

An Anatomical Interface between Memory and Oculomotor Systems

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Abstract

■ Visual behavior is guided by memories from prior experience and knowledge of the visual scene. The hippocampal system (HC), in particular, has been implicated in the guidance of saccades: Amnesic patients, following damage to the HC, exhibit selective deficits in their gaze patterns. However, the neural circuitry by which mnemonic representations influence the oculomotor system remains unknown. We used a data-driven, network-based approach on directed anatomical connectivity from the macaque brain to reveal an extensive set of polysynaptic pathways spanning the extrastriate, posterior parietal and prefrontal cortices that potentially mediate the exchange of in-

formation between the memory and visuo-oculomotor systems. We additionally show how the potential for directed information flow from the hippocampus to oculomotor control areas is exceptionally high. In particular, the dorsolateral pFC and FEF—regions known to be responsible for the cognitive control of saccades—are topologically well positioned to receive information from the hippocampus. Together with neuropsychological evidence of altered gaze patterns following damage to the hippocampus, our findings suggest that a reconsideration of hippocampal involvement in oculomotor guidance is needed. ■

INTRODUCTION

Saccadic eye movements support the active exploration of the visual environment by placing the high-acuity fovea on objects of interest. Saccades are guided by bottom-up elements of the visual environment and by top-down cognitive factors such as attention (Findlay, 2005) and working memory (Theeuwes, Belopolsky, & Olivers, 2009). The additional guidance of saccades by mnemonic information, typically conceptualized as long-term memory, has been consistently documented in both humans and macaques. For example, humans and macaques make more gaze fixations on novel items than on items that have been encountered (Ryan, Hannula, & Cohen, 2007; Zola et al., 2000) and are quicker to fixate a target within a scene on subsequent presentations of the same scene (Chau, Murphy, Rosenbaum, Ryan, & Hoffman, 2011). Moreover, gaze is initially and preferentially directed toward an area of a scene that has changed from a previous presentation (Ryan & Cohen, 2004). These findings suggest that memory of a previously viewed item or scene can guide saccades for the purposes of extracting information from the visual environment (Brockmole & Henderson, 2008; Castelano & Henderson, 2007; Loftus & Mackworth, 1978; Parker, 1978). Consequently, eye tracking has been widely used to probe the integrity of memory in multiple populations. For example, individuals who have amnesia following damage to the hippocampal system (HC) show selective deficits in gaze patterns: Compared with healthy

individuals, memory for the relationships among items is not evident in their visual behavior (Ryan, Althoff, Whitlow, & Cohen, 2000), even over brief delays (Warren, Duff, Tranel, & Cohen, 2011; Ploner et al., 1999).

The neural instantiation of saccade guidance by attention (Bisley & Goldberg, 2010; Awh, Armstrong, & Moore, 2006; Corbetta, 1998) and working memory (Funahashi, 2015; Ikkai & Curtis, 2011; Johnston & Everling, 2008) has been well established in human and nonhuman primates, indicating a highly overlapping frontoparietal network of regions responsible for integrating bottom-up and top-down information for guiding visual behavior. Despite the wealth of behavioral evidence for the guidance of saccades by mnemonic information and observations of altered gaze patterns in amnesic individuals (for review, see Meister & Buffalo, 2015; Hannula et al., 2010), the neural circuitry that supports memory-guided visual behavior remains unknown. Much research is focused on the critical role of HC and its extended system for the formation of memories (Opitz, 2014; Rugg & Vilberg, 2013; Ranganath, 2010). Decades of research have, in parallel, led to a thorough understanding of the network of structures involved in oculomotor control (Gaymard, 2012; Johnston & Everling, 2008; Sparks, 2002). However, no study has yet to explicitly examine the neural circuitry by which mnemonic representations influence the oculomotor system.

Given the extensive interconnections of the primate brain, the task of determining how information may be routed from the HC to the oculomotor system is nontrivial. This issue is complicated by the fact that no direct anatomical

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connections are known to exist between the HC system and the oculomotor structures that control saccade initiation (i.e., FEF and the superior colliculus [SC]) as reported in the macaque literature (Stephan et al., 2001). A large number of polysynaptic pathways therefore exist to potentially serve the flow of information from HC to oculomotor structures. Knowledge of large-scale anatomical connectivity in humans is additionally limited by the inability to infer the directionality of fiber tracts from noninvasive diffusion-weighted imaging techniques. One approach for addressing these challenges is network analysis and the application of graph theoretic tools (Bullmore & Sporns, 2009). For example, functionally specialized subnetworks can be inferred by applying clustering-type algorithms on anatomical networks (Shen et al., 2012; Chen, He, Rosa-neto, Germann, & Evans, 2008; Hilgetag, Burns, O'Neill, Scannell, & Young, 2000). Regions and pathways that support the integration of information can also be identified (van den Heuvel & Sporns, 2011; Sporns, Honey, & Kötter, 2007) and, if directionality of connections is known, the flow of information processing can be inferred (Rubinov & Sporns, 2010). Here, we used network analysis on a large-scale directed network representation of the macaque visual, oculomotor, and memory systems to determine (1) how information may be exchanged between the memory and visuo-oculomotor systems and (2) how mnemonic representations specifically from the HC may directly guide the selection of saccade targets.

METHODS

Anatomical Connectivity Matrix

The CoCoMac database of anatomical tract tracing experiments in macaques (cocomac.g-node.org; Bakker, Wachtler, & Diesmann, 2012; Kötter, 2004; Stephan et al., 2001) was queried using previously described methods (Bezgin, Vakorin, van Opstal, McIntosh, & Bakker, 2012). The result was an anatomical connectivity matrix specifying both the afferent and efferent connections of 75 ROIs (see Table 1 and Figure 1A). An additional comprehensive literature search (limited to the *Macaca* genus) was performed, and 47 connections were manually added to the matrix. Most of these manual additions involved subregions of the BG, medial temporal lobe, and the SC (Figure 1A, red). If information about the connectivity between two regions was not available in CoCoMac or after a thorough literature search, the connection was considered to be absent.

The statistical significance of network measures can be determined by comparing the observed measure to measures obtained from a set of null hypothesis networks that preserve basic network characteristics that may have a large influence on the measures themselves (Rubinov & Sporns, 2010). Using the *randmio_dir_connected* function from the Brain Connectivity Toolbox (BCT; <https://sites.google.com/site/bctnet/>), a null distribution of 1000 randomized networks was created by randomly rewiring the connectivity matrix while preserving the in- and out-degree distribu-

tions (Maslov & Sneppen, 2002). All data analyses were repeated on this set of null networks.

Data Analysis

Fruchterman–Reingold Layouts

The Fruchterman–Reingold layout (FRL) from the force-directed graph drawing class of algorithms was applied to the anatomical network (Fruchterman & Reingold, 1991). Founded in physical principles, force-directed drawing algorithms ensure that vertices (i.e., ROIs) connected by edges (i.e., connections) are drawn next to each other while minimizing clustering. Initial positions of the vertices were randomized, resulting in variable layouts across iterations. One thousand FRLs were therefore generated to determine consistency between layouts. The resulting FRLs translate the three-dimensional anatomical connectivity of the brain onto two-dimensional space and capture network symmetry where possible. One hundred FRLs of each randomized network were additionally generated, for a total of 100,000 FRLs of null networks.

Stream Assignments

The extent to which the anatomical network could be divided into oculomotor and nonoculomotor processing streams was assessed by employing a data-driven approach previously described by Bezgin et al. (2014). Briefly, the center of mass for each FRL was determined and a vector was then rotated around the center of mass in a stepwise fashion. At each step, a similarity measure was calculated based on the Mahalanobis distance (Mahalanobis, 1936) between all points on one side of the vector and each of the points on the other side. The optimal stream separation was taken as the step at which the mean distance was minimal. This method segregates the network based on connectional patterns, such that the symmetry of connections within and across streams is maximized. This symmetry does not impose a prespecified number of regions to either stream (i.e., the two clusters do not have to be equal in size) but instead attempts to maximize the number of connections within streams and minimize the number of connections across streams.

A stream assignment index was computed to describe the consistency of node assignments across the set of FRLs. The assignment index for each node was determined relative to a reference node. For any given node:

$$\text{Stream assignment index} = \frac{(\text{no. appearances in reference node stream} - \text{no. appearances in opposite stream})}{\text{total no. FRLs}}$$

The stream assignment index therefore ranged from -1 to 1 such that consistent assignment to the opposite or reference streams approached -1 or 1 , respectively.

Table 1. ROIs and Their Abbreviations

<i>Abbreviation</i>	<i>Region</i>
29	Area 29
30	Area 30
35	Area 35
36	Area 36
3a	Area 3a
45	Area 45
46	Area 46
6	Area 6
7a	Area 7a
7b	Area 7b
9	Area 9
ACC	Anterior cingulate cortex
AD	Anterodorsal nucleus
AITd	Anterior inferotemporal area (dorsal)
AITv	Anterior inferotemporal area (ventral)
AM	Anteromedial nucleus
AV	Anteroventral nucleus
CA1	CA1 subfield of Ammon's horn
CA3	CA3 subfield of Ammon's horn
Cd	Caudate
CITd	Central inferotemporal area (dorsal)
CITv	Central inferotemporal area (ventral)
CL	Central lateral nucleus
DG	Dentate gyrus
DP	Dorsal prelunate gyrus
ER	Entorhinal cortex
FEF	Frontal eye field
FST	Floor of superior temporal sulcus
GPe	Globus pallidus, external
GPi	Globus pallidus, internal
Id	Dysgranular insula
Ig	Granular insular cortex
LGN	Lateral geniculate nucleus
LIP	Lateral intraparietal area
MD	Mediodorsal nucleus
MDP	Medial dorsal parietal area
MIP	Medial intraparietal area
MSTd	Medial superior temporal area (dorsal)

Table 1. (continued)

<i>Abbreviation</i>	<i>Region</i>
MSTl	Medial superior temporal area (lateral)
MT	Middle temporal area
PaS	Parasubiculum
PCC	Posterior cingulate cortex
oiPFC	Orbitoinferior prefrontal cortex
olPFC	Orbitolateral prefrontal cortex
omPFC	Orbitomedial prefrontal cortex
vlPFC	Ventrolateral prefrontal cortex
PHC	Parahippocampal cortex
PIP	Posterior intraparietal area
PITd	Posterior inferotemporal area (dorsal)
PITv	Posterior inferotemporal area (ventral)
PO	Parietal-occipital area
Pro	Proisocortex
PrS	Presubiculum
Pu	Putamen
Pul	Pulvinar
S	Subiculum
SCd	Superior colliculus, intermediate and deep layers
SCs	Superior colliculus, superficial layers
SEF	Supplementary eye field
Snc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
STPa	Superior temporal polysensory area (anterior)
STPp	Superior temporal polysensory area (posterior)
TF	Temporal area TF
TH	Temporal area TH
V1	Visual area 1
V2	Visual area 2
V3	Visual area 3
V3A	Visual area 3A
V4	Visual area 4
V4t	V4 transitional area
VIP	Ventral intraparietal area
VOT	Ventral occipitotemporal area
VP	Ventral posterior area

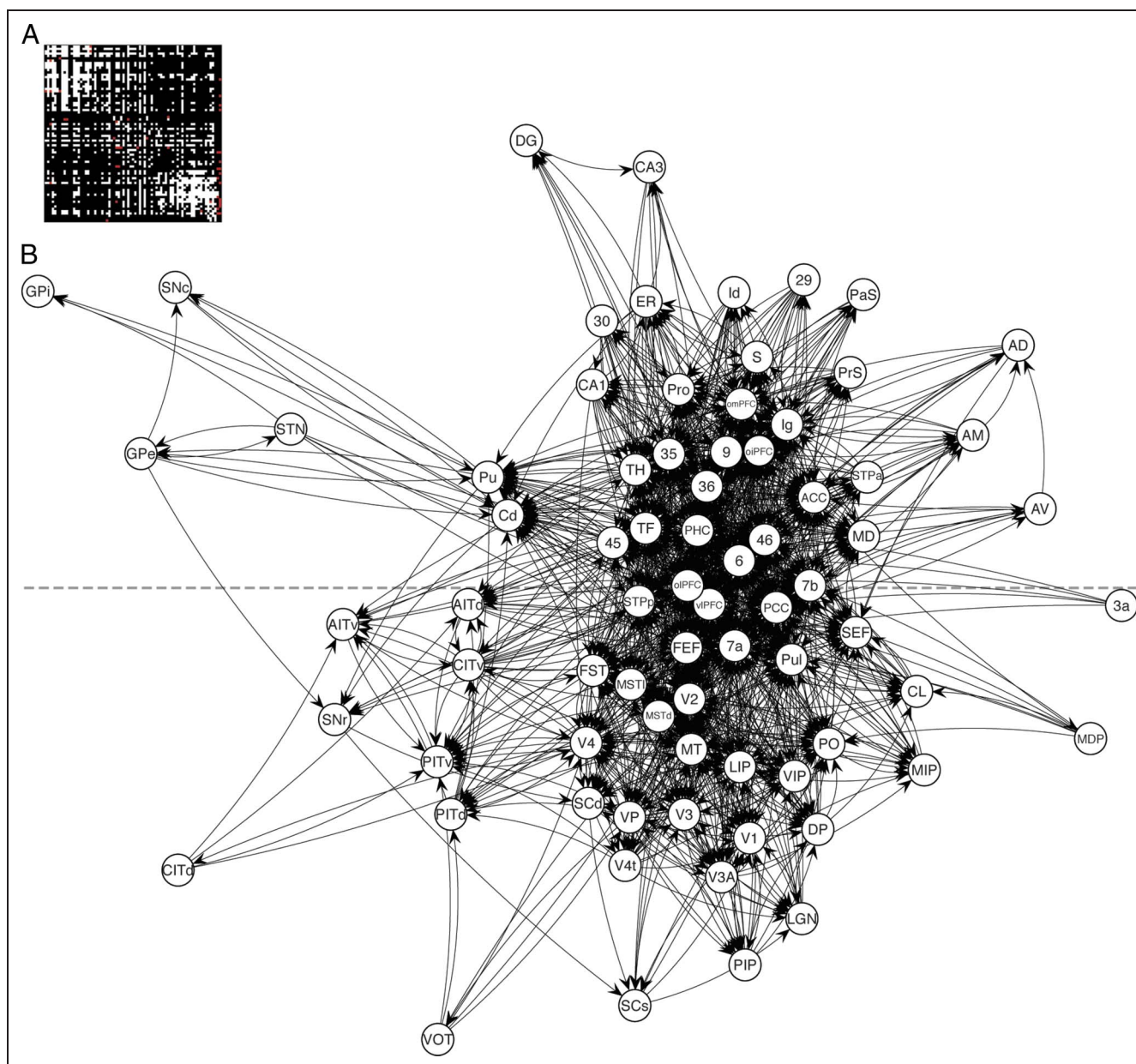


Figure 1. Oculo-memory anatomical network of the macaque. (A) Anatomical connectivity matrix consisting of 75 ROIs from visual, oculomotor, and memory systems. White/red = present connection; black = absent connection. Additions from a manual literature review indicated in red. Node ordering is the same as in Figure 2A. (B) An example FRL of the anatomical network, chosen for its characteristic layout (appearing 24 times out of 1000 FRLs). Dashed gray line depicts the maximum symmetry line that splits the network into two symmetric streams composed of regions subserving (i) visual and oculomotor functions (bottom) and (ii) memory functions (top). See Table 1 for ROI names and their abbreviations.

To quantify the connectivity of each node across streams, the distance of each node from the symmetry line was computed between the orthogonal projection of each node to the split vector and normalized by the maximal distance detected within each FRL. The resulting distance values ranged from 0 to 1 in arbitrary units.

Modularity Partitioning

To validate the stream splitting approach, the connectivity matrix was additionally subjected to a more commonly used community detection algorithm (Blondel,

Guillaume, Lambiotte, & Lefebvre, 2008). Using the *community_louvain* function from the BCT, modules were detected by optimizing the resolution parameter (γ) to achieve the most consistent partitioning having the highest modularity index (Q). This algorithm subdivides the network into groups of nodes with maximal within-group connections and minimal between-group connections. Because the number of modules is not specified a priori, this algorithm provides an alternative data-driven segregation of the network into local communities for comparison with our stream separation approach.

Using the detected community structure, the participation coefficient (BCT function *participation_coef*) of each node was determined to describe the distribution of each node's connections to nodes in other modules (Guimerà & Nunes Amaral, 2005). A coefficient approaching 1 indicates that the connections are uniformly distributed to other modules, whereas values close to 0 indicate that a node's connections are mostly within its own module.

RESULTS

Identifying Anatomical Networks that Support Functional Systems

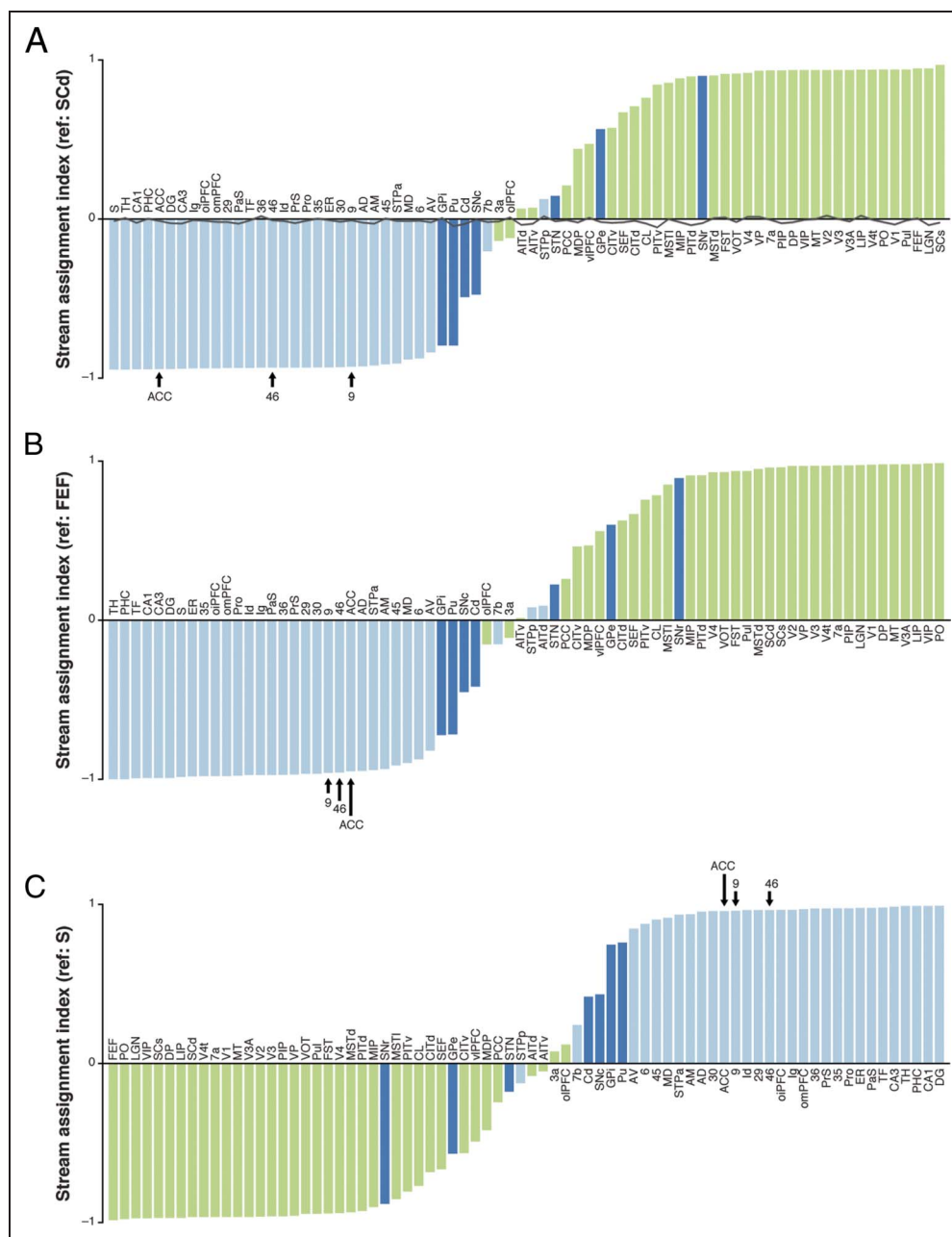
We generated a matrix describing the anatomical connectivity of 75 ROIs by querying the CoCoMac database of macaque axonal tract-tracing studies (Bakker et al., 2012; Stephan et al., 2001). The resulting matrix was a binary and directed intrahemispheric network of cortical and subcortical ROIs known to serve visual, oculomotor, and memory functions (Figure 1A). The network had 1494 directed connections, exhibiting 26.9% of all possible connections. To determine the extent to which the topology of the densely connected anatomical network supports the memory and oculomotor functions of interest, a data-driven approach was used to separate the anatomical network into two functionally specialized streams (Bezgin et al., 2014). First, the connectivity matrix was iteratively subjected to a force-directed drawing algorithm to produce 1000 FRLs (Fruchterman & Reingold, 1991). Using the FRL method, the anatomical network is depicted as a graph, with ROIs represented as vertices and the connections between them as edges. The graph is treated as a physical system whereby the vertices are initially placed randomly in 2-D space. Pairs of vertices connected by edges are given both attractive and repulsive forces, whereas vertices without connecting edges are only repelled from one another. The system then moves to a minimal energy state, resulting in a force-directed layout. FRLs have the added advantage of maximized symmetry and consistent edge lengths. In the context of our network, ROIs that are anatomically connected and especially those that have common connections with other ROIs are pulled closer together whereas those that are not connected and do not share common connections are repelled further apart. Two layouts were consistently detected, one of which is presented in Figure 1B. We took advantage of the symmetry inherent in the FRLs to determine how the ROIs of our anatomical network would cluster into two groups (i.e., processing streams). Each FRL was therefore subjected to a stream-splitting procedure that maximized the symmetry of the graph as indicated by the dashed lines in Figure 2. These examples illustrate how ROIs were generally clustered into what we labeled as either (1) a “visuo-oculomotor” stream composed of striate and extrastriate cortex, inferotemporal and intraparietal areas, as well as FEF and SC (Figure 1B, bottom) or (2) a “memory” stream composed of HC subregions, as well as

areas of the medial temporal lobe and pFC (Figure 1B, top). To assess the consistency of these stream assignments, each ROI's stream assignment index was quantified relative to a reference ROI. In this case, we chose the intermediate and deep layers of SC (SCd) as the reference point for the oculomotor stream because of its well-established role in saccade initiation (Sparks, 2002). An index approaching 1 indicates a consistent assignment with the SCd stream, whereas an index approaching -1 indicates a consistent assignment with the other stream. Figure 2A illustrates how most ROIs were assigned with high consistency to one or the other stream. As expected, the FEF, superficial layers of the SC, and lateral intraparietal area (LIP) were consistently assigned to the same stream as SCd ($\geq 93.8\%$ of FRLs). Similarly, the subregions of the HC (subiculum [S], CA1, CA3, dentate gyrus, and entorhinal cortex) were consistently assigned to the opposite stream ($\geq 93.4\%$ of FRLs), with S—considered the output of HC (Saunders & Aggleton, 2007; Insausti & Muñoz, 2001; Barbas & Blatt, 1995)—at the most extreme end. Unexpectedly, dorsolateral prefrontal (dlPFC) Areas 9 and 46 as well as the ACC were assigned with high consistency to the memory stream ($\geq 93\%$ of FRLs). These areas are well established as functionally important for the cognitive control of saccades in a number of neurophysiological studies (for a review, see Johnston & Everling, 2008). Using FEF or S as the reference nodes produced similar results (Figure 2B, C). It is possible that the unexpected stream assignments of Areas 9/46 and ACC were due to our approach that forced nodes of the network to be assigned to one of two clusters rather than based on true network organization. To test this possibility, we further subjected our anatomical connectivity matrix to an independent modularity partitioning that does not involve an a priori number of clusters (Meunier, Lambiotte, & Bullmore, 2010; Rubinov & Sporns, 2010). Using this partitioning scheme, the network was divided into three modules and was significantly more modular than null models ($Q: 0.296$ vs. $Q_{\text{null}}: 0.2 \pm 1.66 \times 10^{-5}$; $\gamma: 0.80$). Two of the modules were well matched with the visuo-oculomotor and memory stream assignments (Figure 2; green and light blue), with subregions of the BG grouped into a module of their own (Figure 2, dark blue). These results are consistent with the notion that the structural network topology of the macaque is organized into functionally specialized subnetworks (Hilgetag et al., 2000). Even without an a priori specification of number of clusters, Areas 9/46 and ACC were again grouped with regions of the HC system. These results suggest that the dlPFC and ACC, regions known to be involved in the cognitive control of saccades (Johnston & Everling, 2008), are well connected with the HC and broader medial temporal lobe.

Information Exchange between Memory and Visuo-oculomotor Systems

The modularity metric Q was not ~ 1 , suggesting that, although the structural topology is organized in a way to

Figure 2. Stream assignment index and modularity partitioning of the oculo-memory network for reference node set as SCd (A), FEF (B), and S (C). ACC and Areas 9 and 46 of dlPFC were consistently assigned to the stream opposite to that of SCd/FEF (i.e., assigned to the memory stream). The reference node is not shown since by definition it must have an assignment index of +1. Colors denote modularity partitions. See Table 1 for ROI names and their abbreviations.



subserve the more specialized functions of memory and visuo-oculomotor processing, the detected clusters are highly interconnected. To determine which regions may facilitate the exchange of information across streams, the average distance between each node and the symmetry line across all FRLs was computed. Nodes with more connections across streams would be pulled closer to the other stream in an FRL than nodes with fewer connections across streams. Figure 3A illustrates each node's average distance from the symmetry line on the macaque cortical surface (see Figure 3B for subcortical structures). Using the modular partitions described above, a complementary analysis was done by computing the participation coefficient—a measure of intermodular connectivity—for

each node (Guimerà & Nunes Amaral, 2005). A node with a high participation coefficient suggests that that node may act as a hub to integrate information across modules (Rubinov & Sporns, 2010). A node's distance from the symmetry line in the FRL splitting procedure and its participation coefficient were well correlated ($r = -0.67, p < .001$), suggesting that they provide a similar index of intermodular participation. Together, these two measures pointed toward a number of regions that interconnect the memory and visuo-oculomotor systems (Figure 3C), which included prefrontal regions (orbitolateral pFC, ventrolateral pFC [vlPFC], Areas 6 and 45), posterior cingulate cortex, Area 7b, and the caudate. Of the oculomotor control regions, FEF had a high participation coefficient ($> \text{mean} \pm 1 \text{ SD}$),

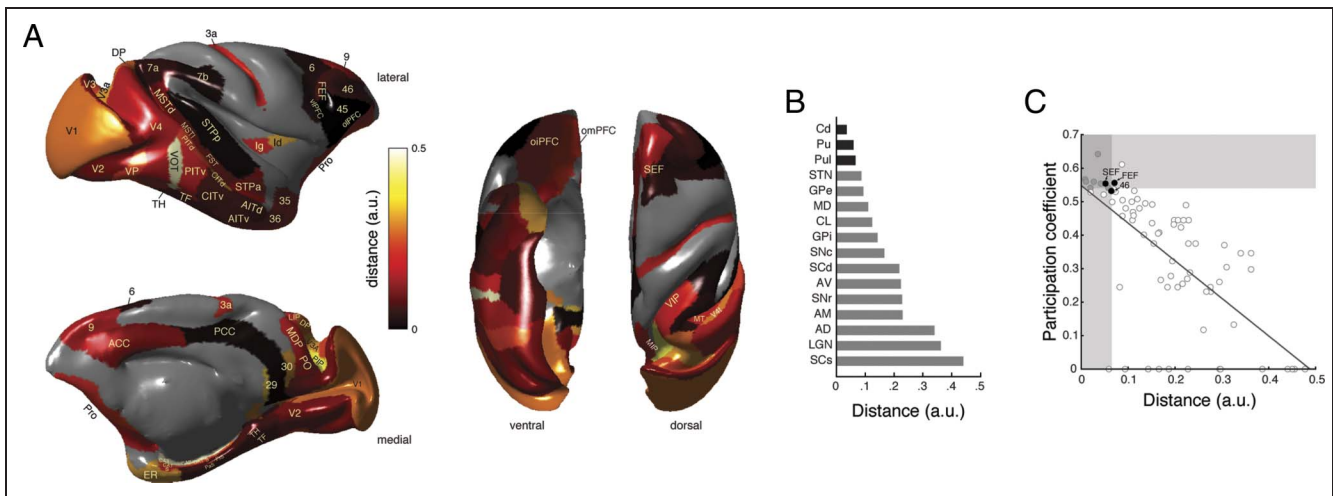


Figure 3. (A) Mean distance from symmetry line for each cortical node depicted on the F99 macaque cortical surface. (B) Mean distance for subcortical distances. Those with notably short distances ($< \text{mean} - 1 \text{ SD}$) depicted with black bars. (C) Distance from symmetry line is correlated with the participation coefficient. Nodes falling in gray zones have a low distance ($< \text{mean} \pm 1 \text{ SD}$) or a high participation coefficient ($> \text{mean} \pm 1 \text{ SD}$) or both.

Area 46 had a short distance to the symmetry line, and supplementary eye field (SEF) had both (Figure 3C). These results suggest that FEF, dlPFC, and SEF are well positioned to bridge information processing across the memory and oculomotor subnetworks.

Information Flow from HC to the Oculomotor System

Thus far, our findings suggest that information processing can occur across the memory and visuo-oculomotor systems. That information processing, however, could subserve various perceptual and cognitive functions aside from memory or oculomotor control. To explicitly test how representations from the HC system guide the selection of saccade targets, the anatomical connectivity arising from HC subregions was examined. We computed a measure of directed reachability (“communicability”) from each HC subregion to all other nodes in the network. Communicability is a generalized measure of shortest paths, taking into account both the direct and indirect paths between any two nodes (Estrada & Hatano, 2008). Communicability therefore expresses the potential for information flow from one region to another. Figure 4A illustrates how every oculomotor control area other than SCd and area LIP have higher communicability with subiculum—the output node of the HC—than expected by chance. Area 46 and FEF are both within the top 10 regions that have the highest reachability from subiculum. FEF’s high communicability is surprising because no monosynaptic connections exist between it and the subiculum. Of note, the majority of highly reachable regions, including many with lower communicability than FEF, are those that receive direct inputs from subiculum (Figure 4A, thick lines). Except in the case of the dentate gyrus, communicability from other HC subregions to the oculomotor areas was similar (data not shown), suggest-

ing that the HC subregions all share common neighbors and therefore common pathways to oculomotor structures. For the dentate gyrus, rank ordered communicability to all regions was under chance levels, suggesting that the HC’s direct and indirect output paths are mostly mediated by subregions other than dentate gyrus.

Finally, we detected the shortest paths between the subregions of the HC and the oculomotor control areas FEF and SCd. FEF and SCd were chosen based on their notable role in the direct control of saccade production (Paré & Hanes, 2003; Hanes & Schall, 1996) as opposed to other oculomotor areas that play a more modulatory role (Curtis, Cole, Rao, & D’Esposito, 2005; Ito, Stuphorn, Brown, & Schall, 2003; Stuphorn, Taylor, & Schall, 2000; Gottlieb, Kusunoki, & Goldberg, 1998). With the exception of the dentate gyrus, all HC subregions had a disynaptic connection to either FEF and/or SCd (Figure 4B). Interestingly, over 94% (34/36) of those disynaptic connections were to FEF, consistent with the finding that FEF has higher communicability from HC subregions than SCd. Together, these results show how regions known to be responsible for the cognitive control of saccades (e.g., dlPFC, ACC, SEF), particularly FEF, are well positioned to receive information from the HC.

DISCUSSION

By applying two independent clustering-type approaches to the anatomical connectivity of the macaque brain, we have identified an extensive network of regions whose pathways may support the guidance of eye movements by memory representations. Our findings suggest that the anatomical architecture of the primate brain is organized such that information can be potentially exchanged between the memory and visuo-oculomotor systems. Importantly, we have also shown that the potential for efficient

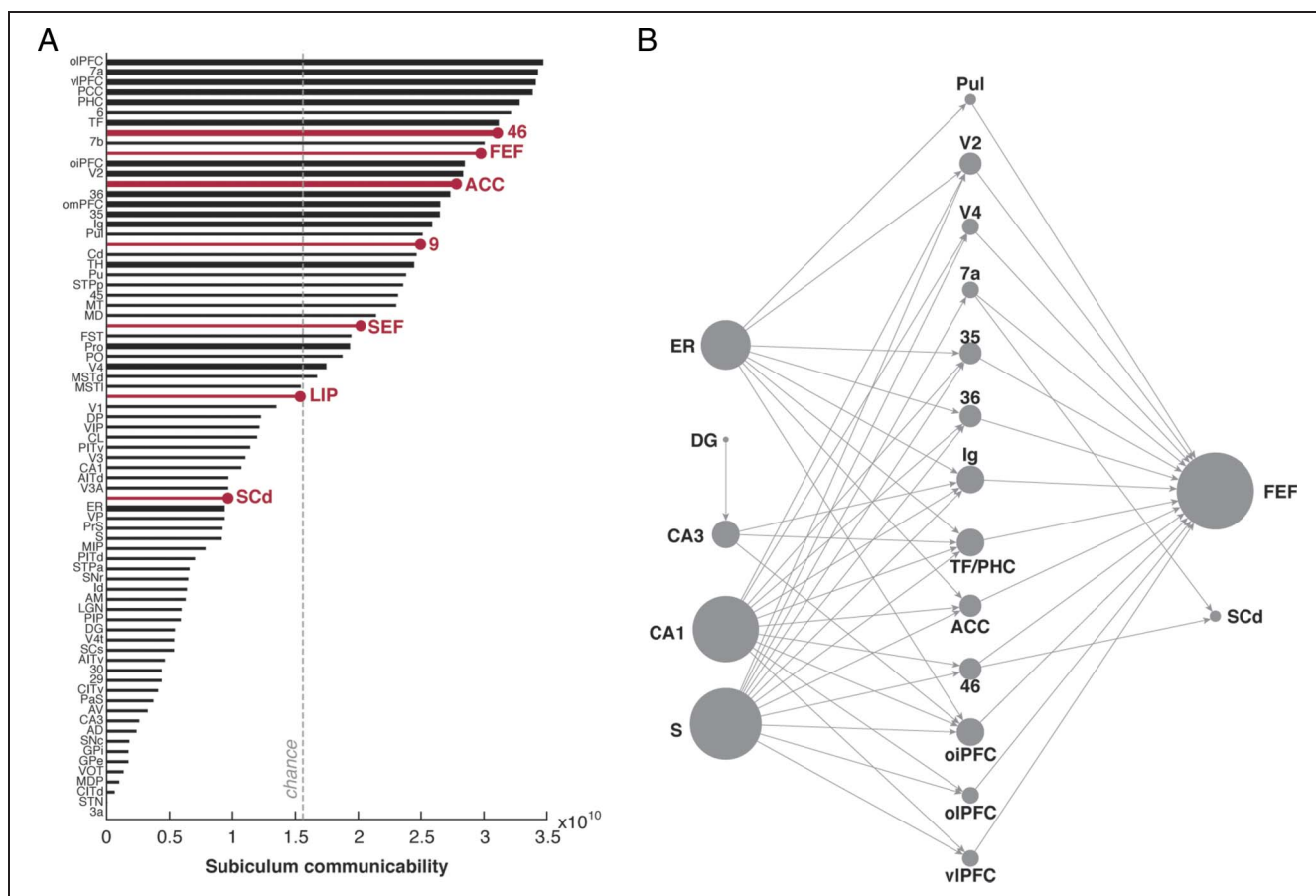


Figure 4. (A) Communicability from the subiculum to all other ROIs, rank ordered. Chance was computed as the maximum mean reachability from the subiculum across 1000 null models. Thick lines indicate regions that receive monosynaptic input from subiculum. Oculomotor ROIs highlighted in red. (B) The shortest paths between the subregions of HC and FEF and SCd. Node size is scaled for the number of shortest paths traversing each node.

and directed information flow specifically from HC to the oculomotor control areas is surprisingly high despite a lack of monosynaptic connections. The collection of disynaptic pathways that may support this directed information flow converges, in particular, on the FEF.

The top-down guidance of saccades by prior knowledge has been consistently documented in humans and macaques (e.g., Chau et al., 2011); consequently, eye tracking has been used as a tool to probe the integrity of memory in multiple populations (Hannula et al., 2010). In healthy individuals, visual behavior reveals memory for single items, as well as memory for the arbitrary relations between objects, temporal sequences, and spatial positions of elements within a scene or event (see Hannula et al., 2010, for a review). For instance, gaze fixations are directed to novel items and, in particular, to more distinct regions of those items as compared with items that have been viewed (Althoff & Cohen, 1999). Gaze fixations are also biased toward previously studied associations, such as the preferential viewing of a target face that had been paired with the presented background scene amongst a set of distractor faces (Hannula, Ryan, Tranel, & Cohen, 2007). Regions of a scene that have changed following a previous presentation also tend to attract gaze fixations; for instance, in cases where an object has

moved in its spatial location (Ryan & Cohen, 2004; Ryan et al., 2000) or a set of objects that have been presented in the same spatial configuration but in a different temporal order than previously studied (Rondina, Curtiss, Meltzer, Barense, & Ryan, in press; see also Pathman & Gheetti, 2015). These findings demonstrate how participants' gaze fixations can be guided by memory for the particular spatial and/or temporal relations among the elements of the scene.

Individuals who have amnesia because of damage to the HC system exhibit altered gaze patterns. On the basis of fixation patterns, some have suggested that the nature of the impairment in amnesia is in relational memory (Ryan et al., 2000; Althoff & Cohen, 1999) that occurs even over brief delays (Warren et al., 2011; Ploner et al., 1999). Others have suggested that amnesia may result in impairments in item memory as well as in relational memory (Smith & Squire, 2008; Smith, Hopkins, & Squire, 2006). More recent evidence has suggested that the effects of HC damage on oculomotor guidance that are suggestive of item memory impairments may be dependent on task conditions that actually reflect relational memory demands (Olsen et al., 2015). Regardless of the nature of the memory formed by the HC system, it is evident that HC representations are used online to guide saccades to

specific locations that contain pertinent information. Additional evidence from nonhuman primates has shown that HC and entorhinal neurons have activity selective for gaze position as well as saccade directions (Killian, Jutras, & Buffalo, 2012; Sobotka, Nowicka, & Ringo, 1997; also see Leonard et al., 2015; Hoffman et al., 2013), and some have suggested that the representation of space within the medial temporal lobe of primates is unlike that of rodents, with a subset of the neuronal population referenced to gaze location rather than the body (Meister & Buffalo, 2015; for a review, see Rolls & Xiang, 2006). This is in line with the view that vision is the primary sensory modality for guiding movement control in primates, as opposed to haptics and olfaction in rodents (Whishaw, 2003; Ellard, 1998). These data suggest that interpreting the findings of HC function in the context of visual behavior from rodent models may be severely limited and that a fuller understanding of the HC system's influence on visual behavior in human and nonhuman primates is needed (also see Murray & Wise, 2010).

We have begun to address this need by using macaque connectivity as a model to identify a putative set of pathways in the primate brain that may mediate the guidance of saccades by mnemonic representations formed by the HC system. Our results suggest that regions of the extrastriate, posterior parietal cortex, medial temporal lobe, and prefrontal cortices may exchange information between the memory and oculomotor systems. It has recently been hypothesized that medial temporal lobe outputs may either directly or indirectly target a network of regions that constitute a "salience map" of the visual world (Meister & Buffalo, 2015). In the macaque, these regions include area LIP (Goldberg, Bisley, Powell, & Gottlieb, 2006), the FEF (Thompson & Bichot, 2005), and the SCd (Shen, Valero, Day, & Paré, 2011), which all exhibit prioritized representations of visual space and whose activity is crucial for the guidance and control of saccades (Belopolsky, 2015; also see Jerde, Merriam, Riggall, Hedges, & Curtis, 2012; Fecteau & Munoz, 2006). Others have additionally posited a role for dlPFC, vlPFC, BG, and thalamus (Micic, Ehrlichman, & Chen, 2010) in the cognitive control of saccades. Consistent with these accounts, we provide evidence using a data-driven network analytic approach that FEF is amongst one of the most reachable areas from HC, whereas area LIP and SCd are decidedly less so. We also found dlPFC, vlPFC, and the pulvinar to have some of the shortest paths between HC and FEF/SCd. Our analyses also revealed a number of other disynaptic pathways via which information from HC can reach FEF and SCd. The functional relevance of many of these pathways is still unknown (e.g., paths via OFC, granular insula, extrastriate cortex) and future studies that map the functional connectivity of these pathways to visual behavior are needed to better understand their contributions to the guidance of saccades. Together, our findings suggest that it is indeed possible for HC information to influence the network of regions that form the visual salience map, especially the FEF.

Some of the regions we extracted from our analysis have been implicated in both memory and oculomotor functions. For example, dlPFC's role in memory function is well documented in humans (Penolazzi, Stramaccia, Braga, Mondini, & Galfano, 2014; Long, Oztekin, & Badre, 2010; Hayama & Rugg, 2009) and macaques (Osada et al., 2015; Petrides, 1991), as is its role in the voluntary control of saccades (Cameron, Riddle, & D'Esposito, 2015; Everling & Johnston, 2013; Pierrot-Deseilligny, Müri, Nyffeler, & Milea, 2005). dlPFC is well positioned to play a major role in integrating information from HC with other task-relevant signals to guide visual behavior, as it provides direct excitatory input to the intermediate layers of the SC (Johnston, Koval, Lomber, & Everling, 2014). A similar argument can be made for ACC given its role in oculomotor control (Johnston, Levin, Koval, & Everling, 2007; Ito et al., 2003; Gaymard et al., 1998; Paus, Petrides, Evans, & Meyer, 1993) and in the signaling of conflicts in information processing (e.g., between prior and novel information) in service of action (Shenhav, Botvinick, & Cohen, 2013; Paus, 2001; Meunier, Bachevalier, & Mishkin, 1997; Parker & Gaffan, 1997). However, much of the literature on the neural substrates of memory or oculomotor functions has been non-overlapping and limited to region-based perspectives, which renders the development of hypotheses difficult with respect to studying the neural basis of memory-guided visual behavior. By adopting a network-based approach, we have demonstrated that a more extensive set of potential pathways exist to support such behavior than previously considered (Meister & Buffalo, 2015; Micic et al., 2010). The anatomical embedding of a region within a network only provides a partial understanding of network communication. The additional consideration of functional dynamics of the network in combination with its structural architecture can provide a more comprehensive understanding of brain function (e.g., Mišić, Goñi, Betzel, Sporns, & McIntosh, 2014; Vlachos, Aertsens, & Kumar, 2012). Future studies of functional connectivity and functional dynamics are therefore needed to gain a fuller understanding of information exchange between the memory and oculomotor systems.

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REFERENCES

- Althoff, R. R., & Cohen, N. J. (1999). Eye-movement-based memory effect: A reprocessing effect in face perception. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *25*, 997–1010.

- Awh, E., Armstrong, K. M., & Moore, T. (2006). Visual and oculomotor selection: Links, causes and implications for spatial attention. *Trends in Cognitive Sciences*, *10*, 124–130.
- Bakker, R., Wachtler, T., & Diesmann, M. (2012). CoCoMac 2.0 and the future of tract-tracing databases. *Frontiers in Neuroinformatics*, *6*, 30.
- Barbas, H., & Blatt, G. J. (1995). Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus*, *5*, 511–533.
- Belopolsky, A. V. (2015). Common priority map for selection history, reward and emotion in the oculomotor system. *Perception*, *44*, 920–933.
- Bezgin, G., Rybacki, K., van Opstal, A. J., Bakker, R., Shen, K., Vakorin, V. A., et al. (2014). Auditory-prefrontal axonal connectivity in the macaque cortex: Quantitative assessment of processing streams. *Brain and Language*, *135*, 73–84.
- Bezgin, G., Vakorin, V. A., van Opstal, A. J., McIntosh, A. R., & Bakker, R. (2012). Hundreds of brain maps in one atlas: Registering coordinate-independent primate neuro-anatomical data to a standard brain. *Neuroimage*, *62*, 67–76.
- Bisley, J. W., & Goldberg, M. E. (2010). Attention, intention, and priority in the parietal lobe. *Annual Review of Neuroscience*, *33*, 1–21.
- Blondel, V. D., Guillaume, J.-L., Lambiotte, R., & Lefebvre, E. (2008). Fast unfolding of communities in large networks. *Journal of Statistical Mechanics: Theory and Experiment*, *2008*, P10008.
- Brockmole, J. R., & Henderson, J. M. (2008). Prioritizing new objects for eye fixation in real-world scenes: Effects of object scene consistency. *Visual Cognition*, *16*, 375–390.
- Bullmore, E. T., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, *10*, 186–198.
- Cameron, I. G. M., Riddle, J. M., & D'Esposito, M. (2015). Dissociable roles of dorsolateral prefrontal cortex and frontal eye fields during saccadic eye movements. *Frontiers in Human Neuroscience*, *9*, 613.
- Castelhano, M. S., & Henderson, J. M. (2007). Initial scene representations facilitate eye movement guidance in visual search. *Journal of Experimental Psychology: Human Perception and Performance*, *33*, 753–763.
- Chau, V. L., Murphy, E. F., Rosenbaum, R. S., Ryan, J. D., & Hoffman, K. L. (2011). A flicker change detection task reveals object-in-scene memory across species. *Frontiers in Behavioral Neuroscience*, *5*, 58.
- Chen, Z. J., He, Y., Rosa-neto, P., Germann, J., & Evans, A. C. (2008). Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cerebral Cortex*, *18*, 2374–2381.
- Corbetta, M. (1998). Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proceedings of the National Academy of Sciences, U.S.A.*, *95*, 831–838.
- Curtis, C. E., Cole, M. W., Rao, V. Y., & D'Esposito, M. (2005). Canceling planned action: An fMRI study of countermanding saccades. *Cerebral Cortex*, *15*, 1281–1289.
- Ellard, C. (1998). Comparative perspectives on multiple cortical visual systems. *Neuroscience & Biobehavioral Reviews*, *22*, 173–180.
- Estrada, E., & Hatano, N. (2008). Communicability in complex networks. *Physical Review E, Statistical, Nonlinear, and Soft Matter Physics*, *77*, 036111.
- Everling, S., & Johnston, K. (2013). Control of the superior colliculus by the lateral prefrontal cortex. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences*, *368*, 20130068.
- Fecteau, J. H., & Munoz, D. P. (2006). Saliency, relevance, and firing: A priority map for target selection. *Trends in Cognitive Sciences*, *10*, 382–390.
- Findlay, J. M. (2005). Covert attention and saccadic eye movements. In L. Itti, J. Tsotsos, & G. Rees (Eds.), *Neurobiology of attention* (pp. 114–116). New York: Elsevier.
- Fruchterman, T., & Reingold, E. (1991). Graph drawing by force directed placement. *Software: Practice and Experience*, *21*, 1129–1164.
- Funahashi, S. (2015). Functions of delay-period activity in the prefrontal cortex and mnemonic scotomas revisited. *Frontiers in Systems Neuroscience*, *9*, 2.
- Gaymard, B. (2012). Cortical and sub-cortical control of saccades and clinical application. *Revue Neurologique*, *168*, 734–740.
- Gaymard, B., Rivaud, S., Cassarini, J. F., Dubard, T., Rancurel, G., Agid, Y., et al. (1998). Effects of anterior cingulate cortex lesions on ocular saccades in humans. *Experimental Brain Research*, *120*, 173–183.
- Goldberg, M. E., Bisley, J. W., Powell, K. D., & Gottlieb, J. (2006). Saccades, saliency and attention: The role of the lateral intraparietal area in visual behavior. *Progress in Brain Research*, *155*, 157–175.
- Gottlieb, J. P., Kusunoki, M., & Goldberg, M. E. (1998). The representation of visual saliency in monkey parietal cortex. *Nature*, *391*, 481–484.
- Guimerà, R., & Nunes Amaral, L. A. (2005). Functional cartography of complex metabolic networks. *Nature*, *433*, 895–900.
- Hanes, D. P., & Schall, J. D. (1996). Neural control of voluntary movement initiation. *Science*, *274*, 427–430.
- Hannula, D. E., Althoff, R. R., Warren, D. E., Riggs, L., Cohen, N. J., & Ryan, J. D. (2010). Worth a glance: Using eye movements to investigate the cognitive neuroscience of memory. *Frontiers in Human Neuroscience*, *4*, 166.
- Hannula, D. E., Ryan, J. D., Tranel, D., & Cohen, N. J. (2007). Rapid onset relational memory effects are evident in eye movement behavior, but not in hippocampal amnesia. *Journal of Cognitive Neuroscience*, *19*, 1690–1705.
- Hayama, H. R., & Rugg, M. D. (2009). Right dorsolateral prefrontal cortex is engaged during post-retrieval processing of both episodic and semantic information. *Neuropsychologia*, *47*, 2409–2416.
- Hilgetag, C. C., Burns, G. A., O'Neill, M. A., Scannell, J. W., & Young, M. P. (2000). Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences*, *355*, 91–110.
- Hoffman, K. L., Dragan, M. C., Leonard, T. K., Micheli, C., Montefusco-Siegmund, R., & Valiante, T. A. (2013). Saccades during visual exploration align hippocampal 3–8 Hz rhythms in human and non-human primates. *Frontiers in Systems Neuroscience*, *7*, 43.
- Ikkai, A., & Curtis, C. E. (2011). Common neural mechanisms supporting spatial working memory, attention and motor intention. *Neuropsychologia*, *49*, 1428–1434.
- Insausti, R., & Muñoz, M. (2001). Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (*Macaca fascicularis*). *European Journal of Neuroscience*, *14*, 435–451.
- Ito, S., Stuphorn, V., Brown, J. W., & Schall, J. D. (2003). Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science*, *302*, 120–122.
- Jerde, T. A., Merriam, E. P., Riggall, A. C., Hedges, J. H., & Curtis, C. E. (2012). Prioritized maps of space in human

- frontoparietal cortex. *Journal of Neuroscience*, *32*, 17382–17390.
- Johnston, K., & Everling, S. (2008). Neurophysiology and neuroanatomy of reflexive and voluntary saccades in non-human primates. *Brain and Cognition*, *68*, 271–283.
- Johnston, K., Koval, M. J., Lomber, S. G., & Everling, S. (2014). Macaque dorsolateral prefrontal cortex does not suppress saccade-related activity in the superior colliculus. *Cerebral Cortex*, *24*, 1373–1388.
- Johnston, K., Levin, H. M., Koval, M. J., & Everling, S. (2007). Top-down control-signal dynamics in anterior cingulate and prefrontal cortex neurons following task switching. *Neuron*, *53*, 453–462.
- Killian, N. J., Jutras, M. J., & Buffalo, E. A. (2012). A map of visual space in the primate entorhinal cortex. *Nature*, *491*, 761–764.
- Kötter, R. (2004). Online retrieval, processing, and visualization of primate connectivity data from the CoCoMac database. *Neuroinformatics*, *2*, 127–144.
- Leonard, T. K., Mikkilä, J. M., Eskandar, E. N., Gerrard, J. L., Kaping, D., Patel, S. R., et al. (2015). Sharp wave ripples during visual exploration in the primate hippocampus. *Journal of Neuroscience*, *35*, 14771–14782.
- Loftus, G. R., & Mackworth, N. H. (1978). Cognitive determinants of fixation location during picture viewing. *Journal of Experimental Psychology: Human Perception and Performance*, *4*, 565–572.
- Long, N. M., Oztekin, I., & Badre, D. (2010). Separable prefrontal cortex contributions to free recall. *Journal of Neuroscience*, *30*, 10967–10976.
- Mahalanobis, P. C. (1936). On the generalized distance in statistics. *Proceedings of the National Institute of Sciences (Calcutta)*, *2*, 49–55.
- Maslov, S., & Sneppen, K. (2002). Specificity and stability in topology of protein networks. *Science*, *296*, 910–913.
- Meister, M. L. R., & Buffalo, E. A. (2015). Getting directions from the hippocampus: The neural connection between looking and memory. *Neurobiology of Learning and Memory*. doi:10.1016/j.nlm.2015.12.004.
- Meunier, D., Lambiotte, R., & Bullmore, E. T. (2010). Modular and hierarchically modular organization of brain networks. *Frontiers in Neuroscience*, *4*, 1–11.
- Meunier, M., Bachevalier, J., & Mishkin, M. (1997). Effects of orbital frontal and anterior cingulate lesions on object and spatial memory in rhesus monkeys. *Neuropsychologia*, *35*, 999–1015.
- Micic, D., Ehrlichman, H., & Chen, R. (2010). Why do we move our eyes while trying to remember? The relationship between non-visual gaze patterns and memory. *Brain and Cognition*, *74*, 210–224.
- Mišić, B., Goñi, J., Betzel, R. F., Sporns, O., & McIntosh, A. R. (2014). A network convergence zone in the hippocampus. *PLoS Computational Biology*, *10*, e1003982.
- Murray, E. A., & Wise, S. P. (2010). What, if anything, can monkeys tell us about human amnesia when they can't say anything at all? *Neuropsychologia*, *48*, 2385–2405.
- Olsen, R. K., Lee, Y., Kube, J., Rosenbaum, R. S., Grady, C., Moscovitch, M., et al. (2015). The role of relational binding in item memory: Evidence from face recognition in a case of developmental amnesia. *Journal of Neuroscience*, *35*, 5342–5350.
- Opitz, B. (2014). Memory function and the hippocampus. *Frontiers of Neurology and Neuroscience*, *34*, 51–59.
- Osada, T., Adachi, Y., Miyamoto, K., Jimura, K., Setsuie, R., & Miyashita, Y. (2015). Dynamically allocated hub in task-evoked network predicts the vulnerable prefrontal locus for contextual memory retrieval in macaques. *PLoS Biology*, *13*, e1002177.
- Paré, M., & Hanes, D. P. (2003). Controlled movement processing: Superior colliculus activity associated with countermanded saccades. *Journal of Neuroscience*, *23*, 6480–6489.
- Parker, A., & Gaffan, D. (1997). The effect of anterior thalamic and cingulate cortex lesions on object-in-place memory in monkeys. *Neuropsychologia*, *35*, 1093–1102.
- Parker, R. E. (1978). Picture processing during recognition. *Journal of Experimental Psychology: Human Perception and Performance*, *4*, 284–293.
- Pathman, T., & Gheetti, S. (2015). Eye movements provide an index of veridical memory for temporal order. *PLoS One*, *10*, e0125648.
- Paus, T. (2001). Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nature Reviews Neuroscience*, *2*, 417–424.
- Paus, T., Petrides, M., Evans, A. C., & Meyer, E. (1993). Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: A positron emission tomography study. *Journal of Neurophysiology*, *70*, 453–469.
- Penolazzi, B., Stramaccia, D. F., Braga, M., Mondini, S., & Galfano, G. (2014). Human memory retrieval and inhibitory control in the brain: Beyond correlational evidence. *Journal of Neuroscience*, *34*, 6606–6610.
- Petrides, M. (1991). Functional specialization within the dorsolateral frontal cortex for serial order memory. *Proceedings Biological Sciences/The Royal Society*, *246*, 299–306.
- Pierrot-Descilligny, C., Müri, R. M., Nyffeler, T., & Milea, D. (2005). The role of the human dorsolateral prefrontal cortex in ocular motor behavior. *Annals of the New York Academy of Sciences*, *1039*, 239–251.
- Ploner, C. J., Gaymard, B. M., Ehrlé, N., Rivaud-Pechoux, S., Baulac, M., Brandt, S. A., et al. (1999). Spatial memory deficits in patients with lesions affecting the medial temporal neocortex. *Annals of Neurology*, *45*, 312–319.
- Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus*, *20*, 1263–1290.
- Rolls, E. T., & Xiang, J. Z. (2006). Spatial view cells in the primate hippocampus and memory recall. *Reviews in the Neurosciences*, *17*, 175–200.
- Rondina, R., Curtiss, K., Meltzer, J. A., Barense, M. D., & Ryan, J. D. (in press). The organization of spatial and temporal relations in memory. *Memory*. doi:10.1080/09658211.2016.1182553.
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage*, *52*, 1059–1069.
- Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Current Opinion in Neurobiology*, *23*, 255–260.
- Ryan, J. D., Althoff, R. R., Whitlow, S., & Cohen, N. J. (2000). Amnesia is a deficit in relational memory. *Psychological Science*, *11*, 454–461.
- Ryan, J. D., & Cohen, N. J. (2004). The nature of change detection and online representations of scenes. *Journal of Experimental Psychology: Human Perception and Performance*, *30*, 988–1015.
- Ryan, J. D., Hannula, D. E., & Cohen, N. J. (2007). The obligatory effects of memory on eye movements. *Memory*, *15*, 508–525.
- Saunders, R. C., & Aggleton, J. P. (2007). Origin and topography of fibers contributing to the fornix in macaque monkeys. *Hippocampus*, *17*, 396–411.
- Shen, K., Bezgin, G., Hutchison, R. M., Gati, J. S., Menon, R. S., Everling, S., et al. (2012). Information processing

- architecture of functionally defined clusters in the macaque cortex. *Journal of Neuroscience*, *32*, 17465–17476.
- Shen, K., Valero, J., Day, G. S., & Paré, M. (2011). Investigating the role of the superior colliculus in active vision with the visual search paradigm. *European Journal of Neuroscience*, *33*, 2003–2016.
- Shenhav, A., Botvinick, M. M., & Cohen, J. D. (2013). The expected value of control: An integrative theory of anterior cingulate cortex function. *Neuron*, *79*, 217–240.
- Smith, C. N., Hopkins, R. O., & Squire, L. R. (2006). Experience-dependent eye movements, awareness, and hippocampus-dependent memory. *Journal of Neuroscience*, *26*, 11304–11312.
- Smith, C. N., & Squire, L. R. (2008). Experience-dependent eye movements reflect hippocampus-dependent (aware) memory. *Journal of Neuroscience*, *28*, 12825–12833.
- Sobotka, S., Nowicka, A., & Ringo, J. L. (1997). Activity linked to externally cued saccades in single units recorded from hippocampal, parahippocampal, and inferotemporal areas of macaques. *Journal of Neurophysiology*, *78*, 2156–2163.
- Sparks, D. L. (2002). The brainstem control of saccadic eye movements. *Nature Reviews Neuroscience*, *3*, 952–964.
- Sporns, O., Honey, C. J., & Kötter, R. (2007). Identification and classification of hubs in brain networks. *PLoS One*, *2*, e1049.
- Stephan, K. E., Kamper, L., Bozkurt, A., Burns, G., Young, M., & Kötter, R. (2001). Advanced database methodology for the Collation of Connectivity data on the macaque brain (CoCoMac). *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences*, *356*, 1159–1186.
- Stuphorn, V., Taylor, T. L., & Schall, J. D. (2000). Performance monitoring by the supplementary eye field. *Nature*, *408*, 857–860.
- Theeuwes, J., Belopolsky, A., & Olivers, C. N. L. (2009). Interactions between working memory, attention and eye movements. *Acta Psychologica*, *132*, 106–114.
- Thompson, K. G., & Bichot, N. P. (2005). A visual salience map in the primate frontal eye field. In *Progress in brain research* (Vol. 147, pp. 251–262). London: Elsevier.
- van den Heuvel, M. P., & Sporns, O. (2011). Rich-club organization of the human connectome. *Journal of Neuroscience*, *31*, 15775–15786.
- Vlachos, I., Aertsen, A., & Kumar, A. (2012). Beyond statistical significance: Implications of network structure on neuronal activity. *PLoS Computational Biology*, *8*, e1002311.
- Warren, D. E., Duff, M. C., Tranel, D., & Cohen, N. J. (2011). Observing degradation of visual representations over short intervals when medial temporal lobe is damaged. *Journal of Cognitive Neuroscience*, *23*, 3862–3873.
- Whishaw, I. Q. (2003). Did a change in sensory control of skilled movements stimulate the evolution of the primate frontal cortex? *Behavioural Brain Research*, *146*, 31–41.
- Zola, S. M., Squire, L. R., Teng, E., Stefanacci, L., Buffalo, E. A., & Clark, R. E. (2000). Impaired recognition memory in monkeys after damage limited to the hippocampal region. *Journal of Neuroscience*, *20*, 451–463.