Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Toward a Better Understanding of the Injured Hippocampus: Multimodal Imaging in Functionally Relevant Substructures

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Review of Voets et al.

In addition to being a focus of cellular and cognitive neuroscience research due to its involvement in multiple cognitive processes, the hippocampus is in the spotlight of clinical neuroscience because of its vulnerability to a broad range of neuropsychiatric disorders (Small et al., 2011). Nevertheless, the mechanisms contributing to the cognitive impact of hippocampal injury and potential subsequent memory reorganization are still poorly understood, because the literature, while abundant, is sometimes perplexing. Part of the confusion arises from the diversity of measures (volume, connectivity, task-related activity, glucose metabolism, etc.) obtained from neuroimaging techniques to assess hippocampal integrity. Although assessing different aspects of hippocampal integrity is a potential strength, existing findings are difficult to compare and integrate because the relationships between these measures and the mechanisms they reflect are poorly characterized. Furthermore, some studies have shown counterintuitive results such as increases of hippocampal activation or connectivity in the face of pathology, and it is unclear whether these reflect compensa-

tory (i.e., beneficial) mechanisms relying on hippocampal plasticity, or aberrant functioning reflecting underlying pathological processes (Maruszak and Thuret, 2014). In addition, the majority of previous research has considered the hippocampus as a unitary entity, whereas much evidence indicates that the hippocampus should be parcellated into functional subunits (Maruszak and Thuret, 2014). Indeed, animal studies indicate that hippocampal efferents vary along its anterior–posterior axis (Aggleton, 2012), consistent with human neuroimaging data showing differential functional connectivity and activity between anterior and posterior hippocampal regions (Poppenk et al., 2013). This gradient is thus expected to influence the functional impact of diseases targeting specific parts of the hippocampus (Small et al., 2011). Exploring these substructures separately could give us more insight into hippocampal function and disorders, and potentially help us reconcile divergent findings.

In a recent article published in *The Journal of Neuroscience*, Voets et al. (2014) took these concerns into account when assessing the hippocampus and related networks in patients with unilateral hippocampal injury due to temporal lobe epilepsy. The authors' approach has several strengths and novel approaches to addressing these pitfalls. They aimed to provide a comprehensive view of hippocampal integrity by combining multiple biomarkers in the same patients, while looking at these

metrics in the anterior and posterior hippocampus separately.

The method used by the authors to define hippocampal subregions is particularly novel and noteworthy. Instead of relying on macroscopic anatomical landmarks to segment the hippocampus along its anterior–posterior axis (Poppenk et al., 2013), the authors used resting-state functional magnetic resonance imaging (rs-fMRI) data to distinguish functionally relevant subregions on the basis of their intrinsic connectivity to multiple cortical regions (i.e., regions showing temporally synchronized fluctuations of the fMRI signal). Multiple metrics were then extracted from these subregions and associated hippocampo-cortical networks.

Although Voets et al. (2014) detected major volume loss in the posterior hippocampus of patients with temporal lobe epilepsy, both anterior and posterior hippocampus showed memory-related activation that was comparable to healthy subjects. Instead, only the posterior parahippocampal gyrus (part of the posterior hippocampus network) showed lower activation than controls during episodic memory encoding. Looking at intrinsic connectivity in patients, Voets et al. (2014) found both increased short-range and decreased long-range hippocampal connectivity: anterior hippocampus-entorhinal and posterior hippocampus-parahippocampal connectivity were enhanced, while the posterior hippocampus showed decreased long-range connectivity with the posterior cingulate. Interestingly, patients' memory

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impairment, assessed on their neuropsychological evaluation, was related to these intrinsic connectivity abnormalities (patients with significant memory impairment showed stronger abnormalities than cognitively spared patients) but not volume or task-related activation.

The hippocampo-cortical networks identified by Voets et al. (2014) echo the two cortical systems that were previously developed and modeled by Ranganath and Ritchey (2012). On one hand, the anterior temporal system, including the anterior hippocampus, and perirhinal, anterior temporal, and orbitofrontal cortices, is thought to be involved in familiarity-based recognition, emotional processing, and social cognition. On the other hand, the posterior medial system, encompassing the posterior hippocampus, parahippocampal cortex, precuneus, posterior cingulate, angular gyrus, and thalamus, is considered crucial for spatial navigation and episodic memory. The results from Voets et al. (2014) confirm these networks' topography and the preferential involvement of the posterior system for episodic memory. Indeed, patients were characterized by a global impairment of the posterior network, as indicated by multiple biomarkers: posterior hippocampal volume loss and aberrant intrinsic connectivity, decreased parahippocampal activation. Although memory impairments were only significantly related to connectivity, the absence of relationships with the other biomarkers should not be over-interpreted due to the limited statistical power, and requires further investigations.

Interestingly, hippocampo-cortical network abnormalities reported by Voets et al. (2014) were not restricted to decreases, but included enhanced hippocampo-parahippocampal connectivity, and both abnormalities were associated with memory deficits. The co-occurrence of increased short-range and decreased long-range connectivity was previously described in patients with amnesic mild cognitive impairment (Das et al., 2013), who also exhibit hippocampal atrophy and episodic memory impairment. Although different pathophysiological mechanisms are likely involved, the similar effects emerging from different disorders emphasizes the detrimental significance of this specific pattern of connectivity dysregulation. In both cases, local hyper-connectivity within the medial temporal lobe (MTL)

may result from the loss of connections with other brain structures reflected by the decreased connectivity to distant cortical regions (Das et al., 2013). Both increased short-range and increased long-range MTL connectivity could therefore indicate cognition-prejudicial disruption of a large-scale network. Complementary investigations of rs-fMRI data using graph-theory analyses to characterize brain subnetworks (or "modules") could further assess this hypothesis. Indeed, studies in children with frontal lobe epilepsy have shown that cognitive deficits were associated with stronger modularity values, indicating the detrimental isolation of functional brain subnetworks (Vaessen et al., 2014).

A major innovation in the study by Voets et al. (2014) is that the hippocampal parcellation was solely driven by each voxel's preferential connectivity to multiple brain regions. Interestingly, the resulting segmentation (Voets et al., 2014; their Fig. 1a) differed from the classically described hippocampal subdivisions (head, body and tail; for an overview, see Poppenk et al., 2013), supporting the idea that connectivity, and potentially function, do not exactly follow macroscopic form and/or that our classical strategies for long-axis segmentation of the hippocampus are not optimal. Complementary to this method, other strategies could be considered to parcellate the hippocampus into subregions, notably segmentation into histological subfields (e.g., dentate gyrus, CA1–3, subiculum), which is now possible *in vivo* thanks to the improvement of image resolution and specific delineation protocols (Wisse et al., 2012). Indeed, these hippocampal subfields are differentially involved in cognitive processes (Small et al., 2011) and have distinct connections (Aggleton, 2012). Moreover, this complementary approach might help researchers understand hippocampal-related disorders, given that subfields seem to be differentially vulnerable to variable pathological processes (Small et al., 2011).

From a different perspective, because they combined multiple techniques in the same patients, Voets et al. (2014) brought us insight into the relationships between different biomarkers. For instance, they showed that, in a given patient group, the same region (the parahippocampal gyrus) could exhibit both enhanced resting-state connectivity (with the posterior hippocampus) and decreased activation in a

memory task. However, only the former was related to cognitive impairment, suggesting that these markers indicate distinct, nonredundant aspects of MTL dysfunction.

Even though additional investigations are needed to better characterize the precise anatomy, function, and relevance to disease of hippocampus-related brain networks, the paper by Voets et al. (2014) illustrates the interest of combining multimodal neuroimaging measurements to assess the integrity of multiple hippocampal subparts. Altogether, our understanding of normal function and pathology in the MTL should benefit from using these recent technical developments and from considering network-based models of brain organization.

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