

Physical Activity and Cognitive Training: Impact on Hippocampal Structure and Function

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Abstract This chapter will review the current state of knowledge on the effects of physical and mental (cognitive) training on hippocampal structure and function. We will primarily focus on normal aging and patient populations, though some relevant examples with young adults will also be described. Where possible, we will briefly review relevant research with animal models, in order to discuss potential mechanisms for beneficial effects of physical activity and cognitive training on hippocampal health.

Introduction

Normal age-related cognitive decline occurs for most individuals (Park and Reuter-Lorenz 2009; Salthouse 2010) and this can have a negative impact on quality of life and independence. In addition, age-related neurological and neurodegenerative conditions such as Alzheimer's Disease are associated with enormous societal cost in terms of morbidity, mortality, loss of independence, loss of employment, and caregiving costs (Barnes and Yaffe 2011; Hurd et al. 2013). Furthermore, because the risk of these disorders increases with age, this problem will likely surge as our population becomes older. The hippocampus is central to these public health concerns because normal aging is known to affect hippocampal structure and function (Nyberg et al. 2012). Furthermore, the hippocampus is a central region where pathology develops in Alzheimer's Disease (Jack et al. 2013), the leading age-related neurodegenerative disorder affecting older adults (Brookmeyer et al. 2011). This increase in the aging population and age-related diseases that affect the hippocampus raises questions about the extent to which such changes in the brain with aging and disease are inevitable or whether they can be prevented, delayed, or

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improved (e.g., Hertzog et al. 2009; Norton et al. 2014). Questions like these have been historically conceptualized under theories of a lifespan view of plasticity (Lindenberger 2014; Lövdén et al. 2010). In general, plasticity can be viewed as the capacity for change within the individual at multiple levels of analysis (e.g., cellular, systems, behavioral), and the concept of lifespan plasticity extends this capacity of modifiability throughout the lifespan (Lerner 1984; Raz and Lindenberger 2013; Reuter-Lorenz and Park 2014).

Recently Lövdén and colleagues proposed a theoretical framework for the study of adult cognitive plasticity that synthesized historical views of lifespan plasticity and asserts several predictions for its realization and measurement (Lövdén et al. 2010). First, they operationalize *plasticity* as the capacity for reactive change, where reactive means in response to a stimulus such as experience or brain injury. A distinction is made between the stimulus and the response to this stimulus. For example, with age-related neurodegeneration or brain injury, the damage itself is the stimulus whereas the actual response of the organism (e.g., repair, compensation) reflects plasticity. With learning new skills, the perceptual demands and the representations during practice would not constitute plasticity, but rather it is the secondary response (improved performance, structural and functional brain alterations) that reflect the plasticity of the organism. Thus, plasticity processes are one component of successful aging because they enable an adaptive response to the brain aging process. Another concept related to successful aging is *flexibility*, which denotes the capacity for the organism to meet the demands of the current context using existing structural and functional resources, limited by existing constraints in the system (Lövdén et al. 2010). The concept of flexibility acknowledges the dynamic range of brain processes that meet everyday demands of cognitive function, while reserving the notion of adaptive plasticity for when this range of performance and functioning has been increased. Finally, in addition to plasticity and flexibility, an equally important process for successful aging is *brain maintenance*, whereby the primary stimulus of brain aging is delayed or slowed and therefore this concept focuses more on postponing age-related changes and pathology rather than on how the brain copes with their presence (Lindenberger 2014; Nyberg et al. 2012).

Given that the hippocampus is a region highly vulnerable to the effects of aging, yet shows tremendous variability in age-related decline in structure and function (suggesting maintenance is possible), and has been shown to increase in size or function in response to interventions (suggesting plasticity is possible), the region represents a valuable test case for determining what types of environmental and lifestyle factors optimize lifespan plasticity (Lövdén et al. 2010; Nyberg et al. 2012). Within this context, the goal of this chapter is to review the current state of knowledge on the effects of physical and mental (cognitive) training on hippocampal structure and function. We primarily focus on normal aging and patient populations, though some relevant examples with young adults are also described. With respect to brain maintenance, we will evaluate whether the evidence supports the preservation of more youth-like brain structure and function. With respect to plasticity processes, we will evaluate whether evidence supports the restoration of structural or functional circuits known to be vulnerable to aging or supports a

compensatory response (i.e., creating new circuits in response to primary aging-related losses of structure and function). This theoretical foundation will create the basis for evaluating the methodological strengths and weaknesses of the empirical literature and for identifying important directions for future research.

Furthermore, for brain maintenance and plasticity to have their broadest impact, it is ideal for lifestyle and intervention-related changes to affect a wide range of cognitive abilities, rather than only skills and abilities that were the targets of training. This type of wide-ranging impact is known as *transfer*, where the target (s) of improvement for training have the capacity to extend to a wide range of functional skills and abilities beyond only the trained capacity (Lustig et al. 2009; Noack et al. 2014). The hippocampus has tremendous potential as an intervention target that could engender wide transfer because of its vulnerabilities to aging (e.g., Nyberg et al. 2012; Persson et al. 2012) and its role in a broad range of skills and abilities that require forming new relational memories that can be flexibly reconfigured (Konkel et al. 2008; Shohamy and Turk-Browne 2013). In general, the concept of aiming interventions at brain regions that could serve as a center for overlap with a broad range of cognitive abilities has been proposed. This proof of concept was demonstrated with the striatum in the context of working memory training (Dahlin et al. 2008, 2009). Therefore, we will evaluate whether there is also evidence supporting the proposal that the hippocampus is a powerful target of interventions because of its potential for broad transfer of training. The easiest case for this concept is non-cognitive training such as physical exercise training that induces change in hippocampal structure and function that is then beneficial for forming new relational memories (e.g., Erickson et al. 2011; Maass et al. 2014; Pereira et al. 2007).

Finally, where possible, we will integrate relevant research with animal models, in order to discuss potential *cellular and molecular mechanisms* for beneficial effects of physical activity and cognitive training on hippocampal health. Such discussion is important for bridging between basic and cognitive mechanisms of *how* interventions with great translational potential engender maintenance, plasticity, and transfer (Voss et al. 2013b).

Cognitive Training

Cognitive training protocols are designed to challenge cognitive functions in order to cause a mismatch between supply and demand in the brain that stimulates structural or functional brain plasticity (Lövdén et al. 2010). Training typically consists of scheduled routines of adaptive mental exercises or games that are either delivered in person or on a computer. Strategy training involves teaching the participant a particular strategy in order to improve performance on a task (e.g. training method of loci to improve memory performance). Process training, on the other hand, involves targeting specific cognitive processes, without explicit strategy training. Process training programs typically include many tasks that place heavy demands on a particular process (e.g. working memory).

As described above, a crucial aspect of cognitive training is the potential for transfer of benefits to untrained tasks. Transfer may depend on overlapping activation across multiple functions, such that when a region underlying the trained task experiences increased volume or altered activation, other functions that engage the same region(s) also demonstrate benefits. Depending on the level of similarity to the trained task, transfer can be defined as near or far. Near transfer is demonstrated when the training of a particular task affects performance on a task that is similar in stimuli, strategy, or outcome. Far transfer, on the other hand, is demonstrated when training of a particular task affects performance on a task that has few common elements with the trained task. Similarity can span many domains (such as knowledge, physical context, temporal context, functional context, social context, and modality), each separately influencing the distinction of near or far transfer (Zelinski 2009). A relevant analogy of near transfer might be training of a forehand swing in tennis followed by improved performance on backhand tennis swings. There are many common elements across dimensions of stimulus-response cues and the movements required to strike the ball. Alternatively, far transfer in this case would be transferring common elements across sports such as applying basics of ball striking to a golf or baseball swing or applying lateral movements from tennis to the same type of movements in basketball (Perkins and Salomon 1992). Similarly, many tasks across varied cognitive domains include demands for rapid and flexible relational binding, such as acquisition of complex task sets, and this could be a basis for far transfer.

An important emerging market for cognitive training is the aging population. Because normal aging is accompanied by deterioration of brain structure (Hedden et al. 2014; Raz et al. 2005) and function (Rieckmann et al. 2011; Shaw et al. 2015), and a broad range of corresponding cognitive abilities (Park and Reuter-Lorenz 2009; Salthouse 2010), cognitive training may offer an especially helpful tool for maintaining or improving mental processes in this population. Within this context, as introduced above, the hippocampus is an important target for training given its central role in Alzheimer's Disease and its capacity for plasticity across the lifespan (Jack et al. 2013). In order to evaluate the extent to which cognitive training has been shown to affect the hippocampus, below we only describe cognitive training studies that included analysis of brain structure or function. We describe evidence from studies where training was focused on functions known to depend on the hippocampus and we consider studies that have focused on multi-domain cognitive training (such as playing video games) or process-specific training of cognitive functions such as working memory training.

Changes in Hippocampal Structure Following Cognitive Training

Although many studies have demonstrated behavioral improvement on both trained and untrained tasks (near transfer) in response to memory training (for review see

Lustig et al. 2009), fewer studies have examined how the brain changes in response to some type of memory training in healthy older adults. However, a few seminal studies of experience-induced brain plasticity should be considered as they found evidence of changes in the hippocampus.

A series of studies investigated the changes induced by visuomotor training in both young and older adults. Draganski et al. (2004) found that in 24 healthy college aged adults, 3 months of juggling practice (to reach juggling fluency), compared to no juggling practice, increased grey matter in the bilateral mid-temporal area and the left posterior intraparietal sulcus. These volumetric changes were positively related to juggling performance and were also transient, such that the grey matter increase vanished after 3 months of no further practice. In a larger study of older adults ($n = 50$) using the same 3-month juggling training protocol, Boyke et al. (2008) found similar training-related transient grey matter increases in mid-temporal area, but in addition they found increased volume in the left hippocampus and bilateral nucleus accumbens. However, the increase in volume was not related to post-training juggling performance or time spent practicing the skill, unlike the positive relationship observed in young adults in other parts of the brain. Further, a much lower percentage of older adults than younger adults became proficient in juggling following training (16% for old, 100% for young), possibly indicating lower limits of potential plasticity. The authors state that hippocampal changes could have resulted from the motor movements, learning and/or spatial skills associated with juggling. Although the hippocampus was not, at the time of these studies, predicted to be involved with juggling, current understanding of hippocampal involvement in motor learning supports and may help explain this finding (Doyon et al. 2009; Schendan et al. 2003).

Based on the involvement of the hippocampus in learning and memorizing abstract and declarative information (Eichenbaum 2004; Squire et al. 2004), Draganski et al. (2006) predicted that extensive studying of medical information in young adults would induce volumetric increases in the parietal lobe and hippocampus. The authors found that 3 months of daily studying in medical students, compared to 3 months during which the control cohort of dental students was not studying for exams, resulted in significant hippocampal grey matter increases. Further, significant increase in hippocampal volume was also found at a 3-month follow up. Given that much less studying presumably occurred between the exam and follow-up date, this result demonstrated consistent plasticity even after the learning period. While hippocampal change was not related to performance on the exam, the authors did not control for additional variables such as IQ, learning strategies, or workload, which may account for some variation in performance.

This series of studies begins to characterize how long it might take to modify the hippocampus and how long that change may last. Although the studies were performed with different populations, with both juggling and extensive studying, 3 months was sufficient to induce and measure changes in human hippocampal volume with MRI methods for measuring brain structure.

More recent studies have better examined the impact of experience with cognitive functions primarily thought to be hippocampal-dependent. Based on cross-

sectional findings that healthy adult London taxi cab drivers had larger hippocampi than comparison individuals, Woollett and Maguire (2011) found that extensive spatial learning over a 3–4 year period resulted in not only increased volume in the posterior hippocampi, but also improved performance on a spatial relations test. In addition, compared to a control sample that either studied but did not pass examinations or had no spatial training over the 3–4 year period, individuals with spatial training performed worse on a complex figure test, a measure of free recall of spatial material after a short delay. Authors explained this pattern of results as a possible trade-off between different spatial abilities. Indeed, the increased volume of the posterior hippocampi was accompanied by decreased volume of the anterior hippocampi (Woollett and Maguire 2011). Although this study lacked a true experimental design, the brain imaging data prior to and following spatial training provide evidence for training-related hippocampal plasticity. Though unfortunately aside from the complex figure test, no other cognitive functions were assessed, which prevents an evaluation of far transfer of training.

Further, it has also been shown that after retiring from taxi driving, hippocampal volume and spatial memory tend to return to normal levels (Woollett et al. 2009). Given that structural plasticity is thought to be dependent on continued use of the hippocampus, this re-normalization is not surprising, and supports that real-life experiences can trigger transient changes in hippocampal volume. This result aligns with the finding that juggling practice in older adults led to increased hippocampal grey matter, followed by decreased volume after termination of practice (Draganski et al. 2004).

As a brief methodological note, the studies summarized above all used Voxel-Based Morphometry (VBM), a technique designed to evaluate local changes in brain structure as a function of training and which allows testing for changes across the whole brain. The advantages of VBM are that it is in principle fully automated and therefore has perfect repeatability, and it does not require time-consuming manual tracing of anatomical structures (Kennedy et al. 2009). However, there are also some limitations to VBM analyses, which include vulnerabilities to bias in areas that commonly have image artifacts and registration errors such as the medial temporal lobes (for methodological reviews, see: Bookstein 2001; Davatzikos 2004; Thomas et al. 2009).

Instead of looking across the whole brain for training-induced change in volume, another approach is to evaluate change in volume of a defined anatomical structure (for methodological reviews, see: Morey et al. 2009; Mulder et al. 2014; Schoemaker et al. 2016; Wenger et al. 2014). For example, a study by Lövdén et al. (2012) used techniques for manually tracing the hippocampus from the rest of the brain and predicted that extensive, long-term engagement of the hippocampus through virtual environment spatial navigation training would modify hippocampal volumes more than an active, no spatial navigation training, control group. Forty-four healthy young and 47 healthy older men were included in the analyses. Individuals in the spatial navigation group learned to navigate through a virtual zoo to learn and memorize the locations of certain animals, while the control group walked comfortably on a treadmill. Both groups completed 42 50-min sessions across a 4-month period. To ensure hippocampal engagement, the spatial

navigation task required numerous functions thought to rely on the hippocampus: allocentric processes, associative memory, encoding of novel information, and consolidation of information. The authors' predictions included improved training-related increases in spatial navigation performance and transfer of training to untrained tasks requiring allocentric spatial processing.

Findings revealed that, compared to the control group, men that underwent spatial navigation training improved more on the navigation task at post-testing. Results also revealed a significant effect of age, such that older adults' performance was worse than young adults' on the navigation task prior to training. However, at post-test, older adults that completed spatial navigation training performed equal to young adults in the control group, demonstrating training-related cognitive plasticity for older adults. Further, performance improvements related to training were partially maintained following 4 months without training. The authors also predicted that integrity (measured by volume and mean diffusivity (MD)) of the hippocampus would increase following spatial training in both young and older adults. Note that both younger and older men in the control group experienced a natural decline in hippocampal volume (0.75% for the left and 1.59% decrease for the right) from the beginning of the study to post-testing. However, both young and older men in the navigation-training group displayed stable volumes across the training period and also throughout the 4 months post-training. Given that the training did not appear to result in increased volume, this may provide evidence for hippocampal maintenance that deters normal age-related decrease in hippocampal volume. These results are interesting, as they reveal maintenance for brain structure (in the face of age-related natural declines), but also cognitive plasticity for performance on the spatial navigation task.

Notably, no main effect of age for hippocampal volume was observed, but there was a main effect of age for MD, such that older men presented with higher MD than young adults. Higher MD is thought to reflect lower structural integrity, possibly by quantifying the density of membranes within a particular region (for review, see Assaf and Pasternak 2008). Within the training group, hippocampal MD decreased during training and then returned to baseline during the 4 months post-training. The control group did not demonstrate significant changes in MD across time. Although the functional relevance of microstructural changes in the hippocampus is still unknown, the evaluation of measures aside from volume is critical, as some experience-dependent changes may take place on a smaller scale than would affect overall volume.

A novel aspect of this study was their investigation of the transfer of navigation training benefits on a variety of other tasks. However, a trend toward better performance for the training group was observed only on a task of spatial orientation. No other tasks showed signs of transfer, including tasks of intelligence (Raven's progressive matrices), mental rotations, vocabulary, processing speed (Digit-Symbol Substitution), route memory, location memory, object-position memory, numerical memory updating, numerical and figural comparison, spatial 2-back, word-list recall, and number-noun pairs.

Thus far the evidence suggests that extensive spatial navigation training can result in structural hippocampal changes and improved spatial abilities, but these spatial ability benefits may not transfer to other tasks, even for tasks that would also seem to evoke hippocampal processing. Greater transfer may occur when individuals are trained on an activity that demands a wide array of cognitive and motor functions, such as playing video games. Given the broad involvement of cognitive processes, this type of activity may have more potential to convey benefits to other tasks. Videogame playing has previously been found to correlate with attention, perception, and executive control abilities (Green and Bavelier 2003), and many have suggested that videogame experience may simultaneously train multiple skills (Basak et al. 2008). Kühn and colleagues (2014) studied young adults' brains before and after 2 months of playing a SuperMario videogame daily. In contrast to the methods used by Lövdén et al. (2012), this study employed VBM to determine training-related group differences in volume. Grey matter increases were observed for the training group, in comparison to the control group who performed no tasks during the training time, in the right hippocampus, right dorsolateral prefrontal cortex, and cerebellum. Interestingly, greater increases in hippocampal volume were associated with the participants' tendency toward an allocentric orientation strategy, suggesting that structural plasticity in the hippocampus was functionally relevant for strategy choice on the SuperMario game.

To summarize, in healthy adults, there are a few studies of interventions that target the hippocampus by training functions like memory and spatial abilities. Changes in the hippocampus have also been seen following other types of training (juggling, abstract learning, video game playing), but evidence is lacking for transfer of benefits. There are many behavioral studies demonstrating improved memory following memory training, but the evidence has not yet shown whether hippocampal plasticity underlies observed benefits.

Because individuals with subjective memory impairment (SMI) or mild cognitive impairment (MCI) are at high risk for developing Alzheimer's Disease (Jessen et al. 2010), studies have also designed interventions for such individuals. Theoretically, bolstering the hippocampus through memory training might decrease the risk or rate of disease progression. In the first of a series of papers by Engvig et al. (2012), the authors found that memory training that employed method of loci to enhance verbal recall in older adults with SMI resulted in increased memory performance, and change in memory was associated with pre-training left hippocampal volume. Following this finding, Engvig et al. (2014) tested for training-related changes in brain structure in the same 19 individuals with SMI from the previous study, along with 42 healthy older adult controls. The authors found that after 2 months of episodic memory training both healthy and impaired older adult individuals experienced improved memory. In particular, a larger training-related effect size for memory improvement was seen in the SMI training group. Both healthy and SMI training groups experienced increased cortical grey matter volume, but only healthy older adults experienced training-related increases in the left hippocampus. The SMI training group showed slightly less (though not statistically significant) negative change in the left hippocampus than the no-training healthy

controls. Notably, change in left hippocampal volume was positively correlated with change in free recall only in the SMI training group. As the authors discuss, the lack of significant structural hippocampal plasticity in the SMI training group could be due to lower potential for plasticity in the impaired hippocampus. However, another likely explanation could be that the training mitigated even greater expected atrophy in SMI individuals, an example of brain maintenance. Unfortunately, the study lacked a no-training SMI control group, so we are unable to discern how much hippocampal atrophy might have occurred during the intervention period in a SMI no-training group.

Changes in Hippocampal Functional MRI Outcomes Following Cognitive Training

Given the relative recency of functional neuroimaging techniques, cognitive training studies in healthy older adults that have demonstrated functional outcomes are limited. Unlike structural changes, which can clearly reflect plasticity, functional changes may reflect change in a variety of processes, including response to familiar stimuli, reallocation of available resources, altering representations, and switching between existing cognitive states (for methodological reviews, see: Kelly et al. 2006; Poldrack 2000). Given these possibilities, it would be misleading to conclude that all functional changes represent experience-dependent plasticity because some training-related patterns of change may stem from more transient adaptive mechanisms associated with flexibility rather than structural changes (Lövdén et al. 2010).

As a first example, a study of 14 healthy older adults by Kirchoff and colleagues (2012) found that change in hippocampal activity, as measured by functional MRI, during memory retrieval following 2 days of memory training was positively associated with training-related improvements in memory encoding and retrieval. Greater hippocampal activity during memory retrieval may represent greater neural activity or recruitment of more neuronal groups within the hippocampus in response to the previously encoded stimuli. Although this training paradigm included only two training sessions across a 2-week period and the sample size was small relative to many other studies, the positive correlation between activation change and memory performance suggests that the hippocampus in older adults can be a key target for improving memory abilities.

Voss et al. (2012) employed a complex skill-learning videogame-based program and examined the effects of various training programs on interactions among multiple neural networks of interest in healthy young adults. Twenty-nine individuals completed 10 2-h training sessions across 2–3 weeks and were randomly assigned to be instructed to focus either on the entirety of the game (fixed priority) or on sub-components of the game (variable priority). Previous studies showed that variable priority training leads to more transfer (Kramer et al. 1995, 1999b), and

this study examined the neural mechanisms of this pattern using functional imaging. For instance, variable priority training may recruit neural networks that are involved with higher-order and flexible goals and actions, such as fronto-parietal networks and regions associated with the declarative memory system such as the hippocampus. In contrast, fixed priority training is thought to invoke a more rigid learning style that is more dependent on procedural learning systems. Such a pattern of systems-level change as a function of training strategy may help explain why variable priority training has been shown to lead to more transfer compared to fixed priority training. Indeed results showed that as expected, the functional connectivity of the hippocampus with regions in a fronto-parietal brain network associated with orienting of attention was most influenced by variable priority training, compared to fixed priority training which increased functional connectivity between the caudate nucleus and the same fronto-parietal brain network. Importantly, the interaction between the fronto-parietal network and the hippocampus was related to a faster learning rate on the videogame across training sessions only for the variable priority group, and connectivity between the caudate and the fronto-parietal system was not associated with learning rate across training sessions for either group. The relationships with learning rate are consistent with the idea that functional plasticity occurred rather than only flexibility of the learning systems. Overall, while the results are promising with regard to understanding the role of the hippocampus in transfer of learning, unfortunately there was little evidence of transfer to other cognitive abilities in this study (Boot et al. 2010). Therefore, it will be important for future studies to replicate this result and examine the role of these network interactions in transfer of learning.

Some studies have also explored functional brain plasticity using techniques other than fMRI (Langer et al. 2013). While techniques such as electroencephalography (EEG) are informative of cortical brain networks, they typically are unable to measure signals within subcortical structures such as the hippocampus. However, Langer et al. (2013) did find that working memory training in 34 young adults (20 30-min sessions across 4 weeks), compared to 32 young adults in the active control group, resulted in increased theta oscillations, which have been tied to functions involving the hippocampus, such as spatial navigation and working memory.

In an attempt to quantify plasticity across multiple time points and multiple structural and functional systems, Lampit et al. (2015) measured a variety of brain outcomes at two times points during and following a randomized, 12-week group-based multi-domain computerized cognitive training program. Participants were 12 older adults from a neuroimaging subsample of a larger cognitive training program in older adults with at least one risk factor for dementia (Lampit et al. 2014). This program consisted of 36 60-min sessions involving exercises of memory, attention, response speed, executive functions, and language. The active control group viewed National Geographic videos and answered multiple-choice questions about the videos, for the same amount and duration of time as the training group. The authors examined training-related changes using structural measures, including VBM, vertex-based analysis, diffusion tensor imaging, and MR spectroscopy

(metabolite signals), as well as fMRI. Results revealed a significant effect of the 3-month training on global cognition (measured as a composite of memory, information processing speed, and executive function). Between baseline and the first follow-up (after 9 h of training), the training group demonstrated increased functional connectivity (FC) between the right hippocampus and the left superior temporal gyrus, whereas the control group showed decreased FC between these regions in that same time period. Interestingly, greater FC increases from baseline to the first follow-up were related to greater increases in global cognition from baseline to the second follow-up (after 36 h of training spread across 3 months). While this may suggest that functional changes occur early on in training and at least partially predict later cognitive changes, the group differences in FC found at the first follow-up were not found after the full 3 months of cognitive training. However, it is critical to note that this study consisted of a relatively small sample (12 participants) and, more importantly, the cognitive training group consisted almost exclusively of women, and the active control group consisted exclusively of men. Therefore, while the results can help guide future hypotheses and continued examination of these outcome measures, there is a chance that the findings described are largely due to sex differences across the groups. This is especially concerning for the functional findings, given that the authors found baseline group differences in whole-brain FC maps for the selected ROIs (right hippocampus and posterior cingulate). Despite the limitations of this pilot study, Lampit and colleagues were able to demonstrate findings of differential training-related effects in early and later stages of training, in addition to semi-converging structural findings between VBM and vertex-based analysis (though these findings did not include the hippocampus).

Functional outcomes of cognitive training have also been examined in patient populations, most often in MCI and Alzheimer's Disease (AD). Most studies focus on memory-based training in an attempt to increase memory abilities and mitigate some symptoms of the diseases. For example, Belleville et al. (2011) employed a training program targeting episodic memory in an older adult population in which half of the participants had a diagnosis of Mild Cognitive Impairment (MCI). The other participants were healthy, age-matched adults. The training program was previously shown to improve delayed word recall, face-name memory, and self-reported daily memory functioning (Belleville et al. 2006). Though effects of training were examined between healthy adults and those with MCI, no training-control groups were used for either population. A key aspect of the study design (Belleville et al. 2011) included two MRI scans prior to the cognitive training. This design helped control for practice effects in the functional MRI measures. The group-based memory training lasted for 12 h spaced across 6 weeks. Neuroimaging outcomes for this study included brain activation during a memory-encoding and retrieval task. No group differences in hippocampal activation during encoding were found prior to training. Healthy adults experienced a training-related decrease in hippocampal activation during encoding, and a training-related increase in hippocampal activation during retrieval processes. In contrast, while training-related increases in cortical activation were found for MCI subjects, no training-related changes in activation were found in the hippocampus. Although the authors

did not find hippocampal-specific plasticity, this study did demonstrate plasticity across a wide network of cortical areas even within this diseased state.

A similar study by Rosen et al. (2011) specifically hypothesized that a training program from Posit Science that included adaptive games would influence the hippocampus and improve memory performance in older adult participants with MCI. Interestingly, the games were designed to improve speed and accuracy in auditory processing, not necessarily to improve memory, but this program has previously been found to improve memory performance in both healthy older adults and those with MCI (Mahncke et al. 2006). Each participant completed the program for 100 min per day for 5 days until criterion performance was reached (asymptotic performance over several days or completion of 80% of the training material), with training lasting approximately 2 months. The control group (also individuals with MCI) completed non-adaptive cognitive engagement tasks (reading, listening to audio books, playing a visuospatial computer game) for 90 min per day, 5 days per week. Consistent with predictions, the adaptive training group did show a significantly greater increase in performance on neuropsychological tests of memory ability than control participants. The control participants experienced a decline in memory ability throughout the intervention, which is not surprising since all participants had been diagnosed with MCI. Brain function was measured during an auditory decision-making task, during which participants chose whether words were concrete or abstract. A small increase in brain activation was found in the left hippocampus exclusively for individuals in the adaptive training group. There was also a trending, though non-significant, positive correlation between increase in activation and change in neuropsychological performance from pre-training to post-training. Although this study consisted of a small number of participants (6 per training/control group), the results suggest that adaptive game training mitigated the negative effects that were seen in the control MCI group.

Finally, Hampstead et al. (2011) and (2012) focused on rehabilitating cognitive impairment using mnemonic strategy training for face-name associations (2011) or object-location associations (2012). In the 2011 study, the training procedure was fairly short (five sessions within a 2 week period), the number of participants was small (6 individuals with MCI), and no placebo training control group or comparison individuals were used. Instead, within-subject comparisons were made across trained and untrained stimuli. Although the mnemonic training resulted in increased performance on laboratory memory tasks, widespread activation increases across the cortex, and increased connectivity within neural networks, this study did not show training-related changes in hippocampal activity or connectivity. In the 2012 study, a healthy older adult group of 16 individuals was included as comparison to 18 MCI patients, and all individuals were randomized to mnemonic strategy training or exposure-matched control training. Critically, group (MCI versus healthy individuals) differences in brain activation were observed prior to training, such that individuals with MCI showed lower encoding and retrieval-related hippocampal activity than healthy comparisons in the head, body and tail of the hippocampus bilaterally. Note that the hippocampus was the main region of interest, so analyses were limited to manually traced bilateral hippocampal regions.

Both MCI and healthy individuals in the mnemonic strategy training group showed greater improvement in object-location memory following the training than the individuals in the exposure-matched control group. This finding was accompanied by greater training-related increases in activation for MCI compared to healthy comparisons, particularly in the hippocampus. These results suggest that the mnemonic strategy training worked to partially restore hippocampal activation during encoding.

Overall, studies of training-related functional changes tend to suggest that, in healthy adults, certain types of cognitive training can result in decreased brain activation during tasks, and this pattern of results may reflect increased efficiency of neural processing (c.f., Poldrack 2015). Evidence also demonstrates that memory training can result in increased activation during memory retrieval and recollection. These differing patterns of training-related changes may depend on the processes involved at the time of measurement. There is little consensus on the type or duration of training that best improves neural function and achieves successful transfer to other tasks. In patient populations, cognitive training may work to restore or mitigate the declines observed due to disease, though the patterns of functional response may differ from healthy individuals and are difficult to interpret unless closely linked to behavioral changes.

Possible Mechanisms Based on Animal Models

Animal and human literature has presented many possibilities for age-related changes in the brain (López-Otín et al. 2013; Thomas et al. 2012; Voss et al. 2013b). Some of these changes include alterations between synaptic connections, cortical thinning and reduced brain volume due to neuronal loss and less efficient neuromodulatory processes. Structural plasticity in the hippocampus can manifest as increased structural volume, which may reflect increased neurogenesis, proliferation of glial cells and astrocytes, increased synaptic density and vascular density, or prolonged cell survival (Kempermann et al. 1998, 2002; Opendak and Gould 2015; van Praag et al. 1999; for review, see Voss et al. 2013b).

In animal studies, increased neurogenesis in the dentate gyrus/CA1 region has been found to relate to better cognitive function, though it is unclear whether neurogenesis itself is the direct cause of improved performance (van Praag et al. 1999; for review, see Voss et al. 2013b). Because it is quite difficult to directly measure neurogenesis in human studies, volume is considered the primary structural adaptation measurable by MRI. Supporting evidence for this is that hippocampal volume has been found to positively relate to some types of learning (Herting and Nagel 2012; Konishi and Bohbot 2013) and memory (Chaddock et al. 2010; Erickson et al. 2009). However, because it is still unknown precisely how microscale cellular, molecular, and synaptic changes translate into macroscale age-related changes in brain structure and function observable with human neuroimaging, further translational research in these areas is needed to improve our

ability to understand whether and how cognitive training might work against the basic mechanisms of brain aging.

Review of Literature for Physical Activity and Fitness Training

Exercise training has also been shown in both animal and human studies to significantly impact the hippocampus. Many studies have now demonstrated evidence for a positive relationship between cardiorespiratory fitness or fitness training and varied cognitive abilities including processing speed, visuospatial processing, attention, and executive function (Colcombe and Kramer 2003; for review, see Erickson et al. 2009, 2014; Kramer et al. 1999a; Smith et al. 2010). Protection from age-related cognitive decline has also been associated with greater self-reported (Benedict et al. 2012; Yaffe et al. 2001) and objectively sensor-based measurements of physical activity (Makizako et al. 2014). Interventions typically aim to increase cardiorespiratory fitness through structured, aerobically challenging exercise sessions. However, some interventions aim primarily to increase physical activity level (particularly if the activity takes place outside the laboratory). Without monitoring heart rate and effort it can be difficult for an intervention to increase cardiorespiratory fitness in all participants. Physical activity is defined as movement that increases the body's energy expenditure beyond resting levels, while exercise is the structured process of completing movement for the purpose of increasing fitness. These distinctions are important when considering whether activity needs to improve fitness in order to improve brain and cognitive health. Further, while most studies use aerobic training, some have examined the effects of other types of training, such as resistance and coordinative training.

Changes in Hippocampal Structure Following Physical Exercise Training

Colcombe et al. (2006) examined changes in fitness and brain volume in 59 healthy but sedentary older adults following a 6-month, 3 times per week, aerobic (walking) exercise-training program. While this study did not find specific volume increases in the hippocampus, this exercise regimen did result in both grey matter and white matter increases in the frontal and temporal lobe. This study used VBM, which, as noted previously, can be vulnerable to bias in areas such as the medial temporal lobes.

Measuring training-related changes in cognition is critical for understanding the relevance of exercise's impact on the brain in everyday life, specifically for cognitive functions that are known to decline with age. To this end, Erickson

et al. (2011) employed a 1-year randomized control trial using an aerobic (walking) exercise training paradigm in 120 healthy older adults and measured hippocampal volume and spatial memory before and after training. Spatial memory is related to hippocampal volume (Erickson et al. 2009) and because hippocampal volume experiences significant decline during aging, training-related changes in the hippocampus may result in improved spatial memory. Significant increases in hippocampal volume were observed for individuals in the training group, compared to control group individuals who experienced decline in hippocampal volume over the course of the year. The increase in volume was found exclusively for the anterior hippocampus. Further, greater increases in hippocampal volume in both the right and left hemispheres were related to greater improvements in fitness, suggesting that increasing fitness may impact the hippocampus in a continuous manner. This study also examined serum BDNF levels, the results of which are discussed below in the possible mechanisms section. Finally, the authors found increases in spatial memory for both the exercise and the control groups. Although this lack of a time x group interaction effect was unexpected, the authors did find that cardiorespiratory fitness both before and after the intervention was positively correlated with performance on the spatial memory task. Further, increased hippocampal volume in the aerobic exercise group was correlated with improvements in spatial memory. These brain and behavior relationships increase the possibility that it was specifically cardiovascular fitness gains that caused plasticity in the hippocampus, here measured by increased hippocampal volume and spatial memory performance.

In addition to volumetric changes of grey or white matter, structural plasticity of the hippocampus has also been measured by vascular plasticity. Maass et al. (2014) conducted a 3-month intervention with 40 healthy, sedentary older adults that were pseudo-randomized to either a program of thrice weekly treadmill interval training or a stretching/relaxation control program that met for the same frequency and duration. The authors found that change in fitness was positively related to change in hippocampal perfusion, a measure of localized blood flow, which may indirectly reflect increased neural activity. However, results also showed that vascular plasticity in the hippocampus might be age-dependent, as fitness-related improvement in perfusion was negatively associated with age. The authors also found a positive correlation between change in fitness and change in hippocampal volume in only the head of the hippocampus, as well as positive correlations between hippocampal volume, perfusion, and memory performance (early recall and recognition on a verbal list learning task). Overall, the results suggest that fitness-related changes in hippocampal volume underlie the subsequent changes in memory performance. Importantly, the relationships that the authors found did not apply to whole-brain measures, and instead appeared hippocampal-specific.

Extending the work on aerobic exercise training, evidence also suggests that training of movements that require extensive motor control (balance, obstacle avoidance, speeded reactions) may facilitate processes in the brain separate from those of cardiovascular training. Niemann et al. (2014) studied 91 healthy older adults and examined whether a 1-year, thrice weekly, group-based coordinative training program would also increase the size of the hippocampus differently from

that of cardiovascular training. The authors found that both cardiovascular and coordinative training, compared to the stretching and relaxation training control group, resulted in increased hippocampal volume. In particular, the right hippocampus was more responsive to coordination training than to cardiovascular training. Interestingly, volume changes could be detected as early as 6 months in the cardiovascular training group, but not until 12 months in the coordination-training group. Although more work is needed to confirm and extend findings of differential time courses for various types of training, this finding may reflect the involvement of both rapid and more stable and longer-lasting neuroplasticity mechanisms that depend on exercise modality.

Exercise training may impact the hippocampus in individuals with certain diseases, particularly diseases that have previously been shown to have hippocampal abnormalities, such as MCI, Alzheimer's Disease and schizophrenia. Reduced hippocampal volume is a well-known feature of schizophrenia. In a randomized, controlled study, Pajonk et al. (2010) randomized 24 schizophrenic patients to either a 3-month aerobic cycling program or a non-aerobic condition of playing table-top football. Further, the effect of exercise training for patients was compared to a group of 8 matched healthy control participants who also did exercise training. Results showed that exercise increased hippocampal volume for both patients and healthy controls, and there was no effect of non-aerobic training on volume. For both patients and controls that did exercise training, greater increases in fitness were related to greater increases in hippocampal volume. Additionally, the authors found a greater training-related increase in a neuronal metabolite marker for schizophrenic exercise group than for the healthy control exercise group. While interesting, this metabolite change was not correlated to the increase in hippocampal volume, which limits the likelihood that this mechanism underlies exercise-related increases in brain volume. Cognitively, only the schizophrenic exercise group experienced increases in memory ability. Within the entire schizophrenic group (exercise and non-exercise), this change in memory was associated with hippocampal volume change, but this correlation was not significant in each separate group. While this study suggests hippocampal plasticity is present in schizophrenia, it is still unknown how the hippocampus differs between the diseased and healthy states and whether those differences alter the capacity for plasticity in any situations.

In a study of 86 women with probable MCI, ten Brinke et al. (2015) found that a twice-weekly, 2-month aerobic exercise program increased hippocampal volume relative to a resistance training or stretching control. However, average change in hippocampal volume was not significantly different from zero, supporting that participants in the aerobic group maintained their hippocampal volume compared to atrophy shown by the other two exercise groups. Unexpectedly, across all participants, while controlling for group membership, greater increase in hippocampal volume was associated with a change towards poorer recall performance on the Rey Auditory Verbal Learning Task (RAVLT). The authors suggested that this may be in part due to other important moderators of the relationship between change in hippocampal volume and memory performance in an MCI population, such as white matter degeneration. Thus, future studies will be needed to more robustly

tie exercise-induced changes in hippocampal volume to improvements in hippocampal-mediated cognitive functions.

Changes in Hippocampal Functional MRI Outcomes Following Physical Exercise Training

The profound effect of exercise training on hippocampal structure has led many researchers to explore how exercise may impact the function of the hippocampus, including measures of blood flow change, indirect measures of brain activation, and degree of connectivity within and between the hippocampus and other brain regions.

Based on evidence of exercise-induced neurogenesis from animal studies, Pereira et al. (2007) examined angiogenesis in mice and humans by measuring cerebral blood volume (CBV) with high resolution MR imaging of the hippocampus. Through a unique comparison of in vivo mouse CBV (accompanied by post-mortem histology data) with human CBV, Pereira and colleagues examined if exercise training would increase CBV in the dentate gyrus for both animal and human participants. Results showed that dentate gyrus CBV increased in 11 healthy young adult humans (9 females, 2 males) following a 12-week (4 times weekly) aerobic exercise intervention and that the CBV increases in the dentate gyrus were related to the increase in cardiorespiratory fitness across individuals. Further, increases in fitness and CBV were related to improvement in the early learning and free recall of a list of words (RAVLT). These correlations were selective for the early learning trial and not other performance measures, such as delayed recall, recognition, and source memory. These findings paralleled the results from the animal model, where rodents that exercised voluntarily for 2 weeks showed increased CBV in the dentate gyrus that corresponded with a measure of increased neurogenesis for the exercise group. Limitations of the study include a relatively small sample for the human exercise training group ($N = 11$) and no control group for either humans or animals to rule out confounds such as increased social enrichment from the exercise program or other lifestyle changes that could have improved fitness. Even despite these limitations, this study provides initial evidence that CBV may be a meaningful outcome measure corresponding to underlying mechanisms related to exercise training.

In the first study to investigate the effect of exercise on functional brain networks in healthy older adults, Voss et al. (2010) employed a 1-year exercise-training program that compared thrice weekly walking to a control group of light stretching and toning. The brain network known as the default mode network (DMN) includes the hippocampus and has been shown to have lower functional connectivity in older compared to young adults (Andrews-Hanna et al. 2007; Buckner et al. 2008; Damoiseaux et al. 2008; Fox et al. 2005). Given that these changes correspond to declines in certain cognitive functions (Andrews-Hanna et al. 2007; Damoiseaux et al. 2008), this network is thought to play an important role in healthy aging. After

12 months of training, Voss and colleagues found that the walking group had greater connectivity within the temporal lobe and between the medial temporal lobe and lateral occipital cortex and prefrontal regions of the DMN. Greater change in DMN functional connectivity was also related to greater change in executive function performance across all participants. Further, exercise training increased the negative association between prefrontal regions and an anterior left hippocampus region, suggesting training-related differentiation between functional networks, an outcome that made older adults' FC patterns look more similar to healthy, young adults. Interestingly, in this study FC outcomes were generally not reliably different after 6 months of training suggesting that functional brain outcomes may continue to increase with greater training durations.

To better understand the training-related changes in the hippocampus, Burdette et al. (2010) examined functional changes in 11 older adults (aged 70–85) by measuring hippocampal blood flow following 4 months of thrice weekly aerobic exercise training compared to a healthy aging educational training program. Of note, all older adults in this single-blinded randomized control pilot trial were at risk for cognitive decline based on age and self-report memory loss. Eligible individuals were randomized into the exercise training ($n = 6$) or healthy aging educational training ($n = 5$) program. Following training, greater hippocampal cerebral blood flow was found in the exercise-training individuals relative to the control group. While there were no overall differences in global brain network metrics for the exercise and control groups, the exercise-training group had higher connectivity between the hippocampus and the rest of the brain after training. In particular, for the exercise-training group, the hippocampus showed higher connectivity with the anterior cingulate cortex (ACC) and anterior medial prefrontal cortex compared to the control group. Finally, greater connectivity between the hippocampus and the medial prefrontal cluster was related to greater perfusion (blood flow) in the hippocampus. However, it is critical to note that all brain measures were assessed only after training. In order to clarify cause and effect, these results will need to be replicated with an assessment of change between before and after an exercise-training program.

Using another yearlong intervention program, Voelcker-Rehage et al. (2011) explored whether the type of training would have a significant effect on outcomes. Evidence from animal and human literature suggest that different types of training may affect brain metabolism and molecular cascades in various ways. This was further supported by the fact that the “control” (flexibility, toning and balance) group in Voss et al. (2010) experienced increased functional connectivity within brain networks, indicating that the non-cardiovascular activities may have beneficially impacted the brain. The use of other types of interventions is also supported by cross-sectional evidence that motor fitness, defined by movement speed, balance, coordination, and flexibility, is associated with greater cognitive ability (Voelcker-Rehage et al. 2011). The interventions used by Voelcker-Rehage et al. (2011) consisted of both a cardiovascular training ($n = 17$) and a coordinative training group ($n = 16$), along with a control group ($n = 11$). The total sample studied included 44 healthy older adults. The authors found that cognitive

performance on the Flanker test was improved over the 12-month study interval for both cardiovascular and coordinative groups, but not the control group. Similarly, while the control group experienced increased activation in cortical regions as well as the parahippocampus following the intervention, the intervention groups experienced no or very little activation change in these regions. Overall, based on changes in cortical activation patterns, the authors concluded that both cardiovascular and coordination training result in brain activation in older adults that is more similar to young adults. The authors also demonstrated that improvements continued to rise across the intervention duration in a linear fashion, suggesting the improvements do not trail off with longer training durations.

Some studies have also investigated whether resistance training can exert a similar beneficial effect as aerobic training. There is some evidence of training-related improvements in cognitive functions, including associative memory, (Liu-Ambrose et al. 2012; Nagamatsu et al. 2012). Such changes were related to changes in functional brain activation patterns in cortical regions, but not the hippocampus. To our knowledge, no studies have shown resistance-training-related structural or functional changes within the human hippocampus.

Possible Mechanisms Based on Animal Models

Evidence from animal studies supports that exercise increases the rate of neurogenesis in the hippocampus (Kronenberg et al. 2003; for review, see van Praag 2008; van Praag et al. 1999). Further, as mentioned in the previous section, a neurogenesis marker was positively correlated with dentate gyrus CBV in exercising mice, and controlling for neurogenesis abolished effects on CBV (Pereira et al. 2007). These observations suggest that exercise-induced increases in neurogenesis may induce increases in hippocampal blood flow. However, more translational studies of this nature are needed to test whether there are other molecular cascades and effects related to exercise-induced increases in cerebral blood volume/flow. It is also possible that the beneficial effect of exercise on angiogenesis may vary with age, as some studies have shown that exercise training can increase neurogenesis and learning in aged rodents without marked changes in angiogenesis (Creer et al. 2010; van Praag et al. 2005).

Training or experience-related neuroplasticity likely occurs in part through a series of growth factor and protein cascades (Nishijima et al. 2015; for review see Voss et al. 2013b). There are two well-known growth factors that are up-regulated in response to exercise. Brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) have been shown in animal studies to increase following exercise training (Fabel et al. 2003; Neepor et al. 1996; Vaynman et al. 2004) and there is evidence that BDNF increases with exercise in humans as well (Pereira et al. 2007; Rojas Vega et al. 2006). Further, there is some evidence that BDNF may play a role in exercise-induced brain and cognitive changes in humans (Ferris et al. 2007; Pereira et al. 2007; Rasmussen et al. 2009; Voss et al. 2013a).

Although Erickson et al. (2011) did not find a difference in training-related change in circulating BDNF between the exercise and control groups, they did find within the exercise group that greater increases in serum BDNF were related to greater increases in hippocampal volume. It is possible that other lifestyle activities could also up-regulate BDNF, which may account for the lack of an exercise-related group difference. Nevertheless, this result suggests that BDNF's response to exercise may be related to the structural plasticity observed in the human adult brain.

Multimodal Interventions that Combine Cognitive and Physical Training

Given the potentially unique effects of cognitive and exercise training, programs combining various types of training may be the most promising for widespread cognitive increases. In these studies, improvements in cognitive function can be described by the cognitive-enrichment theory, in which improving general cognitive capacity overall can affect many different abilities based on greater capacity and resources (Hertzog et al. 2009). Further, multiple reviews of the literature have suggested that multimodal interventions might take advantage of many different molecular pathways (Bamidis et al. 2014; Dhami et al. 2015). Fissler et al. (2013) propose synergistic effects on multiple mechanisms when combining difficult, novel tasks with physical activity components. Such components may interact through “guided plasticity facilitation,” such that cognitive activity guides spatial and temporal characteristics of changes in the brain, while physical activity acts to facilitate, or enhance, these changes. Figure 1 visualizes this interaction and points to relevant papers for each relationship. Further, this physical activity-induced facilitation might be the most effective immediately after a bout of exercise, as it has also been shown that BDNF increases acutely following exercise (Knaepen et al. 2010). Fissler and colleagues conclude that across a population of highly

Fig. 1 Training leads to neuroplasticity that engenders changes in cognitive function and brain health. References denote key papers that demonstrate evidence for each type of relationship in healthy adults (see Table 1)

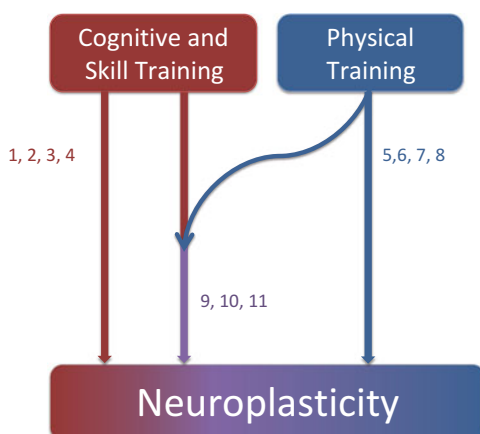


Table 1 Studies referenced in Fig. 1

# in figure	Author (First; Last)	Year	Type of training	Experimental Training Modality (control group)	Population Details <small>unless otherwise stated, controls match population of intervention group</small>
1	Boyke; May	2008	Cognitive and Skill training	Juggling (no-contact)	25 healthy older adults; 25 controls
2	Lövdén; Bäckman	2012	Cognitive and Skill Training	Virtual environment spatial navigation (walk-time yoked, no navigation)	23 healthy young adults; 21 young controls; 23 healthy older adults; 24 older controls
3	Kühn; Gallinat	2014	Cognitive and Skill Training	Video game (no-contact)	23 healthy young adults; 25 controls
4	Lampit; Valenzuela	2015	Cognitive and Skill Training	Multidomain computerized cognitive training (video watching and quizzes)	7 older adults with at least one dementia risk factor; 5 active controls
5	Colcombe; Kramer	2006	Physical activity	Walking (light stretching and toning)	30 sedentary healthy older adults; 29 active controls
6	Erickson; Kramer	2011	Physical activity	Walking (light stretching and toning)	60 healthy older adults; 60 active controls
7	Voss; Kramer	2012	Physical activity	Walking (light flexibility, toning, and balance)	30 sedentary healthy older adults; 25 active controls; 32 young adult controls
8	Maass; Düzel	2014	Physical activity	Treadmill walking (muscle relaxation/stretching)	21 sedentary healthy older adults; 19 active controls
9	Anderson-Hanley; Zimmerman	2012	Multimodal	Cybercycle with virtual reality display (stationary bike)	38 healthy older adults; 41 active controls
10	Li; Li	2014	Multimodal	Cognitive training, Tai Chi & group counseling (lectures on health and aging)	26 healthy older adults; 19 healthy older adult controls
11	Carlson; Fried	2015	Multimodal	Experience Corps (wait-list)	58 healthy older adults; 53 healthy older adult controls

variable individuals, interventions that combine cognitive, social, and physical activities are the most likely to be effective. Although the literature is still sparse concerning brain outcomes from multimodal interventions, we briefly highlight a few promising studies.

In a recent study, Carlson et al. (2015) report the beneficial effects of an intergenerational social health promotion program (Experience Corps) on cortical and hippocampal volume and memory, as measured by the Rey Auditory Verbal Learning Test. The Experience Corps program is a randomized control trial involving older adults volunteering as mentors and tutors at Baltimore area elementary schools for 2 years, which increased their physical, cognitive, and social activity. The Experience Corps group was compared to a wait-list control group of healthy older adults who were referred to lower-intensity volunteer opportunities. A subset of Experience Corps participants were randomized to a Brain Health Substudy (N = 111). Compared to the control group, the experimental group showed intervention-related increases in cortical and hippocampal volume after 2 years, though this relationship was found only in men. Importantly, following the 2 years, male control participants demonstrated age-related atrophy in cortical and hippocampal volume. Thus, the intervention appeared to not only mitigate expected declines, but also facilitate positive plasticity throughout the brain, at least in male participants. For both women and men, greater benefits in the hippocampus were observed after 2 years of the intervention than after just 1 year of participation (although for women the improvements did not reach statistical significance).

Although changes in hippocampal volume were not significantly related to improvements in memory, cortical volume changes were positively associated with changes in recall ability for men in the intervention group. In addition, benefits of the Experience Corps program were found for executive function (Carlson et al. 2008) and neural activity (Carlson et al. 2009), such that greater intervention-related increases in activity in the regions associated with executive function were related to greater behavioral improvement on the Flanker task. The Experience Corps program was proposed as targeting the hippocampus, based on hippocampal plasticity from enriched environments that simultaneously combine physical, mental, and social stimulation (van Praag et al. 2000). Varma et al. (2015) did demonstrate an increase in physical activity in the women from a similar cohort of participants from the Brain Health Substudy of the Experience Corps program (total $N = 114$), as well as a positive relationship between physical activity and hippocampal volume (Varma et al. 2014). This relationship was observed only for women in the Brain Health Substudy. Thus, overall, results suggest this type of volunteer and community-based multimodal intervention is beneficial for hippocampal structure but more research is needed to link these changes to improved hippocampal function.

In a study of 39 otherwise healthy young individuals with schizophrenia, Malchow et al. (2015) examined the effects of a 3-month exercise intervention combined with cognitive training, compared to a non-exercise table soccer intervention that included cognitive training. Compared to schizophrenic patients in the control group there was not a significant effect of endurance exercise + cognitive training on hippocampal volume. This null effect may be a result of the lack of appropriate control (table soccer requires some level of both movement and cognitive engagement). However, the authors did find a significant decrease in hippocampal volume in schizophrenic participants in the non-exercise control group at a follow-up 3 months following the end of the intervention. If nothing else, these data should encourage individuals, particularly those with expected hippocampal decline, to engage in some type of physical or cognitive activity.

In addition, a recent paper by Li et al. (2014) demonstrated functional plasticity following a 6-week multimodal intervention in 26 healthy older adults. Because the prefrontal cortex and the hippocampus are especially sensitive to aging, the authors examined hippocampal-prefrontal connectivity before and after 6 weeks of a multimodal intervention, which was a combination of cognitive training (mnemonic and executive function training), Tai Chi, and group counseling. Of the 45 total participants, 19 individuals were randomly assigned to the control group; these participants received instructions to attend 2 lectures on health and aging. Cognitively, the intervention group improved more on paired associates learning than the control group. The intervention group also showed a greater increase in FC between the prefrontal cortex (PFC) and the left parahippocampal cortex (PHC) than the control group. In an exploratory examination of functional connections with the medial prefrontal cortex, the authors found that the greatest functional connectivity was found with regions in the DMN including the anterior hippocampus. Importantly, in the intervention group, the increase in connectivity

between the PFC and the PHC was related to increased improvement in the Category Fluency Test. Across all individuals, post-training FC between the two regions was also positively related to performance on the Trail Making Test, a measure of executive function. This again demonstrates the potential of functional plasticity in the older adult brain, and suggests that some regions and/or networks may be more responsive than others to cognitive and physical intervention training.

Although the literature concerning mechanisms underlying multimodal intervention is sparse, some evidence can be gleaned from Anderson-Hanley and colleagues' study of cybercycling (2012) in healthy older adults from retirement communities. A 3-month cybercycling intervention was compared to a 3-month stationary cycling program that did not have a cognitive component. The authors found that cybercycling increased plasma BDNF more than exercise alone. This may suggest that combining cognitive and physical activity boosts BDNF-mediated enhancements in brain structure and function. However, this does not explain why the exercise-only group did not also show increases in BDNF given the extent of evidence that supports BDNF up-regulation in response to exercise (Knaepen et al. 2010). It is also still unclear how plasma BDNF relates to BDNF in the hippocampus.

Summary and Outstanding Questions

We have shown that experience-dependent brain plasticity has been demonstrated within the hippocampus in healthy adults and selected patient populations with neurological diseases that affect the hippocampus. Structural changes that take place in response to cognitive or physical training, or their combination, and which correspond with improved cognitive functions reflect the characteristics of plasticity described by Lövdén and colleagues (2010). We detailed many studies that demonstrated these plasticity processes in humans in response to a variety of training programs, with durations ranging from 8 weeks (Engvig et al. 2012, 2014; Kühn et al. 2014) to 2 years (Carlson et al. 2015). These data are consistent with another current theory of plasticity (Walhovd et al. 2015), which proposes that the medial temporal lobe, including the hippocampus, possesses many characteristics that provide a premise for plasticity, including low evolutionary expansion, low genetic correlation or heritability, and high variability in change of cortical thickness and myelin content. As a result, the medial temporal lobe is uniquely positioned for experience-dependent change, in both negative (e.g., neurological disease) and positive (e.g., neurogenesis) ways. However, there are surprisingly few studies that target hippocampal plasticity through the training of specific functions thought to depend on the hippocampus, and which include MR imaging to evaluate changes in hippocampal structure and function in relation to training-related changes in cognitive performance. This is an important gap to address for empirically testing the role of the hippocampus in the broad cognitive decline

associated with aging and its responsiveness to experiential stimulation from cognitive and physical training.

While studies that demonstrate training-induced changes in brain structure can be classified as demonstrating plasticity, it is often more difficult to determine whether changes in functional imaging outcomes reflect plasticity or flexibility. Again, when thinking about functional outcomes, flexibility refers to the behavioral repertoire and functional activity within the range of currently available resources, whereas plasticity refers to changes in behavior that are the result of rejuvenation or reorganization in brain structures and their connections. Flexibility reflects the brain's need for ongoing rapid, transient reconfigurations to support interactions between internal goal states and continually changing external demands. Unless these flexible processes are accompanied by physical changes (such as synaptic connections, density of neurotransmitter receptors, neurogenesis, etc.), they may not indicate training-induced plasticity. An example of a change in functional brain activity or connectivity due to flexibility would be a change in strategy from pre- to post-training that could alter the functional activation observed during performance without altering the structure or functional characteristics of brain regions that give rise to performance.

Given this possible scenario, we can think of several (not mutually exclusive) strategies for studies to examine functional plasticity in the hippocampus with MR imaging that have rarely been applied thus far. First, investigators could include measures of self-reported strategy that are acquired following any behavioral tasks administered during functional imaging. Information about change in strategy would provide context for interpreting change in activation as plasticity or flexibility. In addition, studies could include assessment of changes in the resting FC of hippocampal networks that are known to overlap with networks evoked during behavioral performance, and it would be unlikely that there would be a strategy change in response to instructions to rest quietly in the scanner. Further, studies including either task or resting state functional imaging could more directly test for links between training-induced changes in structure and function. While changes in structure and function do not necessarily occur on the same timescales, this should not be a prerequisite for observing an association between the two and this analytic approach would ground changes in functional outcomes more strongly to plasticity than functional outcomes alone.

Another strategy would be exploring the similarities between various types of learning in animals and humans using cross-species investigations (Mishra and Gazzaley 2015). Animal studies have been able to investigate many variables that cannot be easily measured in humans such as micro-scale tissue changes like dendrite density or receptor density, genetic interactions, or electrophysiology of hippocampal neurons. Therefore, experimental designs that enable connecting training-induced changes in these cellular and molecular outcomes to changes in MR imaging outcomes could provide deep insight into how to measure brain plasticity with human imaging. For example, one study (Sagi et al. 2012) determined that in both humans and rats, as little as 2 h of spatial learning and memory training improved performance and decreased MD in the hippocampus and other nearby regions, suggesting training increased hippocampal tissue density.

Supporting evidence from the animal study provides a conceptual replication and strengthens knowledge of possible cellular changes underlying the change observed with MRI in humans. This study also highlights just how short the “training” period can be before observing structural changes, and may also point out that we need to consider whether and when it is necessary to conceptually distinguish between learning and cognitive training. In any case, future studies comparing effects of cognitive training in animals and humans may help clarify the time-scale of different types of experience-induced changes in hippocampal structure and function and their relationship to changes in performance. Similar to this approach with cognitive training, animal models can provide a parallel foundation of knowledge of basic mechanisms underlying exercise-related plasticity (Voss et al. 2013b). While animal models may not fully translate to humans because of the larger repertoire of human behaviors and experiences that could impact the experience and effectiveness of training, greater understanding of how basic processes studied with animal models relate to human outcomes could inspire interventions that are driven more by an understanding of the mechanisms for change.

We also evaluated examples of brain maintenance, wherein cognitive or physical training delayed decline in hippocampal structure or function, or both. This was most notably demonstrated by Lövdén et al. (2012) in their study of virtual environment spatial navigation training in young and older men. Compared to a group that slowly walked on a treadmill with no spatial navigation training, the authors observed a training ability-related maintenance of hippocampal volume and an increase in spatial navigation. Brain maintenance can also be inferred in studies of individuals with MCI or SMI (Engvig et al. 2012, 2014), when training seems to mitigate greater expected atrophy. However, studies need to include appropriate control and comparison groups to clarify the precise effects of training (similar age groups, cognitive health, and active control conditions). Importantly, ideally plasticity, flexibility, and brain maintenance are each evaluated in the context of accompanying behavioral and cognitive changes thought to rely on the underlying brain regions affected by training.

As alluded to above, a conceptual weakness of this literature is the lack of appropriate control groups that limit the extent to which we can conclude effects of training are specific to the training program (Boot et al. 2013; Thomas and Baker 2013). For cognitive training, researchers should include active control groups that differ from the cognitive training group in one key way. For example, the intervention group may undergo training of various cognitive functions (episodic memory, spatial navigation, task-switching) by completing tasks of increasing difficulty (adaptive training). In this case, the control program could include training of those same functions, but with tasks of fixed difficulty. At a bare minimum, the control group should engage in an active program that acts as a placebo to safeguard against differential expectations and motivation at post-testing. Similarly, with physical training, control programs should be matched on every aspect possible except for the characteristic of interest. For instance, control groups should be matched on social interaction. If training participants are meeting multiple times a week with trainers and other participants, control participants should have the same schedule.

Many exercise studies have used stretching and toning as control exercises, in comparison to aerobic exercises. However, there could be multiple factors that differ between the experimental aerobic and control stretching/toning programs. The level of engagement with trainers, involvement of spatial navigation, or one's own physiologic response (such as monitoring heart rate and reaching heart rate goals) may all vary between aerobic and stretching/toning groups. As an alternative, for maximal experimental control, the control group should experience similar stimulation as the experimental group, with only the variable of interest eliminated or modified. As evident by our review, numerous studies have already demonstrated general benefits of training compared to no training, therefore control groups should now be used to help clarify the critical ingredients for a training program to be effective.

Further, studies should more carefully consider whether the claim of "training-induced" plasticity is appropriately tested and whether sufficient statistics are used to estimate power and control for multiple comparisons (Thomas and Baker 2013). Strong evidence for training-induced change requires an interaction between group and time variables on the outcome measure (either brain or cognitive measures). Some studies have instead reported a main effect of time within the training group, but not the control group, without reporting the interaction effects, and this raises questions about the strength of the finding. Regarding specificity of training-induced change, another conceptual limitation of many studies is the use of targeted analyses of the hippocampus. Such analyses include segmenting or defining the hippocampus as an isolated region of interest without also evaluating other regions for comparison. Although determining the effects of training on comparison regions is not necessary for detecting an effect on the hippocampus, comparison regions are critical for determining the specificity of change in relation to change in performance and for narrowing in on possible mechanistic explanations for change. As discussed more below, limiting analyses to only the hippocampus also limits the ability to evaluate how training impacts the structural and functional connections of the hippocampus with other brain regions. This type of systems-approach will be especially important for understanding how training drives changes in behavior and cognitive performance.

Overall, while many studies did demonstrate changes in the hippocampus, other studies that anticipated hippocampal changes did not find support for this prediction. This mixed support across different studies may in part be driven by the complex patterns of anatomical and functional gains and losses in normal aging (Ballesteros et al. 2015), and the wide variability seen across individuals in the amount and rate of change each person experiences (Baltes et al. 2005). To overcome these intrinsic challenges in the data, the field will benefit from evaluating promising training effects with designs that have enough statistical power to compare change across sub-groups based on baseline demographic, health, cognitive, or brain characteristics in order to identify profiles for responders and non-responders to different interventions. It may also be that timeseries designs would be a valuable complement to reports of change averaged over groups of individuals in traditional clinical trial designs.

We also found little empirical evidence for far transfer of benefits from cognitive training studies that either targeted hippocampal-dependent cognitive functions or which showed change in structure or function of the hippocampus. On the other hand, improvement in hippocampal structure and function from exercise programs may be evidence of far transfer, as improvements in cognitive function are seen in executive function and memory domains and it is unclear how exercise would directly train these processes. As inspiration from this pattern, one strategy for understanding the mechanisms of transfer for cognitive training may be to adopt a more systems-level perspective, rather than focusing on isolated brain regions, as “targets” for transfer. For instance, one reason exercise is proposed to have such broad influence on cognition is its capacity to affect the functional integration of the hippocampus in brain networks known to degrade with age and neurological disease (Voss et al. 2010, 2016). One such network is the DMN, which is also thought to interact with many other systems during cognition, and this interaction may serve as a point of transfer to a broad range of cognitive abilities. Similarly, to better understand the widespread effects of training across the brain, Taya et al. (2015) emphasized the value in characterizing training-related brain outcomes using graph theoretical approaches. In general, a graph approach examines the brain as a complex system of interacting regions, and can reveal which brain regions have the most influence on how well many other regions interact with each other for effective information processing. Therefore, similar to the idea of transfer occurring due to brain regions that have multiple functions and are affected by training, another promising mechanism for transfer could be training-induced plasticity in regions that have broad influence in the overall function of the complex (brain) network by simultaneously affecting many overlapping sub-networks involved in abilities outside of abilities that were explicitly trained (Taya et al. 2015).

In sum, while there is good evidence the hippocampus remains plastic into late life and that cognitive and physical activity can stimulate this plasticity, there is still much to learn in order to optimize the application of this knowledge. One important unknown apparent from our review is the time-scale of various types of training or how much those timescales vary across training type. Although current technology limits the spatial resolution of human imaging with which we can measure structural and functional changes, it is still possible to further define the time course and duration of training effects on brain structure and function across hours, days, weeks, months, and years. This coupled with parallel animal models promises to enhance our understanding of how to drive plasticity over extended periods of time. Determining individual time courses for training gains and change in outcomes for training programs will also be critical for effectively combining interventions for maximum benefit. In addition, current theories of cognitive enhancement and exercise-induced brain plasticity do not yet specify with great detail which aspects of training programs are most effective for engendering primary change and transfer of training. This may occur as more data are collected that allow us to better understand the mechanisms through which experience physically changes the brain and through which transfer occurs. Ultimately, designing interventions based

on components that deliver maximum benefit becomes especially important in the context of the public arena, as certain ingredients of evidence-based interventions will be critical to preserve when implementing any program into realistic guidelines for the public. In this way, studies examining mechanisms in humans with MR imaging are positioned well to increase our understanding of how to take advantage of the natural plasticity of the hippocampus in order to translate training studies from the lab to theoretically-based training programs that are fun, effective, and easily accessible to the broader community.

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