Hippocampal volume and navigational ability: The map(ping) is not to scale.

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Highlights:

- Hippocampal volume has been associated with impaired and expert navigation
- Large pre-registered studies found no such correlation in healthy adults
- Theoretical mechanisms supporting structure-function associations are tenuous
- Navigation is a complex cognitive function, involving multiple brain networks
- Network models offer greater explanatory power for flexibility and individual differences

Abstract

A critical question regards the neural basis of complex cognitive skill acquisition. One extensively studied skill is navigation, with evidence suggesting that humans vary widely in navigation abilities. Yet, data supporting the neural underpinning of these individual differences are mixed. Some evidence suggests robust structure-function relations between hippocampal volume and navigation ability, whereas other experiments show no such correlation. We focus on several possibilities for these discrepancies: 1) volumetric hippocampal changes are relevant only at the extreme ranges of navigational abilities; 2) hippocampal volume correlates across individuals but only for specific measures of navigation skill; 3) hippocampal volume itself does not correlate with navigation skill acquisition; connectivity patterns are more relevant. To explore this third possibility, we present a model emphasizing functional connectivity changes, particularly to extra-hippocampal structures. This class of models arises from the premise that navigation is dynamic and that good navigators flexibly solve spatial challenges. These models pave the way for research on other skills and provide more precise predictions for the neural basis of skill acquisition.

Keywords: Hippocampus, spatial navigation, MRI, functional connectivity, brain volume

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1.1.0 Introduction The human brain is a complex, dynamic organ, capable of highly sophisticated problem solving. A critical question in human cognitive neuroscience is how complex cognitive skills are acquired and how variations in behavioral aspects of those skills manifest in neural differences. Spatial navigation, in part because of its ubiquity across species and ecological relevance, is one example of a complex suite of cognitive abilities which has been extensively studied in cognitive neuroscience. Although all mobile organisms must construct and maintain representations of their environments to find shelter, food, and other resources, human spatial navigation is notable for its need for flexibility and multiple strategy use.

Consider for example the seemingly simple task of finding a new building on campus: one needs an initial bearing, some knowledge of where the building is located relative to other buildings, where the navigator is currently located, and approximately what paths and roads will lead one close enough to the vicinity of known buildings to find the new campus location. If lost along the way, the navigator needs to not only reorient their current position relative to their immediate surroundings, but also to represent their position relative to their eventual goal (or subgoals). As they near the destination, the navigator needs to be able to see the building from a distance and plan a path accordingly. This seemingly simple task involves a myriad of navigation strategies including representing landmarks relative to one's self (egocentric navigation), calculating bearings relative to stable coordinates (perhaps north-south), remembering specific paths, knowing how landmarks are arranged relative to each other in an area unseen (i.e., allocentric navigation), and navigating to an object in sight (i.e., response navigation). Now, consider how much such strategy use might vary for the same task of finding a goal but in a large indoor building or instead an outdoor mountainous environment. As a skill,

navigation is complex and difficult to distill to a single strategy or representation, and shows significant variability depending on the nature of the environment and task at hand.

In addition to its variability and need for flexibility within a specific navigation-task like finding a campus building, navigation is also remarkable for its differences among species and individuals. Among non-human animals, consider: rats in the wild, which construct borrows in the dark within hills to find food sources (Lore & Flannelly, 1978); sea turtles, which use magnetic properties of the earth to find their nesting ground with sub-meter accuracy (Lohmann & Lohmann, 1996); and bees, which use the azimuthal position of the sun for finding pollen and returning to their nest (Gould, 1980). Among humans, we also see a wide variety of different navigational skills. Whereas some people can form detailed representations of large (city-sized) environments, others become easily disoriented even in relatively simple spaces (Weisberg et al., 2014; Weisberg & Newcombe, 2016).

Given that navigation is a complex task, involving rich behavioral variation and individual and inter-species differences, how is behavioral variation instantiated in the brain? In this review, we examine models for a behavioral-neural link in spatial navigation, focusing predominantly on the hippocampus, an area of the brain showing significant multimodal convergence and importance to memory. While certainly a reasonable candidate region for some aspects of navigation, we consider recent evidence and, upon close examination of the literature, argue that this model is likely overly simplistic. We review this evidence and explore an alternative model, consistent with recent advances in network neuroscience, in which variation in behavior is detectable in the human brain by variations in functional and structural connectivity.

1.1.1 Hippocampal growth and navigation: An introduction to an influential model with limitations

Based in part on its anatomical position within the brain as a multimodal convergence zone and its physiology, one prominent theory argues that the hippocampus is the “seat” of the cognitive map, thereby providing storage and access to representations akin to a cartographic map but with information about the position of the navigator (Burgess et al., 2002; O’Keefe & Nadel, 1978). Variability in spatial navigation, some interpretations of this theory suggest, manifests in the brain as the expansion of the hippocampus to accommodate more sophisticated cognitive maps. According to this model, increases in hippocampal volume underlie changes in navigational skill, possibly via increases in synaptic plasticity that could manifest as more sophisticated “cognitive maps” (Burgess, Maguire, & O’Keefe, 2002). Such an idea is supported by findings from London taxi drivers -- expert navigators who have increased posterior hippocampal volume compared to non-taxi drivers (Maguire et al., 2000). On the other end of the spectrum, impaired navigators – patients with Alzheimer’s disease who have relatively smaller hippocampi (Coughlan et al., 2018; Lovden et al., 2012) – show a strong negative correlation with navigation behavior and hippocampal volume. Put succinctly, the larger structurally the hippocampus, the greater synaptic connections, the more developed the cognitive map, and therefore the greater the navigational skills.

Three large-scale efforts evaluating healthy young participants, however, who presumably fall in the non-expert, non-impaired domain, challenge how well this model applies beyond clinical or exceptional groups. Using sample sizes of from 80-100 healthy young volunteers, two studies showed no significant relationship between hippocampal volume and navigational ability, although such participants do vary quite widely in navigation ability (Hao et al., 2016; Weisberg et al., 2019). A third study, using 217 healthy young adults, found no associations between hippocampal volume and a range of tasks, including scene imagination and tasks related to spatial navigation (Clark et al., 2020). In the study by Weisberg and colleagues, participants navigated a large-scale virtual environment and pointed to locations and drew maps of the cities they had explored. Weisberg et al. also measured both anterior

and posterior hippocampal volume, neither of which correlated with any dependent of spatial knowledge (see Figure 1). Contrary to the structure-function model supported by taxi drivers and impaired navigators, the implication of these studies is that hippocampal volume – at least for healthy young participants – is not relevant to understanding navigational skill. We will explore this idea and these studies in more detail shortly, as well as some of the counterpoints raised to them.

Figure 1. A large (N=88, excluding two outliers) pre-registered experiment (Weisberg et al., 2019) revealed no correlation between right hippocampal volume and the accuracy with which a novel virtual environment was recalled. In the model building task, participants placed buildings in an onscreen box in the location they believed the building to be in the virtual environment. Using bidimensional regression, the configuration of buildings on the participants' map was measured in comparison to the actual map, controlling for rotation, translation, and scaling (Friedman & Kohler, 2003). The non-statistically significant negative correlation would be in the opposite direction expected, but also provides evidence in favor of the null hypothesis: $BF_{01} =$

3.52. Note the substantial range of performance on this task in a group of healthy young adults revealing large individual differences.

Weisberg and colleagues' (2019) study raises several possible considerations about the relationship between brain changes and navigational skill. Specifically, we think the following possibilities are all viable: 1) that hippocampal volume correlates with navigation skill but only for "extreme" abilities, i.e., either highly adept or highly impaired; 2) hippocampal volume correlates with navigational skill but only for specific navigational skills, such as allocentric navigation; 3) hippocampal volume itself is not a meaningful measure of the multifaceted skill involved in human spatial navigation and instead, dynamic connectivity patterns and/or extra-hippocampal changes capture the most variance in navigational skill. We explore each of these possibilities in turn and evaluate the strengths and weaknesses with each perspective.

2.1.1 Hippocampal volume in extremes: Hippocampal volume is relevant for expert and impaired navigators but not the "in-betweens"

How can we reconcile findings showing a relationship between navigational skills in experts and patients but not healthy young participants? As suggested in Weisberg and colleagues (2019), one possibility is that volumetric changes are only relevant at the extreme ends of navigational ability. On the one hand, data from impaired and expert navigators suggest a robust structure-function relation between hippocampal volume and spatial navigation behavior. In other words, presumed synaptic density, when impaired as a function of aging or other neurobiological conditions, will result in impaired place cell activity and therefore impaired navigational abilities (Barnes et al., 1980; Erickson & Barnes, 2003), which could manifest grossly at the level of reduced hippocampal volume (an idea we explore in more depth shortly). Conversely, in situations of rapid plasticity, such as might be experienced when learning a large number of new routes or streets as a taxi-driver, one might see hippocampal growth, even if restricted to areas like the posterior hippocampus.

On the other hand, healthy participants show no correlation with hippocampal volume. Under normal circumstances, then, synaptic plasticity may not happen rapidly enough or on a scale large enough to manifest at the level of gross volumetric changes. Notably, however, such changes have been observed in motor areas related to acquiring new skills like juggling (Draganski et al., 2004; Driemeyer et al., 2008). It seems possible, though, that the hippocampus may not be subject to same kind of rapid plasticity at large scale as areas like motor cortex. According to this model, then, hippocampal growth shows a sigmoidal relationship with navigation ability; growth and shrinkage are only relevant at the extreme ends (Figure 2).

Figure 2. A hypothetical plot explaining why hippocampal volume may be correlated with navigation performance in extreme groups, but these correlations do not occur for navigators within typical ranges. Some aspects of the literature remain unexplained by this plot, including whether expert navigators have larger right posterior hippocampal volume than typical navigators. (This figure originally appeared in (Weisberg et al., 2019)).

2.1.2 Strengths of the “extremes” structure-function hypothesis

One of the major strengths of the “extremes” account for hippocampal volumetric changes is that it reconciles classic findings from London taxi-drivers and neurological cases with those from healthy participants. Another strength of this account is that it provides an intuitive explanation for how the brain might acquire new skills – by simply growing (however, see our critique of this explanation). In addition, we think it is worth mentioning several studies that in some form or another might seem to support the arguments.

The structure-function hypothesis draws its initial support from associations between functional properties of the hippocampus that correlate with spatial behavior. Some of the earliest data of this sort were single-cell recordings made in the rodent hippocampus by O’Keefe and Dostrovsky showing individual neuron sensitivity to particular locations in space, which they called place cells (O’Keefe & Dostrovsky, 1971). Later, O’Keefe and Nadel theorized that a collection of hippocampal place cells might serve as a cognitive map of an environment (O’Keefe & Nadel, 1978), drawing on terminology and theory from Tolman (1948). The crux of this idea is that with sufficient representations of individual locations in space, and the anchoring of such neural signals to distal cues, the collection of place cells could serve as a “map” for the both the rats current and future locations.

Over the past 25 years, other lines of research have emerged providing evidence that the size of the hippocampus, not just whether it is activated during a task, relates to individual variability in spatial navigation performance. In several studies, Maguire and colleagues revealed that expert navigators – taxi cab drivers trained on the labyrinthine streets of London – had enlarged posterior hippocampi (Maguire et al., 2000; Maguire, Woollett, et al., 2006) compared to age-matched controls and bus drivers (whose responsibility was to drive around the same streets, but only followed familiar routes rather than traversing the city flexibly). These data also showed correlations between posterior hippocampal volume with how long the cab driver had been driving – those who had been driving longer had larger hippocampi. Beyond single timepoint studies, longitudinal research on taxi cab drivers showed that trainees who

passed “the Knowledge” (the extensive test of geographical information required of London cab drivers) had more enlarged posterior hippocampi after training compared to trainees who failed “the Knowledge” (Woollett & Maguire, 2011).

On the other end of the spectrum, spatial navigation impairments are common among people with hippocampal atrophy or hippocampal lesions. During the course of aging and in particular in mild cognitive impairment and Alzheimer’s disease, the hippocampus atrophies in comparison with some other brain regions (Apostolova et al., 2012; Jack et al., 2000). Numerous studies have documented spatial navigation impairments in patients diagnosed with mild cognitive impairment and Alzheimer’s disease (for review, see Coughlan et al., 2018). Patients with early and late stages of Alzheimer’s disease pathology show navigation impairments that can be dissociated from memory and involve the types of spatial knowledge (allocentric reference frames) that are considered typical of hippocampal function (Serino & Riva, 2013).

2.2.1 Critiques of the “extremes” structure-function hypothesis

There are several areas of weakness of the structure-function hypothesis, both with regard to theoretical interpretations and the empirical studies used to support it. These involve mechanistically how we interpret “growth” in a brain structure, how we interpret a model in which structure-function associations only apply to “extreme” cases, and the fact that the London Taxi driver studies had several shortcomings. We handle each of these issues in turn.

2.2.2 Critiques of the theoretical underpinnings of the structure-function hypothesis

It is instructive to consider other species in which more direct assays of neural changes can be performed and the structure-function hypothesis has been evaluated in some detail. Some species of birds show a dramatic increase in spatial abilities at higher elevations, which may be attributable to the high demands for navigating and remembering multiple locations of

food catches (Sonnenberg et al., 2019). Interestingly, birds living at higher elevations also show fairly large increases in the total numbers of hippocampal neurons compared to those at lower elevations and somewhat modest increases in hippocampal volume compared to lower elevation (Freas et al., 2013). Such differences in hippocampal volume, however, are unreliable and larger sample studies do not show a consistent relationship between hippocampal volume and food hoarding (Brodin & Lundborg, 2003). Overall, while these studies support the idea that navigation skills can undergo dramatic changes which may relate to neuron number within the hippocampus, volume itself does not appear to capture this variance particularly well. In fact, in one of the studies mentioned above, captivity had a much greater effect on hippocampal volume than elevation, suggesting that conditions that impair behavior and movement are more likely to affect brain volume generally.

These studies point to perhaps the biggest limitation with the theoretical backbone of the structure-function hypothesis: it is simply not clear why growth, or certain aspects of gray matter change, in a single part of a brain structure should accommodate a skill as multifaceted as navigation. More specifically, volumetric changes in a brain structure could occur for a variety of different reasons: increases in neuron number (neurogenesis), increases in synapses, increases in vascularization, or even changes in white matter, all of which are difficult to disentangle on standard 3T images used in human MRI. Theoretically, it also seems that shrinkage, within a reasonable range, could reflect increased efficiency of synaptic organization based on synaptic pruning (Grill-Spector et al., 2006).

Notably, the findings from the London taxi-driver studies (and subsequent ones we will discuss) show an increase in posterior hippocampal volume coupled to a decrease in anterior hippocampal volume. Thus, the findings are more consistent with a shifting of potential neural (or glial or vascular) resources than actual growth. But if this is the case, how does this relate to the types of changes in neuron number seen in other species like birds under extreme conditions? Would we not expect the mechanism of hippocampal growth to be equally applied

regardless of the navigator's skill? In other words, the most parsimonious account for a structure-function correlation would suggest a linear relationship, with hippocampal volume increasing as a function of increasing navigational competence.

2.2.3 Critiques of the empirical findings supporting the “extremes” structure-function hypothesis

The London Taxi-driver studies, while ground-breaking at the time of early MRI studies, involved several limitations that would likely complicate support for the structure-function hypothesis. Both taxi-driver studies (Maguire et al., 2000; Maguire, Woollett, et al., 2006) involved underpowered sample sizes for correlation analyses and between subjects comparisons (N=16/17 taxi-drivers, all male) with incomplete corrections for multiple comparisons (Eklund et al., 2016). For example, the correlations reported ($r^2=.25/.36$) in the original study between number of years navigating and posterior hippocampal volume would suggest a large effect size .6-.8, indicating that hippocampal volume changes dramatically based on years navigating. The between subject comparisons also suggest surprisingly large effect size between controls and taxi-drivers. None of these considerations invalidate the findings but they do warrant further consideration, particularly given more recent discussions about sample size, effects size, and correlations, and researcher degrees of freedom (Button et al., 2013; Funder & Ozer, 2019).

One can reasonably ask how reliable correlations are with regard to brain-behavior correlations, particularly given the accumulation of large databases of MRI scans and its dramatic increase in relative ease of access. A recent study using over 10,000 brain and behavioral measures found that the vast majority of large-effects sizes in small samples were spurious; the only reliable correlations in the large-sample size simulations were small effect sizes (Marek et al., 2020). Similarly, a recent effort attempted to replicate behavior/brain correlations reported in the literature related to cognitive and social neuroscience using a fresh

sample of participants. Of the 17 attempted replications, only 1 of 17 effects replicated completely, and all reported effects sizes were substantially lower than the originally reported ones (Boekel et al., 2015). Consistent with these considerations, it seems reasonable that if volume does change with behavioral, such effect sizes would be small and growth itself would see only very small changes with behavioral improvements.

While the taxi-driver study may still replicate in an independent sample, we note that GPS is now widely used by taxi-drivers, and thus replicating and generalizing the reported effects will be challenging outside of those London taxi-drivers who do not use GPS. It is also important to note though that such sample size criticisms can be leveled at a large number of brain-behavior studies and this study is certainly not alone in that collecting MRI data from specialized populations is extremely challenging. One may reasonably argue, however, that definitively establishing the “extreme” end of the spectrum where volume is related to navigational ability (Figure 2), at least with taxi-drivers, may be difficult, if not impossible to establish. Somewhat surprisingly, to our knowledge, no empirical research has revealed altered hippocampal structure in navigation experts besides London taxi drivers, who are likely not the only navigation experts. Orienteers, pilots, geologists, and members of the military all receive extensive navigation training, work with maps, and could be considered navigation experts. One reason could of course be that these groups do have increased hippocampal volume with better navigation ability, but this question, to our knowledge, has not been directly addressed. In the very least, if the “extremes” hypothesis is correct, we would expect to see large differences in highly skilled navigators in other domains compared to controls.

3.1.1 Moving beyond the “extremes” structure-function hypothesis: The specialization argument

It could certainly be the case that the hippocampus does not support memory and navigation generally but has a more specialized role in allocentric navigation (navigation using

distal landmarks) or episodic memory, as indeed some of the authors of the taxi-driver paper have argued in some form (Burgess et al., 2002) as well as many others (Brown & Aggleton, 2001; Eichenbaum, Yonelinas, & Ranganath, 2007). Hippocampal volume changes then would relate to improvements specifically in allocentric navigation and/or episodic memory skills. One way to recharacterize the structure-function association argument described above is that the hippocampus is the seat of one kind of cognitive map which stores memory for spatial locations (and possibly context more generally) but not the only source of spatial representation in the brain. This idea is not new (Aguirre & D'Esposito, 1999; Byrne et al., 2007; Hartley et al., 2003) but is worth re-emphasizing here.

This specialization arguments helps reconcile some of the conflicting findings above: healthy young participants may not always show correlations between hippocampal volume and navigational assays perhaps because memory or navigation was not tapped in the correct way. Another strength of this argument is that it helps account for well-known individual differences in navigation (Weisberg et al., 2014; Weisberg & Newcombe, 2016) because some participants may rely on allocentric navigation to a greater extent and therefore it is those individuals (like taxi-drivers) who might be expected to show enlarged hippocampi. To be clear about our definitions, by allocentric we mean navigating using representations that are invariant to the navigator's facing direction and position (Ekstrom et al., 2014)). According to this argument, then, hippocampal volume should correlate with navigation/memory skills provided we use the correct dependent measures. We explore this perspective in more detail here.

3.1.2 Evidence for the specialization argument

The earliest work to focus on individual differences in spatial navigation related to neural structure come from the idea that the hippocampus is involved in "place" (allocentric) learning and the caudate/striatum is involved in "response" (beacon/egocentric) learning (Bohbot et al., 2007; Iaria et al., 2003; McDonald & White, 1994). These two types of scenarios are perhaps

clearest in the plus maze. The animal first finds a goal from a specific start location, then at test is moved to the location opposite the start. An animal that is a place (allocentric) learner will make a turn toward the goal based on the distal cues, which would be the opposite turn relative to the turn they made during learning. A response learner, in contrast, will take the turn that worked from the previous location based on seeing the junction (or proximal cue) and turning the same way as during encoding. In one human version of this experiment, a participant is taught an array of four objects around an 8-arm radial maze. They learn which object is located in which arm of the maze, then the other four arms are blocked off. At test, they are disoriented and asked to replace the objects they learned initially, with the other four arms now unblocked. The participant can either replace the item with respect to the distal cues (a place strategy, using the mountain ranges in the background) or with respect to their starting position (a response strategy).

In a sample of 30 participants, those who selected a place strategy were observed to have higher gray matter density (measured using voxel-based morphometry) in the hippocampus while those who selected a response strategy had higher gray matter density in the caudate nucleus (Bohbot et al., 2007; Iaria et al., 2003). This work therefore makes the case that individual differences in strategy selection relate (for place learning) to the volume of the hippocampus or (for response learning) to the caudate nucleus. Other studies in humans, albeit also with modest sample sizes, have argued for similar correlations between hippocampal volume and path integration (Chrastil et al., 2017; Sherrill et al., 2018) and configurational knowledge of a real-world environment (Schinazi et al., 2013). Again, these findings suggest that individual differences in specific navigational tendencies may relate to hippocampal volume.

Another line of research has focused on the ratio of posterior to anterior hippocampal volume and episodic memory performance. Poppenk and colleagues (2011) looked at measures of recollection, which provide an assay of detailed memories typically associated with episodic memory (Poppenk & Moscovitch, 2011). Across four different studies, there was a

significant correlation between recollection memory scores (but not simple recognition) and posterior hippocampal volume (see (Snytte et al., 2020) for a replication). Interestingly, anterior hippocampal volume was negatively correlated with posterior hippocampal volume. A similar approach was taken to investigate self-reported cognitive map use. In that experiment, the ratio of poster to anterior hippocampal correlated with the extent to which an individual self-reported using map-like strategies rather than route-like strategies across two separate samples (Brunec et al., 2019). It is intriguing therefore to consider navigation and hippocampal volume within this new light: different participants may rely to different degrees on episodic memory during navigation, which may explain one reason why hippocampal volume and navigation show inconsistent correlations.

3.3.1 Strengths of the specialization argument

Overall, we think the specialization version of the structure-function argument for the hippocampus works better in many ways than the “extremes” argument. It stands to reason, then, that the more the allocentric mapping process is engaged, the more synapses and/or neurons might be recruited to store information, and, like a muscle, the more we might expect the hippocampus to expand to accommodate this capacity. The model helps account for many studies that have shown correlations between hippocampal volume and navigation/memory performance. While we note that many of these studies were still underpowered for brain-behavior correlation analyses (Marek et al., 2020), the collection of the studies would appear to make a case that at least some dependent measures of memory and navigation correlate with hippocampal volume. Important lingering questions remain regarding whether it is memory or navigation skills primary driving this relationship and why exactly growth in the posterior hippocampus should be important to memory. At the same time, assuming this issue can be resolved, using specific behavioral interventions may help to reverse age and disease related decline in the hippocampus.

3.4.1 Weaknesses of the specialization argument: Theoretical and empirical foundations

The specialization argument suffers from both theoretical and empirical weaknesses, many of which are the same or similar to those already covered for the extremes model. These include a poor theoretical conceptualization of why growth should be important to gaining a multifaceted skill such as navigation and mechanistically what is changing with hippocampal growth? These also include empirical considerations regarding sample size: other than Poppenk and Moscovitch (2011), who correlated recollection measures with hippocampal volume across multiple studies, the remaining studies were all significantly underpowered for correlation analyses compared to the preregistered experiments investigating structure-function associations (Clark et al., 2020; Hao et al., 2016; Weisberg et al., 2019). Additional issues we explore here with regard to the specialization argument are why one specific cognitive process should correlate specifically with hippocampal growth, why different behavioral studies appear to suggest variable dependent measures correlate with hippocampal growth, and how one should interpret an anterior/posterior hippocampal shift in volume.

2.4.2 Weaknesses of the specialization argument: Why should hippocampal growth be so specific?

The specialization argument centers around the idea that hippocampal growth is not general to many cognitive processes but specific to a single behavioral process, and therefore a circumscribed set of dependent measures related to the cognitive map and/or episodic memory. Depending on the findings, these two dependent measures are: 1) allocentric navigation efficiency or use of an allocentric strategy 2) recollection/episodic memory. While we consider each of these issues in turn, we think it is helpful to first consider the problem more generally. If hippocampal growth correlates with one specific cognitive process and no others, this might imply that the hippocampus serves a highly specific function in everyday life.

The feasibility of this argument, though, is somewhat questionable. While the neuroanatomy of the hippocampus may be well-suited for memory functions (Levy, 1989; McNaughton & Morris, 1987; Treves & Rolls, 1994), it seems unlikely that a single brain structure is specialized to undergo enhancement if only very specific cognitive processes are engaged, such as allocentric navigation or episodic memory. On the contrary, numerous reports have essentially argued the opposite: that the hippocampus is essentially a jack-of-all-trades and engaged by numerous different memory, language, perception, and navigation tasks (for a review please see: Ekstrom & Yonelinas, 2020). In addition, it seems that in most ecological situations, it is unlikely that a single cognitive process is ever engaged in an sufficiently isolated fashion to trigger growth on its own (Crusio, 1996). While it could certainly be the case that some individuals employ one type of representation or strategy to a greater extent than others (i.e., employing allocentric navigation or episodic memory more frequently, either for experiential or genetic reasons), it seems odd to argue that this factor should be the only one to trigger hippocampal synaptogenesis or neurogenesis.

Posterior to anterior hippocampal comparisons also depend critically on how one defines the anterior vs. posterior hippocampus. There are several different ways to identify the anterior hippocampus as distinct from the posterior hippocampus including the presence of the collateral sulcus and the uncus apex (Duvernoy et al., 2013; Poppenk, 2020). Identifying the uncus apex is one of the more common ways to segment the hippocampus into anterior, medial, and posterior sections and was employed in the original Poppenk and Moscovitch (2011) study as well as Weisberg and colleagues (2019) in exploratory analyses. An issue, however, is that identification of the apex is variable with age (Poppenk, 2020), raising the question if white matter tracts or other brain-wide changes may be producing some of the variability in anterior vs. hippocampal volume. Indeed, as we will explore in the next sections, white matter and connectivity differences are also strong candidates for mediating navigation skill. It is intriguing, although perhaps slightly premature, to consider that at least some of the volumetric differences

we have discussed so far result from changes in connectivity patterns rather than gray matter volume.

2.4.3 Reasons to doubt the specificity of the hippocampus to allocentric navigation

There are several reasons to doubt the specificity of the hippocampus to allocentric navigation. Perhaps the clearest reason is that allocentric navigation is difficult to pin down and define in most ecologically-valid navigation situations (Ekstrom et al., 2014; Wolbers & Wiener, 2014). Specifically, even in cases in which a rat or human can employ distal cues, it is not clear that they do so only in a fashion that is allocentric, i.e., triangulating the goal location based on the combination of all the cues. Instead, in situations in which humans and rats are free to employ short-cuts, they rely on a mixed strategy involving flexible solutions rather than one that involves the optimal shortcut in allocentric coordinates (Bennett, 1996; Gentry et al., 1947; Olton, 1979; Wilson & Wilson, 2018). In addition, strategy choice is malleable in highly similar navigational situations within individuals – varying the instructions for a navigation task can alter whether people choose a novel shortcut or a familiar route (Boone et al., 2019). In this way, there are unlikely to be “pure” allocentric strategies but rather that skilled navigators use a combination of different strategies to find the goal. As such, it seems doubtful that a single cognitive process like “allocentric navigation” relates to hippocampal growth.

The same overall problems apply to models that suggest the hippocampus plays a role in allocentric or “place” navigation while the caudate nucleus plays a role in response-based navigation (Bohbot et al., 2007; McDonald & White, 1994; Packard et al., 1989). The issue with the place vs. response dichotomy is that navigation itself is likely far more dynamic than involving a single strategy at any one time and thus not process pure. That is, it seems unlikely that both strategies engage only behavioral processes that are supported by one region of the brain. In a version of the task in which rats received training at both place and response strategy, lesions to the caudate and hippocampus impaired both aspects of the task

(Ferbinteanu, 2016; Gasser et al., 2020). In addition, while stress results in a greater use of “response” strategies, the caudate nucleus is more active in non-stressed individuals during route planning than stressed individuals (Brown et al., 2020). Overall, it is doubtful whether ecologically-valid situations engage either the hippocampus or caudate nucleus in the dichotomous way proposed and studies would overall support that the hippocampus and striatum plays partial role in both strategies (Goodroe et al., 2018).

2.4.4 Lesions to the human hippocampus do not specifically impair allocentric navigation

If the human hippocampus is central and specific to allocentric navigation, then lesions to this structure should severely and specifically disrupt allocentric navigation. This prediction, though, has not been borne out. Perhaps the most compelling example comes from patient TT, a London Taxi-driver with a bilateral hippocampal lesion (Maguire, et al., 2006). The patient played a virtual taxi-driver game in which the streets, cabs, and other details of London were as accurately rendered as possible. The authors then asked control taxi drivers and patient TT to navigate approximately 15 different routes through London that they would routinely take as taxi drivers. Surprisingly, patient TT was able to get from one place to another through London using short-cuts, and overall, compared to controls, showed little deficit in his overall knowledge of the layout of streets in London. Patient TT did show a tendency to rely on main arteries or roads in the city, which would suggest some impairments in navigation. Such deficits, however, have been demonstrated in other cases of taxi-drivers with medial temporal lobe damage, who show reductions in the details/precisions of their memories but overall intact allocentric navigation (Rosenbaum et al., 2005).

What about situations in which the environment is comparatively novel? Kolarik and colleagues tested patients with focal medial temporal lobe lesions in a widely used task thought to involve reference to distal landmarks, the virtual Morris Water Maze (Kolarik et al., 2016, 2018). Detailed analysis of the search patterns of the patients showed they remembered

hidden locations in the maze with less precision overall than controls. These deficits, however, manifested regardless of whether they approached from the same start point (putative egocentric) or a different start point (putative allocentric). These findings would support the idea that the hippocampus plays a role in the precision of the memories for locations but not in the ability to employ an allocentric strategy. Other studies with patients with hippocampal lesions have suggested little to no allocentric or navigational impairments, instead suggesting that extra hippocampal lesions (to parahippocampal or retrosplenial cortex) produce navigation deficits (Bohbot et al., 1998; Habib & Sirigu, 1987; Kolarik et al., 2016, 2018; Ploner et al., 2000). Such an idea is also supported by fMRI studies with healthy participants under more carefully controlled situations, demonstrating that tasks involving allocentric computations activate areas often outside of the hippocampus, sometimes exclusively so (Committeri et al., 2004; Zhang & Ekstrom, 2013).

4.1.1 An alternative: Dynamic changes in functional connectivity underlie navigational skill

An important alternative articulated in past studies involves the idea that connectivity patterns, rather than focal changes in gray matter, underlie change in navigational skills (Ekstrom et al., 2014, 2017; Huffman & Ekstrom, 2019). These theoretical models have focused in particular on the idea that navigation itself is a highly dynamic ability and that for any given navigation task or even any given moment when navigating, the demands themselves may vary widely (Weisberg & Newcombe, 2018; Wiener et al., 2011; Wolbers & Hegarty, 2010). The idea is that for any given navigational tasks, the brain regions involved may vary depending on the specifics.

Consider first prehistoric navigation vs. urban navigation. When navigating large outdoor environments, the navigator is likely to rely on heuristics like mountain ranges, ocean currents, and star and sun-compass tools (Caudill & Trimble, 2019; Ekstrom et al., 2018;

McNeill et al., 1998). For urban environments, in contrast, the navigator likely relies on street grids and buildings. Also, consider how different an urban environment or experimental room at a lab is in comparison to a mountainous environment: the navigator is likely to rely heavily on boundaries and other information to approximate the positions of objects, both from specific viewpoints and based on the geometry of the room (Cherep et al., 2019; Lynch, 1960; Mou et al., 2004, 2006). Even when navigating something as seemingly simple as finding a campus building, the navigator is likely to employ a combination of different strategies (e.g., allocentric, egocentric, and beacon) dynamically and interchangeably. It seems unlikely that a single brain region such as the hippocampus will capture all of the variance associated with these widely different navigation tasks.

Another advantage of considering connections, rather than single brain regions, is that connectivity patterns dictate not just which brain regions interact with each other but how. For example, if the hippocampus, parietal cortex, and retrosplenial cortex dynamically engage during a task, there are now a combinatorial large set of possible responses recruited than what might be available in one region alone, like the hippocampus. Although not the focus of this review, a core piece of the network connectivity proposal is that between these different brain regions exists both redundancy and unique computational capacities (Bassett & Gazzaniga, 2011). By allowing for previously employed and dynamic configurations of different brain regions, a much larger possible repertoire of solutions is possible. As noted, this can also involve direct feedback in terms of visual input: if the desired location is not found, the set of connections can dynamically reconfigure to find another possible solution (Ekstrom et al., 2020). For example, when the navigator does not find the goal building at the expected location, another solution might be to walk to a courtyard with a view and visually search for the building. While previous papers have elaborated on this model in detail, such models hypothesize a core set of brain regions will be most relevant to this process: hippocampus, parahippocampal gyrus,

retrosplenial cortex, parietal cortex, prefrontal cortex, and visual cortex (Ekstrom et al., 2017; Huffman & Ekstrom, 2019).

4.1.2 Evidence for the connectivity perspective: Connections matter more than focal gray matter changes

An early piece of evidence for the connectivity perspective comes from patients with developmental topological disorientation (DTD). These are patients who have overall normal cognitive skills but suffer from profound spatial orientation problems. Some of the patients described cannot find their way from their home, that they have lived in for years, to nearby locations (Ekstrom et al., 2018). They also fail a battery of tests to assess navigational orientation and knowledge of locations in the neighborhood (Iaria et al., 2009; Iaria & Barton, 2010). Interestingly, detailed analyses of structural and functional MRIs suggest that, compared to controls, they show no reductions in focal gray matter. Instead, one of the hallmarks appears to be impaired functional connectivity between hippocampus and prefrontal cortex (Iaria et al., 2014) and/or retrosplenial cortex and parts of the parahippocampal gyrus and retrosplenial cortex (Kim et al., 2015). Thus, both studies strongly support the idea that functional connectivity, and not focal gray matter changes, underlie profoundly impaired navigation skills – even in the absence of other overt deficits.

Similar findings have also been reported recently for episodic memory. One study employed a large group of patients with focal lesions to the hippocampus. Structural MRI and functional connectivity analyses revealed that almost all of these patients showed impaired connectivity patterns as well as gray matter loss outside of the hippocampus, likely related to the lesion. All associations of hippocampal volume loss with amnesia were fully mediated by connectivity changes. In other words, changes in functional connectivity explained all of the significant variance in amnesia, with hippocampal volume loss contributing only indirectly to amnesia via impaired network interactions (Argyropoulos et al., 2019). In a similar vein, another

study conducted a meta-analysis on patients with amnesia and subsequently analyzed the reported locations of their amnesia. Many of the patients had lesions outside of the hippocampus and a subsequent network analysis based on presumed connectivity patterns from functional connectivity analyses strongly pointed to aberrant connectivity rather than focal gray matter lesions as the best explanatory factor for impaired memory (Ferguson et al., 2019). Together, these findings point to the importance of connectivity patterns, rather than focal gray matter lesions, as necessary for normal episodic memory and navigation.

4.2.1 Testing models of connectivity

To date, connectivity models, particularly in the context of navigation, have undergone significantly less testing than those that rely on gray matter changes within the hippocampus. Although we believe that connectivity models are intuitively more feasible than those that rely on gray matter changes in a single brain region (the hippocampus), it is challenging to constrain such models. One large-scale study (N=190) collected resting state data in healthy volunteers and found a significant correlation with self-reported navigation ability and connectivity patterns: the retrosplenial cortex (and not the hippocampus) served as a “hub” of high degrees of connectivity in good navigators (Kong et al., 2017). We think, however, that more direct measures of navigation are likely needed, including map drawing and pointing of both familiar and novel environments. Such a study would also, hopefully, directly contrast hippocampal volume as an explanatory variable directly against connectivity patterns.

4.2.2 Weakness of models of connectivity

We think that while there is some promising evidence supporting connectivity models, much remains to be done both in terms of formal development of these models and testing. While connectivity models hypothesize that areas like retrosplenial cortex, hippocampus, prefrontal cortex, parietal cortex, and visual cortex form a core network of important brain

regions for navigation, another central part of the model is that other brain regions may dynamically configure depending on navigational demands. For example, the caudate nucleus and cerebellum may be recruited in some instances, depending on navigational demands. Of course, defining these boundary conditions is important and remains an area of development. In addition, while some of past work has attempted to define quantitatively how these models might work, significantly more work is needed in these areas as well (Ekstrom et al., 2020). As we highlighted with many of the studies discussed in favor of the structure-function hypothesis, experimenter degrees of freedom in connectivity models is exceptionally high – how to define nodes, edges, which behavioral tasks to use, and how to validate these models all create a combinatorial explosion of possible analyses. While this is not a weakness per se, it is not as easy to specify in advance how a connectivity model should be configured, what should be controlled for, and how to test hypotheses. This makes pre-registering these experiments even more vital but also more difficult.

Another area of weakness involves determining or specifying what is involved mechanistically in connectivity changes. While research suggested that resting state connectivity may relate to synaptic connectivity changes measure via long-term potentiation (Canals et al., 2009), this idea remains largely untested and underdeveloped. Vascular changes could of course be important for resting state fMRI and if such changes are relevant to behavior, this could shed light mechanistically what is happening in the brain (Webb et al., 2013). Finally, within subject-experiments are also needed to better test connectivity vs. focal gray matter models. These would involve testing a healthy participant at time 1, teaching them how to navigate in some situation, and testing them again at time 2 for changes in functional and structural connectivity. A major advantage of such experiments is that they do not involve the same caveats in sample size, statistical power, and multivariate covariates and thus can potentially provide novel insight into the issue.

5.1.1 Conclusions and future directions

Explaining the neural underpinning of individual differences in a complex skill like spatial navigation has not yielded simple answers. Although early evidence suggested the hippocampus was the seat of the cognitive map and that variation in hippocampal structure correlated with navigation ability, we have reviewed evidence that offers mixed support for this association. To summarize, recent work has shown that correlations between hippocampal volume and navigation ability do not replicate in healthy young adults and may have been more weakly supported in early work. Another possibility we explored is that navigation strategy or episodic memory may be better behavioral targets for this correlation than navigation ability. Instead, we offer the viewpoint that network-based models, which view effective navigation as flexible allocation of resources to spatial tasks as demanded by context, might better capture variability in navigation ability than individual brain region structural changes.

Examining this issue in spatial navigation can also provide new approaches to understanding brain-behavior associations in other areas of cognitive neuroscience. Some research areas, like language, have similarly focused on network approaches to language and beyond individual brain regions (Binder & Desai, 2011; Poeppel et al., 2012). But as neuroscientific inquiry becomes more sophisticated, other complex domains will benefit from a deeper understanding of how to relate complex cognitive processes to neural ones. For example, the cognitive neuroscience of mathematics could build from studies examining numerical processing and arithmetic in single brain regions to a fully-formed theory of how mathematical cognition occurs in the brain (Bellon et al., 2020; Hawes et al., 2019). Other complex domains of cognitive function, like emotional, social processing, and executive function, among many others, may benefit from a set of methods and theories for how to understand behavioral variation and the brain based on dynamic changes in connectivity.

Finally, looking toward the future, we believe rich neural models of complex skills like navigation will yield better outcomes for society. For spatial navigation specifically,

understanding behavioral and neural deficits in spatial function could yield improved diagnostics for navigation-related impairments associated with Alzheimer's disease and better treatments, targeting spatial functions which remain intact. For other domains, a deeper understanding of the neural underpinnings of variability in, say, math performance, may offer better tools for education and better predictions for who might need additional support and what that support might look like. In other words, considering network connectivity patterns and their respective variability based on different cognitive tasks, rather than disruption to a single brain region, allows us to potentially build better therapies that could restore lost connectivity or target other networks that could partially compensate for lost functions.

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