Dissecting the fornix in basic memory processes and neuropsychiatric disease: A review

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Number of words in abstract: 169

Number of tables, figures: 3 tables and 4 figures

Keywords: fornix, white matter, episodic memory, hippocampus, diffusion tensor imaging, Alzheimer's Disease, epilepsy, acetylcholine, theta, obesity, nucleus accumbens, deep brain stimulation, schizophrenia, stress, bipolar disorder, mood

Abstract

The fornix is the primary axonal tract of the hippocampus, connecting it to modulatory subcortical structures. This review reveals that fornix damage causes cognitive deficits that closely mirror those resulting from hippocampal lesions. In rodents and non-human primates, this is demonstrated by deficits in conditioning, reversal learning, and navigation. In humans, this manifests as anterograde amnesia. The fornix is essential for memory formation because it serves as the conduit for theta rhythms and acetylcholine, as well as providing mnemonic representations to deep brain structures that guide motivated behavior, such as when and where to eat. Diffusion imaging research is revealing that the fornix plays a key role in mild cognitive impairment and Alzheimer's Disease, and can potentially predict conversion from the former to the latter. Emerging imaging findings link perturbations in this structure to schizophrenia, mood disorders, and eating disorders, although more research is needed. Cutting-edge research is currently investigating how deep brain stimulation of the fornix can potentially halt memory loss, control epileptic seizures, and even improve mood.

1. Introduction

Seminal work showing that bilateral damage to the hippocampus causes anterograde amnesia (Milner & Scoville, 1957) focused the lens of episodic memory research on the hippocampus, often to the exclusion of other connected brain regions. However, anterograde amnesia can arise from focal damage to other parts of the brain. For instance, prolonged deficiencies in thiamine can cause diencephalic amnesia, which is associated with destruction of the mammillary bodies and/or portions of the thalamus (Gudden, 1896). Anterograde amnesia can also appear after discrete lesions to the basal forebrain (Abe, Inokawa, Kashiwagi, & Yanagihara, 1998). All of these brain regions are linked together by a C-shaped white matter pathway called the fornix. Importantly, fornix damage alone can cause severe and unremitting anterograde amnesia.

However, fornix damage in humans is exceedingly rare. Until recently, it was difficult to know whether the wealth of findings about the fornix from rodents and non-human primates extended to humans. We can now use non-invasive imaging techniques (e.g. diffusion weighted imaging (DWI)) to gain insight into the functional properties, as well as pathological processes, that are associated with various white matter tracts. The goal of this review is to provide a detailed review of the functions and processes supported by the fornix to help researchers interpret their results and plan hypothesis driven DWI research. To achieve this goal, we describe the anatomy of this tract and detail the effects of fornix lesions on memory and other cognitive domains in both humans and animals. In addition, we review the small diffusion imaging literature, discuss the potential information transmission properties of this white matter tract in episodic memory, and point out future directions.

2. Anatomy of the fornix

The fornix, illustrated in **Figure 1**, constitutes the primary efferent and afferent pathway of the hippocampus and is a central component of the Papez Circuit (Amaral & Lavenex, 2007). As an efferent pathway, the fornix begins as the *fimbria*, the attached white matter of the hippocampus, then becomes a detached bundle, forming the fornical crus. The two crura join beneath the splenium of the corpus collosum to form the body of the fornix (Catani, Howard, Pajevic, & Jones, 2002; Douet & Chang, 2015). These fibers descend into the forebrain to become the columns of the fornix, which split around the anterior commissure. The columns then split further into the pre-commissural fibers—which innervate the septal nuclei, diagonal band of Broca, and the nucleus accumbens—and the post-commissural fibers—which extend to the mammillary bodies of the diencephalon. The post-commissural fibers divide into two smaller bundles—one that innervates several anterior hypothalamic areas, and one that carries fibers to the anterior thalamic nuclei (Amaral & Lavenex, 2007). The fornix is bidirectional—it also contains fibers leading from these subcortical regions to the hippocampus. Most external modulators of the products of hippocampal processing—namely the septal nuclei/diagonal band of Broca, locus coeruleus, and raphe nuclei (the latter two regions synapse onto the septal nuclei before progressing to the hippocampus)—enter the hippocampal formation via the fornix (Amaral & Lavenex, 2007). Although some papers state that the hippocampus projects to the medial prefrontal cortex (mPFC) via the fornix, this is inaccurate. There is a separate white matter tract that projects from CA1 and the subiculum to the MPFC that passes through the fornix (Parent, Wang, Su, Netoff, & Yuan, 2010; Godsil, Kiss, Spedding, & Jay, 2013).

Figure 1. **Anatomy of the human fornix.** (A) A schematic depiction of the fornix connecting the hippocampus to other subcortical regions. *Reproduced and adapted with permission from Shi & Toga, 2017.* (B) The fornix reconstructed using diffusion-weighted imaging techniques in a human. *Reproduced with permission from Yeh et al., 2018.*

3. Putative functions of the fornix

3.1. Episodic memory

The literature on the fornix consistently and overwhelmingly links it to long-term forms of memory. In the following sections, we review the relevant literature on non-human animals and humans.

3.1.1. Lesions of the fornix in non-human animals

There is a long history of creating lesions in the fornix of rodents and non-human primates to investigate the causal role of the fornix in long-term forms of memory. In these studies, animals are first trained on a task to a learning criterion, after which they undergo a surgical procedure to sever the fornix, while leaving the hippocampal formation intact. After a period of recovery, the animals are sometimes retested on the previously-learned task to test for retrograde amnesia. They are then taught a new task, after which they are tested to determine whether they were able to acquire new learning, or if they are inhibited by anterograde amnesia. The memory tasks used in non-human primates and rodents are generally spatial or navigational in nature, although some are simply visual recognition tasks. Spatial and navigational tasks require the encoding and retrieval of spatiotemporal context and therefore, serve as a proxy for episodic memory.

Do fornix lesions in non-human animals cause deficits on traditional “hippocampally-dependent” tasks? A rich intellectual history links trace conditioning, contextual fear conditioning, reversal learning, and spatial tasks to hippocampal processing. Performance on all of these tasks is severely affected by lesions to the fornix (detailed in **Table 1**). For instance, one study found that fornix lesions disrupted rabbits’ ability to learn the CS-US association when there was a delay in a trace conditioning paradigm (Oswald, Maddox, & Powell, 2007). Another study used a contextual fear conditioning paradigm and found that rats with fornix lesions do not exhibit freezing behavior upon being returned to the cage in which the CS and US were initially paired (Phillips & LeDoux, 1995; Maren & Fanselow, 1997) nor they do exhibit context-dependent freezing behavior that was previously extinguished (Ji & Maren, 2008). Animals with

fornix transections can learn simple associations when they are repeated many times, but struggle to learn the reversal or reassignments, taking far longer to reach criterion than control animals (Hirsch & Segal, 1972; Wiig, Cooper, & Bear 1996; Wilson et al., 2007). The largest literature of all shows that fornix transection consistently leads to robust impairments in learning new routes and spatial locations, both in non-human primates (Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Kwok & Buckley, 2006) and in rodents (Hirsh & Segal, 1972; O'Keefe, Nadel, Keightley, & Kill, 1975; Walker & Olton, 1979; Ennaceur & Aggleton, 1997; Whishaw & Tomie, 1997; De Bruin, Moita, De Brabander, & Joosten, 2001); see **Figure 2**.

Figure 2. The effect of fornix transection on navigation in non-human primates. Compared to controls, rodents with fornix lesions perform significantly worse on navigational tasks at various delays. *Reproduced with permission from Bussey et al., 2000.*

Crucially, there is robust evidence that fornix lesions do not lead to deficits in non-spatial memory tasks such as object recognition in animals (Markowska, Olton, Murray, & Gaffan, 1989; Gaffan, 1992; Ennaceur, Neave, & Aggleton, 1996; Ennaceur & Aggleton, 1997; Bussey et al., 2000; Wilson et al., 2007). Simple object recognition is thought to be subserved by the perirhinal cortex rather than the hippocampus, however, there is some evidence to the contrary (Bachevalier et al., 1985; Gaffan, 1994; Browning, Gaffan, Croxson, & Baxter, 2010), although the authors in these cases admit to “small and unreliable” effects, or use complex stimuli more akin to “scenes” than objects. Generally, simple object recognition is not impaired by fornix lesions, but once a spatial or contextual component is added to the task, there are consistent and robust deficits in performance.

3.1.2. Lesions of the human fornix

Humans rarely incur damage to the fornix. When it does occur, it is typically in the context of a colloid cyst of the third ventricle (Gaffan, Gaffan, & Hodges, 1991; Hodges & Carpenter, 1991; Poreh et al., 2006; Tsivilis et al., 2008) or some other midline tumor. There are

also rare reports of fornix-specific damage resulting from strokes (Moudgil, Azzouz, Al-Azzaz, Haut, & Gutmann, 2000; Park, Hahn, Kim, Na, & Huh, 2000) or traumatic brain injury (D'Esposito, Verfaellie, Alexander, & Katz, 1995). Findings from this small clinical literature have documented that fornix lesions give rise to a persistent anterograde amnesia best described as a disconnection syndrome (see **Table 1**). This memory deficit occurs against the backdrop of intact intellect and the absence of anosognosia. Working memory, procedural memory, executive and language functioning (except for slightly reduced verbal IQ; Hodges & Carpenter, 1991; Park et al., 2000) are generally in the normal range. When the fornix is completely transected, memory deficits are stimulus invariant, such that they are observed for all types of visual and verbal materials. Even partial damage results in severe decrements, especially if insult is incurred to the left fornix, given the lateralization of language abilities and the import of language to adequate functioning. There is some material specificity in the expected direction, with left fornix damage tending to lead to verbal memory deficits and right fornix damage being more associated with visual memory deficits (Gaffan et al., 1991; McMackin, Cockburn, Anslow, & Gaffan, 1995). However, it is worth noting that the extent of damage is more predictive of deficits than the lesion location on both verbal and visual tasks (Korematsu, Hori, Morioka, & Kuratsu, 2010; Sara, Dyon-Laurent, Guibert, & Levie, 2004 for an animal model).

The episodic memory deficits are generally more profound for recall than for recognition (Calabrese, Markowitsch, Harders, Scholz, & Gehlen, 1995; Tsivilis et al., 2008), although there are deficits in recognition memory as well (Calabrese et al., 1995; D'Esposito et al., 1995; Gaffan, et al., 1991). The clinical profile does not typically include confabulation, distinguishing this form of amnesia from the diencephalic variant. Nevertheless, the episodic memory deficits following fornix lesions in humans are profound, unremitting, and bear an uncanny resemblance to the episodic memory deficits observed after focal bilateral hippocampal lesions.

The multi-trace theory of memory proposes that retrieving past experiences, even remote ones from childhood, necessitates the involvement of the hippocampus (Nadel, Samsonovich, Ryan, & Moscovitch, 2000). Interestingly, there is some evidence that fornix damage causes problems recollecting the far past—deficits in recalling pre-operative learning in animals (Wiig et al., 1996; Squire, Clark, & Knowlton, 2001; Winocur, McDonald, & Moscovitch, 2001) as well as retrograde amnesia in humans (Hodges & Carpenter, 1991; D'Esposito et al., 1995; Poreh et al., 2006). We note that few studies have tested this in humans, but those that have examined it have reported that the retrograde amnesia is primarily for episodic aspects of remote memory, not semantic aspects of remote memory—thus, it is most commonly observed in autobiographical recollection (Hodges & Carpenter, 1991; Poreh et al., 2006). However, other studies find normal levels of pre-operative memory in animals (Gaffan, Parker, & Easton 2001; Buckley et al., 2004; Buckley, Wilson, & Gaffan 2008) or no retrograde amnesia in humans (Park et al., 2000). In sum, the role of the fornix in accessing remote memories is under-developed, but potentially quite interesting.

3.1.2. Diffusion-weighted imaging in humans

Lesion evidence provides strong inferential power about a region's function. However, because fornix lesions are so rare in humans, other means must be sought after to elucidate the role of the fornix in cognitive function. Diffusion-weighted imaging (DWI) can be used to examine how the fornix relates to memory and cognition. This technique uses Brownian motion to create contrast in magnetic resonance imaging (MRI) images—in other words, it tracks the rate and direction that water molecules move in the brain. There are several indices of water

diffusivity, with two of the most commonly used being fractional anisotropy (FA) and mean diffusivity (MD). The interpretation of these indices is not always straightforward, and there is not a one-to-one correspondence between any measure and any particular characteristic of white matter. FA is a composite measure of the degree of anisotropy—symmetry of water movement—in a given voxel, and ranges from 0 (totally isotropic) to 1 (totally anisotropic). It is taken to indicate the degree of directional restriction of water diffusivity within a voxel. MD on the other hand is a measure overall diffusivity (mean of three eigenvalues of the diffusion tensor) in a given voxel, with lower values indicating less diffusivity.

Much of the fornix is located in the third ventricle, inferior (and perpendicular) to the corpus callosum, and, as such, is completely surrounded by cerebrospinal fluid (CSF). This location makes the fornix particularly difficult to image due to ever-present susceptibility artifacts (Sullivan, Rohlfing, & Pfefferbaum, 2010; Gunbey et al. 2014; Hodgetts et al., 2017, 2018). We discuss this issue and potential solutions in Box 1.

Box 1. How to measure the fornix with diffusion weighted imaging

There are several issues that make it difficult to measure the fornix noninvasively. The fornix is small relative to voxel size and it is highly curved, which makes it difficult to reconstruct in DWI. Most importantly, it is difficult to accurately measure due to its location in the third ventricle. Because the diffusion properties of CSF differ greatly from that of white matter—namely, that diffusion is completely free in CSF—this can strongly interfere with the ability to get accurate diffusion measures in the fornix. This can result from inclusion of CSF in many of the voxels identified as part of the fornix, and from pulsatile motion in the CSF surrounding fornical voxels (Sullivan et al., 2010; Gunbey et al., 2014; Hodgetts et al., 2017, 2018). It is therefore paramount that researchers account for this in their analyses that involve the fornix.

Kaufmann and colleagues (2017) proposed the following strategies for CSF remediation. During acquisition, fluid-attenuated inversion recovery prepulses can be used (Cheng, Chung, Chen, & Chou, 2011). Alternatively, during analysis, ventricular volume can be regressed out and free-water elimination can be used (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009). It is essential to consider these strategies when conducting a between-subject design, since ventricular alterations may correlate with age or disease state of one of your populations, thereby biasing your results. For instance, it is known that neurologically normal older adults have relatively larger ventricles than younger adults (Apostolova et al., 2012). In addition, individuals with MCI and AD (Apostolova et al., 2012), multiple sclerosis (Dalton et al., 2006), and schizophrenia (Sayo, Jennings, & Van Horn, 2012) commonly have ventricular enlargement relative to age-matched controls.

It is also difficult to measure the fornix noninvasively because many automated diffusion imaging toolboxes such as AFQ and TRACULA do not include this structure. The majority of published studies on the fornix have used an FSL package called tract-based spatial statistics (TBSS), which is appropriate for some, but not all analyses, and has known pitfalls (Bach et al., 2014). Manual drawing methods can be difficult to reproduce across subjects and laboratories and are time consuming to conduct. A few studies have successfully employed probabilistic fiber tracking techniques using seed, waypoint, and target masks to reconstruct the fornix (Bennett, Huffman, & Stark, 2015; Ngo et al., 2017). Our laboratory uses this method.

An emerging literature is showing that time-of-day modulates resting state, volumetric, and diffusion metrics. In some instances, these effects can swamp the effects of task. The time-of-day changes may reflect important biological rhythms that wax and wane throughout the day (Steel, Thomas, Trefler, Chen, & Baker, 2019). These findings suggest that it is important to test participant populations in a between-subject design at the same time each day, or, if this is not possible, use time-of-day as a factor in regressions.

Last, when conducting DWI research, it is important to know the limitations of the method. DWI is inferior to invasive histology methods used in non-human animals because it cannot reveal the direction of information flow, and it cannot distinguish between the different fibers (e.g. excitatory vs. inhibitory, originating in the lateral septum vs. medial septum, etc.) that constitute a pathway. DWI cannot tell you the biological reason underlying differences in microstructure (Filley & Fields, 2016).

3.1.3. DWI of the fornix in development of episodic memory

The fornix is one of the first major white matter tracts to reach maturity. It can be identified in the fetal brain within the second trimester, and the entire fornical trajectory—the topology—is developed at 19 gestational weeks (Huang, 2010), setting the stage for its developmental course in the first years of life.

Figure 3. **Fornix microstructure in development and aging.** (A) In early childhood, fractional anisotropy increases with age in both boys (in blue) and girls (in red). *Reproduced with permission from Reynolds et al., Jan. 2019 [Preprint].* (B) Increasing age is correlated with decreasing fractional anisotropy in the fornix. *Reproduced with permission from Stadlbauer et al., 2008.*

A small literature describes the development of the fornix and the relationship of DWI metrics to memory performance. While it has been shown that fornix macrostructure is established by the time a human fetus reaches 19 gestational weeks (Huang, 2010), it is less clear when the microstructure reaches maturity. When looking at children beginning at age 2,

researchers found a relationship between age and increased FA in the fornix (Reynolds, Grohs, Dewey, & Lebel, Jan 2019 [Preprint]), suggesting that fornix microstructure is still developing in these very young children (see **Figure 3**). However, no relationship between age and fornix FA was found in studies of children in which the youngest participants were 4 years old (Ngo et al., 2017), 5.6 years old (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008) and 7 years old (Wendelken et al., 2015), which suggests that fornix microstructure reaches maturity before age 4. Relationships between age and fornix MD during development are conflicting, with some evidence suggesting decreased MD in the fornix in children with increasing age (Lebel et al., 2008), whereas other studies show no relationship between age and MD (Reynolds et al., 2019). This discrepancy could be due to the different age ranges and developmental stages of children included in these studies. Wendelken and colleagues (2015) also found a relationship between fornix FA and memory performance in adults, but not in children. This finding is surprising but potentially explained by issues surrounding imaging of the fornix (see Box 1).

3.1.4. DWI of the fornix in adult episodic memory

Consistent with lesion findings, the small diffusion imaging literature in healthy young adults has consistently reported that lower fornix FA and/or higher MD correlates with worse episodic memory performance (Rudebeck et al., 2009; Hodgetts et al., 2017, 2018). These findings suggest that episodic memory impairments that accompany old age should be associated with decreased FA/increased MD.

Indeed, a highly reliable finding in the DWI literature is that in healthy populations of older adults, advanced age is associated with decreased FA and/or increased MD values (Zahr, Rohlfsing, Pfefferbaum, & Sullivan, 2009; Bennett et al., 2015; Bennett & Stark, 2016; Gunbey et al., 2014; Jang, Cho, & Chang, 2011; Metzler-Baddeley, Jones, Aggleton, & O'Sullivan, 2011; Metzler-Baddeley, O'Sullivan, Belaroussi, Aggleton, & Jones, 2011; Pelletier et al., 2013; Stadlbauer, Salomonowitz, Strunk, Hammen, & Ganstlandt, 2008; Zhuang et al., 2012, 2013) in the fornix (see **Figure 3**). A few studies do not find a relationship between increasing age and fornix FA/MD (Doxey & Kirwan, 2015; Kantarci et al., 2011; Rémy, Vayssire, Saint-Aubert, Barbeau, & Pariente, 2015; Metzler-Baddeley et al., 2011b), potentially due to a failure in accounting for age-related differences in ventricular volume/CSF around the fornix (see **Box 1**).

Importantly, the observed decreases in FA correlate with reduced episodic memory performance in older adults (Antonenko et al., 2016; Bennett et al., 2015; Bennet & Stark, 2016; Kantarci et al., 2014; Metzler-Baddeley et al., 2011a & 2011b; Ray et al., 2015; Zhuang et al., 2013), as do increases in MD (Antonenko et al., 2016; Bennett et al., 2015; Zhuang et al., 2013). There are also reduced fornix fiber counts with increasing age (Stadlbauer et al., 2008), and there is some evidence, albeit from a small sample, that higher fornix FA in older adults is related to better performance on measures of working memory and motor control (Zahr et al., 2009).

Only a few studies have looked at multiple within-subject's measures of diffusion. Among those that have was a study by Antonenko and colleagues (2016) that trained a group of healthy older adults on an object-location paradigm, a spatial task designed to index episodic memory. The researchers found increased FA and decreased MD in the fornix from pre- to post-training. They also found that increased FA across training was related to better recall—but not recognition—performance at post-test (Antonenko et al., 2016).

3.1.4. Summary of findings on episodic memory

Findings from the reviewed studies consistently and overwhelmingly converge on the idea that the fornix is essential for memory tasks that are traditionally thought of as “hippocampal.” Fornix damage in rodents or monkeys causes deficits across a range of tasks including trace conditioning, contextual fear conditioning, spatial navigation, object-location pairing, and other visuospatial tasks. Moreover, fornix lesions in non-human primates mirror the temporality that is observed in humans suffering from bilateral hippocampus lesions—anterograde but limited retrograde amnesia after transection of the fornix, evidenced by the primates’ accurate recall of pre-operative memories/experiences in many studies, but inability to form new memories of tasks learned post-operatively (Buckley, Charles, Browning, & Gaffan, 2004; Buckley, Wilson, & Gaffan, 2008; Gaffan et al., 2001). In humans, fornix damage causes anterograde amnesia that is worse for recollection as compared to recognition. The clinical profile is more similar to medial temporal lobe amnesia than it is to diencephalic, due to the absence of confabulation. Are the deficits after fornix lesions of the same duration and of the same magnitude as that observed after hippocampal lesions in non-human animals? Most studies suggest that the deficits are virtually identical (e.g. Aggleton, Keith, Rawlins, Hunt, & Sahgal, 1992; Maren & Fanselow, 1997). Recent findings using non-invasive methods to examine the fornix – DWI – converge on a similar narrative, showing a correlation between diffusion metrics and episodic memory performance across a range of age groups and tasks.

3.2. Spatial cognition, writ large

A second putative role for the fornix in cognition is that it plays a key role in spatial memory and spatial perception. This view stems from a controversial model that proposes that the hippocampus plays a material specific role in cognition: that it is essential for perceiving and remembering scenes and locations, while another medial temporal lobe region - the perirhinal cortex - plays an essential role in face/object perception (reviewed in Graham, Barense, & Lee, 2010). Because the fornix innervates the hippocampus, but not perirhinal cortex, these findings would suggest that fornix transection should cause spatial memory and perception deficits, but not object/face memory and perception deficits. Supporting this view, the literature shows that in non-human primates, memory for objects and faces is usually spared, while spatial memory is impaired, after fornix transection (Markowska et al., 1989; Gaffan, 1992; Ennaceur, Neave, & Aggleton, 1996; Ennaceur & Aggleton, 1997; Bussey, Duck, Muir, & Aggleton, 2000; Wilson, Baxter, Easton, & Gaffan, 2007; Browning et al., 2010; Kwok & Buckley, 2009; Browning et al., 2010; Kwok & Buckley, 2010; but see Bachevalier, Parkinson, & Mishkin, 1985; Gaffan, 1994). In addition, Graham and colleagues used DWI in young healthy participants and found that higher fornix FA was related to better performance on spatial memory measures but did not relate to performance on object memory measures (Hodgetts et al., 2017, 2018; Rudebeck et al., 2009).

As compelling as these findings are, it must be remembered that humans differ from rats and monkeys in several small ways, but also in one major way: we have language. Language, much like flight, is a species game-changer. The ability to remember someone’s name, to communicate instructions, or to follow the narrative of a story is essential for human interactions. And humans with fornix damage fail to remember words and conversations, consistent with a global amnesia (Calabrese et al., 1995; D’Esposito et al., 1995). A quick look at **Table 1** shows that nearly every study of individuals with fornix damage reported verbal memory impairments. Thus, evidence from humans does not support the claim that the fornix is only involved in spatial memory.

As for the claim regarding the role of the fornix in visual perception, there is evidence from non-human primates that fornix transection impairs the ability to discriminate between pictures of complex scenes, while leaving the ability to discriminate between pictures of objects intact (Gaffan, 1992 & 1994; Easton, Ridley, Baker, & Gaffan, 2002; Wilson et al., 2008; Browning et al., 2010). The tiny literature from humans with fornix lesions is mixed (Gaffan et al., 1991; D'Esposito et al., 1995) while the only DWI study found evidence for the material specific role such that fornix microstructure correlated with the perception of scenes (Postans et al., 2014). To summarize, the literature linking the fornix to spatial perception is small and findings are mixed, and potentially confounded by transaccadic memory. Future research should investigate this issue in more detail.

3.3. Working memory, curiosity, and other aspects of cognition

Some researchers have conducted diffusion imaging studies on healthy participants and found associations between working memory performance and higher FA (Zahr et al., 2009) and lower longitudinal and transverse diffusivity in the fornix (measures similar to MD; Sullivan et al., 2010). However, studies of patients with fornix lesions find that they have normal working memory abilities (Calabrese et al., 1995; Gaffan et al., 1991; Hodges & Carpenter, 1991; Park et al., 2000; Poreh et al., 2006; Tsivilis et al., 2008). One case report detailed a patient with deficits in working memory, but this patient sustained a gunshot wound, and the authors speculate her working memory deficit was a result of damage by the bullet to the left posterior parietal region (D'Esposito et al., 1995). In sum, evidence for the fornix playing an essential role in working memory is weak.

Recently, a DWI study linked variation in fornix microstructure to the traits of novelty seeking and curiosity (Valji et al., May 2019 [Preprint]). These findings make sense in light of a large literature showing that the hippocampus is extremely sensitive to novelty, containing a comparator mechanism that allows incoming information to be compared to stored representations (Lisman & Grace, 2005).

Other aspects of cognition—reasoning, attention, language, mathematical abilities, and conceptual knowledge, for instance—do not appear to rely on the fornix, although, admittedly, this has not been an area of interest by researchers studying the fornix.

Table 1: The relationship between the fornix and cognitive performance.

Tasks	Summary of Findings	References
Trace and Contextual Fear Conditioning	<ul style="list-style-type: none"> • Reliable deficits across tasks and non-human species. • No studies in humans. 	Phillips & LeDoux, 1995; Maren & Fanselow, 1997; Oswald et al., 2007; Ji & Maren, 2008
Reversal Learning	<ul style="list-style-type: none"> • Reliable deficits across tasks and non-human species. • No studies in humans. 	Hirsch & Segal, 1972; Wiig et al., 1996; Wilson et al., 2007

Spatial Memory and Spatial Navigation	<ul style="list-style-type: none"> • Reliable deficits across tasks and species. • Reliable relationship between performance on spatial tasks and fornix DWI parameters in humans. 	Hirsch & Segal, 1972; O’Keefe et al., 1975; Walker & Olton, 1979; Markowska et al., 1989; Murray et al., 1989; Aggleton et al., 1992; Gaffan, 1994; Ennaceur et al., 1996; Ennaceur & Aggleton, 1997; Parker & Gaffan, 1997; Whishaw & Tomie, 1997; Bussey et al., 2000; De Bruin et al., 2001; Easton et al., 2002; Buckley et al., 2004 and 2008; Kwok, 2006; Kwok & Buckley, 2010; Kwok et al., 2015; Hodgetts et al., 2017, 2018
Traditional Episodic Memory Tasks, e.g. WMS, CVLT, etc.	<ul style="list-style-type: none"> • Reliable anterograde amnesia for all materials after fornix damage. • Correlational evidence from similar tasks using DWI. 	Gaffan, Gaffan, & Hodges, 1991; Hodges & Carpenter, 1991; D’Esposito et al., 1995; Mougil et al., 2000; Park et al., 2000; Poreh et al., 2006; Tsivilis et al., 2008; Vann et al., 2008; Rudebeck et al., 2009; Fletcher et al., 2013 & 2014; Hodgetts et al., 2017 & Aug. 2019
Remote episodic memory/autobiographical memory	<ul style="list-style-type: none"> • Intact memory for pre-operative learning in non-human primates. • Emerging evidence for link between the fornix and remote episodic, but not semantic, memory in humans. 	Hodges & Carpenter, 1991; Gaffan et al., 2001; Buckley et al., 2004; Poreh et al., 2006; Gilboa et al. 2006; Buckley et al., 2008; Vann et al., 2008; Hodgetts et al., 2017
Object and Scene Perception/Recognition Tasks: (delayed)-(non)-matching-to-sample, spontaneous object recognition, object face, or scene discrimination	<ul style="list-style-type: none"> • Mixed findings. Fornix transection does not produce an impairment in simple object perception or recognition tasks. • Emerging evidence that the fornix is implicated in some types of complex visuospatial processing. 	<i>Deficits:</i> Bachevalier et al., 1985; Gaffan, 1994; Easton et al., 2002; Wilson et al., 2008; Browning et al., 2010. <i>No deficits:</i> Markowska et al. 1989; Gaffan et al., 1991; Gaffan 1992; D’Esposito et al., 1995; Ennaceur, Neave, & Aggleton, 1996; Ennaceur & Aggleton, 1997; Bussey et al., 2000; Wilson et al., 2007; Rudebeck et al., 2009; Kantarci et al. 2011; Postans et al., 2014

4. Mechanistic role of the fornix

The reviewed empirical literature strongly indicates that the fornix plays an essential role in episodic forms of memory. Here we ask what is the mechanistic role of the fornix? Rigorous investigations in rodents have identified several types of information transmitted through the fornix, reviewed next.

4.1. Transmission from basal forebrain to the hippocampus

A key role of the fornix is to transmit an essential neurotransmitter—acetylcholine—from the basal forebrain to the hippocampus. The medial septum (a region in the basal forebrain,

which in turn receives input from the hypothalamus and several brainstem areas (Khakpai, Nasehi, Haeri-Rohani, Eidi, & Zarrindast, 2013) is the brain's primary source for acetylcholine, which is transmitted to the frontal lobe, as well as to the hippocampus via the fornix. Damage or deterioration of the fornix harms acetylcholine delivery to the hippocampus (Rawlins, Feldon, & Gray, 1979; Blaker, Armstrong, & Gage, 1988). We know that acetylcholine plays an essential role in memory based on findings showing that depletion of basal forebrain acetylcholine precedes Alzheimer's Dementia (Muir, 1997), that blocking acetylcholine in rodents with scopolamine inhibits episodic memory formation (Dixon, Bao, Long, & Hayes, 1996), and that supplementing acetylcholine can improve episodic memory (Oswald et al., 2007). It is believed that the mechanistic role of acetylcholine in the hippocampus is to up-regulate memory encoding while simultaneously down-regulating memory consolidation (Hasselmo, 1999). In other words, acetylcholine acts like a switch, allowing the hippocampus to shift to different functional phases. This suggests that organisms with fornix damage would show improved memory encoding (but not consolidation) when taking supplemental acetylcholine (for one example of this, see Oswald et al., 2007). It is thus possible that the observed memory impairments after fornix damage can be completely explained by harkening to essential neurotransmitter depletion. However, there is an orthogonal explanation regarding theta rhythms.

Theta rhythms are found throughout the brain and dominate the local field potential in the hippocampus. There is mounting evidence that hippocampal theta rhythm (4-12 Hz) plays an important role in episodic memory (e.g., Hsieh & Ranganath, 2014) and spatial navigation (Buzsáki, 2005). Theta power at encoding correlates with subsequent word recall (Klimesch, Doppelmayr, Russeger, & Pachinger, 1996), and memory for word-video associations (Staudigl & Hanslmayr, 2013). Furthermore, greater theta-band coherence compared to baseline for the MTL-prefrontal cortex interaction was found during memory recall (Anderson, Rajagovindan, Ghacibeh, Meador, & Ding, 2010). Theta may also play some role in memory binding—remembering the co-occurrence of multiple elements within an event (Buzsaki & Draguhn, 2004; Hanslmayr, Staresina, & Bowman, 2016). Corroborating this view, several studies have found that hippocampal theta-gamma coupling is linked to item-context binding processes (Lega, Jacobs, & Kahana, 2012; Staudigl & Hanslmayr, 2013; Tort, Komorowski, Manns, Kopell, & Eichenbaum, 2009; Backus, Schoffelen, Szebényi, Hanslmayr, & Doeller, 2016). GABAergic neurons in the medial septum serve as generator and pacemaker for theta. These cells burst at theta frequencies in-vivo, and destruction of the medial septum halts whole-brain theta rhythms, while destruction of the fornix halts hippocampal theta rhythms (Rawlins et al., 1979), resulting in episodic memory impairments (Cassel, 1997; Lipponen, Woldemichael, Gurevicius, & Tanila, 2012). There is also evidence that acetylcholine modulates theta power (Zhang, Lin, & Nicolelis, 2010).

4.2. Transmission from the hippocampus to the basal forebrain

The mechanisms we just described only explain one direction of fornix information flow; it does not explain how hippocampal outflow via the fornix modulates subcortical structures. The literature relevant to this question is surprisingly small. However, a few recent studies suggest that this flow of information may be essential for modulating motivated behavior. For instance, a recent study reported that the hippocampus regulates social attack via a circuit from CA2->lateral septum->ventromedial hypothalamus. It is possible that a decision to engage in social attack requires retrieval of memories of past social encounters that allow a prediction to be made about the possible win-lose outcome of aggressive behavior (Pagani et al., 2015). Using a similar

logic, we speculate that the hippocampus, via the fornix, also regulates the decision to engage in sexual behavior, based on older findings showing that direct electrical stimulation of the human septum elicited subjective pleasure and sexual arousal (Olds & Milner, 1954; Heath, 1964; Heath, 1972)

Other studies have reported that a circuit from CA3->lateral septum modulates food intake by regulating learned or emotional aspects of food intake, such as how much time has elapsed since the last meal (Sweeney & Yang, 2015). This finding harkens to studies showing that individuals with anterograde amnesia are unable to recall recent eating and will consume multiple meals in quick succession (Hebben, Corkin, Eichenbaum, & Shedlack, 1985; Higgs, Williamson, Rotshtein, & Humphreys, 2008). It also helps to explain new DWI findings linking fornix microstructure to body mass index (Metzler-Baddeley, Baddeley, Jones, Aggleton, & O'Sullivan, 2013).

The fornix also provides a direct connection between the hippocampus and the nucleus accumbens and there is evidence that this circuit allows memories of reward-predicting environments to guide where animals look for food (Trouche et al., 2019). Taken together, these findings suggest that the fornix transmits mnemonic information that shapes and guides motivated behaviors. Evidence about this role is only beginning to emerge in the literature. It is entirely possible that the third role is broader than our description; the fornix may transmit mnemonic information that guides decision-making in all shapes and forms.

4.3. Summary

The reviewed findings suggest three mechanistic functions of the fornix in episodic memory. One role is in transmitting acetylcholine, which switches the hippocampus from a baseline consolidation state to an encoding state. A second potential role is in transmitting theta, which may serve a binding role in episodic memory. A third role is in transmitting mnemonic information that shapes decisions about where to forage, when to feed, and who to fight.

The reviewed findings and mechanisms allow us to conjecture which brain disorders might be linked to fornix dysfunction. Disorders in which there is a prominent episodic memory component such as MCI and AD should show fornix pathology. In addition, there are disorders with subtle, but consistent episodic memory impairments, such as schizophrenia and major depression, which may involve the fornix (along with other white matter tracts). Last, disorders linked to aberrant reward seeking behavior, such as obesity or substance abuse, may involve the fornix. These disorders are reviewed next.

5. Clinical Disorders and the Fornix

The DWI literature linking the fornix to various clinical disorders has been reviewed in some detail recently by Douet and Chang (2015). These authors reviewed studies linking fornix changes to Parkinson's Disease, multiple sclerosis, frontotemporal dementia, and medial temporal lobe epilepsy (see Douet and Chang, 2015). Other authors have reported changes in the fornix in rare disorders like idiopathic normal pressure hydrocephalus (Hattori et al., 2011; Oishi & Lyketsos, 2014). Most of these literatures are very small and findings tend to be inconsistent. In the following sections, we review larger literatures linking changes in the fornix to mild cognitive impairment (MCI), Alzheimer's Disease, schizophrenia and psychosis, mood disorders, and eating disorders.

5.1. The fornix in Mild Cognitive Impairment (MCI)

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5 Mild Cognitive Impairment (MCI) is a term used to conceptualize the cognitive abilities
6 of older adults whose mental faculties are compromised beyond what would be expected in
7 normal aging. It can be divided into two subtypes: non-amnesic (naMCI) and amnesic (aMCI),
8 with the latter including a memory impairment that exceeds what would be expected in typical
9 aging, but that does not reach the level of dementia (reviewed in Yu, Lam, & Lee, 2017).
10 Diffusion-weighted imaging is particularly useful for examining changes in the early stages of
11 cognitive impairment, as it is sensitive to subtle white matter alterations that would not be
12 evident using traditional MRI (Moseley, 2002). Of particular relevance to pathology of the fornix
13 is the amnesic variant of MCI, as the memory impairments specific to aMCI should be related to
14 fornix microstructural changes.

15
16 Individuals with amnesic MCI have relatively decreased FA in the fornix compared to
17 healthy controls (Kantarci et al., 2014; Zhuang et al., 2012, 2013; Bozoki, Korolev, Davis,
18 Hoisington, & Berger, 2012). Changes in fornix FA or MD appear to precede conversion to AD,
19 making this a potent biomarker for pathological memory profile (Fletcher et al., 2013 & 2014;
20 Zhuang et al., 2013; Yu, Lam, & Lee, 2017), especially since around 40 percent of patients with
21 aMCI will eventually convert to AD (reviewed in Douet & Chang, 2015). It has even been
22 proposed that the “fornix sign,” a discoloration of the fornix in color-coded FA maps of the
23 fornix, can be used to predict conversion to AD (Oishi, Mielke, Albert, Lyketsos, & Mori, 2012;
24 see **Figure 4**). Several findings indicate that white matter alterations in limbic tracts may precede
25 gray matter degeneration in the hippocampus as well as secondary loss of white matter volume
26 due to neuronal loss (Zhuang et al., 2013; Fletcher et al., 2013). Some researchers suggest that
27 using models that incorporate both gray matter volume changes as well as white matter
28 microstructural changes together are optimal for detecting the early signs of MCI (Douaud et al.,
29 2013). Importantly, in a study of older adults with MCI, including fornical crus FA in a logistic
30 regression improved the ability of the model to distinguish aMCI from naMCI participants
31 (Gyebnár et al., 2018), underlining the importance of fornix integrity to the degradation of
32 memory capacity in older adults.

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34 A meta-analysis by J. Yu et al. (2017) indicated that the white matter tracts most
35 consistently linked to aMCI were the fornix, uncinate, and parahippocampal portion of the
36 cingulum bundle. Further, their ROI-based analyses showed a consistent relationship between
37 aMCI and fornix FA, but not MD. The authors note that the inconsistency of free water
38 correction across studies might explain the heterogeneity of results for MD and lack of
39 significant findings for this metric, but also might lead to an overestimation of the association
40 between fornix FA and aMCI pathology (Yu, J., et al., 2017). Indeed, other studies have found
41 the opposite pattern—that increased fornix MD is more strongly associated with MCI pathology
42 than is FA (Nir et al., 2013; Nowrangi et al., 2013; Tang, Dai, Feng, Duan, & Shan, 2017), while
43 still another found that fornix FA and MD are both effective individual predictors of longitudinal
44 cognitive decline in MCI patients (Mielke et al., 2012). It is worth noting, however, that many of
45 these studies do not distinguish between aMCI and naMCI, which may affect the results, as
46 naMCI participants do not always have the memory impairments associated with AD and fornix
47 degradation.

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49 Although this review is focused on the fornix, it is worth mentioning that it is not the only
50 tract implicated in mnemonic impairment and cognitive decline; many studies have reported
51 relationships between cognitive impairment and white matter microstructure of other white
52 matter tracts, particularly the cingulum (Bozoki et al., 2012; Nir et al., 2013; Nowrangi et al.,
53 2013; Yu, J., et al., 2017; Gyebnár et al., 2018). The literature on MCI indicates that changes in
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the microstructure the fornix as well as the cingulum bundle can be important predictors of memory impairment and of eventual conversion to AD. Future diffusion imaging studies should focus on tracking older adults longitudinally to better elucidate which diffusion measures are most sensitive to white matter changes and, as such, are the best predictors of cognitive decline.

Figure 4. **The “fornix sign”.** The colors on fractional anisotropy (FA) maps in people with white matter degeneration indicate decreased FA in the fornix, one of the early signs of cognitive decline. (A) FA map of a healthy 80-year-old woman without a fornix sign (FA 0.6-0.8). (B) FA map of an 80-year-old woman with Alzheimer’s disease with the fornix sign (FA <0.5). *Reproduced with permission from Oishi et al., 2012.*

5.2. The fornix in Alzheimer’s Disease

Alzheimer’s Disease (AD) is a progressive neurodegenerative disease marked by significant mnemonic impairment, in addition to other cognitive, affective, and behavioral deficits. The disease is characterized by the presence of beta-amyloid plaques and neurofibrillary tangles in the brain that generally appear first in the medial temporal lobe (MTL) before spreading to the cortex. An early symptom is significant decline in episodic memory performance and hippocampal atrophy is commonly linked to this condition (Apostolova et al., 2012). However, there is also evidence that changes in diffusion metrics in the fornix are evident in AD, discussed below.

Widespread white matter changes are observed in AD, but changes in the fornix are especially interesting since such changes accord with essential limbic pathology and are consistently observed across different samples and methodologies (Oishi & Lyketsos, 2014). Fornix pathology will necessarily impair cholinergic transmission to the hippocampus. Indeed, it has been known for decades that AD is accompanied by loss of this transmission (Coyle, Price,

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4 & Delong, 1983). Like in MCI, AD pathology is associated with decreased FA/increased MD in
5 the fornix (Agosta et al., 2011; Bozoki et al., 2012; Mielke et al., 2012; Mayo, Mazerolle,
6 Ritchie, Fisk, & Gawryluk, 2017; Tang et al., 2017; Nir et al., 2013; Nowrangi et al., 2013;
7 Kantarci et al., 2017). There is some inconsistency in whether any given study finds a change in
8 FA or MD, however, the fornix is consistently implicated, regardless of the diffusion parameter
9 showing changes. Additionally, fornix diffusivity metrics are consistently linked to worse
10 performance on memory tasks for patients with both MCI and AD (reviewed in Douet & Chang,
11 2015), highlighting the specific connection between fornix pathology and memory impairment.
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14 One of the most important findings regarding the fornix is that white matter abnormalities
15 may *precede* the gray matter degradation in the MTL that is typical of Alzheimer's pathology
16 (Agosta et al., 2011; Fletcher et al., 2013, 2014; Zhuang et al., 2013; reviewed in Douet &
17 Chang, 2015), and often is present in patients with aMCI before they convert to AD. This has led
18 to the controversial suggestion that early white matter disruption (especially in the fornix)
19 triggers an adaptive response of deposition of amyloid and tau along with deficits in cholinergic
20 transmission (Bartzokis, 2011). The change in cholinergic transmission leads to the behavioral
21 manifestation – memory problems – while the accumulation of amyloid and tau potentially cause
22 the secondary deterioration of hippocampal gray matter. This would explain why traumatic brain
23 injury and cerebro-vascular disease, which are both associated with diffuse axonal injury as well
24 as damage to myelin, are also strong risk factors for AD (Filley & Fields, 2016).
25 Clinicians are interested in predicting Alzheimer's disease in vivo. Therefore, tracking changes
26 in white matter diffusion properties could be an effective method for projecting future amnesic
27 symptoms and cognitive decline in older adults. Tissue loss and microstructural changes in the
28 fornix have been found to be predictive of conversion from normal cognition to MCI and AD
29 (Fletcher et al., 2014). In addition, there is some evidence that acetylcholinesterase inhibitors
30 which are commonly prescribed for the treatment of AD, can have a positive effect on
31 myelination (Bartzokis, 2007).
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34 In sum, there is strong evidence that fornix pathology is tightly associated with the
35 development of AD, and tracking this pathology using diffusion imaging can be an effective way
36 to predict cognitive decline and memory impairment in older adults at risk for developing AD.
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41 5.3. The fornix in schizophrenia, psychosis, and mood disorders

42 The diffusion imaging literature on schizophrenia is quite large due to long-standing
43 theories about disrupted circuitry in this disorder (Andreasen, Paradiso, & O'Leary, 1998). In
44 addition, schizophrenia is often accompanied by wide spread cognitive alterations including
45 changes in relational memory (Jung & Lee, 2016), which provides a theoretical justification for
46 looking at the fornix in this disorder. While some studies have reported changes in fornix
47 microstructure in schizophrenia, others have not (reviewed by Douet and Chang, 2015; see also
48 Baumann et al., 2016). However, post-mortem studies of individuals with schizophrenia have
49 not found that the fornix is altered (reviewed by Douet and Chang, 2015) and case reports on
50 humans with fornix damage do not report that they suffer from delusions, thought disorder, or
51 hallucinations. Explanations for inconsistent findings include enlarged ventricles in individuals
52 with schizophrenia (Sayo et al., 2012) which can bias the diffusion metrics (see **Box 1**) and
53 heterogeneous etiologies in the sample population. Nevertheless, this remains an interesting tract
54 to target in this population, using optimized imaging methods.
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57 A stronger case can be made for the fornix in mood disorders. It has been hypothesized
58 that the fornix plays an important role in the mediation of fear and anxiety (Degroot & Treit,
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2004) as well as daily stress, as the conduit of glucocorticoids to the hippocampus (Savransky et al., 2017). Alterations to the fornix microstructure may cause affective dysregulation, which is observed in many mood disorders. For example, variations in the microstructural properties of the fornix body have been associated with early trauma and with symptom severity in individuals with panic disorder (Yu, Lee, & Lee, 2017). Adolescents with bipolar disorder had lower fornix FA compared to age-matched controls, suggesting that alterations in this white matter pathway are present early in the course of the disease (Barnea-Goraly, Chang, Karchemskiy, Howe, & Reiss, 2009). Another study reported that unmedicated patients with bipolar disorder had reduced fimbria volume compared to medicated patients and controls (Elvsåshagen et al., 2012). A recent pilot study reported that deep brain stimulation of the fornix improved mood in individuals with AD (Mao et al., 2018). These results corroborate findings in healthy controls showing that individual differences in sub-clinical anxiety scale with fornix microstructure (Modi et al., 2013). Although the findings we listed are a mixed lot of clinical disorders and methods, they hint that the fornix may play a role in affect regulation, which would not be surprising since the subcortical nuclei at the anterior end of the fornix are involved in many essential limbic functions, including reward signaling. Future research should examine whether the fornix is demyelinated or atrophied in stress-related disorders like post-traumatic stress disorder.

5.4. The fornix in aberrant reward-seeking: eating disorders and substance abuse

Decisions about when to eat and where to optimally forage for food rely on long-term memories (see Section 4.2). Thus, it is possible that alterations in fornix microstructure account for pathology in eating behavior. Some studies report that in humans, variation in fornix microstructure correlates with body mass index (BMI; Metzler-Baddeley et al., 2013; Xu, Li, Lin, Sinha, & Potenza, 2013; reviewed in Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015). These studies generally show that higher BMI is associated with lower FA, higher MD, or both. In addition to degraded fornix microstructure in those who are overweight or obese, there is a similar pattern in those with eating disorders of food restriction, such as anorexia nervosa (AN) and bulimia nervosa (BN). Several studies have investigated this relationship and found decreased FA values, increased MD values, or both in participants with AN (Kazlouski et al., 2011; Frank, Shott, Hagman, & Yang, 2013; Monzon, Hay, Foroughi, & Touyz, 2016; Phillipou et al., 2018) and BN (Kazlouski et al., 2011; Mettler, Shott, Pryor, Yang, & Frank, 2013). This pattern across participants who are both over- and underweight suggests that the fornix may be integral in circuitry related to eating behaviors. However, many of these studies found microstructural changes in tracts other than the fornix, indicating that very high or low BMI (or perhaps frequent vacillations in body weight related to disordered eating patterns) may lead to widespread white matter changes across the brain that are not constrained to the fornix. This is complimented by findings that indicate no group differences in white matter microstructure between women who have recovered from AN and normal controls (Bang, Rø, & Endestad, 2018), suggesting that the white matter abnormalities found in patients with AN may be a result of eating disorder pathology rather than a cause.

One review suggests that such white matter degradation in the brain is related to increased inflammation in the body due to poor physical health, which can in turn impact neurons' myelin sheaths (Porter, Leckie, & Verstynen, 2018). More work is needed to elucidate whether there is a particular role of the fornix in eating behaviors, or if instead having a BMI outside what is considered the normal range is related to nonspecific white matter degradation across the brain. Since abnormal eating behaviors are often related to restriction or bingeing or

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4 both, there is a component of cognitive control and reward seeking inherently tied to disordered
5 eating. Perhaps it is these behaviors that are tied to the altered fornix microstructure in people
6 who are over- or underweight.

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8 Substance abuse is a classic model of reward seeking gone awry. We recently reviewed
9 the diffusion imaging literature on substance abuse (Hampton, Hanik, & Olson, 2019) and found
10 that the literature was highly inconsistent, even when restricted to a particular substance like
11 cocaine. The fornix was mentioned as being affected in only a single study of adolescents with
12 alcohol use disorder (Cardenas et al., 2013). We do not think the absence of findings should be
13 taken as truth, however. We found that this literature suffered from many methodological
14 problems such as imaging methods with poor signal-to-noise ratios, few diffusion directions,
15 reliance on whole brain TBSS analyses, and absence of hypotheses that might point towards a
16 specific tract or brain region. Future research should closely examine the fornix, especially in
17 substance use disorders where pleasurable memories may be especially important in driving
18 behavior (e.g. opioids).
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23 **6. At the cutting-edge: deep brain stimulation of the fornix**

24 There is currently great interest in electrically stimulating the fornix to potentially
25 improve memory in MCI and AD. This idea has its genesis in a now-classic study by Hamani
26 and colleagues, in which the goal was to use deep brain stimulation (DBS) of the hypothalamus
27 to help with weight control in a patient who was morbidly obese (Hamani et al., 2008). DBS
28 functions therapeutically in humans at frequencies between 80 and 185 Hz and with a stimulation
29 current between 1 and 10 mA (Vedam-Mai et al., 2012). The effects of DBS on neuronal
30 function can be excitatory or inhibitory, depending on the stimulation site. In Hamani and
31 colleagues' study (2008), they inadvertently stimulated the fornix (due to the proximity of the
32 fornix to the hypothalamus), which caused the patient to recount extremely detailed
33 autobiographical memories during the surgery, as well as leading to increased activity in the
34 hippocampus and parahippocampal cortex. The patient continued to demonstrate increased
35 performance on verbal recognition and spatial memory assessments after three weeks of
36 continuous stimulation (Hamani et al., 2008).
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40 This compelling finding helped launch a small industry of fornix DBS studies. Studies in
41 rats showed that DBS of the fornix can activate the hippocampus (Gondard et al., 2015) and can
42 reset hippocampal theta, promoting optimal memory encoding (Williams & Givens, 2003). DBS
43 of the fornix in rats also improves performance on hippocampal-dependent spatial memory tasks
44 (Hescham et al., 2013; Zhang, Hu, Wu, Zhang, & Zhang, 2015). Additionally, it can reverse
45 Alzheimer's-type memory impairments in these rats (Hescham et al., 2013), but does not appear
46 to have an effect on the presence of Alzheimer's-related proteins such as beta-amyloid or tau
47 (Gondard et al. 2015).
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49 The benefits to memory in rats with impairments mimicking Alzheimer's deficits raises
50 the question of whether this would translate to humans. Several studies have revealed optimistic
51 findings: fornix DBS in humans can drive neural activity in the entorhinal cortex and
52 hippocampus to reverse impaired glucose utilization in the temporal and parietal lobes (Laxton et
53 al., 2010) and increase metabolism in the medial temporal lobes (Fontaine et al., 2013). In
54 addition, patients with AD who were receiving DBS to the fornix showed slowed hippocampal
55 atrophy relative to AD controls who did not receive stimulation (Sankar et al., 2015). Case
56 studies have also shown that patients whose memory was declining prior to fornix stimulation
57 stabilized after DBS (Laxton et al., 2010; Fontaine et al., 2013), and that even patients with
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4 severe AD showed some improvements in mood, memory, and language ability, as reported by
5 caregivers (Mao et al., 2018).

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7 The memory improvements in these studies are modest, and it has been proposed that
8 more robust results would be obtained if studies employed closed-loop stimulation rather than
9 open-loop stimulation, as closed-loop formats allow stimulation to optimally target memory-
10 related activity in the brain (Senova, Chaillet, & Lozano, 2018). Open-loop stimulation refers to
11 the most common type of DBS in which a constant stimulation, at a constant frequency, is
12 applied. In closed-loop protocols, stimulation is done in targeted intervals at specific frequencies
13 that align with brain activity occurring during either encoding or retrieval periods. Another
14 possibility that can be explored is to use rhythmic DBS of the fornix to pace or replace
15 potentially aberrant hippocampal theta rhythms.
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18 Although the benefits of DBS of the fornix on memory in MCI and AD remain
19 inconclusive, there is some evidence that fornix DBS may have an unexpected benefit for
20 epilepsy. Koubeissi and colleagues (2013) found modest benefits of fornix stimulation on
21 memory recall in epilepsy. More robust was the 92 percent decrease in seizure occurrence,
22 suggesting clinical benefits of fornix stimulation beyond memory improvements (Koubeissi,
23 Kahrman, Syed, Miller, & Durand, 2013).
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25 26 **7. Conclusions**

27 Our review of the fornix literature reveals that it plays an essential role in episodic forms
28 of memory across species and tasks. We were surprised to find that the effects of fornix damage
29 on memory are nearly indistinguishable from the deficits observed after focal hippocampal
30 lesions. Thus, memory processes that are considered “hippocampal” can just as easily be viewed
31 as “fornical”. Classic linkages and functional divisions in the literature on the hippocampus such
32 as episodic vs. semantic memory, recall vs. recognition, explicit vs. implicit, are mimicked in the
33 literature on the fornix, supporting an older idea that damage to any part of the “extended
34 hippocampal memory system” would cause similar memory deficits (e.g., Warrington &
35 Weiskrantz, 1982; Aggleton & Brown, 1999). The mechanistic role of the fornix is, of course,
36 quite different than the computational role of the hippocampus in episodic memory. The fornix is
37 the conduit by which the neurotransmitter acetylcholine—which is crucial for memory encoding—
38 is sent from the medial septum/diagonal band of Broca to the hippocampus. In addition, the
39 GABAergic neurons in the septal nuclei generate theta rhythms which are transmitted through
40 the fornix to the hippocampus. In the absence of these external modulators, the hippocampus is
41 radically dysfunctional.
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44 Without an intact fornix, hippocampal neurons do not have a direct pathway to the basal
45 forebrain or diencephalon, although it retains intact communication with medial temporal lobe
46 regions like the entorhinal cortex, amygdala, and retrosplenial cortex (Aggleton, Wright, Rosene,
47 & Saunders, 2015). It has been suggested that fornix pathology in MCI and AD should lead to a
48 greater reliance on alternative medial temporal lobe pathways, perhaps via the cingulum bundle
49 (Metzler-Baddeley et al., 2012) or uncinate fasciculus. The cingulum bundle, a large limbic tract
50 connecting the parahippocampal cortex, retrosplenial cortex, and cingulate cortex to the frontal
51 lobe, does not appear to play an essential role in episodic memory (Bubb, Metzler-Baddeley, &
52 Aggleton, 2018). Likewise, the uncinate fasciculus, a limbic pathway that connects the anterior
53 temporal lobe and amygdala to the orbitofrontal cortex/ventromedial prefrontal cortex and
54 frontal pole, plays some role in learning and memory (Von Der Heide, Skipper, Klobusicky, &
55 Olson, 2013; Alm, Rolheiser, Mohamed, & Olson, 2015; Alm, Rolheiser, & Olson, 2016), but its
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4 contribution is modest compared to the fornix, and most likely limited to retrieval functions.
5 Thus, there does not appear to be any alternative fiber tracts to support relational memory and
6 recollection if the fornix is compromised.
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8 The findings in the lesion literature are mirrored in the newer diffusion imaging literature.
9 Microstructural properties of the fornix, especially FA, decrease with advanced age, correlate
10 with age-related memory impairments, and decrease in disease states defined clinically by
11 episodic memory problems (amnesic MCI and AD). In fact, it has been suggested that fornix
12 pathology precedes gray matter degeneration in the hippocampus as well as secondary loss of
13 white matter volume due to neuronal loss (Zhuang et al., 2013; Fletcher et al., 2013). The “fornix
14 sign,” a discoloration of the fornix in color-coded FA maps of the fornix, has been used to
15 predict conversion from MCI to AD (Oishi et al., 2012; see **Figure 4**).
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17 It is increasingly recognized that brain rhythms are essential for normal cognition. A
18 simple way to perturb a brain rhythm is to alter myelination of the connecting fibers. There are
19 many avenues to myelin disruption—exposure to toxic reagents, metabolic problems,
20 inflammation, infection, and the list goes on (Filley & Fields, 2016). It is possible that myelin
21 disturbances may cause network disruptions that ultimately lead to neuropsychiatric disorders.
22 The DWI literature has linked changes in the fornix to different psychiatric disorders including
23 schizophrenia and psychosis, bipolar disorder, and eating disorders. We note that in all of these
24 cases, the fornix is not selectively altered, but rather is one of many affected white matter tracts.
25 Unlike the episodic memory literature, the psychosis literature is decidedly mixed on whether or
26 not the fornix plays an important role in the pathophysiology of this disease, potentially due to
27 small and heterogeneous sample populations, and difficulties encountered in imaging the fornix.
28 The literature on bipolar disorder is more promising, and the literature on eating disorders is very
29 small but is beginning to show interesting relationships between fornix microstructure and eating
30 behavior. We suggest that future researchers interested in psychosis and/or bipolar disorder
31 should (a) measure episodic memory performance (preferably using a task with relational and
32 spatial processing demands) as well as stress and allostatic load, and correlate these measures
33 with fornix microstructure, rather than clinical diagnosis *per se*; (b) use optimized imaging
34 methods as described in **Box 1**.
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36 Our review exposed several gaps in the literature that we detail in **Box 2**. We note that the
37 human literature on the fornix would benefit by drawing from the rich literature on the rodent
38 fornix. For instance, lesion and DWI studies of humans should use tasks that depend on an intact
39 fornix in rodents and monkeys (see **Table 1**). Using tasks like reversal learning or trace
40 conditioning in humans would allow for greater cross-species comparison. In addition,
41 delineating the contributions of each MTL subregion has been the primary focus of most
42 memory models in terms of their distinct computational properties (Montaldi & Mayes, 2010;
43 Norman & O'Reilly, 2003) and representation-specific processes (Davachi, 2006; Ranganath,
44 2010). Much controversy surrounds the functional divisions among the MTL gray matter
45 subregions, most notably the hippocampus and MTL cortex including the perirhinal cortex,
46 parahippocampal cortex, and entorhinal cortex. Given the crucial role of the fornix in the
47 multitude of mnemonic processes outlined in this review, integrating this major white matter
48 pathway in these existing theories would generate novel predictions about complex memory
49 capacities expressed as products of an inter-connected circuitry.
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51 In the future, quantitative DWI of the fornix may be able to reliably diagnose AD and
52 predict conversion from MCI to AD. In addition, imaging of the fornix may be able to provide a
53 differential diagnosis of AD, which is important, given that disorders such as depression can
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4 have a clinical presentation of memory impairments in the elderly. Apart from imaging the
5 fornix, the effectiveness of treating neuropsychiatric disorders with DBS of the fornix are modest
6 thus far, but have the potential for added benefit with modifications, such as employing closed-
7 loop formats. Closed loop stimulation of the fornix could even be used to pace or replace
8 potentially aberrant hippocampal theta rhythms in AD (see optogenetic study by Giovannetti et
9 al., 2018) and potentially improve mood, not only in AD, but other disorders like unipolar
10 depression (see Mao et al., 2018). There is emerging evidence that scalp EEG can record theta
11 oscillations (Crivelli-Decker, Hsieh, Clarke, & Ranganath, 2018), opening the door to future
12 research that uses a non-invasive form of brain stimulation, rather than DBS, to modulate theta
13 and. More research is needed to uncover the specific role of the fornix in neuropsychiatric
14 disorders and to discover how best to target this tract for potentially alleviating symptoms or
15 delaying onset of the disorders.
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20 **Box 2. Big Questions for Future Research**

- 21 1. Does fornix degradation in hippocampal or diencephalic amnesia account for some of the
22 deficits in episodic memory? One of the only studies to look at this found that an individual
23 with developmental amnesia had a partially missing and displaced fornix (Rosenbaum et
24 al., 2014). Given the principle of Wallerian degeneration, it is nearly certain that the fornix
25 is abnormal in this patient population.
- 26 2. Is myelin damage in the fornix the catalyst for amyloid and tau deposition, and for later
27 hippocampal cell loss observed in Alzheimer's Disease?
- 28 3. How does inflammation affect fornix myelination and what are the downstream effects on
29 brain rhythms such as theta, acetylcholine transmission, and cognitive state?
- 30 4. Is the fornix damaged by chronic stress? There is evidence that the hippocampus is acutely
31 sensitive to stress and that oligodendrocytes are also sensitive to stress (McEwen, 2017).
32 This literature has evolved along an axis that is quite separate from the literature on
33 episodic memory; thus, it is unclear how different findings in different literatures relate to
34 one another.
- 35 5. Do alterations in fornix microstructure account for pathological eating behavior? The
36 fornix is the conduit by which memories are used to guide decisions; it is part of the
37 interface between the limbic system and action. For instance, decisions about when to eat
38 and where to optimally forage for food rely on a circuit that includes the hippocampus and
39 the fornix. At least one study has reported that in humans, variation in
40 fornix microstructure correlates with body mass index (Metzler-Baddeley et al., 2013).
41 This relationship deserves further attention.
- 42 6. How do changes in fornix microstructure relate to episodic memory and other cognitive
43 faculties in young children? Fornix *macrostructure* is fully developed by age 2, but
44 episodic memory continues to develop for several more years (Ngo, Lin, Newcombe, &
45 Olson, 2019). Future investigators should examine whether variation in fornix
46 microstructure, more than chronological age, relates to the maturity of memory
47 performance in young children.
- 48 7. Is the adult fornix plastic? A ground-breaking study trained both humans and rats on a
49 spatial navigation task. After only two hours of training, there were measurable
50 microstructure changes in the fornix as well as the hippocampus (Hofstetter, Tavor, Tzur
51 Moryosef, & Assaf, 2013). These findings suggesting that the fornix remains plastic in
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4 adulthood, that plasticity in this structure occurs rapidly, and that microstructural changes
5 in white matter and gray matter happen in conjunction. This finding deserves further study.
6 For instance, does this finding generalize to other types of learning (see Hofstetter,
7 Friedmann, & Assaf, 2017)? Is this plasticity maintained in older adults (Vien et al., 2016)?
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10 11 **Acknowledgements**

12
13 We would like to thank David Waxler for helpful comments. This work was supported by a
14 National Institute of Health grant to I. Olson [RO1 MH091113]. The content is solely the
15 responsibility of the authors and does not necessarily represent the official views of the National
16 Institute of Mental Health or the National Institutes of Health.
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