA3	**CA1**	**S**	**PrS**	**PaS**	**ERC**	**35**	**36**	**TF**	**TH**
Observation Node	**CA3**	*0*	2	N/A	23	58	59	47	24	3	6
	CA1	59	*0*	281	22	35	35	7	5	2	4
	S	48	22	*0*	22	34	47	11	8	3	4
	PrS	71	34	N/A	*0*	45	71	13	11	4	3
	PaS	257	21	559	23	*0*	46	9	5	2	21
	ERC	4	4	4	47	70	*0*	2	2	6	7
	35	68	6	21	59	115	2	*0*	1	7	12
	36	82	5	11	10	9	2	2	*0*	5	8
	TF	106	3	N/A	5	68	10	11	8	*0*	3
	TH	8	5	N/A	3	4	10	23	10	3	*0*
	7a	N/A	434	N/A	469	1074	1146	73	49	50	131
	V4	N/A	116	N/A	163	534	747	200	118	8	34
	V2	465	70	N/A	80	127	188	24	13	8	6
	Ig	N/A	397	N/A	505	N/A	44	22	21	244	360
	Pro	186	59	139	9	68	5	5	4	9	10
	5	N/A	516	N/A	374	1331	891	97	61	143	131
	10	328	74	190	97	395	10	9	8	14	45
	11	348	84	210	85	348	8	7	6	32	70
	12	841	188	572	120	500	80	19	9	37	54
	13	268	73	154	95	325	8	7	6	24	44
	14	502	74	306	108	349	47	8	7	24	56
	23	N/A	410	N/A	14	957	471	62	39	94	83
	25	352	84	421	84	132	59	10	7	9	11
	32	538	85	352	120	361	49	9	8	14	45
	24	N/A	214	1171	97	469	143	35	23	38	38
	46	795	120	654	24	317	83	12	10	23	15
	FEF	N/A	340	N/A	121	772	222	36	33	93	109