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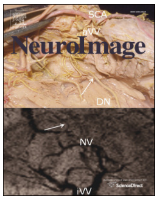

Evidence for an anterior–posterior differentiation in the human hippocampal formation revealed by meta-analytic parcellation of fMRI coordinate maps: Focus on the subiculum

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ABSTRACT

Previous studies, predominantly in experimental animals, have suggested the presence of a differentiation of function across the hippocampal formation. In rodents, ventral regions are thought to be involved in emotional behavior while dorsal regions mediate cognitive or spatial processes. Using a combination of modeling the co-occurrence of significant activations across thousands of neuroimaging experiments and subsequent data-driven clustering of these data we were able to provide evidence of distinct subregions within a region corresponding to the human subiculum, a critical hub within the hippocampal formation. This connectivity-based model consists of a bilateral anterior region, as well as separate posterior and intermediate regions on each hemisphere. Functional connectivity assessed both by meta-analytic and resting fMRI approaches revealed that more anterior regions were more strongly connected to the default mode network, and more posterior regions were more strongly connected to 'task positive' regions. In addition, our analysis revealed that the anterior subregion was functionally connected to the ventral striatum, midbrain and amygdala, a circuit that is central to models of stress and motivated behavior. Analysis of a behavioral taxonomy provided evidence for a role for each subregion in mnemonic processing, as well as implication of the anterior subregion in emotional and visual processing and the right posterior subregion in reward processing. These findings lend support to models which posit anterior–posterior differentiation of function within the human hippocampal formation and complement other early steps toward a comparative (cross-species) model of the region.

Introduction

The hippocampal formation is crucial for mnemonic and spatial representation, as well as an involvement in emotional and stress-related processes. The region is made up of several independent subregions, but functional specialization within the structure remains an area of ongoing experimental and theoretical concern. A variety of evidence supports the presence of functional specialization across a dorsoventral gradient in rodents (Fanselow and Dong, 2010). Shaped as a cashew in these animals, the longitudinal axis extends in a dorsoventral (and septotemporal) direction. Broadly, ventral regions of the hippocampal formation are often considered to play a role in emotional behavior such as anxiety, whereas dorsal regions are thought to play a role in cognitive factors such as spatial and mnemonic processes (Bannerman et al., 2014). In primates, the hippocampal formation is shaped as a ram's horn, extending in the posterioanterior direction. Consequently, the rodent ventral hippocampus is thought to correspond to the anterior hippocampus in humans, whereas the rodent dorsal hippocampus is located posterior in humans (Strange et al., 2014).

Similar evidence for differentiation of function across the region in humans is perhaps sparser (Poppenk et al., 2013), partly due to the technical challenges associated with experimental manipulations, neurophysiological recordings or neuroimaging of the region. Nevertheless, several fMRI studies have reported distinct patterns of activation across

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anterior and posterior regions of the hippocampus (e.g. Baumann and Mattingley, 2013; Hirshhorn et al., 2012; Kuhn and Gallinat, 2014; Nadel et al., 2013; Strange et al., 1999; Voets et al., 2014). Another promising approach has been to examine patterns of resting functional connectivity with other structures, using for example, resting state fMRI (rsfMRI). These methods have proven to be a powerful way to investigate the communication of information across the human brain (Van Dijk et al., 2010), yielding patterns of connectivity that appear to correspond well to known neural circuits, and may reflect underlying anatomical connections (Baria et al., 2013; Damoiseaux and Greicius, 2009) and functional networks. A recent resting state fMRI study described the functional connectivity of the hippocampus with perirhinal and parahippocampal regions as following an antero-posterior gradient: most posterior regions were connected to parahippocampal compared with perirhinal cortex, whereas the reverse pattern was observed in anterior regions (Libby et al., 2012). An intermediate region demonstrated no preferential connectivity. This study implied that zones of differential functional connectivity within the hippocampus may reflect the presence of different functional properties of the more anterior and more posterior portions of the region, and accorded well with anatomical properties of the region as primarily known from animal models. Another recent study identified a gradient of connectivity across the structure with respect to connectivity with ventral striatum and midbrain (Kahn and Shohamy, 2013). While resting fMRI methods infer differential functional connectivity by comparing BOLD variations across time in a single brain state, such networks have the drawback that they lack a functional or neuropsychological context. Resting fMRI studies also tend to focus on particular frequency bands and stationary association, an approach which has proved highly robust but may only reflect a limited range of inter-regional information transmission.

Further characterization of functional connectivity may be obtained by alternative approaches, including meta-analytic connectivity modeling (MACM). In the MACM approach, the inference of functional interactions is based on the co-occurrence of significant activations across studies. While in practice, networks identified by MACM appear to correspond well to those identified by direct covariance using fMRI, discrepancies have also been noted (cf. Clos et al., 2013; Eickhoff et al., 2014; Jakobs et al., 2012). In general, a good corroboration of MACM-based or similar approaches with well-established brain functional connectivity patterns is seen (Clos et al., 2014; Crossley et al., 2013; Di et al., 2013). Nevertheless, distinct properties of MACM-estimated functional connectivity on large scale connectivity networks have been identified, which may reflect, at first approximation, the influence of a general task set (Crossley et al., 2013; Di et al., 2013). Neurofunctional context may be particularly relevant for understanding the functional connectivity of the hippocampal formation, as information transmission to and from the region can be modulated both by behavioral context and input from a third region (e.g. Belujon and Grace, 2008; Gill and Grace, 2013). A recent development for functional mapping has been to examine patterns of differential connections via clustering algorithms to demonstrate distinct subregions with internally coherent connectivity within large anatomical structures ('connectivity-based parcellation'). In particular, data driven clustering based on MACM maps has been employed to demonstrate distinct subregions of the amygdala (Bzdok et al., 2012), supplementary motor area (Eickhoff et al., 2011), temporo-parietal junction (Bzdok et al., 2013) and dorsolateral prefrontal cortex (Cieslik et al., 2013).

To our knowledge, a data-driven parcellation of the hippocampal formation using MACM maps has not been conducted (but see Bonnici et al., 2012). However, given the complexity of the hippocampal formation, with respect to its geometry, anatomical differentiation and connectivity, we focused on the subiculum rather than the entire region. Continuous with the CA1 region of the hippocampus, but located within the parahippocampal gyrus in humans (Duvernoy, 2005), the subiculum provides a central role in the integration of information within the hippocampus (Naber et al., 2000) as well as its transmission to other brain regions (Witter, 2006). The subiculum has also gained attention in the context of pathophysiological models for a variety of psychiatric conditions, in particular those with a component reflecting maladaptive responses to stress (Herman and Mueller, 2006), including schizophrenia, addiction and mood disorders (Belujon and Grace, 2014; Grace, 2010). Consistent with the presence of functional differentiation across the structure, distinct behavioral consequences of dorsal and ventral subiculum manipulations have been observed in rodents (Andrzejewski et al., 2006; Caine et al., 2001). The dorsal-most regions of the subiculum are known to contain place cells which encode location within the spatial domain (O'Mara, 2006). However, as one moves ventrally, this location information is overlaid with limbic inputs. Thus, ventral regions are able to encode the emotional salience of a location, consistent with a contextual signal (Grace, 2012). This functional segregation is mirrored by distinct patterns of anatomical connectivity across the rodent subiculum. The entire structure is connected to the septum, thalamus, mammillary bodies and retrosplenial cortex, although each region receives topographically organized projections. In addition, the ventral subiculum is connected to orbital and medial prefrontal cortex, nucleus accumbens (Aggleton, 2012; Groenewegen et al., 1987; Witter, 2006), and shows bidirectional connectivity with the amygdala (French et al., 2003). Anterior cingulate and prelimbic regions of the rodent prefrontal cortex receive input from the dorsal subiculum, whereas infralimbic regions receive input from ventral subiculum (Witter, 2006). Finally, some investigations have hinted at the presence of an intermediate region with mixed anatomical connectivity (Groenewegen et al., 1987; Strange et al., 2014; Wright et al., 2013).

Although the small size of the subregion and the resolution of imaging studies within the BrainMap database provides an upper limit on our ability to distinguish the subiculum per se from other nearby regions, this region was chosen as a seed for our analyses for two principle reasons: first, as the subiculum is generally considered to be an important output node through which the hippocampus proper communicates with downstream regions, estimates of functional connectivity are likely to be interpretable in terms of the pattern of known efferent connections from the region. Moreover, a prevailing interpretation of local BOLD signals (e.g. Bartels et al., 2008) might suggest that regions which receive synaptic input directly from the hippocampus should provide a promising place for initial focus. Second, the region, as defined by the cytoarchitectonic work of Amunts et al. (2005) is a relatively long, thin structure which traverses the entire anterior/posterior axis of the hippocampal formation. Although this limited resolution in the medial–lateral dimension, it provided a potential for discrimination in the dimension of interest. We were therefore optimistic that a data-driven parcellation of the region would reflect the functional differentiation across the anterior/posterior axis of the hippocampal formation.

In the present study, we aimed to map the subiculum based on regional patterns of functional connectivity using whole brain maps describing the co-occurrence of significant activations across studies. These maps were generated using the BrainMap database for each voxel within the subiculum. The cross-correlation of whole-brain co-occurrence of significant activations between each pair of seed voxels within the subiculum was computed. Clusters of seed voxels with similar patterns of connectivity were determined. The obtained clusters were cross-validated using multivariate clustering methods (Clos et al., 2013). We also aimed to map the (specific) whole-brain interaction pattern of the identified subregions using both task (using MACM) and resting state (examining variation in low frequency resting state BOLD) functional connectivity analyses. We investigated the extent to which the MACM and resting fMRI signals overlapped by using activation loci defined by the former to mask the latter, as well as performing whole brain analyses of each. A final aim was to characterize the functions of the resulting sub-regions with reference to the behavioral taxonomy information in the BrainMap database. We performed a functional characterization of the region via statistical forward and reverse

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