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Abstract

As opposed to earlier beliefs, the brain is altering itself throughout an individual's life. The process of functional or structural alterations is referred to as plasticity, and can be induced by several factors such as experience or physical exercise. In this thesis, the research area of experience-dependent plasticity, with focus on exercise-induced plasticity is examined critically. Evidence from a vast array of studies are reviewed and compared in order to find whether physical exercise can induce neural plasticity in the human brain, how it may be beneficial, and what some of the plausible mediators of exercise-induced plasticity are. The findings demonstrated in this thesis suggest that although there are knowledge gaps and limitations in the literature, physical exercise can indeed result in exhibited plasticity as well as being beneficial for the human brain in several ways.

Keywords: Brain plasticity, experience-induced plasticity, beneficial effects.

Contents

Introduction

The human brain is a remarkably complex organ which has been studied for several centuries. Despite the many decades of research conducted on the brain, knowledge about this complex organ is still far from complete. One thing that is known for sure is that the brain possesses the ability to reorganize itself, both structurally and functionally (May, 2011). Throughout most of the 1900s it was widely believed and accepted within the community of neuroscience that the mammalian nervous system became structurally stable after birth (Leuner & Gould, 2010). It has been shown in more recent times however, that the nervous system is not at all hardwired after birth. In addition, it has been shown that the mammalian brain displays plasticity not only during childhood (Moreno et al., 2009), but also during adolescence (Draganski et al., 2004) and even during old age (Erickson et al., 2011). This remarkable function is referred to as *brain plasticity*, and it is a general term for several different forms of changes, or morphological alterations, occurring in the brain, including for example gliogenesis (generation of new glia cells), neurogenesis (generation of new neurons), changes in the structure of dendrites (such as density), axonal growth, myelination, angiogenesis (the growth of blood vessels from the existing vasculature) and synaptogenesis (the formation of synapses) (May, 2011). These changes can occur due to various reasons such as experience (e.g. Fu & Zuo, 2011), learning (e.g. Mårtensson et al., 2012), practicing a skill (e.g. Groussard et al., 2014), exercising (e.g. Van Praag, Christie, Sejnowski, & Gage, 1999) as well as the environment and our surroundings (e.g. Van Praag, Kempermann, & Gage, 2000).

Since plasticity is a general, and quite broad term, it is quite difficult to give a concise definition without considering in some depth what the concept means. There are for example several different types of plasticity (to be discussed later) one must take into

consideration when thinking of plasticity as a concept. In this essay, the author will give a brief overview of plasticity in general before moving on to more specific concepts and categories regarding neural plasticity and exercise.

Generally speaking, plasticity can largely be thought of as either functional or structural. Functional plasticity refers to alterations in the brain, such as synaptic strengths, that do not involve any anatomical changes. Structural plasticity on the other hand refers to alterations in the brain that involves anatomical changes such as changes in synapse- and neuronal cell numbers, the density of axonal fibres, and the branching of axons and dendrites (Butz, Wörgötter, & van Ooyen, 2009). More specifically, structural changes have been found to be related to neurogenesis, changes in the dendritic structures, axonal growth, myelination and synaptogenesis (May, 2011; Will, Dalrymple-Alford, Wolff, & Cassel, 2008). Furthermore, functional changes on a synaptic level are believed to happen within minutes to hour after experience onset, while structural changes are believed to appear later (Sagi et al., 2012). Changes that affect the system's functioning in more indirect ways (e.g., angiogenesis) also count as structural change, while in contrast, transient variations in the states of the system such as action potentials (a process which play an important role in the communication between neurons), sodium influx, potassium outflow, and release of neurotransmitters (chemicals which transmit signals across synapses), do not by themselves count as anatomical changes (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). Lövdén et al. (2010) further suggest that flexibility can occur in the absence of plasticity. For example, when existing neuronal circuits or other functional supplies become enhanced due to more frequent use, such as when an already learned skill is being practiced, but neural structures remain unaltered.

To break it down further, plasticity can be, according to Kolb and Gibb (2014) either experience-dependent, experience-independent or experience-expectant:

Experience-expectant plasticity is described by Kolb and Gibb (2014) to take place mostly during development. In order for certain brain systems to develop properly, they need specific types of experience. For example, within the primary visual cortex, where ocular dominance columns are found and developed, the columns are alternating and helps producing binocular vision by providing us with a mechanism for the inputs of both eyes. An example demonstrating this is the experiment of Wiesel and Hubel (1963), who showed that keeping one eye closed in newly born kittens, makes the open eye expand its territory which results in shrinkage of the closed eyes column. When the closed eye is eventually opened, the vision becomes compromised.

Experience-independent plasticity is also described by Kolb and Gibb (2014) to be a relatively developmental process, and the researchers state that during development, the many connections of the nervous system is not specified from the beginning. Instead the brain produces a rough structure initially, with an overproduction of neurons and later on connections between the neurons depending on what connections are more frequently used due to internal and external stimuli (Kolb & Gibb, 2014). The neurons firing more frequently together will form stronger connections, and the neurons which are not being frequently used together die out eventually (Kolb & Gibb, 2014). In other words: the brain produces a surplus of neurons during development but as we develop, the less useful neurons dies out, resulting in the surplus of neurons to eventually decrease into a more stable amount.

Experience-dependent plasticity is described by Kolb and Gibb (2014) as changes in the brain that are needed in order to alter neuronal ensembles in the brain that are already existing, thus this type of plasticity is not mainly developmental.

Although all types of plasticity are important areas of research in order to fully understand the concept of plasticity, going into detail and describing all of them would be outside the scope of this essay. Therefore, the main aim of this essay will be to focus on experience-dependent plasticity, followed by an even more specific focus on experience-dependent plasticity induced by exercise and how it may affect the brain positively. Two suggested mediators of exercise-induced plasticity, brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1), which are different types of protein, are discussed as well. The brain area being mostly discussed in this thesis is the hippocampus, which is a formation considered highly plastic and to be involved in functions regarding memory (more information in an upcoming section. Thus, the ultimate goal of this thesis is to conduct a general overview of the relation between brain plasticity and exercise, how exercise-induced plasticity can be beneficial for individuals, and what some of the potential mediators are.

Experience-dependent plasticity

The concept of experience-dependent plasticity is, even though a category within the concept of plasticity itself, a rather broad concept and this type of plasticity can be induced by a vast array of experiences. Experience-dependent plasticity is a good way of studying adult brain plasticity in relation to learning, skill-enhancement and adaptation (Guerra-Carrillo, Mackey, & Bunge, 2014). Kolb and Gibb (2014) stated that virtually every experience possesses the capacity to induce alterations in the brain and in behaviour (at least to a certain extent), experiences and factors such as sensory and motor experience, task learning, psychoactive drugs, a certain diet, engaging in exercise, being exposed to stress, natural aging, prenatal experiences and neurotrophic factors (a family of molecules being typically beneficial for neurons, involving for example BDNF).

A good example of experience-induced plasticity comes from the results reported by Maguire et al. (2000), in which it was reported that taxi drivers in London have significantly greater volume in the posterior hippocampus compared to non-drivers. The researchers suggest that the volume increase in this case is derived from navigational skills. Hence, the general idea of experience-dependent plasticity is that areas of the brain being important and active when engaging in certain activities should alter in relation to the amount of time spent- or improvement displayed in- the specific activity that the individual is engaged in (Lövdén, Wenger, Mårtensson, Lindenberger, & Bäckman, 2013). For example, the brain areas being more highly activated and engaged while an individual is engaged in, for example, some form of learning or practicing of a specific skill (e.g. playing a musical instrument), should display alterations as the individual learns and becomes more skilled at playing that specific instrument (May, 2011). Furthermore, May (2011) claims that in many cases, plasticity is derived from learning or practicing which result in adaptive structural or functional modifications, but other phenomenon such as damage to the nervous system or even amputation of a limb can also cause reorganizations of the brain which may sometimes be maladaptive.

Among the earliest research regarding experience-dependent plasticity involved studying how an enriched environment could affect the brain's cortical structure. Over 50 years ago, Rosenzweig, Krech, Bennett and Zolman (1962) performed an experiment on mice in which they demonstrated that the brains of mice living in an enriched environment differed from the brains of mice who lived in more normal laboratory conditions. Since then, there has been an ample of studies on various experiences, forms of training and environments and how they result in plasticity. However, plasticity has been reported to be exhibited differently depending on what type of experience is inducing the plasticity, and in terms of affected cortical regions as well as the total amount of observed plasticity (Lövdén et al., 2013).

Several studies in the existing literature have reported different results regarding for example increases in volume and weight in various different regions of the brain due to interventions such as exercise, motor skill learning and enriched environments (see Rosenzweig, Bennett, & Diamond, 1972; Rosenzweig & Bennett, 1996; Anderson, Eckburg, & Relucio, 2002; Díaz, Pinto-Hamuy, & Fernández, 1994; Black, Isaacs, Anderson, Alcantara, & Greenough, 1990)

A change in total brain cortical weight indicates some sort of alteration in the brain, and the underlying factors are believed to be, at least in general, activity-specific and area-specific (Lövdén et al., 2013). For example, Mårtensson et al. (2012) found that after high level intensity of learning a foreign language, mostly left-lateralized alterations in cortical thickness of the inferior frontal gyrus, the mid-posterior superior temporal gyrus and dorsal middle frontal gyrus were observed. Draganski et al. (2004) reported transient bilateral expansion in grey matter in the mid-temporal area and in the left posterior intra-parietal sulcus, areas known as task-relevant, in subjects who learned how to juggle over a three-month course compared to a control group. Furthermore, Lerch et al. (2011) found that mice training for five days in a cued version of the Morris water maze displayed volume growth in striatum, whereas mice training on a spatial variant of the maze displayed hippocampal growth.

It seems obvious that different types of experiences result in different types of cortical weight and growth, but what are the most likely underlying factors? Lövdén et al. (2013) states that one probable candidate is synaptic remodelling for alterations in volume due to experience, but Johansen-Berg, Baptista and Thomas (2012) claims that it is quite unlikely for synaptic remodelling alone to result in volume increases. An increase in synapses however, and changes in dendritic structure due to enriched surroundings and learning of

skills might be followed by growth of capillaries and glia cells (Anderson et al., 1994; Anderson et al., 2004). Thus, one single type of alteration in the brain, seeming not to be sufficient to induce any remarkable structural changes, might be accompanied by other alterations. Indeed, Lövdén et al. (2013) states that specific brain changes are unlikely to occur by themselves. The research team suggest that plasticity of regional brain volume is more likely to mirror a wider array of changes in for example dendritic branching, synapses, numbers and size of cells, and also capillaries.

There have been different models of plasticity proposed over the years by researchers within the field and two of them are evaluated below.

The *supply-demand model* is highlighted in the theoretical framework for cognitive plasticity by Lövdén et al. (2010), and it suggests that plasticity occurs due to a mismatch between the structural and functional capacity of the existing neural structures and the present environmental demands. Lövdén et al. (2010) claim that there are two types of mismatch, the first type occurs when the demands of the environment exceed the present capacity of the brain, thus the environmental demands are too challenging for the brains current state to handle. The second type is simply the other way around, i.e. when the present capacity of the brain is higher than the demands of the environment, thus the environmental demands are not challenging enough to stimulate the brain. A good example to demonstrate the idea of the supply-demand model is the study conducted by Draganski et al. (2004), in which 12 subjects (n=12) participated in a three-month long course of learning how to juggle. Using whole brain magnetic resonance imaging (MRI, an imaging technique used to form images of the brain anatomy and processes), the brains of all 12 subjects as well as the brains of a control group (n= 12) were scanned at 3 separate times: before the course started, during the learning period when all the subjects were considered to have reached “fluency” in juggling, and

finally three months after the course was over (during these three months the subjects did not engage in any juggling). Draganski et al. (2004) reported that there were no significant regional differences between subjects and controls before the juggling course started, but at the second MRI scan the jugglers demonstrated a significant transient bilateral expansion in grey matter in the mid-temporal area and in the left posterior intra-parietal sulcus. Interestingly, Draganski and colleagues reported that at the third scan, 3 months after the course, the expansion of grey matter found in the jugglers had decreased and almost returned to base line. The study of Draganski et al. (2004) is thus consistent with the supply-demand model of plasticity presented by Lövdén et al. (2010) in both ways. When the subjects started the course of learning how to juggle from scratch, the environmental demands were higher than the capacity of the subject's brains and plasticity (expansion of grey matter) occurred. After the course, the capacity of each subject had increased, but since their environment however did not contain any juggling or any challenge of similar type for three months, thus the capacity of their brains were higher than the environmental demands and their brains did not receive any stimulation in form of juggling, leading to the initial grey matter expansion to decrease back to (almost) baseline. Even though the supply-demand model seems quite in line with Draganski and collegues study, Lövdén et al. (2010) points out that the model cannot completely explain and predict the manifestation of experience-dependent plasticity due to various reasons. For example, it seems as if all subjects cannot react to- and fully close mismatch gaps (Lövdén et al., 2010) and furthermore, Mercado (2008) demonstrated that due to different genetic makeup, people differ when it comes to predisposition for plasticity, meaning that even though subjects engage in the exact same activity, or are exposed to the exact same environment, they may exhibit plasticity differently from one another.

In order to explain and understand this phenomenon better, additional models needs to be taken into consideration. The additional model, stated by Reed et al. (2011), is

referred to as the *expansion-renormalization model*. The expansion-renormalization model of cortical plasticity suggests that cortical plasticity occurs in order to identify the minimum number of neurons needed in order to carry out a given task (Reed et al., 2011). Within this model, it is believed that there is an initial cortical map extension during which a surplus of neural circuits (the expansion phase) in multiple brain regions that respond to task stimuli are generated. Reed et al. (2011) suggest that later neuronal processes can benefit from the initial surplus by being able to select the most efficient circuitries and get rid of the circuitries redeemed as not useful enough (the renormalization phase). Reed et al. (2011) furthermore suggest that it is during the stage of selecting the most efficient circuitries that learning is achieved, and when organisms preferentially associate these neural responses with the appropriate behavioural responses. Using the example study of Draganski et al. (2004) again, the reported results of increased grey matter could also be a result of the expansion phase, and the decrease after 3 months could be a result of the renormalization phase. Thus, both the supply-demand model, as well as the expansion-renormalization model seem rather valid in terms of explaining the onset of this type of plasticity.

Differences in exhibited plasticity

A vast array of studies indicates that plasticity is normally exhibited differently depending on several factors such as individuals and activity, and other factors such as time course and the amount of displayed plasticity. For example, synaptogenesis and associated changes in dendritic spines can be formed over periods of minutes to hours in both animals and humans, whereas neurogenesis may take days to weeks (Fu & Zuo, 2011; Johansen-Berg et al., 2012; Sagi et al., 2012; Zhao, Deng, & Gage, 2008). Plasticity have furthermore been found to be exhibited differently, even though test subjects have been exposed to the exact same environment and experiences. For example, Prakash, Ambrosio, Alguacil and Del Olmo

(2009) performed a study on two different strains of rats. The two different strains were injected with either saline or cocaine chlorhydrate for seven consecutive days, the goal being to compare the effects of passive chronic cocaine administration on long-term potentiation (LTP), which refers to strengthening of synapses, in two different strains of rats. Prakash et al. (2009) report that LTP depotentiation did not occur in one strain of the rats regardless of the chronic treatment considered, as opposed to the other strain which did, indicating a difference in exhibited plasticity between the strains even in the absence of cocaine. Thus, results of Prakash et al. (2009) suggest that chronic cocaine exposure may alter hippocampal synaptic plasticity inhibiting the process of depotentiation in only in some strains of rats, meaning that although animals of the same species were injected with the same preparation as well as same amount, the exhibited plasticity differed significantly. Furthermore, these observations also support the idea that the genetic background of subjects could underlie differences of hippocampal synaptic plasticity involved in the vulnerability to drugs (Prakash et al., 2009).

Another study by Quallo et al. (2009) was conducted in order to analyse structural MRI images of the brains of three macaque monkeys learning how to use a rake in order to retrieve food. During a period of 21 days during which the monkeys underwent intensive training of using a given rake to retrieve food items, the researchers performed structural MRI scans of the monkey's brains at three different points: before, during and after the period of 21 days. Quallo et al. (2009) reported findings of significant, but differently displayed grey matter volume increases in two cortical areas of the monkey's brains: the right superior temporal sulcus and the right secondary somatosensory area. In convergence with the findings of Prakash et al. (2009), Quallo and colleagues reported that plasticity was exhibited differently among the 3 monkeys. The monkey displaying the fastest learning curve also exhibited the earliest increase in grey matter (within six days), compared to another

monkey with a flatter learning curve (Quallo et al., 2009). Thus, increases of grey matter were found in the brains of both monkeys, but the onset correlated with speed of learning. Furthermore, one of the monkeys displayed increases in grey matter volume in STS and SII by a total of 13% and 14% whilst one of the other monkeys displayed lesser increases, a total of 10% and 13% (Quallo et al., 2009). Another interesting finding reported by the researchers, converging with the supply-demand model by Lövdén et al. (2010) as well as the expansion-renormalization model by Reed et al. (2011), was that despite continued training, grey matter volume decreased after it peaked. In other words, post training, the volume was bigger than before the training started, but total volume decreased compared to when total volume peaked.

The time course of plasticity and when it is first displayed is an additional variable that tends to vary to quite a great extent when observing displayed plasticity. In the study conducted by Quallo et al. (2009) reviewed above, structural plasticity in form of increased grey matter volume was observable after six days at the earliest. Lerch et al. (2011) who performed a study on rats receiving training in the Morris water maze found that merely five days were enough in order for the researchers to observe and locate increases of regional grey matter volume in the brains of the trained mice.

Lövdén et al. (2013) claims that out of all studies (available at that present time) using comparison of experimental and control groups in order to find observable cortical plasticity induced by some sort of experience, the study reporting the fastest observable cortical alterations was a study conducted by Takeuchi et al. (2011). This study by Takeuchi et al. (2011) was conducted in order to find out whether sections of working memory training could induce observable grey matter morphology in the brains of human subjects. Using voxel-based morphometry (VBM), Takeuchi et al. (2011) found that engaging in 5 days of 4

hour sessions of training working memory in form of mental mathematics (multiplication and addition) training, resulted in trends for *decreases* of grey matter in fronto-parietal areas as well as the superior temporal gyrus for the experimental group. This study and the observed results are interesting because training resulted in volume decreases. The underlying reason for this phenomenon of cortical thinning in relation to improving cognitive functions is, suggested by Takeuchi et al. (2011), the process of selective elimination of synapses. The researchers of this study furthermore state that this phenomenon has been gaining growing evidence and refer to Kanai and Rees (2011) for a review. Another interesting part of Takeuchi and colleagues study is the fact that human subjects were used, and only five days of training sessions were enough to observe cortical alterations, in comparison to e.g. Draganski et al. (2004) who reported that human subjects learning how to juggle displayed plasticity after a period of three months.

The studies mentioned above all suggest that plasticity is flexible and varies depending on a vast array of factors such as time course, activity, cortical areas, individuals and species. The previous sections have discussed, and given a general overview of plasticity and experience-dependent plasticity to provide some insight to the topic of brain plasticity. The following sections will focus on a more specific type of experience-dependent plasticity: namely experience-dependent plasticity induced by physical exercise, and how it can be beneficial for individuals.

Plasticity induced by physical exercise

Physical exercise has long been thought to have adaptive effects on both humans and animals, and it has for long been accepted as a type of activity that aids in keeping us healthy and our bodies strong and in shape. As research have been progressing however, exercise have been studied more widely in relation to the brain and how it may alter both

structure and function, and a vast array of research, as will be reviewed in the upcoming sections, indicates that exercise can affect plasticity as well. Cotman and Berchtold (2002) stated as much as 15 years ago that "it is now clear that voluntary exercise can increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, stimulate neurogenesis, increase resistance to brain insult and improve learning and mental performance". Research within this area has doubtlessly increased since, and a vast array of evidence further points to exercise being adaptive for the brain.

Colcombe and Kramer (2003) found, when surveying the existing research at that present time, that physical exercise had several positive influences on cognition. The researchers stated that physical exercise has been found to influence quite a broad variety of cognitive processes, but that the largest positive effects have been observed for executive control processes. The executive control processes mentioned by Colcombe and Kramer (2003) as being affected positively by exercise, included several components of cognition such as planning, scheduling, working memory, inhibitory processes, and multitasking. More recently, Vivar, Potter and van Praag (2012) stated that a formidable amount of evidence from research, mostly on animals but also on humans, suggests that physical exercise is beneficial for the brain and cognitive functions in terms of learning and memory, that exercise may reduce the risk for neurodegenerative diseases, and could also postpone the natural cognitive decline caused by aging. These improvements in learning and memory which are suggested to be induced by physical activity are correlated with enhanced adult hippocampal neurogenesis as well as increased activity-dependent synaptic plasticity (Vivar et al., 2012). Exercise have furthermore been found to significantly increase brain volume (both gray and white matter) in humans as compared to controls (Colcombe et al., 2006)

Van Praag et al. (1999) reported that running leads to significant enhancement of LTP in the dentate gyrus (DG) in the hippocampal formation, increased neurogenesis and improved learning in mice compared to sedentary controls. Consistently, results from an in vivo study by Farmer et al. (2004) showed that running mice displayed significantly more short-term potentiation as well as LTP compared to non-running litter mates of similar age. Exercise have also been reported to enhance repairing systems in the brain against processes related to neurogenerative diseases (such as Alzheimer's disease) (Radak et al., 2010), and to heighten the birth rate of new neurons in the hippocampus, increase neuronal spine density, synaptic plasticity, neurotrophin levels, and also improve spatial memory function in mice compared with non-running controls (Voss, Vivar, Kramer, & van Praag, 2013). Consistently, using human subjects, exercise and higher fitness levels have been found to correlate with higher synaptic plasticity in the left abductor pollicis brevis muscle motor circuit (Cirillo, Lavender, Ridding, & Semmler, 2009), increased neurotrophin levels (Rasmussen et al., 2009) and better performance in spatial recognition tasks (Déry et al., 2013).

Several studies further suggest that engaging in exercise correlates positively with improvements in several cognitive functions, especially those that are theorized to require the hippocampus. Van Praag (2008) stated that it has been shown in adult rodents that engaging in both voluntary and forced exercise improves spatial memory in rats, as observed when tested in the Morris water maze, Y-maze, T-maze and radial arm maze tests. Cassilhas and colleagues found that engaging in physical exercise, both aerobic and resistance exercise, can lead to improvements in spatial learning and memory in both humans (Cassilhas et al., 2007), and in rodents (Cassilhas et al., 2012). Furthermore, Eadie, Redila and Christie (2005) found that rats who engaged in voluntary running exhibited changes in the dendritic morphology of dentate granule neurons in terms of length, spine density and complexity. Quite consistent

with the results of Eadie et al. (2005), Stranahan, Khalil and Gould (2007) reported findings of voluntary running for two months resulting in increased dendritic spine density in granule neurons of the DG, CA1 pyramidal neurons, as well as in layer III pyramidal neurons of the entorhinal cortex.

Exercise has furthermore been found to be effective in both protecting against- and helping people suffering from several neurodegenerative diseases and other disorders. Exercise has been found to play a preventive role against Alzheimer's disease (Radak et al., 2010), against dementia in humans aged 65 years and older (Larson et al., 2006), and a study based on twins conducted by Andel et al. (2008) suggests that exercising during midlife can reduce the chance of developing dementia decades later in life. Exercise can help in alleviating attention deficit hyperactivity disorder (ADHD) symptoms (Archer & Kostrzewa, 2012), and it is strongly associated with lower levels of neuroticism, anxiety and depression and higher levels of extraversion (De Moor, Beem, Stubbe, Boomsma, & De Geus, 2006)

As seen in this section, the suggested positive effects of exercise on the brain are quite widespread and seems to be derived from a combination of several factors such as enhanced neurogenesis, modifications in synaptic plasticity, spine density, neurotrophins, and angiogenesis. These underlying beneficial factors generated or upregulated by exercise seem to be beneficial for both humans and animals in several ways, such as enhancing learning and memory, reducing the risk of neurodegenerative diseases and delaying of age-related cognitive decline. The upcoming sections will revise research about suggested underlying factors behind exercise-induced plasticity (BDNF and IGF-1), followed by sections regarding research on the effects of exercise on the hippocampus, as well as the aging brain.

Mediators of exercise-induced plasticity:

Brain-derived neurotrophic factor (BDNF)

BDNF is part of the neurotrophin family of structurally related proteins and it is considered a central operator of brain plasticity (Cowansage, LeDoux, & Monfils, 2010). Although a handful of proteins and neurotrophins have been studied in parallel with physical exercise besides from BDNF and IGF-1 (which is discussed in the upcoming) such as vascular endothelial growth factor (VEGF) (e.g. Nieves, D'amore, & Bryan, 2009), the author will focus on BDNF and IGF-1 as molecular mediators of the effects of exercise on brain and cognition.

Cassilhas, Tufik, and de Mello (2016) describes BDNF as being the most, out of all neurotrophins, sensitive to the effects of physical exercise. Voss et al. (2013) describes BDNF as being of particular interest in regard of proteins and neurotrophins because it supports neural survival, neural growth, as well as synaptic plasticity, thus making it highly relevant not only to exercise but also to neural plasticity. BDNF has been widely studied in parallel with the effects of exercise on the brain and is further considered, in consistency with results of Voss et al. (2013), a potent promoter of neurite growth (Weishaupt, Blesch, & Fouad, 2012), the survival of neurons (Lipsky & Marini, 2007), synaptic plasticity (Cowansage et al., 2010) and it has been found to influence learning and memory (Tyler, Alonso, Bramham, & Pozzo-Miller, 2002).

The many effects of BDNF in the nervous system makes it a great candidate for several factors, such as being involved in neuroprotective strategies, promoting axonal regeneration, plasticity and re-myelination (Weishaupt et al., 2012). BDNF have furthermore been suggested to play a functional role in the expression of LTP in the hippocampus (Korte

el al., 1995). Using genetic deletion of coding of BDNF in a strain of mice, Korte et al. (1995) reported significantly less LTP in the CA1 area of the hippocampus. The findings of Korte et al. (1995) is consistent with those of Farmer et al. 2004, who conducted an experiment demonstrating that BDNF is associated with aerobic exercise-induced increases in LTP in rats engaging in voluntary running. Cotman and Berchtold (2002) describes BDNF as having both neurotrophic and neuroprotective properties with the ability to affect functions underlying brain plasticity, and they furthermore, quite consistently with Weishaupt et al. (2012), state that "BDNF promotes the differentiation, neurite extension and survival of a variety of neuronal populations in culture including hippocampal, cortical, striatal, septal and cerebellar neurons" (Cotman and Berchtold, 2002).

Back in the 1990's, Neeper, Gomez-Pinilla, Choi and Cotman (1995) was the first to conduct a study aiming to find out whether physical exercise could affect BDNF gene expression in the brains of rats. Neeper et al. (1995) reported that rats engaging in voluntary running could exhibit increased BDNF gene expression in the hippocampus and in the caudal region of the neocortex. The research team furthermore reported a positive correlation between running distance and levels of BDNF mRNA in both the hippocampus, as well as in the caudal region of the neocortex. Neeper, Gómez-Pinilla, Choi and Cotman (1996) found that, in addition to running being related to increased levels of BDNF in the hippocampus and the caudal cerebral cortex in rats, also the total running distance correlated positively with the levels of expressed BDNF in the regions recently mentioned, as well as the cerebellum. Furthermore, in the studies of Neeper et al. (1995) and Neeper et al. (1996), the participating rats engaged voluntarily in running, thus mimicking as closely as possible the human way of engaging in exercise, and results showed increased levels of BDNF in the hippocampus, the caudal nucleus and also the cerebellum. In addition to the hippocampus, caudal nucleus and cerebellum (Neeper et al., 2005; Neeper et al., 2006), exercise has furthermore been found to

increase levels of BDNF in areas such as the lumbar area of the spinal cord (Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002), the amygdala (Liu et al., 2009) and the perirhinal cortex (Hopkins & Bucci, 2010). Widenfalk, Olson and Thorén (1999) found that not only do running increase levels of BDNF in the brains of rats, but also do the levels of BDNF decrease if the rats are being prevented from running, a finding that strengthens the suggestion that increases in BDNF levels is indeed can be a direct result from running.

Using both rats and humans, Rasmussen et al. (2009) conducted an experiment in order to find evidence for increased levels of BDNF from the brain during exercise. In the human study, 8 subjects engaged in 4 hours of rowing while the researchers simultaneously took frequent blood samples. In the mice study, subjects engaged in treadmill-running for 2 hours before being euthanized to have their brains checked for alterations. The human results reported by Rasmussen et al. (2009) displayed BDNF to be released from the brain at rest, and increased two- to threefold during the exercise. Results from the human experiment furthermore showed that the brain contributed 70-80% of the circulating BDNF, indicating that the brain is a major, but not unique, contributor to circulating BDNF. Results from the mice experiment displayed a three- to fivefold increase of expressed BDNF in the hippocampus and the cortex (Rasmussen et al., 2009).

Berchtold, Chinn, Chou, Kesslak and Cotman (2005) conducted an experiment using rats divided into three different groups. One group engaged daily in voluntary running, the second group in intermitted running and the third group of mice were fully sedentary throughout the study. Mice in the intermitted group were only allowed to use the running wheel on controlled, alternating days. Using this paradigm, Berchtold et al. (2005) found that intermitted running was just as effective as daily running in order to increase BDNF protein levels in the hippocampus. Furthermore, Berchtold et al. (2005) found that the peak levels of

BDNF, occurring while being active, were re-induced rapidly by re-engaging in running, even after up to 14 days of quiescence. In addition to the two findings recently mentioned, the researchers reported BDNF levels to remain elevated for several days after cessation of running. In line with the reported results of Berchtold et al. (2005), Berchtold, Castello and Cotman (2010) reported findings of BDNF remaining upregulated for as long as 14 days after mice were deprived of their access to a running wheel, and that a total of 3-4 weeks was required in order for BDNF levels to fully return to baseline. Berchtold et al. (2010) furthermore reported running mice to perform better on the radial arm water maze compared to sedentary controls.

In another study, Seifert et al. (2010) conducted two parallel experiments to find whether endurance training would affect levels of released BDNF in both humans and mice. Using 12 human participants (test subjects n=7 and controls n=5), Seifert et al. (2010) found that 3 months of endurance training resulted in significantly enhanced release of BDNF during resting, but not whilst engaging in the endurance training. Similarly, in the experiment with mice subjects, the researchers found that 5 weeks of treadmill running resulted in significantly increased levels of BDNF in the hippocampus.

BDNF seems to be an important factor to take into consideration when studying the effects of exercise on the brain and plasticity. Research reviewed in this section suggests BDNF to be involved in a vast array of alterations and processes in the brain that are often being highlighted in research regarding neuronal plasticity, alterations and processes such as neural survival, growth and protection, axonal regeneration and re-myelination, neurogenesis, synaptic plasticity, and the expression of LTP. Since levels of BDNF have been shown to increase due to physical exercise, it seems fair to consider exercise and BDNF an important

component in terms of inducing neural plasticity, and especially beneficial neural plasticity. However, additional mediators need to be taken into consideration.

Insulin-like growth factor 1 (IGF-1)

IGF-1 is a peptide hormone with similar structure to insulin. IGF-1 is involved in a vast array of physiological processes in which it acts in different manners to promote growth, and it is being produced mainly by the liver in response to pituitary growth hormone (Livingstone, 2013). Although IGF-1 is predominantly produced in the liver, essentially every tissue possesses the ability to secrete IGF-1 for various purposes (D'Ercole, Applewhite, & Underwood, 1980) and the actions carried out by IGF-1 includes, but are not limited to tissue growth and development, insulin-like activity, proliferation (the growth and division of cells), pro-survival/anti-aging and antioxidation (Puche & Castilla-Cortázar, 2012). The current section will review research regarding IGF-1 and its relation to the brain and exercise.

IGF-1 have been studied quite widely in relation to the development of the nervous system. In addition to having plenty of various effects in the adult animal, IGF-1 appears to be important for normal brain development (Anderson, Åberg, Nilsson, & Eriksson, 2002), and neurogenesis in the DG (Trejo, Carro, & Torres-Alemán, 2001). The influence of IGF-1 on the developing nervous system has been studied quite abundantly, with demonstrated effects on several stages of brain development including cell proliferation, cell differentiation and cell survival (Anderson et al., 2002). IGF-1 have been suggested to be an important promoter of embryonic processes of growth (Liu, Baker, Perkins, Robertson, & Efstratiadis, 1993) as well as an important mediator of the majority of the growth-promoting effects of growth hormones after birth (Woods, Camacho-Hübner, Savage, & Clark, 1996).

O'Kusky, Ye and D'Ercole (2000) conducted an in-vivo study in which the researchers found that overexpression of IGF-1 limited to the brain resulted in producing an increase in total numbers of neurons and synapses in the DG, thus indicating IGF-1 to promote both neurogenesis and synaptogenesis. Overexpressed levels of IGF-1 in mice have furthermore been found to result in larger brain volumes as well as increased total contents of myelin, indicating IGF-1 to be a potent inducer of brain growth and myelination (Carson, Behringer, Brinster, & McMorris, 1993). In consistency with Carson et al. (1993), Dentremont, Ye, D'Ercole and O'Kusky (1999) reported overexpression of IGF-1 to result in larger brain volumes as well, and the research team suggested the underlying factor to be an increase in total numbers of neurons. In support of these previously mentioned findings, Beck, Powell-Braxtont, Widmer, Valverde and Hefti (1995) reported that disruption of IGF-1 reduced brain volume, with reduction exhibition distributed evenly across all major brain areas, as well as reduced white matter structures in the spinal cord. Similar findings have been observed in humans as well, Woods et al. (1996) performed clinical and molecular studies on a patient with a homozygous defect in the IGF-1 gene, leading to decreased growth before and after birth. At the age of 15, the patient's height was 119.1 cm and the weight was 23.0 kg. The homozygous defect in the IGF-1 gene furthermore led to declines in cognition such as mental retardation, short attention span and hyperactivity. These reported results further indicate IGF-1 to be critical for prenatal and postnatal growth, as well as normal development of the central nervous system.

IGF-1 have been studied quite widely in correlation with physical exercise and neuroplasticity. For both humans and laboratory animals, exercise has stimulatory effects on IGF-1 (Carro, Trejo, Núñez, & Torres-Aleman, 2003), and exercise have been suggested to increase neuronal survival and plasticity in the adult brain by enhancing the uptake of IGF-1 (Chang, Yang, Wang, Kuo, & Wang, 2011). Exercise may increase expression and release of

IGF-1 from the liver in rodents (Zanconato et al., 1994) and may also induce the uptake of IGF-1 in the brain of rodents (Carro, Nuñez, Busiguina, & Torres-Aleman, 2000). Nakajima, Ohsawa, Ohta, Ohno, & Mikami (2010) found voluntary exercise to significantly increase levels of IGF-1 protein in the cerebral cortex, as well as significantly increased levels of IGF-1 mRNA in the liver compared to controls. Trejo et al. (2001) found IGF-1 to be an important underlying factor for the impact of exercise on neurogenesis in the DG. More specifically, Trejo et al. (2001) found the uptake of of blood-borne IGF-1 to be necessary for the stimulatory effects of exercise on the number of new granule cells in the adult hippocampus.

Ding, Vaynman, Akhavan, Ying, and Gomez-Pinilla (2006) conducted a study in which rats were engaged in voluntary exercise for 5 days, as well as two trials per day in the Morris water maze for 5 consecutive days followed by a probe trial 2 days later.
Ding et al. (2006) reported that levels of IGF-1 mRNA in the hippocampus were significantly increased due to running exercise, but blocking the IGF-1 receptors in running mice during exercise resulted in significant nullification of the exercise-induced increases in IGF-1 expression. Different results were reported for sedentary mice, in which blocking the IGF-1 receptors did not have any significant effects on the expression of IGF-1. Further convergent findings were made in regards of spatial memory. Using a probe trial, Ding et al. (2006) found that running mice being free of IGF-1 receptor blockades displayed improved performance in the Morris water maze, whereas running mice with blocked IGF-1 receptors did not improve. These findings indicate IGF-1 to be an important promoter in mediating the positive effects of exercise on spatial memory. Ding et al. (2006) reported an additional interesting result from their study regarding levels of BDNF. It was found that rats engaging in running exhibited significant increases of BDNF levels in the hippocampus compared to sedentary controls, but these increases of BDNF levels were fully abolished when blocking

the IGF-1 receptor. Once again, the researchers further report that blocking the IGF-1 receptor did not have any effect on hippocampal BDNF levels in sedentary mice.

Another interesting study was conducted by Chang et al. (2011), in which rats with ischemic brains (characterised by insufficient blood flow to the brain in order to meet metabolic demands) were engaged in forced running on a treadmill in order to find out whether running could have any effects on IGF-1 in the ischemic brain. Reported results displayed running to increase the entrance of IGF-1 into the ischemic brain, as well as increasing IGF-1 signalling expression.

Just like BDNF, IGF-1 seems to be an important factor to take into consideration when studying the effects of exercise on the brain and plasticity. As seen in this section, IGF-1 is suggested to be highly important and involved in several processes such as the development of the central nervous system, tissue growth, cell proliferation, differentiation and survival, neurogenesis and synaptogenesis. Exercise seems to promote expression and uptake of IGF-1, and IGF-1 seems to mediate several of the positive effects induced by exercise. Note however, that additional suggested mediators can be found in the literature (such as VEGF), but the author are under the impression that BDNF and IGF-1 are the most frequently mentioned mediators throughout the existing literature, and deem that adding additional ones would be outside the scope of the current thesis.

The remaining sections before the completive discussion will revise research on the effects of exercise on the hippocampus, as well as the aged brain

Exercise and the hippocampus.

A great amount of research suggests that the hippocampus first of all is highly plastic and plays a crucial role in neocortical experience-dependent plasticity (Sutherland,

Gibb, & Colb, 2010), and second of all that exercise can have compelling effects on the hippocampus (see examples below). Kramer et al. (2006) state that the hippocampus in more specific terms contains a handful of subfields, each playing their own specific role in the forming of new memories, and that these subfields and their functions may be affected by exercise. These subfields include, but are not limited to, the DG, Cornu Ammonis 1 (CA1), and Cornu Ammonis 3 (CA3) (Kramer et al., 2006). Other areas of the brain have certainly been suggested to be affected by exercise as well, at least to some extent, areas such as the prefrontal cortex (e.g. Berchicci, Lucci, & Di Russo, 2013) and the amygdala (e.g. Lin et al., 2012). This section will however focus on the impact of exercise solely on the hippocampus and its sub regions. Kramer, Erickson and Colcombe (2006) claim that the hippocampus of rodents, for quite long have been a structure frequently associated with cognitive functions such as spatial learning and certain memory tasks such as the Morris water maze.

Studies have shown that exercise can lead to increases of hippocampal volume in both rodents (e.g. Biedermann et al., 2012) and humans (e.g. Erickson et al., 2011). The birthrate of new neurons in the hippocampus can be upregulated by exercise, but research suggests that this phenomenon is specific solely for the DG of the hippocampus, and exercise has furthermore been shown to improve hippocampus-dependent spatial memory in rodents (Voss et al., 2013). Studies using human participants have shown that fitness and exercise is beneficial for several cognitive factors involving the hippocampus, such as pattern separation, spatial memory performance and relational memory performance (Voss et al., 2013). Van Praag et al. (1999) found that running resulted in significantly higher cell proliferation (the growth and division of cells), cell survival and neuronal differentiation in the hippocampus of adult mice. Pereira et al. (2007) found that higher levels of cerebral blood volume (CBV) in the DG was exhibited in participants engaging in exercise, and it has further been reported

that forced treadmill running resulted in enhanced LTP, as well as increased expression of BDNF in the DG of adult rats (O'callaghan, Ohle, & Kelly, 2007)

Herting and Nagel (2012) tested weather higher levels of fitness correlated with cortical volume and performance on memory and learning tasks in humans aged 15-18 years. The research team found that aerobic fitness levels correlated positively with hippocampal volume, as well as better learning during a virtual Morris water task. That is, participants with higher fitness levels displayed greater hippocampal volumes and performed better on the Morris water task. In consistency with these findings, Erickson et al. (2011) suggests that increased hippocampal volume translates into improved memory function and higher serum BDNF. Lou, Liu, Chang and Chen (2008) found a significant correlation between the intensity of running and neurogenesis and gene expression in the hippocampus of juvenile rats. Their results indicate that neurogenesis and mRNA expression of (among else) BDNF benefits more from low intensity running compared to high intensity. These results are consistent with those of Kim et al. (2003) who found that cell proliferation in relation to exercise was enhanced the most in rats engaging in light-intensity running.

The hippocampus is known to undergo changes along with aging, changes that are mostly in relation to cognitive decline and shrinkage that may lead to impaired memory and increased risk for dementia (Erickson et al., 2011). Indeed, Jack et al. (1998) found, in a study with participants aged 70-89 years, that the hippocampus underwent a significant yearly decline of 1-2%. Erickson et al. (2011) found however that hippocampal and medial temporal lobe volumes are larger in higher-fit adults. The research team furthermore report that physical activity training increases hippocampal perfusion and the size of the anterior hippocampus, leading to improvements in spatial memory. In the study of Erickson et al. (2011), elderly participants engaged in aerobic exercise for a period of one year. The reported

results suggest that aerobic exercise training increased total hippocampal volume by 2%, and was effective in reversing age-related loss in volume by 1 to 2 years.

Erickson et al. (2010) conducted a study with 299 older adults (mean age of 79 years), in which the amount of walking distance per week was tested to see if it had any impact on hippocampal volume. Using high resolution brain scans 9 years after the onset of the study, Erickson et al. (2010) found that greater distances in walking correlated with greater gray matter volumes of several structures, with significant results in the hippocampus. Erickson et al. (2010) furthermore report that greater gray matter volume found in structures involving the hippocampus is related to reduced risk of developing dementia and mild cognitive impairment, and that distances of at least 6-9 miles of walking per week was necessary in order to find differences in gray matter after 9 years. Another interesting founding was made by Pajonk et al. (2010), who found that engaging in 12 weeks of exercise, three sessions a week for 30 minutes per session, resulted in significant hippocampal volume increase for not only healthy participants, but also in patients suffering from Schizophrenia, compared to a non-exercising control group.

The research reviewed in this section suggests the hippocampus to be a highly plastic region, and a region being affected to a very high extent by exercise. Several factors related to the hippocampus such as the total volume, neurogenesis, CBV and levels of BDNF is suggested to increase due to exercise. Since increases/ improvements in these factors have been found to correlate with improved performance in tasks requiring activation of the hippocampus, exercise may improve performance in certain tasks involving cognitive functions such as spatial memory, as well as overall hippocampal health and preserving. It seems however, that there has been no evidence yet for exercise to increase neurogenesis in humans.

Exercise-induced plasticity and the aging brain

As individuals grow older, functional and structural changes can be observed in the brain. Raz, Rodrigue and Haacke (2007) argue that the present literature provides clear evidence that even normal aging (i.e. aging in individuals not suffering from any neurodegenerative deficit) is related to neural and cognitive decline. Aging of the brain results in several changes such as decline and loss of synaptic contacts and neuronal apoptosis (an active, highly regulated and natural form of cell death) which in turn incites factors such as age-dependant decline of sensory processing, motor performance, and cognitive function (Rossini, Rossi, Babiloni, & Polich, 2007). Research have further suggested that older age is correlated with other factors of decline such as decreased tissue volume (Jernigan et al., 2001), decline of synaptic density (Terry & Katzman, 2001), reduced neurogenesis in the hippocampus (Kuhn, Dickinson-Anson, & Gage, 1996), as well as cognition and brain function (Kramer et al., 2006) such as processing speed (Schaie, 1989), attentional shifting (Cona, Bisiacchi, Amodio, & Schiff, 2013) and poor decision making (Boyle et al., 2012)

There is indeed a vast array of converging studies suggesting various forms of decline in both brain structure and cognitive functions in relation to aging. For example, Jernigan et al. (2001) conducted a study involving 78 subjects in ages ranging from 30 to 99 years (mean age of 64 years). Jernigan et al. (2001) reported that their results estimates that between the age of 30 and 90 years, volume loss in the brain averages 14% in the cerebral cortex, 35% in the hippocampus, and 26% in the cerebral white matter.

Terry and Katzman (2001) argued that throughout the lifespan, provided that an individual goes through natural aging, between the age of 20 and 100 years the population density of neocortical synapses declines up to a level rather close to the one found in individuals

suffering from Alzheimer disease, which according to Terry et al. (1991), occurs when roughly 40% of the total neocortical synapses have been lost.

Boyle et al. (2012) conducted a study containing 420 older, nondemented participants in which the research team found that poor decision making as well as high susceptibility for scams, are consequences of cognitive decline that follows the natural course of aging. Furthermore, several studies converge on neurogenesis in the hippocampus declining steadily with age. Using bromodeoxyuridine (BrdU, a technique used to mark proliferating cells and determine whether the brain is undergoing neurogenesis) labelling in four different age groups (6, 12, 21 and 27 months of age) of F344 rats, Kuhn et al. (1996) found that rats aged 12 – 27 months exhibited significant declines of neurogenesis in the DG compared to rats in the age of 6 months. Similar findings were reported by Siwak-Tapp, Head, Muggenburg, Milgram and Cotman (2007) when studying neurogenesis in the canine hippocampus. Using doublecortin (DCX) and BrdU immunostaining in five older dogs (13-15 years of age) and five younger dogs (3.4–4.5 years of age), Siwak-Tapp et al. (2007) found that cellgenesis and neurogenesis in the canine hippocampus decreased significantly with age.

As seen in this section so far, there is a wide selection of converging evidence for cognitive functions and cortical structures being altered as a result of aging. However, there is also a wide selection of converging evidence for neuronal and structural brain preservation as a result of physical exercise.

Kramer, Erickson and Colcombe (2006) reviewed the literature available at that time and they stated that their findings suggests that physical activity such as aerobic exercise training can be beneficial in terms of moderation of undesirable age-related alterations in several factors such as cognition, brain function, and brain structure (note that these three are

all mentioned above as declining due to aging). Kramer et al. (2006) furthermore state that the information they reviewed, and the conclusions they drew from it, is a substantial addition to the growing literature which suggests that both cognitive- and brain plasticity is maintained in older age, although to a certain lesser extent compared to young individuals. Vivar et al. (2012) state that reduced neurogenesis is indeed reduced naturally by aging, but engaging in exercise may not only just mitigate the reduction, exercise may even reverse it to some extent in some, but not likely all conditions. Furthermore, the robust effects that exercise has on neurogenesis is maintained throughout life in rodents (Vivar el al., 2012).

The effects of exercise have also been evaluated in terms of being helpful against neurodegenerative diseases being more commonly seen in elderly people compared to younger peers. Hamer and Chida (2009) found exercise to be protective against future risks of dementia and Alzheimer's disease. In certain models of Alzheimer's, exercise can be helpful in order to reduce pathology and enhance cognition (Vivar et al., 2012). Thus, it seems possible to tackle age-related cognitive and structural decline, and below follows research in support of the positive effects of exercise on the brain and cognition.

Using the Morris water maze, Van Praag, Shubert, Zhao, and Gage (2005) found that exercise helped aged, sedentary mice to restore spatial learning and neurogenesis in the hippocampus. The mice used in this study had been sedentary until 19 months of age. During the experiment, the mice had unlimited access to running wheel for 45 days, during which the aged mice ran a similar total distance to the one mice aged 3 months ran. Van Praag et al. (2005) reported that 45 days of voluntary running resulted in the aged mice performing better in the Morris water maze in terms of faster acquisition of the hidden platform, and that the aged mice also exhibited a higher rate of newborn neurons in the DG compared to sedentary controls of similar age.

Rogers, Meyer and Mortel (1990) conducted a longitudinal study over four years, on a total of 90 elderly humans aged 62-70 years. Participants who were active, either in work or as an active retiree, sustained higher levels of cerebral blood flow (CBF) and scored higher on a general measure of cognition compared to retired peers who were not physically active. Cassilhas et al. (2007) found that both medium- and high intensity resistance training over a period of 6 months had beneficial effects on cognitive functions, more specifically in memory performance and verbal concept formation in men aged between 65 to 75 years. In a similar study, Liu-Ambrose et al. (2010) found that senior women (65 to 75 years of age) who engaged in resistance training once or twice every week for 12 months exhibited enhanced selective attention as well as conflict resolution.

Another study using elderly human participants was conducted by Erickson et al. (2011). This study involved 120 older participants who were being randomly divided into two groups. 60 subjects were assigned to a group for engaging in aerobic exercise and the other 60 were assigned to a control group in which they were to engage in stretching and toning exercise. Erickson et al. (2011) reported that after one year of engaging in moderate-intensity aerobic exercise, the participants displayed increased size of both the left side (by 2.12%) and the right side (by 1.97%) of the hippocampus. Interestingly, the participants in the control group displayed a decline in size of the hippocampus (1.40% and 1.43%). Moreover, the researchers found that higher levels of fitness were positively correlated with higher levels of hippocampal growth, and higher changes in BDNF serum was positively correlated with higher changes in hippocampal size (Erickson et al., 2011). It was furthermore reported that higher baseline level of physical fitness of all subjects correlated with better performance in a spatial memory task at the very beginning of the study, and later on the researchers found that increases in hippocampal volume in the aerobic exercise group correlated with improvement in memory performance (Erickson et al., 2011). Results from this study involves several

interesting findings that correlates with findings in other studies mentioned above, such as the hippocampus being modifiable even in old age, aerobic exercise being helpful in preventing natural volume loss, and that an increase in hippocampal size which can be achieved through aerobic exercise is correlated with improved memory function and higher serum levels of BDNF (Erickson et al., 2011). Consistent with the evidence provided by Erickson et al. (2011), studies with similar scientific quality have been conducted (see Ruscheweyh et al., 2011; Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2012)

As we have seen in this section, there is a vast array of suggested evidence converging on the brain undergoing several alterations of decline due to aging. Engaging in different forms of exercise such as aerobic training (e.g. Erickson et al., 2011) and resistance training (e.g. Cassilhas et al., 2007) have been suggested to be beneficial for the aging brain. Thus, it seems to be as if brain preservation can be induced by exercise, and the evidence from the literature reviewed above suggests that the brain is not plainly doomed to declination as a result of the natural course of aging.

Discussion

This discussion section will aim mainly at widening the previously discussed sections, especially in terms of considering knowledge gaps and limitations in the research related to brain plasticity and exercise-induced plasticity. A conclusion of this paper is also included at the very end of this section.

As in any field of research, regardless of the extraordinary progress in both knowledge and technology, there are a handful of limitations, knowledge gaps and problematics within the field of neuroplasticity. First of all, a vast majority of conducted research regarding experience-induced plasticity has been carried out using animals,

especially rodents, as subjects. One must address the question of to what extent results generated from animals can be generalized to humans. Research conducted on human subjects regarding neural plasticity induced by experience and physical exercise have been relatively limited, but modern neuroimaging technologies may enable the field of cognitive neuroscience to initiate bridging of the gap between studies using animal and human subjects (Voss et al. 2013).

When comparing evidence from research using animal subjects and randomized controlled trials (RCTs) and intervention trials using human subjects, Voss et al. (2013) reported several findings from animal research that have not been reported in results from human studies. For example, in adult animals', exercise have been reported to enhance angiogenesis, neurogenesis, proliferation, LTP and adaptation. In human studies, none of these factors have been reported to be affected by exercise. Although differently exhibited, on a more general level there are convergent evidence across humans and animals regarding exercise-induced plasticity as well. Much research has been carried out with results indicating similar neural effects generated by exercise in both humans and rodents, such as volume alterations, synaptic plasticity and alterations in neurotrophic levels (Ruscheweyh et al., 2011; Erickson et al., 2011; Rasmussen et al., 2009; Voss et al., 2013; Cirillo et al., 2009; Biedermann et al., 2012). Moreover, cognitive functions, and especially those suggested to rely on the hippocampus, have been suggested to exhibit enhancement due to exercise and higher levels of physical fitness not only in animals, but also in humans (Rogers et al., 1990; Erickson et al., 2011; Liu-Ambrose et al., 2010). Regardless, there are obviously differences in how plasticity is exhibited in humans and non-human species. As mentioned, the existing studies using animal subjects outnumber the studies using human subjects greatly for several reasons.

Conducting human studies are in general costlier and more difficult to design, especially when conducting longitudinal studies. (Voss et al., 2013) Whereas animals can be studied easily over a longer period of time within the lab even from birth, the same does not apply for humans. The researchers are fully able control for how long the animals are to engage in the testing, and possess the ability to euthanize the subjects in order to retrieve their brains for closer examination. Moreover, rodents used generally represent two extreme types of activity: either highly active or completely sedentary, which is hardly the case for human subjects (Seo et al., 2014). Differences in other factors in human vs animal studies, such as access to food and water as well as time of the day when exercise is engaged may further complicate comparison (Seo et al., 2014). Additional complications involve for example measuring and imaging techniques in terms of several techniques, such as BrdU labelling are not easy to use on human subjects due to safety concerns.

To summarize the aspect of research conducted on animals contra humans: animal experiments provide insight into desirable outcomes generated by exercise, possibly generalizable across species. Animal studies are not always translatable to humans however, but can provide foundations for corresponding human studies and guidelines for predictions which can be useful in several ways when searching for the impact of exercise on the human brain and cognition. With the knowledge generated from the vast literature of animal studies, future research should focus more on longitudinal studies using large human samples with human control groups included. Following paragraphs will discuss the existing limitations in the literature of human studies.

Although much of the existing literature involve animal samples, there is a vast array of research conducted on plasticity induced by experience and exercise with human samples as well. However, quite a few studies within the area contain various flaws making

parts of the generated evidence questionable. Lövdén et al. (2013) point out several flaws and methodological limitations in a handful of studies regarding experience-dependent macrostructural alterations in grey matter, such as stating that several of these studies are using quite liberal corrections of the threshold for significance (the alpha level) for the multiple test problem in the mass univariate statistics approach, generating less trustworthy results, and several studies report effects of experience-dependent macrostructural alterations without considering comparison of results to a control group.

According to the criticism delivered by Lövdén et al. (2013), it seems as if several studies contain flaws making them less trustworthy and difficult to interpret. Studies conducted on neural changes should apply appropriate statistical analyses, use control-group design with the groups being measured closely to each other in time and being managed identically during measurement, as well as appropriate imaging techniques.

MRI techniques using voxel-based morphometry (VBM) are very commonly used when studying regional changes in brain morphology (Lövdén et al., 2013). In addition to the many strengths of VBM, it also comes with a handful of weaknesses important to address. For example, when studying alterations in grey matter, the feasibility of each voxel in a generated image being actual grey matter is not fully reasonably forthright to relate to the macrostructure of the biological brain (Lövdén et al., 2013). It is furthermore quite difficult to distinguish white matter from grey matter in VBM, and observed differences may be difficult to interpret (for a review of the limitations of VBM, see Davatzikos, 2004). Thus, VBM may generate measures reflecting a mixture of morphological changes, changes such as density, cortical surface area, cortical folding, and cortical thickness, rather than reflecting the exact morphological changes of interest and should therefore be used with caution. In order to generate stronger evidence and achieve a more comprehensive understanding, more than one technique should be used when studying neural plasticity.

There are further aspects to consider in order to present valid results and for progress to strive in this field of research. There are quite a lot of cross-sectional studies comparing brains of different subjects with one another, such as musicians' vs non-musicians (e.g. Bengtsson et al. 2005). However, with cross-sectional studies it is difficult to fully determine whether the experience preceded the structural alterations or the other way around (May, 2011). Longitudinal studies on the other hand, provide more robust evidence for experience-dependent structural alterations due to the experience being directly manipulated, and the alterations are constantly measured within participants. Future research should thus consider longitudinal studies rather than cross-sectional in order to provide robust results regarding dependent and independent variables. In addition, control groups engaging in a separate training task should always be included, as well as direct comparison between the experimental and control group, and ideally large samples (Thomas & baker., 2013).

To summarize the aspect of existing problematics in human studies and imaging methods: Although there are some questionable studies in the existing literature, there are also several studies with high scientific quality and solid evidence, suggesting both exercise and other experiences to correlate with various types of plasticity such as increases in regional grey matter (Mårtensson et al., 2012; Colcombe et al., 2006), white matter (Lövdén et al., 2014; Colcombe et al., 2006), increased hippocampal volume (Erickson et al., 2011) changes in levels of neurotrophins and enhanced cognition (Erickson et al., 2011; Ruscheweyh et al., 2011). Furthermore, the evidence from Erickson et al. (2011) and Ruscheweyh el al. (2011) (see also Liu-Ambrose et al., 2012) was generated using elderly humans, suggesting exercise to be highly beneficial for the aged brain in terms of preservation, improved cognition, altered levels of neurotrophins and prevention of natural volume loss. All studies mentioned above are longitudinal studies with human samples, adequate alpha levels and all except for Lövdén et al. (2014) include a control group, thus

providing trustworthy results. These scientific applications which increase the empirical quality of research should be applied more often in future studies in order to increase knowledge within this field.

In conclusion: The existing literature on plasticity induced by experience and exercise does most certainly contain limitations and knowledge gaps. There are however compelling evidence of exercise and experience affecting the brain of both humans and animals, both functionally and structurally. The aim of this thesis was to conduct a general overview of the relation between brain plasticity and exercise and whether exercise can induce beneficial plasticity in humans, as well as pinpointing certain suggested mediators of the effects of exercise on the brain and its functions. The existing literature provides strong evidence for exercise as being able of inducing functional and structural plasticity in humans, and quite strong evidence for exercise to have beneficial effects on humans in a handful of ways such as enhancing neural functions, increasing cortical volume, preventing natural volume loss and improving cognitive abilities. These findings are evident in elderly humans as well. On a molecular level, neurotrophins such as BDNF and IGF-1 seem to play quite an important role for plasticity induced by exercise and experience. However, an increased number of well-designed studies are needed before any extensive understanding can be achieved within this field. Future research should focus more on longitudinal studies using large human samples with proper human control groups included, as well as appropriate statistical analyses and imaging techniques.

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