Identifying and Characterizing the Effects of Nutrition on Hippocampal Memory

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ABSTRACT

In this review we provide evidence linking relational memory to the hippocampus, as well as examples of sensitive relational memory tasks that may help characterize the subtle effects of nutrition on learning and memory. Research into dietary effects on cognition is in its nascent stages, and many studies have cast a wide net with respect to areas of cognition to investigate. However, it may be that nutrition will have a disproportionate effect on particular cognitive domains. Thus, researchers interested in nutrition-cognition interactions may wish to apply a more targeted approach when selecting cognitive domains. We suggest that hippocampus-based relational memory may be extraordinarily sensitive to the effects of nutrition. The hippocampus shows unique plastic capabilities, making its structure and function responsive to an array of lifestyle factors and environmental conditions, including dietary intake. A major function of the hippocampus is relational memory, defined as learning and memory for the constituent elements and facts that comprise events. Here we identify several sensitive tests of relational memory that may be used to examine what may be subtle effects of nutrition on hippocampus and memory. We then turn to the literature on aerobic exercise and cognition to provide examples of translational research programs that have successfully applied this targeted approach centering on the hippocampus and sensitive relational memory tools. Finally, we discuss selected findings from animal and human research on nutrition and the hippocampus and advocate for the role of relational memory tasks in future research. Adv. Nutr. 5: 337S–343S, 2014.

Introduction

Long thought of as the top of the body’s food chain, the brain has been shown in recent research to be sensitive to processes occurring elsewhere in the body. Lifestyle factors such as dietary intake, body mass, and physical fitness that affect bodily health can also influence brain structure and function in both humans and animals.

One area of the brain particularly sensitive to bodily health, lifestyle factors, and environmental conditions is the hippocampus (1). For instance, the size of the hippocampus is smaller in individuals with hypertension, type 2 diabetes, obesity, clinical depression, or a history of mild traumatic brain injury (2–6). Hippocampal size is also known to increase in response to lifestyle factors including aerobic exercise, education, and intensive cognitive training, such as that experienced by London taxi drivers in training or medical students studying for a certification exam (7–10). Interestingly, as further discussed below, components of dietary intake have beneficial or detrimental effects on hippocampal health (11).

The hippocampus’s responsiveness to these disparate factors and conditions likely stems from its high metabolic demand and extraordinary capabilities of plasticity. For instance, the hippocampus is 1 of just 2 structures in the brain known to undergo neurogenesis, the creation of new neurons, beyond the gestational period (12,13). This form of plasticity is related to lifestyle factors, with both exercise and dietary intake modulating the rate of neurogenesis and other forms of structural change (see below).

In terms of cognitive expression, the hippocampus has been linked to memory processes since the seminal 1957 report by Scoville and Milner (14) on the patient known as “H.M.” H.M. suffered from intractable epilepsy and underwent an experimental procedure in which doctors removed most of both his hippocampi. After the surgery, H.M. became densely amnesic, losing the ability to form new memories for daily life events, as well as losing the ability to recall

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what happened even years before the surgery. Since this report, the nature of the precise memory representations dependent on the hippocampus has been thoroughly investigated in patients with hippocampal damage like H. M. as well as with fMRI in healthy individuals. In the next section, we provide evidence indicating that the hippocampus subserves a particular cognitive process, relational memory, which is critical for flexibly binding together elements of events or ideas into memory.

**Current Status of Knowledge**

**Relational memory and the hippocampus.** Cognitive neuroscience research has uncovered that the brain has multiple memory systems (15). A large research area in the field centers on delineating the brain structures and networks that underlie these individual memory systems. There are a multitude of memory system classification schemes, but 1 well-established and agreed-upon dissociation involves the brain systems responsible for procedural memory versus relational/declarative memory (15,16). Procedural memories entail processes learned gradually over time, such as the skills required to type efficiently on a computer or play professional golf or a musical instrument. Relational memories are characterized by memory for facts and events and are composed of a rich set of interconnections of elements, essentially binding together the who, what, where, and when of an experience. Examples of the use of relational memory include learning a new acquaintance’s name, acquiring factual knowledge about the world, or remembering a visit to a research center (Fig. 1). Relational memory formation and retrieval rely on a memory system with the hippocampus serving as the central hub and include contributions from the surrounding medial temporal lobe (MTL) cortex and from the prefrontal cortex (PFC) (17).

One reason for the dependence of relational memory formation on the hippocampus is because of its anatomic connections in the brain. The hippocampus is intricately connected with a variety of neocortical processing streams and serves as a convergence zone for disparate pieces of information. For example, visuospatial and visual object information is initially segregated in 2 cortical processing streams but converges in the hippocampus via inputs from the MTL cortex (18). As the hippocampus receives this plethora of multimodal information, it is able to link these elements into a coherent, distinct representation and embed it in a vast network of relationally organized information.

A wealth of empirical research from a variety of converging cognitive neuroscience methods exists, identifying relational memory processing as a key function of the hippocampus [for review see (19)]. One critical line of evidence comes from neuropsychological research in patients with circumscribed lesions to the hippocampus. The surgery performed on H.M. has never been done since, because of the dire consequences. However, because the hippocampus has such high oxygen requirements, it is highly sensitive to situations in which the brain is deprived of oxygen. Even short periods of inadequate oxygen supply, such as during cardiac arrest, can produce circumscribed hippocampal lesions. In 1 study with such patients, Konkel et al. (20) tested the necessity of the hippocampus for relational memory processing. The results demonstrated that patients with hippocampal damage were impaired at remembering all manners of associations among novel objects, such as their spatial and temporal relations, even though their memory for the individual objects was mostly intact (20).

Complementary evidence tying the hippocampus to relational memory is available from experiments using fMRI in healthy adults. fMRI allows investigators to discern which brain regions are actively involved in specific cognitive processes with high spatial resolution. A study by Staresina and Davachi (21) found that when participants had to simply encode a particular item, activity was greatest in the perirhinal cortex, located in the MTL adjacent to the hippocampus (21). However, when participants were instructed to bind

**FIGURE 1** The hippocampus underlies relational binding of elements of experience. In this example, the constituent elements of a visit to the Beckman Institute at the University of Illinois at Urbana-Champaign are represented by the hippocampus (shown in red). These may include details such as the time of day you visited, an interesting sculpture you observed, the architecture of the building, what room the talk you attended was in, and a lively discussion you had with a colleague afterwards. The hippocampus flexibly binds these elements together into memory and allows you to later recall the experience. The central image was reproduced from reference 66 with permission.
an item with a color (cross-modal association), brain activity shifted more to the hippocampus. Furthermore, adding an additional relation that required participants to bind an item and color across a temporal gap elicited even more hippocampal activity. Thus, because one must bind more elements together, the hippocampus becomes more engaged.

A historical point regarding the hippocampus and relational memory concerns how much of a temporal delay must occur between encoding and retrieval for a memory to be hippocampus-dependent. The classic view in neuropsychology is that the hippocampus governs long-term memory, and remembering information over short time periods (e.g., several seconds) can be accomplished without a hippocampus. This view is rooted in early work with H.M. and other hippocampal amnesic patients, showing that these patients were grossly impaired at remembering declarative information (e.g., a word list) after several minutes had passed but seemed to be able to retain simple information over a span of just a few seconds (22–24). However, a large amount of empirical data now indicates that this might be misleading [for review see (25)]. In particular, converging evidence from fMRI and patient studies indicates that if the information to be retained is relational, the hippocampus is involved irrespective of temporal delay (26–30). This updated view of the timescale of hippocampal memory is critical to the study of nutrition and memory, because one need not be limited to experimental paradigms that impose cumbersome delays between study and test. Indeed, the examination of nutritional enhancement of memory depends decisively on the choice of the proper memory assessment tools.

**Sensitive tools of assessment for relational memory and hippocampal function.** Given the exquisite plasticity displayed by the hippocampus in response to multiple lifestyle factors or events, the hippocampus may be an opportune target to show effects of nutritional intervention. Furthermore, the relation between the hippocampus and relational memory indicates that tasks measuring relational memory can provide an index of hippocampal function.

Traditional neuropsychological tasks of hippocampal memory typically involve an examiner reading aloud a story or list of words and asking the participant to recall this information after some delay (e.g., usually ~10–30 min). These tasks have proven useful in identifying gross hippocampal damage or pathology, such as that suffered by the amnesic patients mentioned above or in Alzheimer disease patients. However, the use of only these tasks to detect differences in hippocampal function resulting from nutrition will likely be less successful for a variety of reasons. First, the change in hippocampal structure and function resulting from differences in nutrition will be subtler than that caused by Alzheimer disease or a hippocampal lesion. This is not to say that cognitive changes from nutrition are not meaningful in day-to-day life but rather that they will require more sensitive tests to detect them.

Another reason that researchers may need to expand their toolbox beyond using traditional word lists to assess nutritional effects of memory concerns the type of memory representations needed to successfully complete these tasks. It is the case that having to remember words read by an experimenter invokes relational memory given that the participant must bind the auditory perception of the word to the experimental setting in order to recall it 30 min later. However, because the words used on these tasks are familiar (e.g., diamond, crocodile) participants generally have pre-existing neocortical representations of these words that they can use to aid later recall. Therefore, contributions to successful performance on these tasks may emanate from extrahippocampal areas and could potentially muddle any effects of nutrition on the hippocampus. To this end, relational memory formation for pre-experimentally unfamiliar materials, such as novel faces, scenes, or other computer-generated images, is more likely to rely on the hippocampus, given that novel stimuli and associations are known to disproportionately engage the hippocampus (31).

Finally, the all-or-nothing nature of the recall in traditional neuropsychological tasks (i.e., the word is remembered or not) lacks validity to real-world memory function. Individuals often retain some information about an event while forgetting other pieces. Therefore, instances in which the relational memory task reflects the graded nature of human mnemonic function more closely resemble the use of memory in the real world. One example of this approach to studying relational memory uses eye-tracking to record eye movements during memory retrieval. This technique is noninvasive and can be used independently of subjective behavioral reporting. Our laboratory has used this method extensively to investigate hippocampus-based relational memory [for review see (32)]. A prototypical experimental design involves showing participants novel face-scene pairs and requiring them to remember the association between the face and the corresponding scene during the encoding phase. During the test phase, on each trial participants are shown a scene from the encoding phase that serves as a background and 3 previously viewed faces simultaneously superimposed on the scene. One of the faces was shown with that particular scene during encoding, whereas the other 2 faces were associated with other scenes that are not displayed again during the test phase. Individuals with an intact hippocampus rapidly, robustly, and disproportionately fixate their eyes on the face associated with the scene when viewing the 3-face display (“disproportionate viewing effect”); however, those with hippocampal damage fail to show this effect (33).

Furthermore, research simultaneously using fMRI and eye-tracking discovered this disproportionate viewing effect to be tightly linked to activation of the hippocampus, whereas correct behavioral responses indicating which face went with the scene relied on both the hippocampus and PFC regions (34). Thus, the disproportionate viewing effect may be a purer measure of hippocampal function than asking participants to provide memory judgments via verbal or motor response. Moreover, the position of the eye is often recorded at a rate of 500–1000 times/s, thereby providing...
a rich temporal data set from which researchers can extract information about how encoding or retrieval processes unfold across time. Finally, multiple analytic techniques can be applied to such data sets, allowing the researcher to untangle more nuanced or subtle memory effects (32).

Another powerful experimental technique to assess hippocampal function involves the use of memory tasks with open-ended response conditions, as opposed to forced-choice tasks. For example, Watson et al. (27) used a spatial reconstruction task in amnesic patients with hippocampal damage. In this task, participants studied the location of several objects on a table. The patients’ view was then obstructed for several seconds while the experimenter aligned the objects at the top of the table. The participant was then asked to move the objects back to their original locations. The minimal constraints placed on the participant during the recall phase allowed for a rich investigation of the types of errors one could make, and these are, in turn, informative of the organization of participants’ underlying memory representations. For instance, a metric based on distance could be used to determine how far a participant placed the object from its original location. Other measures indexing relational memory can also be derived.

One such measure, termed “swap” errors, were situations in which participants placed object A in object B’s original location, and vice versa. This was interpreted as failure in object-location bindings (relational memory) among pairs of objects. When this paradigm was used in hippocampal-amnesic patients, they were overwhelmingly more likely to make this swap error compared with healthy comparison participants [40 times more likely (27)]. Through the open-ended nature of this task, the researchers were able to identify a specific behavioral marker of relational memory sensitive to hippocampal amnesia. Detecting the effects of nutritional intervention on the brain will likely entail the use of tasks similar to the ones described above because of their ability to hone in on the intricacies of hippocampal representations.

Exercise, hippocampus, and relational memory. Powerful examples of hippocampal sensitivity to lifestyle factors, and the use of sensitive tasks to detect relational memory differences arising from these factors, can be found in the literature on exercise and cognition. In addition to augmented neurogenesis and neurogenesis in the dentate gyrus of the hippocampus resulting from aerobic exercise, animal models also indicate that wheel-running leads to more complex dendritic branching in the hippocampus, allowing for the formation of more synapses (35). Furthermore, hippocampal long-term potentiation, a potential physiologic marker of memory formation, is amplified after chronic wheel-running, and this effect co-occurs with more accurate performance on hippocampus-dependent tasks in mice (36).

Direct quantification of certain measures of hippocampal plasticity in humans, such as neurogenesis, is not feasible because of the invasive techniques used for assessment. However, noninvasive neuroimaging methods using MRI have been applied with great success to confirm exercise-related hippocampal changes. In 1 elegant study, Pereira et al. (37) used rodents to find that change in cerebral blood volume, as measured through MRI, was strongly related to neurogenesis in the dentate gyrus of the hippocampus. The researchers then applied this MRI technique to humans before and after an exercise intervention and confirmed the increase in cerebral blood volume localized to the dentate gyrus, providing strong evidence of exercise-induced neurogenesis in humans (37). Similar changes to the hippocampus in older adults have been reported. After a 12-mo exercise intervention, older adults who walked 3 times/wk for 45-min sessions increased their hippocampal volume, whereas those in the stretching and toning group displayed the usual shrinkage of the hippocampus associated with late adulthood. Moreover, this exercise-induced brain growth was specific to the hippocampus, because other subcortical regions showed no group differences in volume stemming from the exercise intervention (10).

Eye-tracking has also been successfully used to study relational memory enhancement after aerobic exercise. One study from our laboratory adapted an eye-tracking paradigm from Hannula and Ranganath (34), involving faces and scenes, similar to the tasks described above, in an effort to assess the cognitive effects of a 9-mo after-school exercise intervention in preadolescent children. During the test, when the participants behaviorally selected which of the 3 faces had been originally paired with a scene, there were no differences between the exercise and control groups. However, compared with the control group, participants in the exercise group displayed a greater degree of disproportionate viewing to the face they had studied with the scene (38). Moreover, this paradigm included an item memory condition in which the background scene was held constant and participants were shown a 3-face display with 1 familiar face and 2 novel faces. In this condition, participants were instructed to find the familiar face; no effect of the exercise intervention was evident in these data. Together, these data illustrate the sensitivity of eye-tracking to exercise-induced modification of relational memory, even when overt behavioral measures fail to detect any difference. Furthermore they demonstrate the specificity of relational memory (and presumably the hippocampus) to this lifestyle factor.

Nutrition, hippocampus, and memory. The techniques used to study the effects of exercise on memory and the hippocampus can also be applied to the investigation of nutritional impact on learning and memory. Bridging this gap, physical activity and dietary intake have been shown in animal models to interact with one another (39). Rodent models have shown that exercise can act synergistically with dietary intake to enhance hippocampal function. Rodents who were given access to running wheels combined with intake of either flavonoids or the omega-3 FA DHA showed enhanced neurogenesis and behavioral memory performance relative to either exercise or dietary supplementation alone. All 3 exercise and/or nutritional supplement groups showed superior memory performance and a
greater degree of neurogenesis than did an unsupplemented sedentary control group (40). Similarly, exercise has been shown to ameliorate the negative consequences of an unhealthy diet in rodents. Animals who were fed diets high in saturated fat and sugar and were additionally given access to running wheels showed levels of markers of neurogenesis and behavioral memory performance comparable to that of sedentary animals fed a control diet (41).

Independent of physical activity, studies are beginning to show that nutritional intake can have beneficial or detrimental effects on hippocampal structure and function. For example, nutrients with antioxidant or anti-inflammatory properties, such as omega-3 FAs and polyphenolic compounds, increase hippocampal neurogenesis in rodent models (42–44). Furthermore, these compounds have been shown to reduce Alzheimer’s-like pathology in rodents (45–47). In contrast, low intakes of micronutrients or high intakes of saturated fat, refined sugar, and alcohol have each been shown to negatively affect hippocampal memory function (11,48).

There are many possible mechanisms that may underlie the observed interactions between nutritional intake and hippocampal function in animals. First, nutrients can modulate the expression of critical growth factors known to promote plasticity in the hippocampus, including brain-derived neurotrophic factor and insulin-like growth factor 1. Expression of these growth factors leads to neurogenesis, angiogenesis, and synaptogenesis in rodent models (see reference 49 for review). For instance, a high–saturated fat and sugar diet reduces hippocampal brain-derived neurotrophic factor in 2-mo-old female rats (39), whereas antioxidant foods such as blueberries can augment the concentrations of insulin-like growth factor 1 in 19-mo-old male rats (43) Compounding these effects, dietary components may exacerbate (e.g., saturated fat) or protect against (e.g., omega-3 FAs) inflammation in the brain, which has been linked to cognitive decline in aging and risk of developing Alzheimer disease (39,50). Second, it is well known that diet can affect insulin signaling and insulin sensitivity in somatic tissues, and a recent study showed that high saturated fat intake in male rats can interfere with insulin signaling in the hippocampus as well (51). Accordingly, this can degrade hippocampal function and corresponding relational memory abilities. Third, a diet high in saturated fat and refined sugar in male rats can increase signs of oxidative stress, thereby decreasing the efficacy of cellular communication in the hippocampus (52). Taken together, these proposed mechanistic links provide clear functional pathways for the action of particular components of diet on the structural and functional integrity of the hippocampus.

Translating these effects from rodent models to humans has been complicated, however. On the positive end, several epidemiologic studies suggest a role for nutritional patterns and the maintenance of cognition in late adulthood (53–55). Furthermore, intervention studies indicate both beneficial and deleterious effects of nutrition on cognitive aging and brain health. For instance, in older adults with mild cognitive impairment (a potential precursor to Alzheimer disease or other dementias) and high homocysteine concentrations, a 24-mo B-vitamin supplementation (vitamin B-6, folate acid, and vitamin B-12) reduced brain atrophy in areas implicated in Alzheimer disease, including the hippocampus (56). Investigators testing the negative impact of certain diets conducted a 4-wk intervention providing participants with foods with a high glycemic index and high in saturated fat (“High” group) and compared them with those receiving a diet of foods with a low glycemic index and low in saturated fat (“Low” group). After just 4 wk, the High diet participants displayed higher indications of oxidative stress and Alzheimer disease pathology in their cerebrospinal fluid and worse memory performance, whereas the Low group displayed the opposite patterns (57). Other measures of diet composition, such as glycemic load, may be even more sensitive to dietary influences on the brain and cognition. Given that these studies have been conducted in adult populations, these results likely do not transfer to the nutritional needs of all populations, namely infants, in whom the benefits of breast-milk feeding outweigh its saturated fat and simple sugar content.

Despite the above experiments reporting nutritional intervention effects, the majority of large-scale nutritional intervention studies in older adults have produced null results (58–62). These null results may be due to a variety of factors, including the administration of single nutrients (vs. combinations of nutrients) and population selection (e.g., Alzheimer disease vs. healthy older adults). It may also be the case that rather than testing global cognition, as many studies have done, a more targeted approach centered on certain neural systems or cognitive domains would prove more effective (63). Given the responsiveness of the hippocampus to a multitude of health and lifestyle factors, coupled with its accelerated rate of aging-related atrophy (64,65), the hippocampus and relational memory provide excellent targets for the investigation of nutritional enhancement of learning and memory.

Conclusions
On the basis of the evidence discussed, we suggest that the hippocampus and associated relational memory function are opportune targets for assessing relations between nutritional intake and cognitive and brain health. Indeed, beneficial or detrimental effects of nutrition have been shown in animal models of hippocampal structure and function, and such effects are becoming apparent in humans as well. Given that it is one of the most highly metabolically active structures in the brain and has been shown to be sensitive to other health factors including physical activity, the hippocampus, and consequently hippocampus-based memory, shows great promise as a target for characterizing the effects of nutrition on the brain.

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Literature Cited


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