Title: Space and Memory (far) beyond the Hippocampus: Many Subcortical Structures also Support Cognitive Mapping and Mnemonic Processing

Shane M. O'Mara¹ and John P. Aggleton²

1. School of Psychology and Institute of Neuroscience, Trinity College, Dublin, D02 PN40, Ireland

2. School of Psychology, Cardiff University, Cardiff, Wales, UK CF10 3AT

Acknowledgements

The work described here was supported in part by a Wellcome Trust Senior Investigator Award to JPA and SMOM, and a Science Foundation Ireland Principal Investigator Award to SMOM.

Word Count

Abstract: 215 words

Main body: 5263 Words

References: 108

Key Words: memory, hippocampal formation, space, anterior thalamus, claustrum, diencephalic amnesia

Abstract

Memory research remains focused on just a few brain structures – in particular, the hippocampal formation (the hippocampus and entorhinal cortex). Three key discoveries promote this continued focus: the striking demonstrations of enduring anterograde amnesia after bilateral hippocampal damage; the realisation that synapses in the hippocampal formation are plastic e.g., when responding to short bursts of patterned stimulation ('long-term potentiation' or LTP); and the discovery of a panoply of spatially-tuned cells, principally surveyed in the hippocampal formation (place cells coding for position; head-direction cells, providing compass-like information; and grid cells, providing a metric for 3D space). Recent anatomical, behavioural, and electrophysiological work extends this picture to a growing network of subcortical brain structures (including the anterior thalamic nuclei, rostral midline thalamic nuclei, and the claustrum). There are, for example, spatially-tuned cells in all of these regions, including cells with properties similar to place cells of the hippocampus proper. These findings add new perspectives to what had been originally been proposed - but often overlooked - half a century ago: that damage to an extended network of structures connected to the hippocampal formation results in diencephalic amnesia. We suggest these new findings extend spatial signalling in the brain far beyond the hippocampal formation, with profound implications for theories of the neural bases of spatial and mnemonic functions.

Introduction

An intensive research effort over the past four decades has revealed that discrete populations of cells, present in widely distributed networks in the brain, code for differing aspects of three-dimensional space (for comprehensive reviews, see Grieves and Jeffery; 2017; Hunsacker and Kesner, 2018). There has been a particular and substantial research emphasis on the precise roles played by two connected structures (the entorhinal cortex and the hippocampus; collectively, the hippocampal formation), because these structures have been identified as playing key roles in certain types of memory (and, particularly, in spatial memory). Less attention has been given to the roles played by certain structures connected to the hippocampal formation, although these structures also play similarly vital roles in memory.

Here, we will focus on spatial mapping functions subserved by particular brain regions and networks, similar to those performed by the hippocampal formation: namely, the rostral midline and anterior nuclei of the thalamus, as well as the claustrum. These regions are less investigated and less well-understood than the hippocampal formation; they are not as frequently incorporated into theoretical accounts of spatial coding in the brain, and are less well-recognised as spatial processing nodes. (The one possible exception concerns the appreciation that the anterodorsal thalamic nucleus contains head-direction cells; Taube, 1995; 2007). Unexpectedly, there are cells in all of these regions that code for aspects of three-dimensional space, including positional information, boundary or perimeter information, as well as head directional and object information (Jankowski et al., 2014; 2015; 2017; Jankowski and O'Mara, 2015; Matulewicz et al., 2019). Moreover, it is now clear that lesions of the rostral and anterior thalamic nuclei can result in deficits in the performance of spatial and non-spatial tasks that appear comparable to those resulting from lesions within the entorhinal-hippocampal axis. The few lesion investigations of the claustrum indicate that claustral lesions also disrupt certain aspects of spatial processing.

Memory research has focused especially on the hippocampal formation

The effort to understand how the brain encodes and supports memory functions has been underway for well over a century (Squire, 1987; Aggleton and Morris, 2018). Over that time, substantial progress has been made in elucidating the brain structures that support memory (including spatial memory), with one particular region remaining in the spotlight, namely, the hippocampal formation Buzsaki and Moser,

2013). Memory research has focused particularly on the hippocampal formation for at least three interrelated reasons. The early description of the amnesic Patient HM demonstrated a clear and striking case of amnesia that has often been attributed to bilateral loss of the hippocampal formation (Scoville and Milner, 1957). Despite the fact that the surgery clearly involved additional grey and white matter (Annesse et al., 2014), HM's amnesia case-study continues to exercise a powerful hold on theoretical and experimental analyses in the memory literature. His near life-long, enduring and non-resolving amnesia, has provided, and continues to provide, a source of fertile hypotheses regarding the neural bases of learning and memory. A second reason for focusing on the hippocampal formation was the important and influential demonstration that synapses in the hippocampus were plastic ('long-term potentiation' or LTP), resulting from a brief period (~1 s) of high-frequency electrical stimulation; LTP was initially comprehensively demonstrated by Bliss and Lomo (1973), after an original prediction by Hebb (1949). Subsequent demonstrations that pharmacological inhibitors of hippocampal long-term potentiation effectively inhibited learning and memory in spatial memory tasks, have also provided a rich source of theory and experiment focused on the role of the hippocampal formation in learning and memory (e.g., Bliss and Collingridge, 1993; Grewe et al., 2017; Larkin et al., 2008; Lynch, 2004; Malenka & Bear, 2004; Tsokas et al., 2016; Van Praag et al., 1999). Added information has come from recent 'engram' studies, which appear to show that the stimulation of specific hippocampal cell ensembles can reactivate a representation, e.g., a particular context (Park et al., 2016; Tonegawa et al., 2015).

The third powerful impetus derives from the work of John O'Keefe and his collaborators over the past four decades (e.g., Krupec et al., 2015; O'Keefe & Burgess, 1996; O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978, 1979). In particular, O'Keefe's work reanimated earlier suggestions by Edward Tolman (1948) that there must be a 'cognitive map' within the brain. Tolman's experiments showed that rats were capable of engaging in 'latent' learning – learning 'on the fly' whilst exploring mazes, and subsequently using this information to solve route finding problems on these self-same mazes when usual routes to reward were blocked (see also O'Mara, 2017). Tolman speculated that, contrary to the motor movement reinforcement theories of Clark Hull and others (e.g. Hull, 1943; Spence, 1956), rats were inducing or inferring something like a 'survey map' of their environment, which allowed them to flexibly navigate that environment. O'Keefe's demonstration of the existence of place cells in the hippocampus (O'Keefe and Dostrovsky, 1971) and his subsequent elaboration of the cognitive mapping theory with Lynn Nadel (O'Keefe and Nadel, 1978) in their book *'The Hippocampus as a Cognitive Map'* ensured that the hippocampus would be a focus for investigations of spatial processing by the brain.

In the decades after O'Keefe's initial demonstration of the existence of place cells, further discoveries indicated that the brain coded for differing aspects of three dimensional space. In particular, the head-direction cells described by Ranck and Taube (Taube et al, 1990a,b) suggested that, in addition to representations of place, the brain also maintains a representation of a compass-like heading in relation to the external three-dimensional world. However, missing from this picture was a sense for how the brain might code a metric for space – a sense of relative distance, and how a metric for space might play a role in spatial processing. The discovery of 'grid cells' within the entorhinal cortex by Hafting et al. (2005) provided this missing link, powerfully reinforcing the idea that the entorhinal-hippocampal axis plays *the* central role in how the brain codes for space.

Current theories (e.g. Moser & Buzsaki, 2013) of the means by which the brain represents space (and memory) rely on an anatomical model revolving around the existence of cells representing position (place cells), heading (head-direction cells) and relative distance (grid cells). The key structures implicated are the hippocampal formation (principally concerned with representing spatial position), parahippocampal and related anterior thalamic areas (principally concerned with representing heading information), and entorhinal cortex (principally concerned with representing metric information). This tripartite anatomical-structural model now dominates theoretical views of spatial navigation and spatial representation. Biologically-inspired models of spatial navigation rely similarly on core ideas revolving around the dissociation of place information from heading information and their subsequent integration in other downstream areas to facilitate goal-directed navigation (e.g. Barrera & Weitzenfeld, 2008). We suggest that there are important components of this overall theoretical picture missing, in particular relating to evolutionarily-conserved brain regions under-explored to this point. We further suggest that significant revision of current models of how the brain controls behavioural choices in a spatial context may be warranted.

Here, we briefly review evidence suggesting that this dominant picture needs a considerable degree of extension. The hippocampal formation has vital interconnections with a wide variety of brain regions, so much so, in fact, that Aggleton and Brown (1999) suggested we should more properly think of an 'extended hippocampal formation' when considering memory (see also Delay & Brion, 1969; Ranganath & Ritchey, 2012). Key elements within the extended hippocampal formation include the fornix, the mammillary bodies, the anterior thalamic nuclei, and retrosplenial cortex (Bubb et al., 2017). What are now archaic neuroanatomical constructions (such as 'the trisynaptic loop') are giving way to recent neuroanatomical and neurophysiological investigations, suggesting that interactions between the

hippocampal formation, as a key spatial hub, in association with a distributed network of other key locations is a more appropriate functional neuroanatomical conception of the structures that support cognitive mapping.

Evidence from neodecorticate animal preparations

In the 1970s and 1980s a number of investigators investigated what functions could continue to be performed in the absence of a cerebral cortex and hippocampal formation. These preparations usually involved a bilateral removal of the developing cerebral cortex and hippocampus (decortication) at various time points postnatally. Such studies are rarely performed now. However, these early studies indicated that in the absence of a cortex and hippocampus, decorticate rats were capable of learning a variety of spatial and non-spatial tasks. These included nesting, food retrieval and foraging, and successfully returning to a point of origin, and the learning of complex spatial tasks where errors were prevented (for reviews, see Kolb & Whishaw, 1989; Whishaw, 1990). Furthermore, decorticate animals were also capable of successfully learning stimulus relations and responses in a variety of classical conditioning tasks, suggesting that the learning of classically-conditioned avoidance responses dependent on temporal relations remains intact in these animals. Subsequent investigation suggested that such learning requires intact cerebellar and brainstem nuclei, particularly using the rabbit classically-conditioned nictitating membrane (NMR) preparation (McCormick and Thompson, 1984; Thompson, 1986). In an interesting convergence, more recent work by Rochefort et al. (2011) has demonstrated that genetically-modified L7PKCI mice with deficits in PKC-dependent plasticity at parallel fiber–Purkinje cell synapses in the cerebellum have defective place cell processing in tasks requiring vestibular self-motion cues.

Event memory and the anterior thalamic nuclei

More than 80 years ago, James Papez (1937) proposed that ‘the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, and the hippocampus, and their interconnections, constitute a harmonious mechanism which may elaborate the functions of central emotion as well as participating in emotional expression’. Although sometimes overlooked by certain theorists, the notion of a ‘*Papez circuit*’ was and continues to be a highly influential concept, in particular because Papez, firstly, correctly highlighted a major circuit critical for overall hippocampal function; and secondly, Papez placed the hippocampus clearly within a network connected to a wide variety of anatomically-connected and functionally-

conserved structures (Bubb et al., 2017). Papez' emphasis on emotion was, in certain respects, somewhat misplaced (although ventral hippocampal structures certainly play a role in regulating the HPA axis, and therefore, the stress response; Herman & Mueller, 2005; Lowry, 2002; Myers et al., 2017; Ulrich-Lai & Herman, 2009).

A considerable volume of data from diverse sources support the idea that the anterior thalamus also plays a critical and central role in explicit, event memory. The phenomenon of diencephalic amnesia (the best known example of which is Korsakoff's amnesia or syndrome; Albert et al., 1979) strongly suggests that the mnemonic deficits seen in these patients derives from degeneration of the anterior thalamic and closely-related nuclei, especially the mammillary bodies (Harding et al., 2000; Segobin et al., 2019; Vann & Aggleton, 2004; Vann & Nelson, 2015). Similarly, studies of patients with rostral thalamic strokes that disrupt the projections from the mammillary bodies to the anterior thalamic nuclei (Carlesimo, 2011) add further support for the importance of these sites for episodic memory. Moreover, patients with bilateral fornix damage show deficits in memory on verbal and non-verbal tasks that tax supraspan item memory, while short-term memory tasks are spared (Hodges & Carpenter, 1991; McMackin et al., 1995). Significant correlations between recollective memory and mammillary body volume in such cases further reinforce the notion that hippocampal – medial diencephalic interactions have a vital role in aspects of episodic memory (Tsivilis et al., 2008). Complementary observations have been made in both fornix-transected monkeys (e.g., Gaffan, 1994) and fornix-transected rats (e.g., Ennaceur & Aggleton, 1997). The key finding across differing patient groups is that the pattern of memory deficits in diencephalic amnesia appears both qualitatively and quantitatively similar as that in amnesiacs with relatively selective hippocampal pathology (Aggleton, 2008).

Spatial coding by neurons in the main hippocampal output: the subiculum

The subiculum is the main, yet largely underexplored, output target for hippocampal area CA1 (and thus for the hippocampus proper). There have been relatively few investigations of the firing properties of subicular cells, compared to area CA1 place cells; we briefly survey some here. Unlike area CA1, the subiculum displays a remarkable heterogeneity of spatial responding. Sharp and Greene (1994) found that there were indeed neurons in subiculum showing location-specific activity; their firing fields tended to be somewhat larger and more variable than those of area CA1. Subicular cells also displayed ectopic spiking – that is, they showed much higher rates of 'out-of-field' firing compared to hippocampal CA1 place cells. They also found that subicular neurons could be classified as bursting and non-bursting

types, based on their spiking, similar to previous observations in vitro (see also Anderson and O'Mara, 2003; Jung et al., 2001; Staff et al., 2000; Stewart and Wong, 1993). Anderson and O'Mara (2004) reported that subicular cells do not respond to the presence or movement of objects within an arena, but instead their activity is best predicted by the position and movement of the rat within the arena (behaviourally, the animal did respond to the movement of the objects, suggesting such spatial-object manipulations are subserved by a network independent of subiculum). Subsequently, Brotons-Mas et al. (2011) showed that about 45% of subicular place cells showed remarkable stability in across multiple light and dark transitions: these cells showed no evidence for remapping during multiple transitions across light and dark explorations of an open field. The remaining cells showed some degree of remapping, with some units replicating their locational firing across specific light-to-dark conditions, whereas others were strongly affected by light–dark transitions. Brotons-Mas et al. suggested that because a plurality of units were stable across light–dark transitions, the subiculum participates in or supports the neurocognitive processing underlying path integration, because subicular units appear relatively unresponsive to visual inputs, and are perhaps more responsive to cues arising from whole-body movement. Subsequently, Brotons-Mas et al. (2017) conducted extensive spatial phenotyping of subicular spatial responses using a foraging task in two experimental paradigms – a variably-sized recording arena (small, medium, large), and an arena with systematically inserted barriers in differing locations. Subicular units showed strongly heterogeneous spatial coding, with place cells, barrier- or perimeter-related cells, as well as boundary-vector cells, and certain units that showed grid-like patterns of activity in larger arenas. The subiculum, therefore, seems to code space in a flexible manner, being involved in the processing of allocentric information, external cues, and path integration, thus broadly supporting spatial navigation.

Spatial coding by neurons in the anterior thalamic nuclei

It has been known for some time that the anterodorsal nucleus of the thalamus has a substantial population of head-direction cells, with head direction cells present in both the anterodorsal nucleus (Blair and Sharp, 1995; Goodridge and Taube, 1997) and the anteroventral nucleus (Tsanov et al., 2011) of the thalamus. The former contribute to path integration (Frohardt et al., 2006), and navigation in 3D space (Laurens et al., 2017; Page et al., 2017). Less is known regarding spatial coding in the other anterior thalamic nuclei and other rostral thalamic nuclei. These sites are of particular interest as the subiculum provides dense, direct inputs to the anteromedial and anteroventral nuclei, while the postsubiculum (presubiculum) projects directly to the anterodorsal thalamic nuclei (Bubb et al., 2017;

Meibach & Siegel, 1977; van Groen & Wyss, 1999a,b). Of the various midline nuclei, nucleus reuniens stands out because of its inputs from the subiculum and CA1, as well as its dense, direct projections to the hippocampus, especially to CA1 (Herkenham, 1978; Vertes et al., 2007). Based on their respective connectivity, it had previously been predicted that the anterior thalamic nuclei process information with high spatial and temporal resolution (Aggleton et al., 2010), whereas rostral midline thalamic nuclei would have more diffuse roles in attention and arousal (Van der Werf et al., 2002; Vertes et al., 2007). Our current findings strongly support the first prediction but appear to substantially moderate the second prediction, because they show the widespread presence of a diverse population of spatially-responsive neurons in these nuclei.

In nucleus reuniens, for example, there is an (unexpected) population of cells coding for head direction (Jankowski et al., 2014), extending the numbers of brain regions coding for head direction to at least 10 (Grieves and Jeffery, 2017). The head-direction cells found in nucleus reuniens are similar in a great many respects to those found in other regions that show head direction coding: they are not affected by changing visual conditions from light to dark and back to light, or by changing arena shape; they do not remap across days, maintaining a constant orientation. They are also present from the first exposure to the recording environment. Interestingly, theta-cycle skipping cells are also present in nucleus reuniens, similar to the theta-skipping cells found in entorhinal cortex (e.g., Brandon et al., 2013); these nucleus reuniens theta-skipping cells do not code either for head direction or for place, and may instead perform a clock-like or timing function. Finally, nucleus reuniens head directions cells are not place cells: they are not spatially-modulated in the sense of having of a place-related signal (Jankowski et al., 2014).

Nucleus reuniens also provides a substantial anatomical output to hippocampal area CA1, offering a means by which its head-direction cells can modulate spatial coding in the hippocampus proper. Cholvin et al. (2018) have found that combined lesions of the rhomboid nucleus and nucleus reuniens (ReRh) do not affect place cell spatial characteristics of hippocampal CA1 neurons, in familiar, but not unfamiliar, environments. In their experiments, rats explored either familiar or a novel environment; they found no changes post-ReRh lesion in the spatial characteristics of CA1 place cells while rats explored a familiar environment. However, after ReRh lesions, spatial coherence decreased for the first exploration session in a novel environment. Recordings conducted over a five-day period showed that ReRh lesions resulted in a marked and enduring decrease in place field stability and lower firing variability. These data suggest that the input from ReRh modulates spatial remapping in the hippocampus; it may be that the head directional signal provides a stabilising directional signal while exploring unfamiliar environments.

Jankowski et al. (2015b) recorded in the parataenial (PT) nucleus, anteromedial (AM) nucleus, and nucleus reuniens (NRe), finding place cells and other spatial cells in each of these nuclei. In PT 29.2% of cells recorded were place cells, whereas 6.2% of cells recorded in AM were place cells, with head direction cells a further 9.7% of recorded cells, with a small number of perimeter/border cells (0.5%). The percentages of place cells recorded in NRe was 2.0%, and 2.0% perimeter/border cells; head direction cells were described separately (Jankowski et al., 2014) and quantified at 8.7%. The variation in the percentage of place cells present across these nuclei suggests that the spatial code is more or less sparse for the differing nuclei. More than this, the phenotypic characteristics of the place cells vary in these differing nuclei, with the place fields of cells in nucleus reuniens being the largest and, thereby, carrying the lowest spatial information. Meanwhile, the place fields in the parataenial nucleus occupy the smallest percentage of the recording arena, carrying the highest spatial information. The anteromedial nucleus occupies an intermediate position. In other words, across these anatomically-related nuclei, there appears to be a spatial information content gradient.

In addition to place cells, there is also a population of neurons that respond to the presence of impassable perimeters in the recording arena. These neurons are found in nucleus reuniens and the anteromedial thalamic nucleus (Jankowski et al., 2015). Temporal evolution analyses suggest that the perimeter cells and place cells in these nuclei appear on the first exposure of the animal to the arena. Finally, recordings in the anteromedial nucleus of the thalamus also disclose a population of head-direction cells in a hitherto unsuspected and untheorised-about location. These head-direction cells are active also from the first exposure of the animal to the arena, suggesting that early preprocessing of spatial information occurs rapidly in subcortical brain structures.

Perimeters are an important part of the environment, as they formally shape the geometry of the perceptible environment, as well as constraining behavioural trajectories. Perimeters can comprise vertical walls, vertical drops, water courses, etc.; they can be impassable, or can be passed through at crossings of various types (some perimeters may be perceptual, as in light-to-dark perimeters, perhaps signalling danger or safety). Matulewicz et al. (2019) have surveyed perimeter-related discharge of units in the anteromedial and parataenial nuclei. Matulewicz et al. found neurons whose firing patterns reflected the presence of walls and drops, irrespective of arena shape (circular or square). Moreover, the firing patterns of these perimeter-responsive units were stable across multiple sleep-wake cycles, and were independent of either light or dark conditions, suggesting that these units are not directly modulated by visual input. Furthermore, these neurons respond in similar ways to both opaque and

clear barriers; this latter feature is remarkable, because ‘see-through’ or clear barriers (such as Plexiglas) are not part of the natural environment. These neurons respond to perimeter modifications by remapping their firing when two walls of the four present in a rectangular recording arena are removed from recording session to recording session.

Summary of spatial coding by anterior thalamic nuclei

Overall, recordings within the various rostral thalamic nuclei reveal the presence of spatially-responsive cells. The origin of their spatial signals is not yet known, leaving us with (at least) three hypotheses to entertain. The first is that the hippocampal and rostral thalamic spatial systems operate in parallel (in a fashion similar to the accessory optic system); secondly, that one is subordinate to the other, for example the hippocampal formation provides information necessary for the spatial activity observed in the rostral thalamus, or vice versa; and thirdly, that there are reciprocal and interdependent relationships between these spatial nodes.

Current findings only provide an incomplete data-set with regard to these three hypotheses. Most of the focus has been on the consequences of anterior thalamic lesions upon hippocampal and parahippocampal activity, stemming from the significance of the anterodorsal nucleus for head-direction signals (Taube, 1995). Consequently, it is known that anterior thalamic lesions cause an absence of postsubiculum head-direction signals (Goodridge & Taube, 1997). While postsubiculum lesions change the properties of anterodorsal head-direction cells, these cells are still present (Goodridge & Taube, 1997), reflecting an asymmetric relationship. Likewise, a disruption of the head-direction network following anterior thalamic lesions impairs parahippocampal ‘grid cell’ activity (Winter et al., 2015), although the opposite relationship has yet to be investigated. Meanwhile, CA1 place cells appear largely unaffected after anterior thalamic lesions (Calton et al., 2003). Consequently, with the exception of the head-direction network, little is known about the interdependencies of the various spatial cell types found in the hippocampal formation and anterior thalamus.

Spatial signalling and other possible functions performed by the claustrum

The claustrum is an underexplored and enigmatic paracortical structure. The claustrum of the rat is a bilateral subcortical sheet of grey matter, spanning approximately the rostral half of the telencephalon, almost to the frontal poles, and caudally to the motor strip. It is bordered by the orbitofrontal cortex, rostrally, both caudally and medially by the caudoputamen, and by the insular cortex laterally

(Dillingham et al., 2017; 2019). Anatomically, the claustrum receives projections from the entire cortical mantle. These projections are organised in a topographic fashion, with association cortex projecting to anterior claustrum and sensory cortices projecting to the posterior portion of the claustrum. In addition, there are also claustrum connections to and from the hippocampal formation, retrosplenial cortex, entorhinal cortex, and a wide variety of subcortical structures (although the existence of projections from the anterior thalamus to the claustrum continues to be a matter of debate (Dillingham et al., 2017; 2019). Comprehensive lesion investigations of the claustrum have yet to be undertaken for technical reasons: the claustrum is a difficult target for the injection-targeting used in lesion analyses, although chemogenetic approaches (such as DREADDs) may prove more tractable.

There have been many hypotheses regarding the functions of the claustrum over the years, notably that it orchestrates consciousness in the mammalian brain (Crick and Koch, 2005). There have been intermittent anatomical explorations of the claustrum that conclude it does not comprise striatal tissue, but rather can be thought best of as a paracortical tissue. Functional investigations of the claustrum are relatively few in number; we briefly survey some relevant studies here. There have been very few lesion studies of the claustrum. Aclaustral humans are rarely reported: one study of a patient with striking, transient, but symmetric, bilateral, claustral lesions arising from mumps encephalitis; Ishii et al. (2011) reported that during the acute phase of infection this patient experienced visual and auditory hallucinations which resolved with treatment for concurrent epilepsy. The infection resolved and subsequent imaging showed no persisting lesions of the bilateral claustrum. Intriguingly, Cascella et al. (2011) report that schizophrenic patients with delusions may have an atrophic left claustrum. Another study (Koubeissi et al., 2014) of a human epilepsy patient implanted with deep-brain electrodes in the claustrum reported loss of consciousness on stimulation onset, and return of consciousness on stimulus offset. The patient had previously undergone a left hippocampal resection for epilepsy; she was seizure-free for four years, after which her seizures returned. Depth electrodes were implanted for seizure sampling. The results of stimulation of the claustral electrode were dramatic: stimulation ‘resulted in immediate impairment of consciousness, in 10 out of 10 times, with arrest of reading, onset of blank staring, unresponsiveness to auditory or visual commands, and slowing of spontaneous respiratory movements. The patient returned to baseline as soon as the stimulation stopped with no recollection of the events during the stimulation period.’

Olson and Graybiel suggested (1980) that there is a somatosensory map of the complete surface of the body, arranged longitudinally in the claustrum (in the anaesthetised cat preparation). Remedios et al. (2010) have recorded claustral neurons in the conscious, behaving, head-fixed non-human primate, finding neurons responsive to a variety of naturalistic sensory stimuli, especially auditory and visual stimuli. They concluded that the claustrum overall is a multisensory structure, but that individual claustral neurons are unimodal, and these unimodal neurons are the prevalent neurons present in this preparation. Remedios et al. (2012) also reported in conference proceedings that when a claustral rats were placed in the center of an eight-arm radial arm maze, they would freeze, apparently unable or unwilling to explore any of the arms. These data await a full report, however.

Jankowski and O'Mara (2015) conducted what appears to be the first freely moving recordings in the rat claustrum. These recordings, remarkably, disclose the existence of a population of spatially-responsive neurons in the claustrum, including place cells, perimeter cells, and object responsive cells. Claustral place cells do not remap during light-dark-light transitions, although their spatial information content falls a little in the dark, and is restored in the light. Visual input, therefore, does not seem to affect claustral place cell position, although it does have some effect on claustral place cell spatial information content. Analyses of the temporal evolution of claustral place cells show that they appear to be present from the earliest exposure to the environment. Object responsive cells in the claustrum respond to an initial presentation of an object (for example, a glass bottle) with increased firing activity around the object, and near-zero firing activity away from the object. These cells track the repositioning of the object. Moreover, claustral place cells do not respond to the presence of an object. By contrast, the firing fields of claustral object-responsive cells track the positioning and repositioning of the object in the environment. Claustral units also respond to the perimeter of the environment, showing a penumbra of activity associated with an impassable perimeter. This firing field is very tightly bound to the perimeter, and such cells exhibit near-zero firing rates away from the perimeter itself. Finally, Jankowski and O'Mara (2015) also noted the presence of both theta-modulated and fast-firing bursting cells in the claustrum. The fast-firing cells fired up to 30 Hz or more. These fast-firing cells are not spatially-modulated or spatially-responsive.

One hypothesis that accounts for this unexpected pattern of activity is that the claustrum dynamically represents extended space (in a similar fashion to hippocampal area CA1) but that the claustrum also incorporates landmark (or object) information. We have not, however, observed the presence of head-direction cells in the claustrum. The existence of these claustral spatial cells is remarkable, as they are

currently unpredicted by any current theory of claustral function, or indeed, any more general theory of the representation of space within the mammalian brain. It may be that the claustrum provides dynamic information about body position and landmark information to the cortex in order to enable moment-to-moment control of behaviour.

Some speculations and conclusions

The hippocampus, anterior thalamus, and claustrum show a remarkable rapidity and speed (instantaneity) of spatial coding. Maps of space emerge very rapidly and are representationally rich. At present, we do not have a good theoretical account for why there is such redundancy in spatial representations in the brain, nor do we have a good theory to predict across differing neural systems the rapid emergence of such representationally rich coding. One hypothesis worth considering is that of Barsalou (2010) who suggests that 'The cognitive system utilises the environment and the body as external informational structures that complement internal representations...internal representations of a situated character, implemented via simulations in the brain's modal systems, making them well suited for interfacing with external structures'. There has been comparatively little consideration given in contemporary neuroscience to the idea that the brain uses the external environment as a kind of 'cognitive surface', or that it supports the structure of cognition. This might reflect the bias in sensory neuroscience, which has followed the stimulus from the receptor surface into the brain. However, behavioural responses are not aligned along sensory axes; rather, intrinsic activity within the brain determines, in large part, the nature of the processing of sensory stimuli are subjected to (Dadarlat & Stryker, 2017; Raichle, 2015; Stringer et al., 2019; Yamins & DiCarlo, 2016).

The hypothesis that the anterior thalamus engages in extensive preprocessing of stimuli, and generates the elements, or at least some elements of a cognitive map, is an attractive one, for it allows an exploration of the idea that differing types of maps are important at differing temporal scales. Such maps might be adaptively significant, depending on the behavioural and environmental context the organism is in. Invoking action maps to escape a predator requires instantaneous action selection and route selection, whereas latent learning during safe periods of exploration might operate on an entirely different temporal scale instead. It may be that the claustrum, given its cortical anatomical position and connectivity allows the rapid selection of action responses in 3D space, when there are temporal constraints requiring the rapid co-ordination of adaptive behavioural responses. The extended hippocampal formation (entorhinal cortex-hippocampus-anterior thalamus) might, by contrast, more

specifically engaged in richer representational action over longer time scales (an idea that finds merit in the possible role of the extended hippocampal formation in imagination and prospection: Buckner, 2010; Maguire & Hassabis, 2011; Zeidman & Maguire, 2016).

Finally, we note that biologically-inspired models of spatial navigation rely on core ideas revolving around the dissociation of place information from heading information and their subsequent integration in other downstream areas to facilitate goal-directed navigation (e.g., Barrera & Weitzenfeld, 2008). Here, we suggest that there are important components of this overall theoretical picture missing, in particular relating to an extended and extensive variety of evolutionarily-conserved brain regions (particularly the thalamic nuclei, but also the claustrum), which support a wide range of spatial functions. These brain regions continue to be under-explored to this point. We further suggest that significant revision of current models of how the brain controls behavioural choices in a spatial context may be warranted.

References

- Aggleton, J.P. (2008). Understanding anterograde amnesia: disconnections and hidden lesions. *Quarterly Journal of Experimental Psychology*, 61, 1441-1471.
- Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal–anterior thalamic axis. *Behavioral and Brain Sciences*, 22(3), 425-444.
- Aggleton, J. P., & Morris, R. G. (2018). Memory: Looking back and looking forward. *Brain and Neuroscience Advances*, 2, 1-9, 2398212818794830.
- Aggleton, J. P., O'Mara, S. M., Vann, S. D., Wright, N. F., Tsanov, M., & Erichsen, J. T. (2010). Hippocampal–anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. *European Journal of Neuroscience*, 31(12), 2292-2307.
- Albert, M. S., Butters, N., & Levin, J. (1979). Temporal gradients in the retrograde amnesia of patients with alcoholic Korsakoff's disease. *Archives of Neurology*, 36(4), 211-216.
- Anderson, M. I., & O'Mara, S. M. (2003). Analysis of recordings of single-unit firing and population activity in the dorsal subiculum of unrestrained, freely moving rats. *Journal of Neurophysiology*, 90(2), 655-665.
- Anderson, M. I., & O'Mara, S. M. (2004). Responses of dorsal subicular neurons of rats during object exploration in an extended environment. *Experimental Brain Research*, 159(4), 519-529.
- Annese, J., Schenker-Ahmed, N. M., Bartsch, H., Maechler, P., Sheh, C., Thomas, N., ... & Klaming, R. (2014). Postmortem examination of patient HM's brain based on histological sectioning and digital 3D reconstruction. *Nature Communications*, 5, 3122.
- Barrera, A., & Weitzenfeld, A., 2008. Biologically-inspired robot spatial cognition based on rat neurophysiological studies. *Autonomous Robotics*, 25, 147-169.
- Barsalou, L. W. (2010). Grounded cognition: Past, present, and future. *Topics in Cognitive Science*, 2(4), 716-724.

Blair, H.T., & Sharp, P.E. (1995). Anticipatory head direction signals in anterior thalamus: evidence for a thalamocortical circuit that integrates angular head motion to compute head direction. *Journal of Neuroscience*, 15, 6260–6270.

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, 361(6407), 31.

Bliss, T. V., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, 232(2), 331-356.

Brandon, M.P., Bogaard, A.R., Schultheiss, N.W., Hasselmo, M.E. (2013). Segregation of cortical head direction cell assemblies on alternating θ cycles. *Nature Neuroscience* 16:739–748.

Brotons-Mas, J. R., Montejo, N., O'Mara, S. M., & Sanchez-Vives, M. V. (2010). Stability of subicular place fields across multiple light and dark transitions. *European Journal of Neuroscience*, 32(4), 648-658.

Brotons-Mas, J. R., Schaffelhofer, S., Guger, C., O'Mara, S. M., & Sanchez-Vives, M. V. (2017). Heterogeneous spatial representation by different subpopulations of neurons in the subiculum. *Neuroscience*, 343, 174-189.

Bubb, E. J., Kinnavane, L., & Aggleton, J. P. (2017). Hippocampal–diencephalic–cingulate networks for memory and emotion: An anatomical guide. *Brain and Neuroscience Advances*, 1, 1-20. DOI: 10.1177/2398212817723443

Buchanan, K. J., & Johnson, J. I. (2011). Diversity of spatial relationships of the claustrum and insula in branches of the mammalian radiation. *Annals of the New York Academy of Sciences*, 1225(1).

Buckner, R. L. (2010). The role of the hippocampus in prediction and imagination. *Annual Review of Psychology*, 61, 27-48.

Buzsáki, G., & Moser, E. I. (2013). Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nature Neuroscience*, 16(2), 130.

- Calton, J. L., Stackman, R. W., Goodridge, J. P., Arcey, W. B., Dudchenko, P. A., & Taube, J. S. (2003). Hippocampal place cell instability after lesions of the head direction cell network. *Journal of Neuroscience*, 23(30), 9719-9731.
- Carlesimo, G. A., Lombardi, M. G., & Caltagirone, C. (2011). Vascular thalamic amnesia: a reappraisal. *Neuropsychologia*, 49(5), 777-789.
- Cascella NG, Gerner GJ, Fieldstone SC, et al. (2011) The insula–claustrum region and delusions in schizophrenia. *Schizophrenia Research*, 133, 77–81.
- Cholvin, T., Hok, V., Giorgi, L., Chaillan, F. A., & Poucet, B. (2018). Ventral midline thalamus is necessary for hippocampal place field stability and cell firing modulation. *Journal of Neuroscience*, 38(1), 158-172.
- Crick, F. C., & Koch, C. (2005). What is the function of the claustrum? *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1458), 1271-1279.
- Dadarlat, M. C., & Stryker, M. P. (2017). Locomotion enhances neural encoding of visual stimuli in mouse V1. *Journal of Neuroscience*, 37(14), 3764-3775.
- Delay, J., & Brion, S. (1969). *Le syndrome de Korsakoff*. Masson.
- Dillingham, C. M., Jankowski, M. M., Chandra, R., Frost, B. E., & O'Mara, S. M. (2017). The claustrum: Considerations regarding its anatomy, functions and a programme for research. *Brain and Neuroscience Advances*, 1, 2398212817718962.
- Dillingham, C. M., Mathiasen, M. L., Frost, B. E., Lambert, M. A., Bubb, E. J., Jankowski, M. M., ... & O'Mara, S. M. (2019). The anatomical boundary of the rat claustrum. *bioRxiv*, 596304. (in press, *Frontiers in Neuroanatomy*)
- Ennaceur, A., & Aggleton, J. P. (1997). The effects of neurotoxic lesions of the perirhinal cortex combined to fornix transection on object recognition memory in the rat. *Behavioural Brain Research*, 88(2), 181-193.

- Frohardt, R. J., Bassett, J. P., & Taube, J. S. (2006). Path integration and lesions within the head direction cell circuit: comparison between the roles of the anterodorsal thalamus and dorsal tegmental nucleus. *Behavioral Neuroscience*, 120(1), 135-149.
- Gaffan, D. (1994). Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. *Journal of Cognitive Neuroscience*, 6(4), 305-320.
- Goodridge, J.P. & Taube, J.S. (1997). Interaction between the postsubiculum and anterior thalamus in the generation of head direction cell activity. *Journal of Neuroscience*, 17, 9315–9330.
- Grewe, B. F., Gründemann, J., Kitch, L. J., Lecoq, J. A., Parker, J. G., Marshall, J. D., ... & Lüthi, A. (2017). Neural ensemble dynamics underlying a long-term associative memory. *Nature*, 543(7647), 670.
- Grieves, R. M., & Jeffery, K. J. (2017). The representation of space in the brain. *Behavioural Processes*, 135, 113-131.
- Hafting, T., Fyhn, M., Molden, S., Moser, M. B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature*, 436(7052), 801.
- Harding, A., Halliday, G., Caine, D., & Kril, J. (2000). Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. *Brain*, 123(1), 141-154.
- Hebb, D. O. (1949). *The organization of behavior: A neuropsychological theory*. Psychology Press.
- Herkenham, M. (1978). The connections of the nucleus reuniens thalami: Evidence for a direct thalamo-hippocampal pathway in the rat. *Journal of Comparative Neurology*, 177(4), 589-609.
- Herman, J.P., & Mueller, N.K. (2006). Role of the ventral subiculum in stress integration. *Behavioural Brain Research*, 174, 215–24
- Hodges, J. R., & Carpenter, K. (1991). Anterograde amnesia with fornix damage following removal of IIIrd ventricle colloid cyst. *Journal of Neurology, Neurosurgery & Psychiatry*, 54(7), 633-638.
- Hull, C. L. (1943). *Principles of behavior: An introduction to behavior theory*.

Hunsaker, M. R., & Kesner, R. P. (2018). Unfolding the cognitive map: The role of hippocampal and extra-hippocampal substrates based on a systems analysis of spatial processing. *Neurobiology of Learning and Memory*, 147, 90-119.

Ishii, K., Tsuji, H., & Tamaoka, A. (2011). Mumps virus encephalitis with symmetric claustrum lesions. *American Journal of Neuroradiology*, 32(7), E139-E139.

Jankowski MM, O'Mara SM (2015a) Dynamics of place, boundary and object encoding in rat anterior claustrum. *Frontiers in Behavioral Neuroscience*, 9, 00250, DOI=10.3389/fnbeh.2015.00250.

Jankowski, M. M., Islam, M. N., Wright, N. F., Vann, S. D., Erichsen, J. T., Aggleton, J. P., & O'Mara, S. M. (2014). Nucleus reuniens of the thalamus contains head direction cells. *Elife*, 3, e03075.

Jankowski, M. M., Islam, M. N., & O'Mara, S. M. (2017). Dynamics of spontaneous local field potentials in the anterior claustrum of freely moving rats. *Brain Research*, 1677, 101-117.

Jankowski, Maciej M., Johannes Passecker, Md Nurul Islam, Seralynne Vann, Jonathan T. Erichsen, John P. Aggleton, and Shane M. O'Mara. (2015b). Evidence for spatially-responsive neurons in the rostral thalamus. *Frontiers in Behavioral Neuroscience*, 9, 256.

Jung, H. Y., Staff, N. P., & Spruston, N. (2001). Action potential bursting in subicular pyramidal neurons is driven by a calcium tail current. *Journal of Neuroscience*, 21(10), 3312-3321.

Koubeissi, M. Z., Bartolomei, F., Beltagy, A., & Picard, F. (2014). Electrical stimulation of a small brain area reversibly disrupts consciousness. *Epilepsy & Behavior*, 37, 32-35.

Laurens, J., Kim, B., Dickman, J. D., & Angelaki, D. E. (2016). Gravity orientation tuning in macaque anterior thalamus. *Nature Neuroscience*, 19(12), 1566.

Lowry CA (2002). Functional subsets of serotonergic neurones: implications for control of the hypothalamic–pituitary–adrenal axis. *Journal of Neuroendocrinology*, 14, 911–23.

Kolb, B., & Whishaw, I. Q. (1989). Plasticity in the neocortex: mechanisms underlying recovery from early brain damage. *Progress in Neurobiology*, 32(4), 235-276.

- Krupic, J., Bauza, M., Burton, S., Barry, C., & O'Keefe, J. (2015). Grid cell symmetry is shaped by environmental geometry. *Nature*, 518(7538), 232-235.
- Larkin, A. E., Fahey, B., Gobbo, O., Callaghan, C. K., Cahill, E., O'Mara, S. M., & Kelly, Á. M. (2008). Blockade of NMDA receptors pre-training, but not post-training, impairs object displacement learning in the rat. *Brain Research*, 1199, 126-132.
- Lynch, M. A. (2004). Long-term potentiation and memory. *Physiological Reviews*, 84(1), 87-136.
- Maguire, E. A., & Hassabis, D. (2011). Role of the hippocampus in imagination and future thinking. *Proceedings of the National Academy of Sciences*, 108(11), E39-E39.
- Malenka, R. C., & Bear, M. F. (2004). LTP and LTD: an embarrassment of riches. *Neuron*, 44(1), 5-21.
- Matulewicz, P., Ulrich, K., Islam, M. N., Mathiasen, M. L., Aggleton, J. P., & O'Mara, S. M. (2019). Proximal perimeter encoding in the rat rostral thalamus. *Scientific Reports*, 9(1), 2865.
- McCormick, D. A., & Thompson, R. F. (1984). Cerebellum: essential involvement in the classically conditioned eyelid response. *Science*, 223(4633), 296-299.
- McMackin, D., Cockburn, J., Anslow, P., & Gaffan, D. (1995). Correlation of fornix damage with memory impairment in six cases of colloid cyst removal. *Acta Neurochirurgica*, 135(1-2), 12-18.
- Meibach, R. C., & Siegel, A. (1977). Thalamic projections of the hippocampal formation: evidence for an alternate pathway involving the internal capsule. *Brain Research*, 134(1), 1-12.
- Myers, B., Scheimann, J. R., Franco-Villanueva, A., & Herman, J. P. (2017). Ascending mechanisms of stress integration: Implications for brainstem regulation of neuroendocrine and behavioral stress responses. *Neuroscience & Biobehavioral Reviews*, 74, 366-375.
- O'Keefe, J., & Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature*, 381(6581), 425-428.
- O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map: preliminary evidence from unit activity in the freely-moving rat. *Brain Research* 34, 171-175.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map* Clarendon Press.

O'Keefe, J., & Nadel, L. (1979). Précis of O'Keefe & Nadel's 'The hippocampus as a cognitive map'. *Behavioral and Brain Sciences*, 2(4), 487-494.

Olson, C. R., & Graybiel, A. M. (1980). Sensory maps in the claustrum of the cat. *Nature*, 288(5790), 479 - 481.

O'Mara, S. M. (2017). Place cells: knowing where you are depends on knowing where you're heading. *Current Biology*, 27(17), R834-R836.

Page, H. J., Wilson, J. J., & Jeffery, K. J. (2017). A dual-axis rotation rule for updating the head direction cell reference frame during movement in three dimensions. *Journal of neurophysiology*, 119(1), 192-208.

Papez, J. W. (1937). A proposed mechanism of emotion. *Archives of Neurology & Psychiatry*, 38(4), 725-743.

Park, S., Kramer, E. E., Mercaldo, V., Rashid, A. J., Insel, N., Frankland, P. W., & Josselyn, S. A. (2016). Neuronal allocation to a hippocampal engram. *Neuropsychopharmacology*, 41(13), 2987-2993.

Raichle, M. E. (2015). The restless brain: how intrinsic activity organizes brain function. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 370(1668), 20140172.

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience*, 13(10), 713-726.

Remedios, R., Logothetis, N., & Kayser, C. (2012). *The Claustrum and the Orchestra of Cognitive Control*. Talk presented at Francis Crick Memorial Conference: Consciousness in Human and Non-Human Animals. Cambridge, UK. 2012-07-07. Available at: <http://fcmconference.org/#program>

Remedios, R., Logothetis, N. K., & Kayser, C. (2010). Unimodal responses prevail within the multisensory claustrum. *Journal of Neuroscience*, 30(39), 12902-12907.

- Rocheffort, C., Arabo, A., André, M., Poucet, B., Save, E., & Rondi-Reig, L. (2011). Cerebellum shapes hippocampal spatial code. *Science*, 334(6054), 385-389.
- Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, 20(1), 11-21.
- Segobin, S., Laniepce, A., Ritz, L., Lannuzel, C., Boudehent, C., Cabé, N., Urso, L., Vabret, F., Eustache, F., Beaunieux, H. & Pitel, A.L., & Pitel, A. L. (2019). Dissociating thalamic alterations in alcohol use disorder defines specificity of Korsakoff's syndrome. *Brain*, 142(5), 1458-1470.
- Sharp, P. E., & Green, C. (1994). Spatial correlates of firing patterns of single cells in the subiculum of the freely moving rat. *Journal of Neuroscience*, 14(4), 2339-2356.
- Spence, K. W. (1956). *Behavior theory and conditioning* (Vol. 35). New Haven: Yale University Press.
- Squire, L. R. (1987). *Memory and brain*. Oxford University Press.
- Staff, N. P., Jung, H. Y., Thiagarajan, T., Yao, M., & Spruston, N. (2000). Resting and active properties of pyramidal neurons in subiculum and CA1 of rat hippocampus. *Journal of Neurophysiology*, 84(5), 2398-2408.
- Stewart, M. & Wong, R. K. (1993). Intrinsic properties and evoked responses of guinea pig subicular neurons in vitro. *Journal of neurophysiology*, 70(1), 232-245.
- Stringer, C., Pachitariu, M., Steinmetz, N., Reddy, C. B., Carandini, M., & Harris, K. D. (2019). Spontaneous behaviors drive multidimensional, brain-wide activity. *Cell*, 1(10), 100.
- Taube, J. S. (1995). Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *Journal of Neuroscience*, 15(1), 70-86.
- Taube, J. S., Muller, R. U., & Ranck, J. B. (1990a). Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *Journal of Neuroscience*, 10(2), 420-435.

Taube, J. S., Muller, R. U., & Ranck, J. B. (1990b). Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *Journal of Neuroscience*, 10(2), 436-447.

Taube, J. S. (1995). Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *Journal of Neuroscience*, 15(1), 70-86.

Taube, J. S. (2007). The head direction signal: origins and sensory-motor integration. *Annual Review of Neuroscience*, 30, 181-207.

Thompson, R. F. (1986). The neurobiology of learning and memory. *Science*, 233(4767), 941-947.

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review*, 55(4), 189-208.

Tonegawa, S., Liu, X., Ramirez, S., & Redondo, R. (2015). Memory engram cells have come of age. *Neuron*, 87(5), 918-931.

Tsanov, M., Chah, E., Vann, S. D., Reilly, R. B., Erichsen, J. T., Aggleton, J. P., & O'Mara, S. M. (2011). Theta-modulated head direction cells in the rat anterior thalamus. *Journal of Neuroscience*, 31(26), 9489-9502.

Tsivilis, D., Vann, S. D., Denby, C., Roberts, N., Mayes, A. R., Montaldi, D., & Aggleton, J. P. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. *Nature Neuroscience*, 11(7), 834 -842.

Tsokas, P., Hsieh, C., Yao, Y., Lesburgueres, E., Wallace, E. J. C., Tcherepanov, A., ... & Farese, R. V. (2016). Compensation for PKM ζ in long-term potentiation and spatial long-term memory in mutant mice. *Elife*, 5, e14846.

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, 10(6), 397-409.

van Groen, T., & Wyss, J. M. (1990a). The connections of presubiculum and parasubiculum in the rat. *Brain Research*, 518(1-2), 227-243.

van Groen, T., & Wyss, J. M. (1990b). The postsubicular cortex in the rat: characterization of the fourth region of the subicular cortex and its connections. *Brain Research*, 529(1-2), 165-177.

Van der Werf, TD, Witter, MP, Groenewegen, HJ The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Research Reviews*, 39, 107-140, 2002.

Van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences*, 96(23), 13427-13431.

Vann, S. D., & Nelson, A. J. (2015). The mammillary bodies and memory: more than a hippocampal relay. In *Progress in Brain Research* (Vol. 219, pp. 163-185). Elsevier.

Vann, S. D., & Aggleton, J. P. (2004). The mammillary bodies: two memory systems in one?. *Nature Reviews Neuroscience*, 5(1), 35-44.

Vertes, R.P., Hoover, W.B., Szigeti-Buck, K., Leranth, C. Nucleus reuniens of the midline thalamus: Link between the medial prefrontal cortex and the hippocampus. *Brain Research Bulletin*, 71, 601-609, 2007.

Whishaw, IQ (1990). The decorticate rat. In B. Kolb & RC Tees (Eds.), *The cerebral cortex of the rat* (pp. 239-267). Cambridge, MA, US: The MIT Press.

Winter, S. S., Clark, B. J., & Taube, J. S. (2015). Disruption of the head direction cell network impairs the parahippocampal grid cell signal. *Science*, 347(6224), 870-874.

Yamins, D. L., & DiCarlo, J. J. (2016). Using goal-driven deep learning models to understand sensory cortex. *Nature Neuroscience*, 19(3), 356-365.

Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: the anatomy of perception, imagination and episodic memory. *Nature Reviews Neuroscience*, 17(3), 173-182