EFFECTS ON THE HIPPOCAMPAL VOLUME AND FUNCTION
Stress and Depression Versus Physical Exercise

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Abstract

In this essay, changes in the human hippocampal volume and function induced by stress, depression and physical exercise are examined. Hippocampus is crucially involved in the acquisition and retrieval of episodic and spatial memory, and hippocampal volume correlates with episodic and spatial memory performance. Hippocampus has substantial plasticity and changes with age, but also in response to experiential factors across life. Stress and, under at least some circumstances, also depression have negative effects on hippocampal volume and memory function. The negative effects are believed to accelerate age-related decline in volume and function, mediated by exaggerated cortisol levels and dysfunction in the HPA-axis. Physical exercise is examined from two perspectives; aerobic and strength exercise. Aerobic exercise increases hippocampal volume across various ages and decelerates age-related hippocampal degeneration, whereas support for strength exercise-induced effects are mixed and need to be studied further. The positive effects are believed to be mediated by increased BDNF levels and regional cerebral blood volume. Although hippocampal volume normally correlates with hippocampus-dependent memory, studies on exercise-induced changes in human hippocampus-dependent memory have reported inconsistent results. Animal studies have observed both the negative and positive effects on hippocampal volume to relate to changes in neurogenesis, cell proliferation, and dendritic complexity. The negative and positive effects on hippocampal volume have been observed to be non-permanent, suggesting that physical exercise may prevent, attenuate and possibly reverse hippocampal degeneration induced by stress and depression. Further, more studies on sex and age differences, exercise intervention designs and functional values of physical exercise would be of value.

Keywords: hippocampus, hippocampal volume, hippocampal function, memory, stress, depression, physical exercise
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Introduction

To be able to successfully recall events you experience while walking through life, such as your graduation long ago, who you met in the store last week, or what you read in the news app this morning, your hippocampus-dependent memory is required (Baddeley, Eysenck, & Anderson, 2015). It is also necessary for daily activities such as to follow your favorite TV-show to continue where you left off before dinner, to find your way to the bus stop, or to be disturbed by your partner not doing the dishes for the fourth night in a row.

Hippocampus is commonly called the center of learning and memory, a somewhat simplified description of what we currently know about memory from a neuroscientific perspective. Memory is not a single thing, it is made up of multiple types of memory and these are related to various brain structures (Baddeley et al., 2015). This essay will focus on factors that affect hippocampal volume and function, a brain region that experts agree is essentially involved in spatial and episodic memory (Burgess, Maguire, & O’Keefe, 2002; Morris, 2007a). Spatial memory provides you with the capacity to navigate around an environment, whereas episodic memory allows you to recollect episodes of your past experiences which are tied to a specific context of what, when and where it occurred. Without it, you would be doomed to live permanently in the present. Until your memory starts to fail you, it may be easy to take the above mentioned daily activities for granted.

Hippocampus-dependent memory is known to correlate with hippocampal volume, suggesting that volumetric changes in the hippocampus may have functional values for related memory functions (Doxey & Kirwan, 2015). Prior research has suggested that increasing age affects hippocampal volume as well as hippocampus-dependent memory negatively (e.g. Driscoll et al., 2003; Erickson et al., 2011). Further, we know that extensive cognitive training improves hippocampal volume and function in both animals and humans (Dudai, 2002).

Spatial learning increases neurogenesis selectively in the hippocampus in rats (Gould, Beylin,
Tanapat, Reeves, & Shors, 1999) and similarly studies of taxi drivers with extensive training in spatial navigation have found them to have greater hippocampal volume compared to controls, which moreover positively correlates with years of training (Maguire et al., 2000; Maguire, Woollett, & Spiers, 2006). Nonetheless, it is not only aging and cognitive training that affects the hippocampal volume and function, but several other, experiential factors can impact it as well, negatively as well as positively (Leuner & Gould, 2010).

The notion that lifestyle aspects such as stress and physical exercise influence brain structures and functions is growing (Hillman, Erickson, & Kramer, 2008). On one hand, animal studies have made it clear that extreme or prolonged exposure to stress results in excessive levels glucocorticoids, which is associated with accelerating age-related hippocampal atrophy as well as impaired hippocampus-dependent memory (Morris, 2007b). Since depression is a common psychiatric disorder closely related to dysfunction in the glucocorticoid-regulating HPA-axis (Pariante & Lightman, 2008), it is of interest to examine the effects of both stress and depression on the hippocampus and related memory in humans. On the other hand, physical exercise is a hot topic in the search for hippocampal enhancement (van Praag, 2008). Animal studies have also consistently reported physical exercise to increase hippocampal volume as well as improving hippocampus-dependent learning in memory. This raises the question whether these negative as well as positive effects also apply to humans and, if so, if physical exercise may prevent, decrease or reverse the effects of stress and depression on the hippocampal volume and function.

The aim of this essay is to review the effects of stress, depression and physical exercise on hippocampal volume and memory function in humans, where physical exercise will be reviewed in the terms of aerobic and strength exercise. First, a presentation of the anatomy of the hippocampus, related brain structures, and their neural connectivity will be provided, followed by a description of hippocampus-dependent memory functions. Second, publications
on the correlates between stress and depression, hippocampal volume and hippocampus-related memory as well as between aerobic and strength exercise, hippocampal volume, and hippocampus-related memory will be provided. Finally, the reviewed research will be discussed, with concluding remarks.

Hippocampus

Anatomy

To fully understand the hippocampus and its relation to experiential factors and memory, an introduction of the hippocampus is in order. Hippocampus is an infolding of the medial temporal lobe located bilaterally in the inferior part, and it consists of the three subfields CA1, CA2, CA3, the dentate gyrus and the subiculum (Squire & Zola, 1996). The definition can also be distinguished as the hippocampus proper and the hippocampal formation where the hippocampus proper consists of the CA1-3 and the hippocampal formation consists of the hippocampus proper together with several functionally related brain structures; the entorhinal cortex, the dentate gyrus, and the subicular complex. The entorhinal cortex is viewed as the gateway enabling sensory input from cortex to reach the hippocampal formation (Amaral & Lavenex, 2007). The dentate gyrus is one of few known areas in the brain where new cells are born in adulthood, a process called neurogenesis (Morris, 2007b). The subicular complex consists of three regions called the presubiculum, subiculum, and parasubiculum (Amaral & Lavenex, 2007). In this essay, the first definition presented, referring to the hippocampus as consisting of the CA1, CA2, CA3, the dentate gyrus and the subiculum, will mainly be used.

To understand hippocampus-dependent memory it is also relevant to briefly describe further adjacent, functionally related regions. The perirhinal and parahippocampal cortex, also
located in the medial temporal lobes, are essentially involved in the flow of information between the cortex and the hippocampus occurring during learning and memory (Squire, 1992). The perirhinal cortex is believed to convey sensory input about the features of an item (what), whereas the parahippocampal cortex passes on information about the item’s context (where) (Diana, Yonelinas, & Ranganath, 2007).

**Hippocampal Connectivity**

In hippocampus-dependent memory, experience-related information is conveyed from various sensory-specific regions of the cortex to the parahippocampal and perirhinal cortex (Schultz & Engelhardt, 2014; Amaral & Lavenex, 2007). From there, it enters the hippocampus through the entorhinal cortex, where the cortical information associated with the specific experience converges. As information enters the entorhinal cortex, a unidirectional flow of information, the intrinsic hippocampal connectivity, is initiated. From the entorhinal cortex, the majority of the axons connect to the dentate gyrus, and from the dentate gyrus continue unidirectionally to the CA3, then to the CA2, and to the CA1, which in turn projects to the subiculum. The CA1 and subiculum close the intrinsic connectivity loop by projecting back to the entorhinal cortex, the same site where the information first entered the hippocampus. The entorhinal cortex ends the intrinsic hippocampal connectivity and continues an extrinsic neuronal circuitry by projecting output back to the multiple sources in the brain (Amaral & Lavenex, 2007; Zeidman & Maguire, 2016).

**Hippocampus and Memory**

Memory is the result of learning information over time and it can be viewed from the perspective of being formed in interacting steps; encoding, consolidation, storage, and
retrieval of information (Dudai, 2002). Encoding is the initial step, which transforms information into memory traces in appropriate neuronal code, to make the information available to consolidation, storage, and retrieval. Brain areas involved in the encoding of memory vary depending on the kind of memory, but the structures involved during encoding are commonly also involved in the retrieval of the same information. Consolidation is the stabilization of encoded memory traces in the brain. It can take from minutes or hours up to days, weeks, months or even years to stabilize information into long-term memory.

Consolidation is divided into two processes; synaptic and system consolidation. Synaptic consolidation occurs within hours after learning and is a process of change on a cellular level. System consolidation, on the other hand, is a more long-term process of stabilization in which memories are gradually transferred from one system in the brain to another. Retrieval is the process of making the encoded, consolidated and stored information in long-term memory accessible for usage (Dudai, 2002). Various brain structures contribute to various memory functions, and it has become widely accepted that the hippocampus is crucial in the neural mechanisms of episodic and spatial memory (Strange, Witter, Lein, & Moser, 2014). The involvement of the hippocampus in the steps of memory formation in episodic and spatial memory will be presented below.

**Episodic Memory**

Long-term memory is divided into two subcategories, declarative and nondeclarative memory, where episodic memory falls under declarative memory together with the subcategory semantic memory (Baddeley et al., 2015). In contrast to semantic memory which refers to factual knowledge, episodic memory is context-dependent, it comprises personal experiences of events bound to a specific time and setting. Episodic memories do not only allow you to consciously declare them but also to mentally reexperience them, e.g. recalling
the context of your first kiss or the day you graduated high school, but also where you put your keys or what you had for lunch the other day. This kind of memory requires an association between the what, when, and where of an event, which Morris (2007a) claims to be a characteristic with neurobiological implications related to the hippocampus, because the hippocampus is essential in the process of binding various context aspects of an event together into an associational representation in memory. To encode and consolidate an episodic memory, information about the context reaches content-specific regions of the cortex. The hippocampal connectivity is initiated, to converge the item-related information via the perirhinal cortex, and the location-related information via the parahippocampal cortex, to the hippocampus. The hippocampus is then believed to bind the converged contextual information together and form a memory representation or associational network in the brain.

In sum, in the process of encoding and consolidation, the hippocampus provides our memory system with associational networks of content-specific regions across the brain, to bind the contextual information of an event together (Morris, 2007a).

According to Maguire (2014), there is consensus in that episodic memories are hippocampus-dependent also during retrieval, but that the retrieval process might become less dependent on hippocampal involvement over time. Maguire highlights two perspectives on this. First, the standard model of consolidation which proposes that there is a time aspect involved. This model suggests that the associational cortical connections of a memory become stronger over time, and that memories would ultimately not require hippocampal involvement to be able to retrieve the memory since it has been completely established in the associational connections across the cortex. Second, she presents a view which suggests that hippocampus is always essential in the ability to bring episodic memories to mind, regardless of the time aspect. There is evidence supporting both views. Patients with bilateral hippocampal damage suffer from impairments in the encoding of new episodic memories (i.e. anterograde
amnesia), but the extent to which they suffer from problems with retrieving episodic memories acquired before the lesion (i.e. retrograde amnesia) may vary. On one hand, some patients have trouble remembering the more recent events but not more remote ones, which supports the hypothesis that hippocampal involvement in retrieval is time limited and vital only until the memory is fully established in the cortex (Maguire, 2014; Squire, 1992). On the other hand, there are also patients with bilateral hippocampal damage who cannot remember any personally experienced events at all, which supports the view of hippocampus being crucial in retrieval throughout life (Maguire, 2014).

Interestingly, studies using event-related fMRI support the view that the hippocampus is active during encoding and retrieval of long-term memory, but only when the information is correctly recollected (Baddeley et al., 2015). Due to this distinction, it is relevant to specify the difference between episodic memory (i.e. recollection-based recognition), and familiarity-based recognition (Morris, 2007a). As stated, episodic memory is mainly characterized by the ability to recollect the context of an event, whereas familiarity-based recognition is characterized by the feeling of something being familiar but with no actual recollection of memory. Episodic memory has been shown to correlate with activation in the hippocampus and parahippocampal cortex, whereas familiarity-based recognition is correlated with activation in the perirhinal cortex only (Diana et al., 2007). Thus, hippocampus is involved in the encoding, consolidation, and at least under some circumstances in retrieval of episodic memory, but not in familiarity-based recognition.

Spatial Memory

Spatial memory contains representations of environmental information which is essential to provide spatial context in the formation of episodic memories, as well as for the ability to navigate through complex environments, and to remember where objects or places
are located in the surroundings (Burgess et al., 2002). Spatial memory is dependent on the hippocampus, and also on the entorhinal cortex (Pilly & Grossberg, 2012).

In 1978, O’Keefe and Nadel presented hippocampus as a cognitive mapping system, similar to a representational mental map of the surrounding environment. Animal studies have discovered so-called place cells, specific neurons in the hippocampus which respond to an organism’s own position in the environment. Place cells are activated by a unique position, meaning that some are triggered to fire when the animal is in one field of the environment, whereas others fire selectively as a response to when the animal is in other fields of the environment. As they move, the hippocampus can form a memory representation of the environment that the animal is moving within. In and around the hippocampus are also certain neurons which fire in response to a certain direction of the head, at a certain distance to objects, and so-called grid cells in the entorhinal cortex which provide a representation of the surrounding environment (Burgess & Bisby, 2018). Together, these cells in and around the hippocampus provide a mental representation system of position and orientation in relation to the current environment, something believed to be important to the ability to navigate through the surroundings. This system seems to apply to the human hippocampus as well (Maguire, 2014). Using virtual reality (VR) and fMRI, a correlation between a person’s spatial location in a VR environment and the activity pattern in the hippocampus has been observed, indicating that certain neurons in the hippocampus represent specific locations in the environment. Taxi drivers in London, who require extensive experience in spatial navigation and memory, have also provided support for a relationship between spatial memory and the human hippocampus (Maguire et al., 2000). As noted earlier, Maguire and colleagues (2000) found taxi drivers to have significantly greater posterior hippocampal volumes compared to controls, which correlated positively with number of years of experience. Interestingly, in addition to the experience-related increase in the posterior hippocampus, they also observed
an experience-related decrease in the anterior hippocampus, which suggests that experience in spatial navigation is associated with structural alterations in the hippocampus. Maguire et al. (2006) suggest that the structural changes are associated with functional consequences. Taxi drivers with corresponding structural changes performed better in a spatial memory representation task, but worse in learning new spatial information as compared to the control group, suggesting that the anterior region may be more involved in encoding of spatial information than the posterior part, whereas the posterior region may be more involved in representations of stored spatial memory necessary in the process of retrieval than the anterior part. The authors suggest that this supports what has been observed in animals, that there is a mental representation of the environment similar to a map, in the posterior region of the human hippocampus. As the memory of spatial knowledge expands, so does the volume in this region. At the same time, the expansion seems to be at the cost of the volume in the anterior hippocampus (Maguire et al., 2006).

**Changes in Hippocampal Volume and Function**

In accordance with the research of Maguire and colleagues (2000, 2006), the hippocampus is a highly plastic brain structure with the ability to structurally change through the lifespan (Leuner & Gould, 2010). Hippocampal volume can be modified through reorganization of existing neural connections in the number of synapses (formation or elimination) or the complexity of its dendrites (extension or retraction). Further, in the light of hippocampus as one of the few sites in the brain with substantial processes of neurogenesis, the volume can also change through alterations in the process of formation of entirely new neurons. What we know about hippocampal plasticity is initially based on research in animals, but Leuner and Gould (2010) explain that studies in humans support the capacity of adult neurogenesis and dendritic modification in the hippocampus, suggesting that findings of the
hippocampus as a plastic brain structure in animal studies also apply to the human hippocampus.

Hippocampus as a structure is not fully developed at birth; it develops and matures first in childhood and adolescence, the time when it generates new cells at the highest rate (Leuner & Gould, 2010). During young adulthood, the process of neurogenesis gradually decreases. Some of the newborn cells in adulthood die if they are not needed, whereas some undergo maturing phases to become functionally incorporated neurons in already existing neural circuits in the hippocampus. Later on, in middle-aged adulthood, neurogenesis continues to decrease. So does cell proliferation, the balance between cell increase and cell loss resulting in an increased number of neurons, which is involved in the well-established age-related decline in hippocampal volume (Leuner & Gould, 2010). The age-related hippocampal reduction has been detected bilaterally, along with age-related impairment of hippocampus-dependent spatial and episodic learning and memory (Driscoll et al., 2003). Further, Doxey and Kirwan (2015) found that when age is controlled for, the volume of the CA3 and the dentate gyrus in the left hippocampus predict episodic memory performance. This was measured in a memory discrimination task where subjects were presented with pictures and asked to separate them as new, similar or repeatedly presented pictures, which demands hippocampal engagement. Volumetric changes in the hippocampus are not only associated with age and cognitive training, but also with various experiential factors, suggesting that hippocampal plasticity is related to the environment throughout life (Leuner & Gould, 2010). The hippocampal sensitivity to environmental experience is believed to have positive as well as negative consequences.
Hippocampus and Stress

Stress is beneficial in small amounts, but high or prolonged exposure is generally not (Gazzaniga, Heatherton, & Halpern, 2010). Stress is a behavioral and physiological response to a subjectively stressful situation when the perceived ability does not match the perceived requirements of the situation, a response that begins in the brain. An individual’s health issues, such as stress, are according to the biopsychosocial model the result of a combination of biological, psychological and social factors (Engel, 1978). Such factors include everything from brain development and genetic predispositions, lifestyle, behaviors, thoughts, and beliefs, to relationships, culture, and the environment. In relation to stress, this means that what induces stress can be a combination of many factors in daily life, it is highly individual and can vary over time, depending on one’s biological, psychological, and social situation at the time. For example, social circumstances that induce a stress response in a person in one situation may not elicit a stress reaction in the same person under other circumstances, or in another person with different experiences and biological predispositions.

The factors inducing a stress response increase the activity in the hypothalamus-pituitary-adrenal (HPA) axis, a neuroendocrine system which affects the release of the human stress hormone cortisol from the adrenal cortex (Frodl & O’Keane, 2013). Cortisol is what is called a glucocorticoid, a steroid hormone that binds to two kinds of receptors in the brain and one of them, glucocorticoid receptors, is highly present in the hippocampus. By binding to the glucocorticoid receptors, cortisol is also involved in a feedback inhibition of the HPA activation and cortisol secretion, to prevent a prolonged stress response and return to a balanced state. This means that hippocampus is a central structure in the cortisol-induced feedback system to prevent chronic stress (Frodl & O’Keane, 2013). However, the hippocampus is not only involved in the regulation, it is also a target for cortisol. According to the glucocorticoid cascade hypothesis, a hypothesis derived from animal studies that
originally describes the relationship between glucocorticoids and hippocampal degeneration in aging, cumulative exposure to glucocorticoids (i.e. cortisol in humans) lead to down-regulation of the number of glucocorticoid receptors per neuron especially in the hippocampus, which progressively impairs and desensitizes the feedback inhibition system (Sapolsky, Krey, & McEwen, 1986). This process is believed to ultimately lead to loss of hippocampal neurons through a feed forward cascade of degeneration; a loop of hypersecretion of cortisol and degeneration of the hippocampal structure. Prolonged or extreme exposure to stress is argued to speed up this age-related hippocampal atrophy by further increasing the cumulative levels of cortisol.

Studies in humans have, in line with studies in animals, presented support for the view that elicited levels of glucocorticoids are associated with structural as well as functional changes in the hippocampus (Lupien et al., 1998). Structural changes in humans have commonly been examined through brain imaging correlational studies based on animal studies which have investigated the structural degeneration in ways providing more regionally specific details (Pinel, 2011). Such animal studies have found stress to suppress neurogenesis and cell survival in the dentate gyrus, and to remodel the structure of hippocampal neurons (McEwen, 2007). For example, adult tree shrews that were exposed to acute psychosocial stress lasting for one hour showed a rapid reduction of cells involved in neurogenesis in the dentate gyrus compared to controls (Gould, McEwen, Tanapat, Galea, & Fuchs, 1997). In another study, rats exposed to chronic psychosocial stress induced by a dominance hierarchy among males showed retracted and simplified dendrites in the CA3 field of the hippocampus, which was not observed in the control condition (McKittrick et al., 2000). The stress-induced rats also showed a reduction in glucocorticoid receptors and a desensitization of the glucocorticoid feedback system, as described in the glucocorticoid cascade hypothesis.
In humans, healthy older adults with prolonged increased levels of cortisol were found to have a 14% reduction in hippocampal volume compared to subjects with decreased cortisol levels over time (Lupien et al., 1998). Several brain regions were measured, but structural changes were only observed in the hippocampus, suggesting the correlational degeneration to be selectively distributed in the brain. The magnitude of hippocampal degeneration correlated with the level of increased cortisol over time as well as with the basal level of cortisol. Functionally, the increase in cortisol was associated with impaired hippocampus-dependent spatial memory. The authors explain the association between size and memory by referring to the detrimental effects of the glucocorticoid cascade hypothesis. More precisely, they imply that increased levels of cortisol are associated with decreased neurogenesis in the dentate gyrus.

The relationship between cortisol levels and hippocampal volume has also been observed in middle-aged adults (Knoops, Gerritsen, van der Graaf, Mali, & Geerlings, 2010). Interestingly, this study, which investigated both middle-aged and older adults, found an association with cortisol levels in the evening, but not at other times during the day. In healthy populations, cortisol secretion shows a diurnal rhythm with a rapid increase within the first 30 minutes after awakening followed by a steep decrease as the day goes by (Smyth, Hucklebridge, Thorn, Evans, & Clow, 2013). Therefore, the level of cortisol was measured at 7 times during a day to identify differences in cortisol secretion over the day. The results found higher cortisol levels in the evening to correlate with smaller hippocampus, regardless of the total brain volume. Knoops et al. (2010) mean that a reduced hippocampus also means a reduction in receptors involved in the cortisol feedback system, which in turn gradually results in increased levels of cortisol in the evening. In their study, 0.5 mg of dexamethasone was administered in the evening with the purpose to desensitize the feedback inhibition of cortisol in the next morning. The study demonstrated that higher cortisol levels after
dexamethasone were correlated with smaller hippocampus as well, suggesting dysfunctional cortisol regulation to be related to reduced hippocampal volumes.

Sindi et al. (2014) suggest that the current environment in which the cortisol levels are measured also may play a part. When in a stressful environment, both young and older adults showed a correlation between high cortisol levels and smaller hippocampal volume, but not when tested in a favorable environment. Since both young and older adults with smaller hippocampus showed greater increase in cortisol in the stressful environment, Sindi and colleagues discuss that hippocampal volume may reflect a level of stress resistance. Since stress is a subjective implication of a current situation, memory retrieval of past experiences is needed to evaluate the current situation. When the size of the hippocampus is reduced, so may also the functional capacity to recall past experiences and realistically evaluate the level of stress in a situation, thus the level of stress resistance may be diminished (Sindi et al., 2014).

A study in preadolescent children observed associations which do not coincide with the glucocorticoid cascade hypothesis or the observed pattern in adults (Wiedenmayer, et al., 2006). Wiedenmayer and colleagues (2006) found cortisol levels to correlate with specific regions in the hippocampus, and these changes were most prominent in the right hemisphere. Cortisol was measured at one time in the morning, and in contrast to previously presented findings in adults, higher levels of cortisol were associated with larger volumes in the CA3 field and the dentate gyrus, whereas lower levels were associated with larger volumes particularly in the CA1. Age did not correlate with either hippocampal volume or cortisol levels, also inconsistent with studies in adults. However, in this age, the hippocampus is still developing, and related plastic features of the development and maturation are discussed as probably involved in the results of this study. Although this study in children did not observe a relationship between cortisol levels and hippocampal decline, childhood is thought to be an important period involved in stress-induced hippocampal decrease (Lupien, McEwen,
Gunnar, & Heim, 2009). Lupien et al. (2009) state that both human and animal studies support that stress-related effects on the hippocampus seem to differ depending on when during the lifespan one is exposed to chronic stress or trauma, with early childhood and late adulthood being especially sensitive. The authors mean that the hippocampus is highly vulnerable to stress exposure in early childhood when the hippocampus is developing, whereas in late adolescence it is fully developed and supposedly not as vulnerable. Since age-related atrophy in the hippocampus is well-known to occur in mid and late adulthood, a time in life characterized by cumulative cortisol levels, it is also assumed to be more sensitive to additive effects of stress exposure (Lupien et al., 2009).

Functional effects of stress on hippocampus-dependent memory in humans have been examined by eliciting cortisol levels medically as well as with psychosocial stress exposure (de Quervain et al., 2003; Kuhlmann, Piel, & Wolf, 2005). In a study with the aim to explore if increased levels of cortisol would affect the cerebral blood flow (CBF) in the medial temporal lobe during memory retrieval, young men received medical treatment that significantly increased their cortisol concentrations (de Quervain et al., 2003). It did. The decrease in CBF was selectively affected in the hippocampal region in the right hemisphere, which also was associated with significantly impaired episodic memory retrieval. This suggests that increased cortisol concentrations decrease hippocampal activity, impairing the process of memory retrieval. Another research group wanted to explore whether increased cortisol levels induced by stress also reduced the capacity to retrieve episodic memory, which it did (Kuhlmann et al., 2005). The subjects received a list of 30 words to learn. Subjects were exposed to a psychosocial stressor prior to a free recall task, and the results showed a correlation between increased levels of cortisol and significantly reduced long-term memory recall.
Hippocampus and Depression

Major depressive disorder (MDD) is a psychiatric mood disorder defined in the DSM-5 (Morrison, 2014). It has an essential feature of at least one major depressive episode with a duration of most of the days for at least 2 weeks of depressed mood or loss of pleasure and at least 4 more symptoms, which have resulted in distress or disability for the patient. The defined symptoms are fatigue, feelings of guilt or being worthless, impaired concentration, psychomotor retardation, sleep disruption, change in appetite and weight, death wishes, suicidal thoughts. MDD is divided into two categories; single episode or recurrent. In recurrent MDD, at least 2 months free from symptoms separate the episodes. MDD can occur at any stage of life but is most common to begin between the age 25 to 30. The duration of an episode varies a lot, from 2 weeks up to several years (Morrison, 2014).

Although MDD is a mood disorder it is also associated with other abnormalities. Pariante and Lightman (2008) state that hyperactivity in the HPA, thus hypersecretion of cortisol, is one of the most consistent findings in MDD. A meta-analysis on 64 MRI studies examining volumetric brain abnormalities in patients with MDD compared to healthy participants demonstrated that MDD is also associated with moderate reductions of hippocampal volume (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009). In 2000, a study on hippocampal volume in patients with remitted major depression found them to have significantly smaller left hippocampal volume compared to the control group (Bremner et al., 2000). The authors suggested three explanations; that decreased levels of neurotrophic factors during depressive episodes may lead to decreased hippocampus; that increased levels of cortisol may cause reduced hippocampal volume; or that smaller hippocampus is a pre-existing risk factor for major depression.

Brain-derived neurotrophic factor (BDNF) is essentially involved in neurogenesis and it has been suggested that MDD correlates with abnormal levels of BDNF in the brain as well
Kishi and colleagues (2017) reviewed 8 meta-analyses on the topic and they found patients with MDD to have smaller hippocampal volumes as well as lower levels of BDNF compared to healthy controls. Interestingly, these levels increased in patients after treatment. However, the authors conclude that the level of BDNF is a biomarker for the current intensity of MDD, but not a risk factor for the illness.

Colla et al. (2007) observed reduced total hippocampal volume in hospitalized patients with MDD compared to healthy volunteers, which they explain as a result of increased levels of cortisol and the glucocorticoid cascade hypothesis. The volumetric changes were not associated with cortisol levels at baseline, but with the duration of illness. The authors suggest that baseline levels of cortisol represent the intensity of depression at the time of measure, whereas the time of suffering from MDD, thus exposure to elicited cortisol levels due to HPA-hyperactivity, might be a more relevant predictor of the volumetric changes. In a meta-analysis of 32 MRI studies, McKinnon, Yucel, Nazarov, and MacQueen (2009) support the duration of illness as a predictor of the size of the hippocampus in MDD. They found the duration of illness to predict hippocampal volumetric decrease in patients with MDD for at least 2 years or at least 2 episodes, where the number of depressive episodes correlated with total hippocampal volume. This correlation was found in children, middle-aged and older adults, whereas young adults with MDD showed no volumetric difference compared to controls. The authors present two possible explanations for this deviation; that young adults may experience less burden of the illness compared to children and older patients, or that young adulthood is a time in life when the hippocampus is not as vulnerable to structural changes as in childhood and mid and older adulthood.

Frodl and O’Keane (2013) propose that changes in the hippocampal structure during childhood, during the hippocampal development, affect the function of the HPA-axis and the cortisol regulation in adult life. In combination with stress exposure further on in life is
reduced hippocampus and HPA-hyperactivity induced in childhood believed to increase the risk for depression or other stress-related illnesses in adulthood. In line with this, Vythilingam et al. (2002) hypothesized that MDD patients with a history of abuse early in life would have smaller hippocampal volumes compared to subjects without such experience, with or without MDD. The hypothesis was confirmed in the study where female inpatients with experience of early childhood abuse occurring at least once a month for a year have smaller left hippocampus compared to both patients and healthy controls without such experience. The authors propose that reduced hippocampus in adulthood may be a result of childhood trauma, or a combination of adverse factors. The authors speculate further about an interaction of factors to be necessary to result in decreased hippocampus in patients with MDD, which they call the combined insult hypothesis (Vythilingam et al., 2004). A combination of elevated levels of cortisol, adverse experiences such as childhood trauma or chronic stress, aging etc. may have additive effects on decreased hippocampal volume in patients with MDD.

Burt, Zembar, and Niederehe (1995) analyzed 148 memory studies to explore the relationship between MDD and memory function. The results showed mild to moderate impaired recall and recognition memory in MDD patients over 18 years old. Another observed pattern was that subjects who were older or suffered from more severe forms of depression showed greater memory impairment than younger or less severely depressed subjects. The authors propose that this pattern might be related to age at the point of onset of MDD rather than actual age of subject, and that early onset or duration may be a more relevant predictor of impaired memory in MDD. However, when MacQueen and colleagues (2003) examined the relationship between duration of MDD and hippocampal memory function in young and middle-aged adults, they found impairments to be present independent of duration. They conducted a study with participants in three groups; patients in their first depressive episode, patients with a history of multiple episodes and healthy subjects in young
and middle adulthood. Memory was assessed through a questionnaire, a recollection memory task, and a computerized task with the aim to measure hippocampus-dependent memory. The cognitive failures questionnaire examines the subjective experience of memory impairment, whereas the two tasks examine hippocampus-dependent memory performance. Both groups of patients reported high self-experienced memory impairments compared to controls, as well as showed impaired hippocampus-dependent memory performance, with no difference between the two groups, pointing to a decline in memory appearing already in the first depressive episode without accelerating in this study. In relation to volumetric decline, the association between duration of MDD and hippocampal reduction was evident, patients with a history of at least two depressive episodes showed hippocampal reduction whereas the first episode subjects did not. The authors propose a quite rapid hippocampal degeneration to occur after the first episode but in the early course of illness, to gradually slow down in prolonged depression.

Impaired hippocampus-dependent memory is found to correlate with altered hippocampal activity in patients with MDD compared with healthy controls, both in encoding and retrieval of memory (Dietsche et al., 2014; Milne, MacQueen, & Hall, 2011). Milne and colleagues (2011) used fMRI to examine hippocampal activity in patients with an extensive history of MDD, at least 3 depressive episodes or 5 years of illness, during a recollection memory task. MDD patients showed significantly impaired recollection memory performance associated with decreased activity in the right hippocampus compared to in healthy controls, suggesting that reduced recall memory function correlates with attenuated hippocampal engagement in MDD (Milne et al., 2011). To assess the neural correlates of encoding of hippocampus-dependent memory in patients with MDD, Dietsche et al. (2014) also used fMRI, to measure brain activity while subjects conducted a memory task where they were supposed to remember pictures of faces. In contrast to healthy controls, MDD patients showed
decreased hippocampal activity during encoding. The level of hippocampal activity during encoding predicted the performance outcome for healthy controls whereas this relationship was not observed in MDD, suggesting that the hippocampal function in encoding is altered in MDD patients (Dietsche et al., 2014).

**Hippocampus and Physical Exercise**

Research on the relationship between physical exercise and the hippocampus focuses primarily on aerobic exercise (Hillman et al., 2008), and the definition of physical exercise is a specified, planned and repetitive form of physical activity with the aim to improve or maintain physical fitness (Caspersen, Powell, & Christenson, 1985). Physical fitness, in turn, is defined as various health- or skill-related attributes, and in the context of exercise and the human hippocampus, physical fitness commonly refers to aerobic fitness, which is measured in maximal oxygen consumption (VO\textsubscript{2} max).

**Aerobic exercise.** Research on exercise-induced volumetric changes in the hippocampus has initially been studied in animals where running has been linked to increased neurogenesis in the hippocampus, specifically in the dentate gyrus (van Praag, 2008). The exercise-induced neurogenesis correlates with several mechanisms. In a study in running mice, it was found to correlate with increased cerebral blood volume (CBV) in the dentate gyrus, suggesting that changes in CBV in the region is a measure of exercise-induced neurogenesis (Pereira et al., 2007). A study in voluntary running rats observed increased neurogenesis to correlate with regionally higher levels of BDNF in the dentate gyrus compared with controls (Farmer et al., 2004). Stranahan et al. (2009) also found exercise-induced neurogenesis to increase hippocampal BDNF levels in mice, as well as the density of dendritic spines in the hippocampus.
In addition to increased neurogenesis, van Praag, Christie, Seinowski, and Gage (1999) found voluntary running mice to increase cell proliferation, and to show functional improvements in spatial learning and memory compared to sedentary controls. Mice who had free access to running wheels for 2 to 4 months performed better in a *Morris water maze*, a spatial learning task where the mouse is put in a water container to find a platform located 1 cm below the surface somewhere in the container. The mice were inserted 2 to 4 times a day for 6 days in a row in 6 different starting points, and spatial learning and memory was measured in how fast they could find their way to the platform. Van Praag et al. (1999) imply that the increased neurogenesis and cell proliferation is involved in functional improvements of hippocampus-dependent spatial memory.

Erickson et al. (2011) designed a 12-month long aerobic exercise program to examine if aerobic exercise would provide similar beneficial effects on human hippocampal volume and spatial memory in older adults. First, the exercise intervention improved level of aerobic fitness. Structurally, the improved aerobic fitness correlated significantly with increased anterior hippocampal volume bilaterally over time, compared to a stretching control group which demonstrated a corresponding volumetric decrease instead, in line with normal age-related decline. After the intervention, the anterior hippocampus increased by approximately 2.0% compared to the control group’s decrease of approximately 1.4%, while the posterior hippocampus showed no significant alterations in either the exercise group or the control group. Erickson and colleagues discuss changes in levels of BDNF as the underlying mechanism to the exercise-induced increase in hippocampal volume since greater elicits in the level of BDNF correlated with the volumetric increase in the exercise group. Functionally, both groups performed better in a spatial memory task after 12 months. Although the exercising older adults did not show greater improvements than the control group, there was a correlation between hippocampal volume and spatial memory performance. Therefore, the
authors imply that aerobic exercise results in elicited levels of BDNF, associated with increased anterior hippocampal volume, and that larger hippocampus is associated with improved spatial memory. With a similar aim, Jonasson et al. (2017) conducted a comparably shorter 6-month aerobic exercise intervention study on sedentary older adults as well, examining participants’ changes in brain structures and cognitive functions before and after the intervention. This study also found hippocampal volume to correlate with improved aerobic fitness over time, replicating the results of Erickson et al. (2011). Unlike Erickson and colleagues who measured hippocampus-related memory in a spatial memory task, Jonasson and colleagues measured it in three verbal episodic memory tasks. Functionally, hippocampal volume predicted verbal episodic memory performance at baseline, but not over time in this study. The authors discuss that this absence of correlation may be linked to increased neurogenesis where newborn cells may not have become functionally incorporated yet, or that spatial memory tasks are more sensitive to structural changes in the hippocampus, compared to verbal memory tasks.

Pereira et al. (2007) conducted a 3-month aerobic exercise intervention which also induced aerobic fitness and structural changes in the hippocampus, this time in young and middle-aged adults. They found exercise to induce selectively increased CBV in the dentate gyrus over time, which they interpret as an indication of increased neurogenesis, thus increased volume, in this particular region. Functionally, they measured hippocampus-dependent memory through verbal episodic memory in a free recall task before and after the intervention, but Pereira and colleagues did not find the structural changes to be associated with functional values in episodic memory either. Thomas et al. (2016) found exercise-mediated changes in hippocampal volume to be non-permanent. As Pereira et al., they did also study sedentary young and middle-aged adults but during a 6-week aerobic exercise intervention, to investigate if such a short time period of exercise would increase hippocampal
volume. Indeed, post-intervention measures demonstrated a significant correlation between physical exercise, aerobic fitness and volume in the anterior hippocampus after only 6 weeks of aerobic exercise. Interestingly, Thomas and colleagues also concluded that these effects were non-permanent since without further regular aerobic exercise during the six weeks between the post-intervention measure and the follow-up measure, the volume of hippocampus returned to baseline. The authors did not observe increased cerebral blood volume (CBV) after the intervention, but they did find support in favor of an exercise-induced increase in myelin as the possible explanation to volumetric change in the hippocampus. The authors speculate that the intervention might have been too short to elicit increases in CBV in the dentate gyrus, as Pereira and colleagues observed in their 3-month long intervention. Thomas et al. assessed hippocampus-dependent function through contextual memory in a list-learning task, and as Jonasson et al. (2017) and Pereira et al. (2007), they did not find evidence for exercise-induced improvements in verbal episodic memory. Thomas et al. did also measure hippocampus-dependent function through a spatial memory task, without significant improvements after the intervention, in contrast to Erickson et al. (2011) who observed exercise-induced improvements in spatial memory. Thomas and colleagues put forward the short duration, the choice of measurement tasks, and the age of the subjects as possible reasons for lack of support of functional changes and propose that age-related cognitive decline in older adults may enable exercise to induce recovery of memory function rather than to improve it.

These presented studies have demonstrated that aerobic exercise interventions of various lengths clearly correlate with improved aerobic fitness as well as hippocampal volumetric increases. However, they vary in the specificity of hippocampal changes. Firth and colleagues (2018) conducted a meta-analysis on 14 studies to examine the effects of aerobic exercise on human hippocampal volume in clinical and non-clinical subjects. They found the
volumetric effects to differ laterally, with a significant increase in the left hippocampus compared to controls. Firth and colleagues claim that the effects of aerobic exercise in healthy older adults attenuate age-related hippocampal deterioration, rather than to actually increase its volume. This means that control groups showed neuronal loss, whereas exercise groups showed retained neuronal mass in the hippocampus. Firth et al. suggest aerobic exercise to increase the level of BDNF in the hippocampus, thus increasing neurogenesis in the region. The authors conclude that the length, frequency, and intensity of exercise vary considerably across the studies analyzed, making it hard to distinguish the most important factors of exercise interventions involved in hippocampal volume.

Chaddock et al. (2010) studied the relationship between aerobic fitness levels and hippocampal volume and function in preadolescent children. Aerobic fitness assessed at one time was found to correlate with both volume and function, because children with high aerobic fitness level had larger bilateral hippocampal volumes and performed better in a relational memory task but not in a non-hippocampus-dependent memory task compared to children with low aerobic fitness. Additionally, the size of hippocampus correlated with relational memory performance. Hayes and colleagues (2015) suggest that exercise-related effects on hippocampal function are associated with age. They observed physical activity to be positively correlated with improved episodic memory in older adults but not in younger adults. In this study, physical activity was defined as total number of steps, and episodic memory performance was found to improve in a visual memory task and a face-name relational memory task, but not in a verbal episodic memory task.

Roig, Norbrandt, Geertsen, and Nielsen (2013) analyzed 41 papers on aerobic interventions and found the intervention design to be involved in the effects on memory performance. They did not distinguish long-term memory in episodic versus semantic memory, however, they discuss that the effects on memory induced by aerobic exercise seem
to differ depending on whether the exercise is acute or long-term. Acute exercise refers to a single session, whereas long-term exercise refers to several sessions during a period of weeks to months. Regarding improvements in long-term memory performance, they found acute exercise to have moderate to large effects, in contrast to long-term exercise that showed no significant associations to long-term memory improvements. The authors propose that acute exercise affects memory in a way that facilitates the process of encoding and consolidation during a certain time period induced by exercise, and in that way enhances the consolidation into long-term memory. Although long-term exercise interventions did not show significant improvements in long-term memory per se, they seem to provide favorable conditions for memory processing. Roig et al. believe that long-term and acute exercise have complementing effects improving long-term memory.

**Strength exercise.** Strength exercise, or resistance exercise as it is also called, is a planned and repetitive form of activation of muscle groups with external resistance (e.g. weights or machines) with the aim to improve or maintain physical fitness (Kim, Shin, Hong, & Kim, 2017; Caspersen et al., 1985). As mentioned, most research on the relationship between the human hippocampus and physical exercise focus on aerobic exercise, but a few studies on strength training have been conducted as well (Kim et al., 2017). In a 6-month long strength exercise program, Kim and colleagues (2017) evaluated its effects on functional fitness and hippocampal volume in older women. Functional fitness was defined as the ability to engage in everyday activities and assessed through several tests measuring body strength, flexibility, balance, and aerobic endurance. Strength exercise was found to correlate with improved functional fitness as well as with significant bilateral increase in the hippocampal volume, whereas the control group instead showed a decrease in line with age-related decline. Kim and colleagues suggest the theory of increased neurogenesis in the hippocampus due to
increased cerebral blood flow as a possible explanation for the volumetric increase. The authors propose that strength exercise is beneficial in that it may reduce age-related hippocampal atrophy, similar to what has been associated with aerobic exercise. Best, Chiu, Liang Hsu, Nagamatsu, and Liu-Ambrose (2015) is another research group who have investigated the effects of strength exercise on brain volume in older women, in relation to a 12-month intervention. The participants were divided into three groups; two strength exercise groups, one which exercised once a week, and the other twice a week, and one active control group following a balance and toning program twice a week. In contrast to Kim and colleagues’ results, Best and colleagues (2015) found none of the strength exercise groups to increase in hippocampal volume.

Animal research has also provided mixed results regarding the relationship between strength exercise and hippocampal plasticity. Novaes Gomes et al. (2014) found rats, after 4 weeks of strength exercise on a vertical ladder, to have increased cell proliferation in the hippocampus. In contrast, Nokia and collaborators (2016) conducted a similar study on rats which after 6 to 8 weeks of strength exercise on a vertical ladder showed no support for strength exercise to be associated with increased neurogenesis in the hippocampus. Park et al. (2005) suggest that variations in the relationship between strength exercise and hippocampal volume relate to the intensity of exercise. The authors found young rats in a light-intensity exercise group to show increased cell proliferation in the dentate gyrus, whereas those in the heavy-intensity exercise group showed decreased cell proliferation. Additionally, the heavy-intensity group showed a decrease in number of glucocorticoid receptors in the hippocampus after the intervention, which was observed in neither the light-intensity group nor the control group. This lead the authors to suggest that heavy-intensity exercise may induce a stress response, thus also stress-related decrease in cell proliferation and glucocorticoid receptors in the region. Functionally, has animal research found support for strength exercise to elicit
enhanced spatial memory (Cassilhas et al., 2012). In a study comparing the effects of 8 weeks of strength exercise versus aerobic exercise on spatial memory in rats, strength exercise was executed on a vertical ladder and aerobic exercise on a treadmill. Spatial memory assessed in a Morris water maze task improved in both exercise groups compared to the control group, indicating that strength exercise is associated with spatial memory improvements similar to those induced by aerobic exercise. Interestingly, strength exercise correlated positively with levels of insulin-like growth factor 1 (IGF-1) in the hippocampus, while the aerobic exercise group showed higher levels of BDNF in the region. The authors mean that the results of this study indicate that strength exercise and aerobic exercise both improve spatial memory, but that it is mediated by the levels of two distinct growth factors related to each type of exercise. Both IGF-1 and BDNF are growth factors involved in adult hippocampal neurogenesis and cell survival, leading the authors to speculate in that the observed strength exercise-induced improvements in hippocampus-dependent spatial memory may be associated with strength exercise-induced changes in the hippocampal volume as well (Cassilhas et al., 2012).

In humans, older adults participating in a 6-month strength exercise intervention have shown improvements in hippocampus-dependent visuo-spatial memory (Cassilhas et al., 2007). The aim of the study was to assess the effects of moderate- contra high-intensity strength exercise on cognitive functions in older adults where both exercise groups trained three times a week. The design of the sessions was identical except for the intensity (i.e. load) where the moderate-intensity group trained with loads of 50 % of their maximum capacity in one repetition, whereas the high-intensity group trained with 80 % of their maximum capacity. The visuo-spatial memory assessment required the participants to reproduce a complex figure of lines twice, first by drawing a copy of the figure and then by drawing after recollecting the figure from memory. Regardless of intensity, strength exercise was associated with improved memory performance compared to controls in this study. In addition, both
exercise groups showed significantly increased levels of IGF-1 after the intervention compared to the control group, however, neither of them showed increases in cerebral blood flow as was expected. The authors discuss underlying mechanisms in terms of growth factors. The association between higher concentrations of IGF-1 and improved visuo-spatial memory in both exercise groups but not in the control group indicate that strength exercise induces elevated levels of IGF-1, which in turn correlate with improved hippocampus-dependent visuo-spatial memory (Cassilhas et al., 2007).

Loprinzi, Frith, and Edwards (2018) state that the relationship between strength exercise and episodic memory in humans is a novel research topic since when they reviewed the relationship between strength exercise and episodic memory they found only eight publications on the subject, where seven of them were published between 2012 and 2017, including both clinical and non-clinical subjects. Loprinzi and collaborators concluded that the study results vary extensively and that the support for strength exercise-induced improvements in episodic memory in humans is very limited. Best et al. (2015) reported mixed results about the effect of strength exercise on hippocampus-dependent contextual memory. Cognitive functions as well as brain volume were assessed at three times; before, after, and one year after the 12-month intervention. Memory was measured in a list-learning task and none of the groups showed improved memory performance immediately after the intervention, however, the strength exercise group exercising twice a week showed improvements in memory performance in the 1-year follow-up assessment, in contrast to the once-a-week group and the control group.

An interesting observation of strength exercising older adults who experience fewer memory problems was reported by Iuliano et al. (2017). After a 3-month long high-intensity strength exercise intervention, the participants reported improved subjective experience of memory compared to before the intervention. However, the objective measures of episodic
memory performance did not show significant improvements. Memory was measured in a contextual list learning task in addition to a task where the participants were supposed to listen to, remember, and recall a short story. Worth mentioning is that another group followed an aerobic exercise program during the same time period, and they also reported improvements in the subjective experience of memory function, but not in the objective assessments (Iuliano et al., 2017).

**Discussion**

Animal studies have presented substantial support for negative effects of stress on hippocampal volume as well as function (Gould et al., 1997; McEwen, 2007; McKittrick et al., 2000; Sapolsky et al., 1986), and corresponding positive effects in relation to physical exercise (Farmer et al., 2004; Novaes Gomes et al., 2014; Pereira et al., 2007; van Praag et al., 1999; van Praag, 2008). The aim of this essay was to examine whether this pattern also applies to humans by reviewing studies regarding hippocampal volume and function in relation to the experiential factors stress, depression, aerobic exercise, and strength exercise in humans. The human hippocampus is a complex field of research and it is difficult to study underlying mechanisms on a cellular level in humans as is possible in animal research, which is why animal studies have been reviewed as well.

Hippocampus is a brain structure located bilaterally in the medial temporal lobes that is essentially involved in the acquisition and retrieval of episodic and spatial memory. Hippocampus is also established to possess neuroplastic characteristics throughout life, processes that are involved in regulation of hippocampal structure and volume and are sensitive to increasing age as well as to various types of experiential factors (Leuner & Gould, 2010). Age-related hippocampal degeneration is accompanied with functional decline in hippocampus-dependent memory, and certain experiential factors are found to accelerate the
normal age-related decline, whereas other experiential factors attenuate it (Doxey & Kirwan, 2015; Leuner & Gould, 2010). In the following discussion, the effects of the experiential factors stress and depression on hippocampal volume will first be considered, with emphasis on the reviewed aspects of cortisol, duration, sex differences, and vulnerability related to age, HPA-hyperactivity, childhood trauma and combinations of adverse factors. Second, the associations between aerobic as well as strength exercise and hippocampal volume will be looked upon, mainly focusing on region-specific differences in exercise-induced hippocampal volumetric increase and the potential importance of intensity in strength exercise. Next, the negative and positive volumetric effects of the reviewed experiential factors will be considered from the view of whether physical exercise may prevent, attenuate or reverse the effects of stress and depression, and lastly, the functional values of the experience-induced volumetric changes will be discussed.

Regarding the findings on stress and depression and its relation to hippocampal volume, extreme or prolonged exposure to stress in humans is, as well as major depressive disorder (MDD), associated with hypersecretion of the glucocorticoid cortisol (Lupien et al., 1998; Pariante & Lightman, 2008), a human stress hormone that in excessive concentrations is associated with degenerative effects on the hippocampal volume. This fits with the findings of a negative correlation between stress-induced cortisol levels and hippocampal volume (Lupien et al., 1998), as well as with the negative correlation between duration of MDD and hippocampal volume (MacQueen et al., 2003; Colla et al., 2007). The research on negative effects of stress and depression in adulthood is extensive, especially in older adults, in contrast to research in children. Besides, children studies reviewed in this essay have presented contradicting results. For instance, Wiedenmayer et al. (2006) did not find preadolescent children with high cortisol levels to have smaller hippocampus than those with low levels, but Colla et al. (2007) observed children’s hippocampal volume to correlate
negatively with the duration of MDD, which in turn is correlated with increased cortisol levels. Wiedenmayer et al. assessed the children’s cortisol level at one time in the morning, but since cortisol levels vary during the day (Smyth et al., 2013) this is an aspect of the study design that may affect the results. Additionally, Knoops et al. (2010) found evening cortisol levels but not morning levels to correlate with hippocampal volumes, and although this was found in older subjects, it cannot be ruled out that it may also apply to children, which also suggests that Wiedenmayer et al. results are inconclusive. Therefore, it would be of interest to study the relationship of cortisol levels in children and hippocampal volumes based on multiple measures over the day in future studies.

Stress-related hippocampal degeneration is evident in humans and so are MDD-related hippocampal changes, at least to some extent, although additional potentially involved factors need to be further explored. Worthy of discussion is the relationship between childhood experiences and dysfunctional HPA-axis in adulthood (Frodl & O’Keane, 2013; Vythilingam et al., 2002), because even though human studies have presented consistent findings of stress-induced volumetric reductions in the hippocampus, and several studies and meta-analyses have reported a significant correlation between duration of MDD and decline in hippocampal volumes (Colla et al., 2007; McKinnon et al., 2009; MacQueen et al., 2003), experts do not fully agree on the relationship between MDD and smaller hippocampal volumes. There are studies that argue for that multiple adverse experiences are necessary for hippocampal volumes to be reduced in patients with MDD, and not only hypersecretion of cortisol due to dysregulation of the HPA-axis (Frodl & O’Keane, 2013; Vythilingam et al., 2002; Vythilingam et al., 2004). For instance, Vythilingam et al. (2002) only found smaller hippocampus in patients with MDD if they also had a history of childhood abuse. Since the hippocampal structure is sensitive during the developmental period in childhood, Frodl and O’Keane (2013) mean that traumatic and stressful experiences, such as abuse, at this age can
alter the hippocampus in a way that alters the function of the HPA-axis later on in life. In that way, adverse experiences in childhood can result in dysfunctional HPA-regulation and heightened cortisol levels in response to psychosocial stress (Frodl & O'Keane, 2013). In combination with stress-inducing factors, this dysregulation increases the risk of MDD as well as reduced hippocampal volumes not only at that time but also further on in adult life; a theory that could be argued to be compatible with the biopsychosocial model (Engel, 1978).

In addition, Vythilingam et al. (2004) did not find patients with mild to moderate depressive symptoms to have reduced hippocampal volumes, and MacQueen et al. (2003) found that the first depressive episode does not result in volumetric decrease, but later on during the illness does. Based on this, it could be speculated that mild to moderate symptoms as well as first episode patients do not elicit hippocampal degeneration as is seen in severe, prolonged or hospitalized MDD patients, if not in combination with other adverse factors such as childhood trauma, increasing age, stress exposure etc., factors which are related to hippocampal degeneration, increased cortisol levels, and HPA-dysfunction. Another angle on the various results in MDD could be due to sex differences. Most studies are conducted on male subjects because the circadian rhythm of cortisol secretion is not necessarily the same in men and women. For example, women with oral contraceptives show lower levels of cortisol in the morning whereas premenopausal women elicit higher levels in the morning compared to men (Pruessner et al., 1997). The studies conducted by Vythilingam et al. (2002; 2004) which support a need for a combination of adverse experiences to cause hippocampal degeneration in MDD only studied women. In the future, it would be of interest to investigate possible sex differences in relation to the mixed results on hippocampal decrease in relation to MDD.

According to Kuhlmann et al. (2005), stress effects have been mostly studied in men because of the sex differences in relation to cortisol, which means that it cannot be ruled out that there are sex differences in the effects on hippocampus induced by stress, and that further research
would be of interest for the field. Another view on the relationship between cortisol and hippocampal volume is that elicited cortisol levels may not be the final degenerative mechanism. Conrad (2008) suggests that cortisol alters the hippocampus in a reversible way that creates a time window where the hippocampus is more vulnerable to threats that can induce irreversible damage, which could also be further examined as an aspect involved in the inconsistent results in patients with MDD.

To sum up the reviewed research on stress, depression and the hippocampal volume in humans, extreme or prolonged stress exposure and at least prolonged and severe forms of depression, as well as milder forms in combination with adverse factors inducing HPA-dysregulation, are supported to induce an acceleration of the established age-related hippocampal degeneration. In relation to MDD does duration of illness and adverse childhood experiences seem to be two influential aspects when it comes to hippocampal degeneration. Animal studies have found stress to induce volumetric hippocampal degeneration through decreased neurogenesis and cell proliferation (Gould et al., 1997; McEwen, 2007), retracted or simplified dendrites, and reduction of glucocorticoid receptors (McKittrick et al., 2000) selectively in the hippocampus. Since stress and MDD, at least under some conditions, are associated with reductions of hippocampal volume, these changes are plausible to occur also in humans. However, the impact of aspects such as time of day, sex differences, age differences and combinations of factors need to be studied further.

Moving on to the aspects of physical exercise and its effects on hippocampal volume, this essay has examined two types of exercise; aerobic and strength exercise. Both aerobic (Erickson et al., 2011; Firth et al., 2018; Jonasson et al., 2017; Pereira et al., 2007; Thomas et al., 2016) and strength (Kim et al., 2017) exercise have been ascribed beneficial effects on human hippocampal volumes, however there is extensively more research to back up the positive effects of aerobic exercise than of strength exercise. Aerobic exercise studies in
humans in various ages and various length of exercise programs have found exercising people to increase their level of aerobic fitness as well as their hippocampal volumes compared to sedentary as well as active control groups. In animal studies have exercise-induced increases in hippocampal volume been associated with increased neurogenesis, cell proliferation, dendritic branching and cerebral blood volumes (CBV) as well as increased levels of BDNF selectively in the hippocampus. However, experts do not seem to agree on what particular part of the hippocampus that is increased as an effect of aerobic exercise. Since rodents who have been exercising in an enriched environment have been found to increase neurogenesis as well as cell survival in the hippocampus compared to those exercising alone (Thomas et al., 2016), one explanation could be that differences in the results are impacted by variations in the environment of the subjects. It could also be speculated that sedentary humans who start a new habit such as an exercise intervention, are enriched by this experience and that this also may impact the results. Another view on the variations in regions affected is that since it takes time for the newborn neurons in the dentate gyrus to mature and become fully incorporated into the neural circuits of the hippocampus (Jonasson et al., 2017), it may be possible that there is a time sensitive aspect that impacts the observations at measures post-intervention. It may be difficult to control the environment of human subjects as can be done in caged rodents, but it would be of interest to study this further as well as to examine potential variations in relation to time.

Research on strength exercise is, as mentioned, novel and thus quite limited and has yet provided mixed results on strength exercise-induced effects on the hippocampus, in both animals and humans. Kim et al. (2017) did find strength exercise to correlate with hippocampal increase in their intervention study in older women, whereas Best et al. (2015) did not observe such a relationship in their study in older women. Also animal studies have reported mixed results, for instance, Novaes Gomes et al. (2014) observed strength exercising
rats to increase cell proliferation in the hippocampus, whereas Nokia et al. (2016) found no such relationship. Park et al. (2005) bring up that the intensity of strength exercise seems to be involved in whether strength exercise is beneficial in terms of hippocampal volumetric increase or not, where light-intensity was associated with enhanced cell proliferation in the hippocampus, whereas high-intensity showed suppression of cell proliferation as well as a reduction of glucocorticoid receptors in the hippocampus, similar to the effects of stress and depression. This suggests that the intensity of strength exercise is an important factor involved in regulating the effects of strength exercise on the hippocampus, and that conducted in a favorable intensity it may have positive effects, whereas unfavorable intensity may have detrimental effects on the hippocampal volume. It is possible that this correlation applies to the mixed results presented above, because although it is difficult to determine the intensity they used, it is evident that the strength exercise intervention in Kim et al. study was differently designed compared to in Best et al. study. Additionally, Nova Gomes and colleagues’ exercise intervention consisted of comparably lower intensity over 5 days of exercise a week, whereas the intervention conducted by Nokia et al. consisted of 3 days of exercise a week with a comparably higher intensity of resistance, also supporting the intensity to play a part in the hippocampal effects. However, this is speculative and should be interpreted cautiously. Although there is some support for strength exercise to be associated with increases in hippocampal volume in humans, human studies have not supported the negative associations of inhibited cell proliferation and reduced number of glucocorticoid receptors, as suggested by Park et al. (2005). Therefore, it would be of considerable interest to further study the relationship between strength exercise and hippocampal volume in humans, as well as the potential involvement of exercise intensity, and whether very high intensity may have stress-like effects instead. On the other hand, it could be speculated that the observed positive effects open up for the possibility that strength exercise, potentially under favorable
circumstances, may elicit hippocampal increase, as aerobic exercise does. Interestingly, there are studies indicating that the beneficial effects on hippocampal volumes induced by these two forms of physical exercise are mediated through different growth factors that both are related to neurogenesis in the hippocampus, where aerobic exercise-induced increases in hippocampal volume is mediated by BDNF (e.g. Firth et al., 2018), and strength exercise-induced increases in hippocampal volume is pointing towards being mediated by IGF-1 (Trejo, Carro, & Torres-Alemán, 2001).

To summarize the reviewed studies on physical exercise; aerobic exercise induces hippocampal volumetric increase in various ages and in response to interventions of various lengths between 6 weeks up to 12 months. The studies reviewed on strength exercise in humans are few and inconsistent, making it hard to draw conclusions, but there is some support in favor for positive effects, indicating that future research in the area is needed to accept or dismiss strength exercise to have similar effects on the human hippocampus as aerobic exercise does.

In order to consider the negative and positive volumetric effects of the experiential factors stress, depression and physical exercise in relation to each other, it is of importance to clarify that not only do physical exercise effects on hippocampal volume seem to be non-permanent (Thomas et al., 2016), but hippocampal degeneration does not seem to necessarily be permanent either. For instance, patients with severe MDD treated with 2 weeks of repetitive transcranial magnetic stimulation have been observed to significantly increase in hippocampal volume (Hayasaka et al., 2017). Moreover, a 2-year follow-up study observed MDD patients without further depressive episodes to show normalizing hippocampal volume over time, compared to patients with further episodes who kept decreasing (Dohm, Zaremba, Redlich, Grotegerd, & Dannlowski, 2017). The view of hippocampal degeneration to be reversible provides a reason to discuss the mechanisms in the hippocampus during stress,
depression and physical exercise in relation to each other. Since the relationship between increased cortisol levels and decreased hippocampal volumes is found in both animals and humans, it is plausible to believe that neurogenesis, cell proliferation, dendritic remodeling and reduced number of glucocorticoid receptors in the hippocampus that have been found in animals also occur during degeneration in humans. Interestingly, what has been found in animals in relation to exercise-induced hippocampal changes is, in contrast to the effects of stress and depression, increased neurogenesis, cell proliferation and dendritic complexity in the hippocampus. This argues for that the processes that are suppressed in response to stress and MDD may be enhanced in response to physical exercise, especially aerobic, suggesting that physical exercise may prevent stress- or depression-induced hippocampal degeneration. Firth et al. (2018) stated that aerobic exercise has a decelerating effect on age-related hippocampal atrophy, and since excessive cortisol concentrations are related to accelerating age-related hippocampal atrophy, this can be developed further into the suggestion that physical exercise is a lifestyle factor that may also reverse or at least attenuate what is already degenerated due to stress or depression.

Regarding the functional values of stress-, depression-, and physical exercise-induced volumetric changes, the decrease in hippocampal volume has consistently been associated with negative effects also in hippocampus-dependent memory. Stress exposure and increased cortisol levels correlate with impaired hippocampus-dependent spatial (Lupien et al., 1998) and episodic memory (de Quervain et al., 2003; Kuhlmann et al., 2005), which is associated with decreased hippocampal activity during the process of retrieval (de Quervain et al., 2003). Hippocampus-dependent memory impairment has also been consistently observed in MDD patients, from onset (Burt et al., 1995; Dietsche et al., 2014; MacQueen et al., 2003; Milne et al., 2011), which is associated with altered hippocampal activity in encoding and retrieval (Dietsche et al., 2014; Milne et al., 2011). In terms of exercise-induced increases in
hippocampal volume, Firth et al. (2018) suggest that there is lack of support for a direct association with enhanced cognitive functions. Although many of the reviewed physical exercise studies have observed volumetric changes in the hippocampus, and hippocampal volume has been found to correlate with hippocampus-dependent memory (Doxey & Kirwan, 2015; Erickson et al., 2011), far from all of them supported the volumetric changes to have such functional values. Erickson et al. (2011), Chaddock et al. (2010) and Hayes et al. (2015) have provided some support for aerobic exercise to functionally enhance hippocampus-dependent memory performance, whereas Jonasson et al. (2017), Pereira et al. (2007) and Thomas et al. (2016) did not observe such improvements in hippocampus-dependent memory. Cassilhas et al. (2007) have also reported positive effects on hippocampus-dependent memory in response to strength exercise, however, Loprinzi et al. (2018) argue that it is too early to draw conclusions and more research is needed on strength exercise and hippocampus-dependent memory to extend the current indications.

One view is that age may be involved in whether exercise improves hippocampus-dependent memory or not; Hayes and colleagues (2015) observed physical activity to correlate with improvements in an episodic memory task in older adults but not in younger adults. Another view is proposed by Jonasson and colleagues (2017) who measured multiple cognitive functions with several function-specific tasks to examine the relationship between aerobic exercise and cognition in a broader way. The results led them to suggest that aerobic exercise improves cognitive functions generally rather than specifically, and that this could be a reason for why studies on its effects on hippocampus-dependent memory have yielded mixed results. Moreover, physical exercise studies have been conducted in many different ways, indicating that design could be involved in the mixed results. Roig et al. (2013) found the intervention design to be involved in the effects on memory performance in that acute and long-term exercise differed. Since Driscoll et al. (2003) found men to perform better in spatial
navigation compared to women across all ages, even after controlling for hippocampal
volume, it would also be of interest to deepen the understanding of sex differences in
hippocampus-dependent memory, since that may also impact the results.

Another interesting finding is that Iuliano and colleagues (2017) found exercising older
adults to report improved subjective experience of memory, regardless of whether the type of
exercise was strength or aerobic. At the same time, none of the groups showed improvements
in the objective measures of episodic memory. Taking this into account, in combination with
the inconsistent results regarding exercise-induced effects on hippocampus-dependent
memory, it could be argued that cognition is affected broadly rather than generally, as
suggested by Jonasson et al., or that episodic and spatial memory are affected differently, with
spatial memory being enhanced whereas episodic memory is not. It could also be affected by
the choice of assessment tasks to measure hippocampus-dependent memory, where spatial
memory tasks might be more responsive to volumetric changes than episodic memory tasks
are. Since many studies differ in what part of the hippocampus is increased in response to
exercise, and that for example Milne and colleagues (2011) observed parts of the memory
formation process to be associated with specific regions of the hippocampus, this may also be
involved in the inconsistent results of memory improvements. It could be speculated that what
part of the hippocampus that is increased in volume is impacted by e.g. exercise design or
environmental demands, and that the functional values may vary due to this, making it hard to
observe specific effects in episodic or spatial memory. The studies on physical exercise
reviewed in this essay have covered healthy subjects and as Thomas et al. (2016) discuss, it is
possible that the functional effects are more relevant in terms of recovery and not in further
improvement, suggesting that physical exercise attenuates and reverses decline in
hippocampus-dependent memory, rather than to improve it. In line with the inconsistent
results on exercise-related hippocampus-dependent memory improvements, it could be argued
that such functional recovery not only relates to age-related decline, but also to stress- and depression-induced memory impairments.

Based on this review, it could be argued that the volumetric changes in hippocampus induced by stress and exercise observed in animals apply also to humans. Stress, and to some extent also depression, accelerates age-related hippocampal degeneration, whereas physical exercise, aerobic in particular, decelerates atrophy in the aging hippocampus, suggesting that physical exercise is a lifestyle aspect with the capacity to not only prevent, attenuate or reverse age-related decline but also decline induced by stress and depression. Since greater hippocampal volumes are associated with greater hippocampus-dependent memory, and physical exercise induces hippocampal volumetric increases, it could be expected that the experience of hippocampus-dependent memory in daily life also would be affected positively. However, more research is needed to determine how the volumetric changes induced by physical exercise affect related memory functions. Until then, stay grateful for the capacity of remembering your graduation, following your favorite TV-show and being able to be disturbed by your partner not doing the dishes, this night either.
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