The Effects of Aging on Visual Perceptual Learning and Plasticity

BY

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This dissertation by Li-Hung Chang is accepted in its present form by the Department of Cognitive, Linguistic, and Psychological Sciences as satisfying the dissertation requirement for the degree of Doctor of Philosophy.

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Choi, H., Chang, L.-H., Shibata, K., Sasaki, Y., & Watanabe, T. (2012). Resetting capacity limitations: Long-lasting elimination of attentional blink by training. *Proc Natl Acad Sci*, Jul;109(30):12242-7.

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Electroencephalogram (EEG) acquisition
Event-Related Potential (ERP) data analysis
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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACC	anterior cingulate cortex
BOLD	blood-oxygen-level-dependent
CRUNCH	compensation-related utilization of neural circuits hypothesis
CT	computed tomography
dHb	deoxygenated hemoglobin
DLPFC	dorsoalateral prefrontal cortex
DTI	diffusion weighted tensor imaging
DWI	diffusion-weighted imaging
FA	fractional anisotropy
FT	fiber-tracking analysis
FWHM	full width at half maximum
fMRI	functional magnetic resonance imaging
FLH	frontal-aging hypothesis
HAROLD	hemispheric asymmetry reduction in older adults
HDR	hemodynamic response
IFG	inferior prefrontal gyrus
IPS	intraparietal sulcus
LPFC	lateral prefrontal cortical areas
MFG	middle frontal gyrus
OFC	orbitofrontal cortex
SBM	surface-based morphometry
SPG	superior parietal gyrus
SPM	statistical parametric mapping
TBSS	tract-based spatial statistics
TDT	texture discrimination task
TIPL	task irrelevant perceptual learning
TMS	transcranial magnetic stimulation
TRPL	task relevant perceptual learning
RF	radio-frequency
ROI	regions of interest
RSVP	rapid serial visual presentation
SOA	stimulus-to-mask onset asynchrony
UFOV	useful field of view
VBM	voxel-based morphometry
VPL	visual perceptual learning

1. Chapter 1: Introduction

1.1 Visual perceptual learning and plasticity

Visual perceptual learning (VPL) is defined as long-term improvement on a visual task and is regarded as a manifestation of the plasticity in the visual system (Sasaki et al., 2010). Several studies have shown that the repetitive and intensive practice of a visual task leads to enhanced performance in younger adults (Sagi, 2010). VPL can be divided into two types: task-relevant perceptual learning (TRPL) and task-irrelevant perceptual learning (TIPL).

1.1.1 Task-relevant perceptual learning (TRPL)

TRPL refers to the learning of a feature that is relevant to the trained task. Some studies have suggested that TRPL is related to the changes in the primary visual area for younger adults. For example, Yotsumoto, Watanabe, and Sasaki (2008) conducted perceptual learning training using four different functional magnetic resonance imaging (fMRI) scans before, between, and after the training. The younger subjects were asked to identify the central letter in the fixation and discriminate the orientation of the targets that differ from the background during the texture discrimination task (TDT; Karni and Sagi, 1991), which is a standard VPL task. The results indicated that only the blood-oxygen-level-dependent (BOLD) signal changes in the early visual area V1 corresponded to task performance improvement. In contrast, task performance did not correspond to the BOLD signal changes in the other brain regions, including the higher cortical brain areas, such as the intraparietal sulcus (IPS), the superior

parietal gyrus (SPG), and the middle frontal gyrus (MFG). These results suggest that the visual plasticity induced by TRPL training is due to the local alteration within the early visual areas in the younger adults. Thus, perceptual learning can be used to evaluate age-associated changes in the behavior task performance related to the occipital cortex, including early visual areas.

1.1.2 Task-irrelevant perceptual learning (TIPL)

On the other hand, TIPL refers to learning a feature that is irrelevant to the trained task. Some studies suggest that TIPL might involve the effect from a higher cortical area in addition the lower-level visual processing in the visual area. For instance, by using rapid serial visual presentation (RSVP) with the selected direction motion exposure, which is regarded as a task-irrelevant stimulus, younger subjects' motion perception of the trained task-irrelevant signal will be enhanced after the 14-day RSVP exposure; interestingly, the results also suggest that motion perception related to task-irrelevant stimulus can only be enhanced by subthreshold exposure in younger participants (Seitz and Watanabe, 2003; Tsushima et al., 2008). The results from another fMRI study suggested that it might due to the inhibition from the higher cortical area, which the signal from the super-threshold stimulus in RSVP task might suppress through its inhibitory control system (i.e., lateral prefrontal cortical areas [LPFC]) in the higher cognitive process stage (Tsushima et al., 2006). Such evidence indicates that the absence of TIPL in a suprathreshold feature could stem from the attentional control system detecting the signals from the feature and then inhibiting the signals. Yet the occurrence of TIPL in a subthreshold task-irrelevant

feature might be because the attentional system does not detect and, therefore, fails to inhibit the signals to enhance the learning.

Although VPL has been widely applied to enhance visual ability for those with different visual impairments, including amblyopic (Levi and Li, 2009a, b), low myopic (Tan and Fong, 2008), and presbyopic (Polat, 2009) adults as well as those with abnormal development, including schizophrenia patients (Norton et al., 2011), the effect of perceptual learning among elderly adults has not been fully investigated.

1.2 Aging and the brain

What is the effect of aging to the human brain? In this section, we will review some studies from structural as well as functional observations on cognitive neuroscience in aging.

1.2.1 Brain structural changes associated with normal aging

The structure of the human brain can be generally segmented into gray matter, white matter, and cerebrospinal fluid. Gray matter, which is known as the cortex, consists of the cell bodies of nerve cells and is located in the exterior of the brain. White matter, which is known as the medulla, transmits the electrical signals that carry the messages between neurons; it is located in the interior of the brain. Cerebrospinal fluid, which contains transparent fluid, fills ventricles and surrounds the brain and spinal cord; it can also absorb the shock and protect the brain. In the human brain structural analysis, the quantifying anatomical features can be obtained from these parts in terms of shape, mass, and volume, like grey matter density and white matter connectivity, cortical thickness, or the amount of cerebrospinal fluid. To analyze the gray matter, one of the most common

parameters is cortical thickness, which refers to the distance from the outer cortical surface to the inner cortical white matter–gray matter boundary (Fischl and Dale, 2000). It can imply the indirect measure of the complex cortical architecture, with changes in the cortical myelination synaptic pruning and cell density being the candidate cellular events (Huttenlocher and Dabholkar, 1997). On the other hand, in the white matter, one of the most common parameters is to measure fractional anisotropy (FA), which can quantify the directional selectivity of the random diffusion of water molecules in white matter (Beaulieu, 2002). The changes in regional FA during the lifespan might be due to changes in cerebral myelin levels and myelin packing (Mädler et al., 2008; Song et al., 2003; Song et al., 2005, see Chapter 2 for details).

Traditionally, we can only get histological brain information from the dissection after the individual passes away. For example, Flood and Coleman (1988) compared a human brain and a monkey's brain by measuring the neuron numbers and sizes during a postmortem analysis and demonstrated that the neuron numbers and sizes in the CA1 area of the hippocampus showed some similar age-related changes between the two brains. Today, the devolvement and application of brain-imaging techniques allow for the in vivo observation of the brain's structural changes during normal aging. The structural analysis of the aging brain can be divided into two different approaches: whole brain analysis and regional analysis. The whole brain analysis normalizes and averages the anatomical features as a homogeneous unit. Thus, we can observe the longitudinal development of the brain structure changes at different ages and

calculate the effect of aging. Some studies have suggested that the human brain structure in different regions is not purely homogenous. For example, the cortical thickness varies in different brain areas. In general, the sensory cortex is thinner and the motor cortex is thicker than other areas (Kruggel et al., 2003). Thus, it is worth segmenting different brain areas and observing the effect of normal aging in a region by region manner. Here we review the previous aging studies focusing on the whole brain analysis first; then we discuss the effect of aging in different regions.

1.2.2 Effect of aging in the whole brain analysis

Studies focusing on aging and brain structural differences by applying whole brain analysis started from postmortem studies (Dekaban, 1977; Skullerud, 1985), suggesting that normal brain aging is an overall cerebral atrophy that includes the shrinkage of gray and white matter and the enlargement of the cerebrospinal fluid spaces. It has been concluded that such changes might be due to a direct loss of neuron fibers rather than a direct loss of neurons, which is relatively limited with age (Pakkenberg et al., 2003; Peters et al., 1998). However, such studies have used a biased population in terms of either age or gender. For example, in Dekaban's study (1977), the time window of the observations was from newborn to twenty years old only. Thus, the timing of such age-related decreases and increases remains uncertain. Postmortem analyses of brain structures are also influenced by other factors, like the duration between death and fixation and timing of measurements (Messert et al., 1972; Miller et al., 1980). Postmortem studies might also limit the results in terms of the

skimpy medical and behavioral history. Furthermore, it is impossible to conduct a concurrent assessment (Raz and Rodrigue, 2006), and it is hard to explain the changes related to the cortical thickness and cortical space.

With the development of MRI, scientists started to explore the brain's structural changes in vivo, including more populations with more longitudinal designs. The early MRI studies of aging using a whole brain analysis started with Good et al. (2001), whose results indicated that grey matter volume decreased linearly with age in the whole brain analysis; it significantly declined in males. In contrast, the global white matter did not decline with age, although some local areas showed relatively accelerated loss and preservation. The authors concluded that, although the majority of structural MRI data indicated micro-structural changes in cerebral white matter (Raz et al., 1997; Wahlund et al., 1990), the total white matter volume loss was not expressed. Their results suggested that the different brain structures might have different effects from normal aging. Good et al.'s (2001) study only reported the decline in gray matter; no significant decline in white matter was found.

Observations have varied and are controversial in different studies. For example, Courchesne et al. (2000) suggested that both gray matter and white matter decline late in the lifespan. In their report, gray matter increased 13% from early childhood (19–33 months) to later childhood (6–9 years), and it decreased linearly by approximately 5% per decade throughout life, which supports Good et al.'s (2001) finding. More importantly, white matter volume increased 74% from early childhood and reached a plateau by the fourth decade of life before

decreasing by 13% in the oldest volunteers (aged 70–80 years). These results suggest that the differences between Good et al.'s (2001) and Courchesne et al.'s (2000) studies are due to different time windows in their older group distribution. As a result, the observation of a more detailed and larger range of ages is necessary.

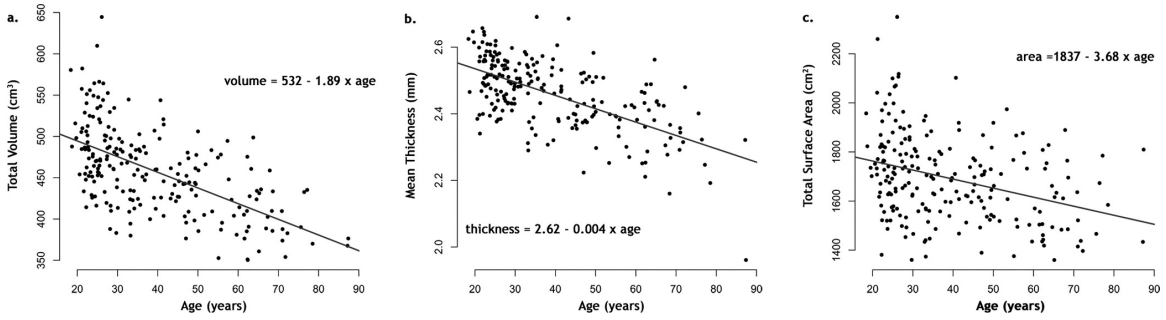

Figure 1. Age-associated changes in the whole-brain analysis

Scatter plots and simple linear regressions of total volume (a) mean thickness (b) and total surface area (c) (Lemaitre et al., 2012)[1].

In 2012, Lemaitre et al. (2012) recruited 216 individuals (ages 18–87 years) and conducted a whole-brain analysis. In addition to gray matter, which has been examined in early studies (Courchesne et al., 2000; Good et al., 2001), Lemaitre et al. (2012) included more structural indexes, such as cortical thickness and surface areas. In their report, the linear regressions revealed significant age-related reductions ($p < 0.001$) in cortical gray matter ($r = -.059$),

[1] Reprinted from *Neurobiology of Aging*, 33/617, Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., and Mattay, V.S., Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? 611-619, Copyright © 2012, with permission from Elsevier.

surface area (r = -0.34), and cortical thickness (r = -0.62) (see Figure 1; Lemaitre et al., 2012). Their results provided more detailed information, with a larger sample size and wider age distribution than previous studies. The results also suggested a common pattern of a global age-related reduction in cortical thickness, surface area, and cortical volume (gray matter).

One question that remained was whether the white matter shared similar patterns with the gray matter in terms of the brain's structural measures. Regarding the aging effect on white matter, Kochunove et al. (2011) recruited 1031 participants (ages 11–90 years) and used the whole brain to measure the cortical thickness and FA as white matter. After controlling the factors from age and gender effects, both cortical thickness and white matter FA index were found to be significantly correlated with aging. In addition, a non-linear (quadratic) positive relationship was found between the age trajectories of cortical thickness and white matter's FA value. The authors' finding suggests that an age-related reduction in gray matter might share a common biological mechanism related to the changes in cerebral myelination. Both Lemaitre et al.'s and Kochunove et al.'s findings, with better control over both age population and gender effect, provide more evidence of the global changes in both gray and white matter.

In addition, these studies provide strong evidence of biological and structural reduction with normal aging in the human brain across different brain structures, like gray matter volume, white matter, cortical surface, and cortical thickness; however, these characteristics on the aging effect have not been found in other animals. For example, Sherwood et al. (2011) compared the brain

structures of 99 chimpanzees and 87 adults. The results showed that, in the human group, a significant reduction in cortical gray matter occurred, which replicated the previous studies in gray matter reduction; however, the aging effect was not observed in chimpanzees' gray matter. The results suggest that this increased magnitude of brain structure shrinkage in human brain is a human-specific phenomenon and might imply some evolutionarily implements on the human brain related to the extension of the lifespan.

1.2.3 Effect of aging in the regional analysis

Postmortem analyses of mammalian brains have suggested that our brain is not homogeneous, and different brain regions might have their own developing processes throughout the lifespan. The effect of aging might be universal for the whole brain, but not uniform in every brain region. Early studies have found that there may be a gradient of aging from the prefrontal brain areas to the primary sensory regions (Flood and Coleman, 1988). As a result, it is worth observing the effect of aging on local representation. In general, aging effects are significantly strong on frontal cortices, but more moderate in the temporal and parietal areas. In contrast, the sensory area seems more preserved than the frontal area (Allen et al., 2005; Raz et al., 2004; Raz and Rodrigue, 2006). In this section, we will review and discuss the effect of aging on different brain regions.

Among the different regions, the prefrontal area has been regarded as the most vulnerable area with advancing age (Allen et al., 2005; Brickman et al., 2007; Fjell et al., 2009; Lemaitre et al., 2012; Raz et al., 1997; Raz et al., 2004; Salat et al., 2004; Salat et al., 1999). For example, Raz et al. (2004) suggested

that the prefrontal cortices are more significantly affected than the rest of the neocortical regions. Moreover, Raz et al. (1997) investigated 148 healthy adults and found that the most substantial age-related decline occurred in the volume of the prefrontal gray matter, including the dorsolateral prefrontal cortex (r = -0.51, DLPFC) and orbito-prefrontal cortex (r = -0.48). In addition, Fjell et al. (2009) reported that the strongest age effect in cortical thickness measures occurs in the superior middle and inferior frontal cortex. Salat et al. (2005) also found that younger subjects have significantly larger white matter volume than older people in the prefrontal area based on measurements of FA. The authors indicated that the white matter in the prefrontal area is developed late in the early 20s and remains relatively preserved until late aging; however, FA was significantly reduced by middle age in superior, inferior lateral orbital, and medial orbital frontal areas. These results are consistent with Lemaitre's (2012) large population of global and regional observation. In Lemaitre's report, all of the brain's sub-regions in the prefrontal cortex showed the greatest age-related reduction in volume, thickness, and surface area. In particular, the superior frontal and middle frontal gyri showed the greatest age-related reduction (see Figure 2: Lemaitre et al., 2012). Some studies suggested that this significant vulnerability to aging in the prefrontal area might relate to the aging-related declines in several cognitive processes, which we discuss in later parts of this chapter.

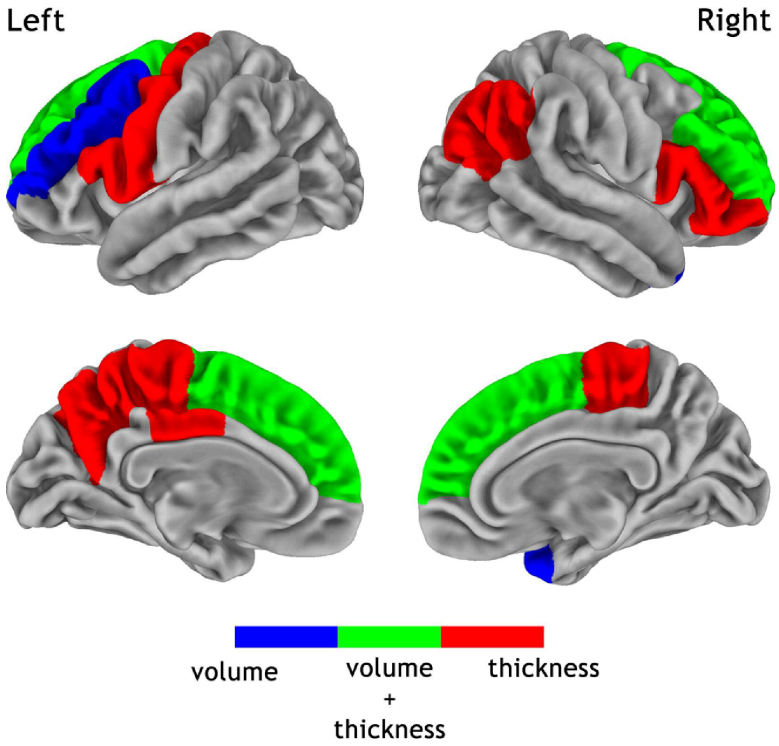

Figure 2. Age-associated changes in the regional analysis

Cortical areas showed significant age-associated reduction in cortical volume (blue), thickness (red) or both (green) (Lemaitre et al., 2012)[2].

In terms of the gradient age reduction from the anterior to posterior brain areas, most studies have also reported the age effect in the parietal areas (Abe et al., 2008; Brickman et al., 2007; Good et al., 2001; Resnick et al., 2000; Salat et al., 2004). For example, Good et al. (2001) found the accelerated loss on gray matter in insula, superior parietal gyri, central sulci, and angula gyri. In addition, Resnick et al. (2000) controlled the differences in absolute volumes across different regions and found that the age differences were even greater in the

[2] Reprinted from *Neurobiology of Aging*, 33/617, Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., and Mattay, V.S., Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? 611-619, Copyright © 2012, with permission from Elsevier.

parietal region than in the frontal area. In 2007, Brickman et al. (2007) found similar evidence on both gray and white matter volume lost in both frontal and parietal areas. In their study, both frontal and parietal lobes indicated the greatest regional aging reduction effect at approximately 5.4 and 2.4 cm^3 between older (n = 29, mean age = 73.1) and younger control groups (n = 84, mean age = 24). In contrast, Lemaitre et al. (2012) found that only cortical thickness showed a significant reduction in inferior parietal gyrus, which is consistent with results of other cortical thickness studies (Fjell et al., 2009; Salat et al., 2004; Ziegler et al., 2010). No significant reduction occurred in gray matter volume or the cortical surface area. Generally speaking, although most of the studies reported some age-related atrophy in the parietal area, the evidence in different brain structures varies, which might suggest that the parietal area encounters different histological development during normal aging than the other brain regions.

Compared to the frontal and parietal areas, temporal lobes have been studied relatively less often in terms of age reduction (Cowell et al., 1994; Lemaitre et al., 2012; Sullivan et al., 1995). For example, Raz et al. (1997) only found smaller age-related differences in the volume of inferior temporal areas; in terms of white matter, Good et al. (2001) found that the temporal lobe has relative preservation of white matter volume. In addition, the age-associated declination seems varied in the sub-region among the temporal lobes. For instance, Fjell et al. (2009) found a significant age-related reduction of cortical thickness in superior and middle temporal gyri, but less effect in the inferior temporal lobe. In addition, the temporal area seems to have a larger gender

effect than the other regions. For instance, Murphy et al. (1996) found that the male brain showed greater age-related loss in temporal lobes. Raz et al. (1997) also indicated an increased trend of aging in the inferior temporal cortex in males. Finally, previous clinical studies have suggested that the temporal area and medial-temporal regions are related to memory processing. The aging effect in the temporal area might relate to the function of memory in cognitive declination (Braak and Braak, 1991; Mesulam, 1999).

On the other hand, a large number of studies have suggested that the sensory area and occipital lobes are preserved from the effect of aging, unlike other brain areas (Bartzokis et al., 2001; Good et al., 2001; Raz, 2005; Raz et al., 1997). For example, Good et al. (2001) found no significant association between white matter and the effect of aging in the occipital area. Raz et al. (1997) reported that both motor and primary sensory areas have been either minimally affected or remain intact throughout the lifespan. Compared with the other cortical areas, like the frontal area (r = -0.56), temporal area (r = -0.37), and parietal area (r = -0.2), the occipital cortex (r = -0.19) is the least associated with aging in terms of gray matter (Raz, 2000). Furthermore, Lemaitre et al. (2012) did not find any significant age-related reduction in volume, thickness, or surface area of the occipital cortex, and they found fewer aging effects on cortical thickness in the motor-sensory area.

However, some studies suggest that the effect of aging on the occipital lobes is still controversial (Fjell et al., 2009). For example, significant structural declinations were found in gray matter volume (Allen et al., 2005; Resnick et al.,

2003) and cortical thickness (Salat et al., 2004), and a similar delineation was found in white matter volume and white matter integrity (Allen et al., 2005; Head et al., 2004; Madden et al., 2004; Nusbaum et al., 2001; Resnick et al., 2003) in the occipital area.

Finally, some studies have also investigated the relationship between the sub-cortical areas and normal aging. For example, Good et al. (2001) found little or no age effect (relative preservation) in the cingulate sulci, amygdala, hippocampi, or entorhinal cortex. In the anterior cingulate cortex (ACC), the researchers found inconsistent results between the effect of aging and ACC. For example, some studies (Abe et al., 2008; Salat et al., 2004) found that ACC is more preserved than other regions. Other studies (Brickman et al., 2007; Kalpouzos et al., 2009; Tisserand et al., 2002; Vaidya et al., 2007) found age-related reductions in ACC. Lemaitre et al. (2012) also found that entorhinal and parahippocampal cortices showed relative preservation with aging. Their results were supported by previous studies on the parahippocampal area, which is relatively less affected by age than other cortical regions (Raz et al., 1997; 2004; Salat et al., 2004). In contrast, Raz and Rodrigue (2006) found that the hippocampal volume shows a moderately negative association with age, like the amygdala, the cerebellum, and the neostriatum (median correlations ranging: r = -0.30 to -0.43). In addition, some studies reported significant age-related reductions in the volume of the hippocampal region (Bigler et al., 2002; Du et al., 2006; Walhovd et al., 2005). On the other hand, Grieve et al. (2005) observed the sub-cortical regions with a large age scale (7–79 years), demonstrating that

the hippocampal volume is more preserved with other limbic and paralimbic structures. Interestingly, Allen et al. (2005) found that the volume of the hippocampal region remains constant until the seventh decade; it then starts to show a sharp decrease after the eighth decade. Such results suggest that the different regions in the sub-cortical area might have different temporal patterns associated with normal aging, and a large age scale is necessary to observe the subtle differences.

1.2.4 Human cognition changes associated with normal aging

The previous section reviewed both global and regional structural analyses, comparing the findings from postmortem studies as well as the brain image data. These studies concluded that normal brain aging is an overall cerebral atrophy that includes the shrinkage of gray matter volume, cortical thickness, surface area, white matter, and the enlargement of the cerebrospinal fluid spaces in the whole brain analysis. Specifically, the aging effects are significantly strong on frontal cortices, but more moderate in the temporal and parietal areas. In addition, the sensory area seems controversial during aging (Allen et al., 2005; Fjell et al., 2009; Raz et al., 2004; Raz and Rodrigue, 2006). These results suggest that the different brain regions experience aging effects to varying degrees. Although previous studies focusing on the cognitive function have found that human cognitive functions, like memory, attention, inhibition, and processing speed, decline with normal aging (Grady, 1998), it remains unclear whether the declining cognitive functions related to the brain's structural changes are due to normal aging. Are the varying age-associated patterns in different

brain regions related to specific cognitive functions' declination? In this section, we first review the studies on human cognitive functions associated with normal aging. We also discuss the functional changes in brain-imaging studies associated with cognitive functions with aging. This discussion might provide more information on the effect of aging between structural reduction and functional declination.

Plenty of studies have examined the aging declination in cognitive functions across the lifespan. In particular, much of the research focuses on the effect of normal aging associated with various memory declinations in the cognitive task. Episodic memory is especially impaired in normal aging (Brickman and Stern, 2009). For example, Nilsson et al. (1997) found that the cognitive tasks of episodic memory included free recall, cued recall, source recall, and recognition of actions while short sentences, free recall of words, and recognition of names and faces significantly declined. It has been suggested that episodic memory is related to the networks among the frontal, temporal, and parietal lobes (Wagner et al., 2005). In addition, for semantic memory, it has been found that older individuals have significantly impaired performance on memory tests, vocabulary, and general knowledge (Nilsson et al., 1997). Similar results are evident in other semantic-related memory tasks, such as the remembering of proper names (Crook and West, 1990), the naming of common objects (Au et al., 1995; Mitrushina and Satz, 1995), word fluency (Bäckman and Nilsson, 1996), and word production (Maylor, 1990). On the other hand, short-term memory and priming seem to have a relatively stable performance level across the entire

lifespan (Herlitz et al., 1997; Nilsson et al., 1997). Bopp and Verhaeghen (2009) used separate working memory tasks on verbal and visuospatial domains and found that older adults have slower and less accurate controls than younger adults. Other studies have found similar results (Gilinsky and Judd, 1994; Hultsch et al., 1992) by applying different working memory tasks (e.g., reading span, computational span, listening span).

Previous studies have also indicated impairment in the executive function (e.g., attention or inhibition) with normal aging. For example, Guttentag and Madden (1987) found that older adults have impaired attention capacity compared with younger controls on the letter-matching task. In addition, Commodari and Guarnera (2008) conducted a series of multi-tasked computerized assessments, including seven tasks assessing simple reaction times and choice reaction times, visual-spatial and auditory selectivity functions, digit span, divided attention, resistance to distraction, and attentive shifting. The results indicated that older adults have significant age-related reductions in terms of attention span, selectivity, attentive shifting, and inhibition. Even older subjects (over 60 years) showed slow processing on complex tasks and a reduced capacity to inhibit irrelevant stimuli. Anderson, Craik, and Naveh-Benjamin (1998) applied different attention-demanding tasks (e.g., free recall, cued recall, and recognition tasks) to find age-associated impairment in divided attention.

Processing speed also declines on different cognitive tasks. For example, Salthouse (1996) found a systematic lower processing speed in various attention tasks (including memory spend, digit search, stroop task); they concluded that

the decreased speed is due to the fact that the task-relevant operations cannot be successfully executed and the early processing might no longer be available when later processing is complete. Interestingly, Kramer et al. (1999) found that—although older adults showed significantly impaired ability with slower reaction time on task-switching paradigms when the subjects were presented with rows of digits and asked to indicate whether the number of digits (element number task) or the value of the digits (digit value task) were greater than or less than five—the lower performance in older adults can be improved by practice. Moreover, the effect of the extra practice is only obtained with lower memory loads, and older adults were unable to capitalize on practice under high memory loads. Such findings might suggest that the impaired executive ability or cognitive loading in older adults might be able to be compensated with limited resources by recruiting more cognitive resource.

Yet previous studies have also found impaired inhibition related to the attention task (Healey et al., 2008). When older adults were asked to ignore the distracted information during the cognitive task, they maintained a better memory of the distracting features, not the target feature, than the younger controls. These results provide more information on the age-related reduction in inhibitory ability. In summary, the previous works focused on the age difference in cognitive functions and demonstrated that older adults have difficulty with different memory categories (e.g., episodic memory, semantic memory and working memory), executive functions (attention and inhibition), and processing speed. Although cognitive functions declined with aging, some subjects might still achieve the

cognitive task, suggesting that the impaired function could be enhanced or compensated to overcome the task. The next section discusses the current findings related to brain-associated changes with impaired cognitive function using fMRI.

1.2.5 Early studies on de-asymmetric brain activations

The early studies on the cognitive task with fMRI (see Chapter 2 for more details about fMRI) mainly discussed de-asymmetric brain activations in older brains. Generally speaking, some of the cognitive functions in younger adults have been accompanied with asymmetric brain activity. For example, during language processing, the brain is highly activated in the left inferior prefrontal gyrus (IFG, Broca area), angular gyrus, superior and posterior temporal gyrus, and supra-marginal gyrus (Wernicke's areas). Stroke patients with left inferior prefrontal gyrus lesion experience impaired phonological processing (Benson, 1988), language production (Goodglass, 1993), and semantic language suggesting that language is related to left-lateralized brain functions. A similar lateralized effect is also observed in memory and perception ability (Grady, 2012); however, this lateralized phenomenon has been found to decrease in older adults, especially in the frontal areas. For example, Reuter-Lorenz et al. (2000) used different memory tasks to demonstrate that brain asymmetry reduction occurs in verbal working memory and spatial working memory: Older adults have high significant activations in both hemispheres, whereas younger participants only showed high activation in one hemisphere. Moreover, Cabeza et al. (1997) investigated the effects of aging on brain activity during episodic

memory encoding and retrieval stages. In the encoding condition, participants studied word pairs (e.g., parents–piano). In one retrieval condition, the subjects were shown the first word of each pair and had to recall the second word (e.g., parents–???). The results indicated that, compared with younger subjects, older adults showed a more bilateral pattern of prefrontal cortex activity during verbal recall. Cabeza (2002) called this de-asymmetry phenomenon in the aging brain hemispheric asymmetry reduction in older adults (HAROLD), which suggests that, under similar conditions, the brain activity during cognitive tasks tends to be less lateralized in older adults than in younger adults. The evidence from Cabeza's model is supported by functional brain imaging in the domains of episodic memory, semantic memory, working memory, and inhibitory control (Cabeza, 2002). Few theories have tried to explain the de-asymmetric brain activations. The next few sections will introduce some theories to explain the different patterns in brain activations between older and younger adults.

1.2.6 Compensation theory

In compensation theory, early studies on the de-asymmetric brain activations have indicated that older adults might be able to engage some brain areas, particularly from the other side of the frontal area (which have more plasticity to support the extra cognitive loading) to compensate for impaired functioning in the brain. Some studies have indicated that these de-asymmetric brain activations in different cognitive functions are positively associated with performance improvement (Davis et al., 2009; Grady et al., 2005; McIntosh et al., 1999; Reuter-Lorenz et al., 2000). For example, McIntosh et al. (1999) tested

visual short-term memory with positron emission tomography (PET) in both young and old individuals. The results demonstrated that old individuals recruited more areas, including medial temporal and dorsolateral prefrontal cortices, and the amount of these areas was strongly related to their task performance.

Another study applied transcranial magnetic stimulation (TMS) to provide more causation effectuation between de-asymmetric brain activations and performance in cognitive tasks. Manenti et al. (2011) applied TMS to interfere in the brain areas related to episodic memory. TMS uses electromagnetic induction to produce weak electric currents with a rapidly changing magnetic field. Weak electric currents can cause activity in specific brain regions to enhance or interfere with brain functions. In Manenti et al.'s study, subjects were asked to respond to the word pair task. The TMS stimulation was delivered when subjects were encoding or retrieving word pairs on the DLPFC. Their results indicated that, when the left DLPFC was interrupted by the TMS stimulation, older subjects had significantly impaired performance on the word pair task. No significant interference occurred when TMS was induced on the right DLPFC. In addition, younger subjects only showed impaired performance when the right DLPFC was interrupted by TMS. This is the first direct evidence to show that older adults recruit more brain regions to compensate for the impaired function in cognitive tasks. The results suggest that the right DLPFC is necessary during encoding for younger subjects as the interruption on the right DLPFC produced an impaired performance in younger subjects. On the other hand, for older adults, the function of the right DLPFC had already declined, so the effect of TMS

interference on the right DLPFC was not significant. Thus, older adults need to recruit more brain areas in the left DLPFC; then we can observe the largest interference when TMS interrupted the right DLPFC.

1.2.7 Compensation and/or over-recruitment

Compensation can explain some of the early studies that observed de-asymmetric brain activations with improved performance in cognitive tasks. In contrast, the compensation on recruiting more brain areas is not always a benefit to the performance; some studies have also indicated that recruitment of brain activity does not necessarily come with better task performance as over-recruitment. For example, Grady (2012) conducted a meta-analysis comparing the brain activities between two similar experiments, but with different brain activation patterns (see Figure 3; Grady, 2012). Figure 3 shows that the IFG, left inferior parietal lobe, and MFG are highly activated in the older brain, but not in the younger brain as an effect of HAROLD. In one study, the activated brain areas are associated with better accuracy in older adults as compensation. Yet in another study, the same areas are associated with slower responses in older adults and regarded as over-recruitment. Grady (2012) concluded that over-recruitment might reflect a less efficient use of neural resources or a greater demand in the older brain than compensation; thus, greater activation in older adults can sometimes be associated with a poorer, not better, performance. Rypma et al. (2007) also indicated that it might be due to “partial compensation,” suggesting that the compensation might assist older adults’ cognition in a general way, but it cannot replace the specific function required in some cognitive tasks.

For example, the recruitment of the right PFC might help adults carry out more information in an encoding task when the left PFC becomes less efficient; however, this additional right PFC activity cannot compensate for a reduction in encoding effectiveness of the left PFC, meaning it does not provide a benefit for subsequent memory of the encoded items.

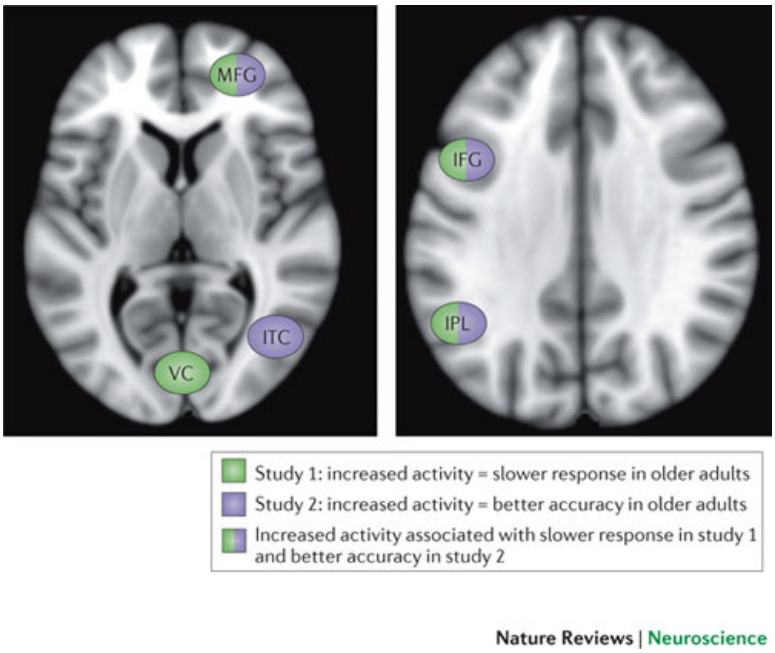

Figure 3. Compensation and/or over-recruitment

Increased brain activity in older adults might be associated with better or worse task performance. This figure summarizes the results of two studies that differ in how increased brain activity in older adults was associated with task performance (Grady, 2012)[3].

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1.2.8 Compensation-related utilization of neural circuits hypothesis (CRUNCH)

Although traditional compensation theory tried to explain the de-asymmetric brain activations in the cognitive tasks, it unfortunately cannot fully explain why some older subjects have de-asymmetric brain activations in the same activation area but with lower performance or slower processing speed, suggesting that compensation does not seem to work for the aging brain in different tasks, such as over-recruitment. For some people, the frontal area might be too rigid and less efficient; thus, the aging brain does not have enough plasticity with the task requiring higher cognitive loading. Reuter-Lorenz and Cappell (2008) demonstrated a more advanced model to include both compensation and over-recruitment reports with different cognitive tasks; this model refers to the compensation-related utilization of neural circuits hypothesis (CRUNCH). In the CRUNCH model (see Figure 4; Reuter-Lorenz & Cappell, 2008, modified by Grady, 2012), different cognitive tasks are classified by different levels of cognitive loading. The model divided different subjects by normal younger subjects (red line), low risk for Alzheimer's disease older adults (low-risk older adults, green line) and high risk for Alzheimer's disease older adults (blue line). According to the model, old adults can engage neural resources, such as the prefrontal areas, in lower task loads for compensation. The relationship between brain activity and cognitive loading is "S" shaped. For example, in relatively lower cognitive tasks (purple shaded area), younger adults (red line) can easily complete the task without increasing any brain activity or

recruiting more brain areas. In contrast, both high- and low-risk older adults need to increase their brain activity and recruit more brain areas to support the task with compensation. However, when the task becomes even harder (green shaded area), the younger adults and low-risk adults can still overcome the cognitive loading with higher brain activity as compensation, but the brain activation of high-risk older subjects has already peaked and is unable to support the cognitive loading with over-recruitment. Finally, when the cognitive task becomes extremely hard (orange shaded area), the increased brain activity from both low- and high-risk older adults becomes less efficient with over-recruitment, and only younger adults can overcome the tasks. This hypothesis included the idea that load-dependent functions can explain why previous studies have reported both under- and over-recruitment in older adults compared to younger adults and in high-risk older adults compared to low-risk older adults. Although the high- and low-risk groups are defined by the risk of Alzheimer's disease in the original report, it can also refer to older subjects who have different levels of cognitive declination and account for both age-related increases and decreases of brain activity described in the previous literature. The results have been found to support the advanced model, like working memory tasks (Schneider-Garces et al., 2010). In such tasks, both older and younger adults were required to report on whether the cue letter is the same as the previous target letter or not. The target letter changed from two letters to six letters to represent different cognitive loads. The results indicated that, when four target letters were used as low set sizes, no significantly increased activation occurred in the younger subjects'

brains; however, older subjects' brains showed significant activation in the left occipital, bilateral parietal, bilateral premotor, bilateral inferior frontal, and medial frontal cortex as compensation. In contrast, when more than four target letters were used (four to six targets as a high set size), no significant activation occurred in the older subjects' brains, and only younger subjects have significant activation in the bilateral parietal and frontal cortex and left occipital cortex. The results provided strong quantitative support for the utilization of neural networks proposed by CRUNCH (Reuter-Lorenz & Cappell, 2008), suggesting that the difference in brain activation that exists between younger and older adults can be entirely accounted for by the difference of cognitive loads for specific cognitive tasks.

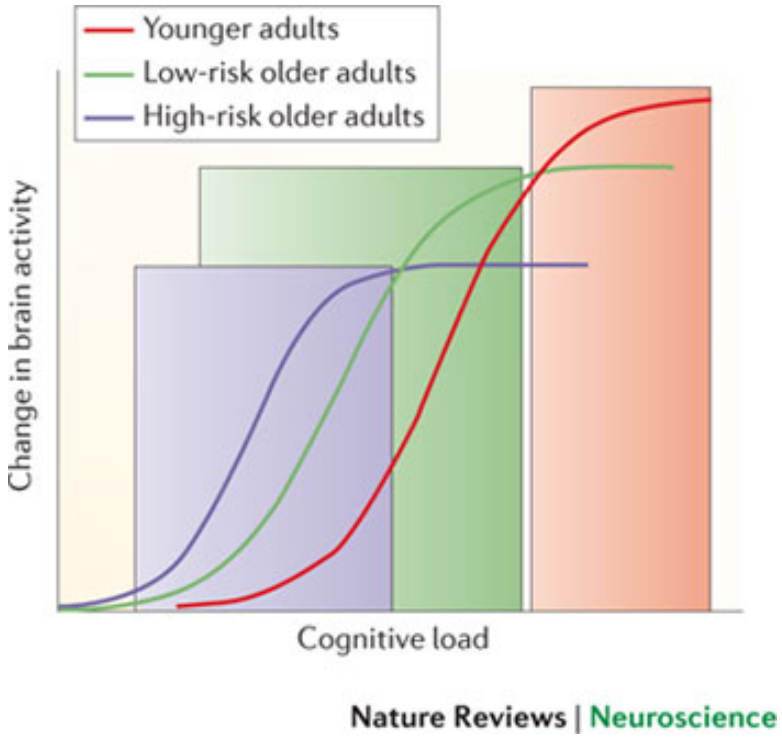

Figure 4. CRUNCH model
(Reuter-Lorenz & Cappell, 2008, modified by Grady, 2012)[4]

1.2.9 Theories of the aging brain

In the previous sections, we discussed the structural and functional changes with normal aging with the cognitive declination. In addition, we found that CRUNCH model can explain how the age-associated brain reduction induced the increased brain activity as compensation from the other cortical areas based on different cognitive loading. In the studies focusing on structural and functional cortical changes, fairly extensive literature has reported that the frontal area and the cognitive function related to the frontal areas (e.g., attention, inhibition) are the most vulnerable areas or functions in the aging brain (Abe et

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al., 2008; Brickman et al., 2007; Good et al., 2001; Resnick et al., 2000; Salat et al., 2004). This raises some important questions: Why does the frontal area have a large aging effect in both cognitive and structural reductions? Moreover, why does aging have a different degree of effect on different brain regions? The following theories will further discuss the relationship between the aging effects among different brain areas.

1.2.9.1 Frontal-aging hypothesis (FLH)

The frontal-aging hypothesis (FLH) focuses on the vulnerability of the frontal lobe and its associated functional declination in the aging brain is frontal-aging hypothesis (FLH). FLH suggests that functions largely dependent on frontal regions decline with normal aging while functions largely independent of frontal lobes remain relatively spared (Dempster, 1992; Hartley, 1993; Moscovitch and Winocur, 1992; West, 1996). FLH further predicts that age-related brain change selectively affects frontal regions. Although we have already found a large number of studies that reported on the reduction in both structural and functional changes associated with declined cognitive function, other cortical areas (e.g., parietal and medial areas) are also significantly influenced by aging and associated with different cognitive functions. Thus, Greenwood (2000) suggested that, whereas the frontal lobes are subject to age-related changes reflecting the cognitive declination, only weak and conflicting evidence exists to suggest that frontal regions are selectively and differentially affected by aging, which might indicate that the effect of aging is not only largely associated with the frontal

regions selectively, but also an age-associated pattern in multiple brain regions. Thus, what is the pattern that is selectively affected by normal aging?

1.2.9.2 Last in, first out and first in, last out: A sequential declination pattern of aging brain

Regarding the previous question, the last in, first out model hypothesis suggests that the brain regions that are late to mature or develop are first to be affected by aging (Raz, 2005). The last in, first out model not only includes the concept of the frontal-aging hypothesis, but also extends the age-associated regions to the brain structural maturation patterns. Notably, the last in, first out model is strongly supported by Flechsig's myelinogenesis theory. German neuroscientist Paul Flechsig (1901) found that the development of myelins, which are the sheath around nerve fibers in the brain, are followed by sequential development processing. He studied the brains of the fetuses and newborns by staining for myelin. His findings suggest that the time window is about two months before and after birth, during which time most of the cerebral cortical areas are myelinated, but the myelination continues its final development until adolescence. According to Flechsig’s observation, the first cortical region starts to myeline from motor and sensory areas, followed by the myelination in the anterior cingulate cortex and the inferior temporal cortex. Finally, the prefrontal cortex is one of the last regions to complete maturation. Raz et al. (2000) measured 11 cortical regions in the regression of the magnitude of age effect based on the report of the Flechsig myelination precedence rank, including DLPFC, orbitofrontal cortex (OFC), inferior temporal area, inferior parietal lobule,

superior parietal cortex, anterior cingulated gyrus, motor cortex, visual cortex, hippocampus, somatosensory cortex, and fusiform gyrus. The results indicate that the relationship between the effect of aging and those regions linearly follow the Flechsig myelination precedence. Moreover, the DLPFC and OFC seem have even larger aging effects than predicted from Flechsig's model. Lemaitre et al. (2012) found that the age-associated reduction in cortical thickness and the gray matter volume changes showed a diffused pattern as the last in, first out model. The reduction was observed largely in inferior, middle, and superior frontal gyri, followed by precentral, paracentral, precuneus, and posterior cingulate gyri.

In addition to the observation on the gray matter, the similar evidences from white matter analysis also support the last in, first out model hypothesis. Davis et al. (2009) conducted tractography measures on FA values between older and younger adults based on diffusion-weighted images. They selected the five main white matter tracks: the genu and the splenium part of the corpus callosum, the inferior longitudinal fasciculus (ILF), the uncinate fasciculus (UF), and the cingulum bundle (CB). Their results indicated that the age-associated difference was significant, followed by the linear relationship from more posterior parts (occipital lobe) to anterior regions specific to the frontal lobes, which indicated that age-related white matter in the FA values was more pronounced in the anterior (prefrontal lobe) than in the posterior brain regions (medial and occipital lobes).

In summary, the early studies found that that there might be a gradient of aging effect from the prefrontal brain areas to the primary sensory regions (Flood and Coleman, 1988). In addition, the last in, first out model suggests that the age-associated declination is highly related to the neural maturation precedence. The late maturation brain areas (e.g., frontal lobe) have a larger aging effect on both structural and cognitive declinations and further suggest that early maturation should have less of an aging effect on the brain's structural and preserved performance in cognitive tasks. If so, during aging, the occipital cortex (including early visual areas) might reserve more function and plasticity, which relates to the occurrence of VPL in older adults.

1.3 Problem statement and study rationale

1.3.1 Can older people achieve VPL like younger adults?

The literature review on aging and the brain suggests that the frontal area is more significantly affected during normal aging whereas the occipital area seems more preserved. As VPL is related to the cortical changes in the early visual area in younger adults, it might also be related to the cortical plasticity in the early visual area; therefore, older adults should be able to enhance their ability through perceptual learning training, as younger adults can. The performance between older and younger adults should be less distinct compared with other cognitive tasks, which might rely on the cognitive loading in the higher cortical area with larger age-associated declinations. Thus, it is worth investigating the effect of visual perceptual learning in older adults.

1.3.2 Underlying neural mechanism of VPL in older adults

If older adults can obtain VPL, what is the underlying mechanism of VPL in them? Will older adults have different neural mechanisms than younger adults due to the impaired cortical functions? It has been suggested that VPL is related to cortical changes in the early visual area. For example, Yotsumoto et al. (2008) found that VPL is associated with BOLD activation changes in the early visual area V1 as cortical plasticity. Thus, the examination of VPL might also help us test the effect of aging in the occipital lobe, including early visual areas. For example, if the occipital area is more preserved than other areas, does older adults' early visual area have the same plasticity as that of younger adults? If the cortical area corresponding to VPL is better able to resist the effects of aging due to the reserved cortical structure, we should be able to observe similar cortical activity changes as in younger adults. On the other hand, if the cortical area corresponding to VPL has more impairment due to aging, we might not be able to observe the VPL in older adults or might not see the similar cortical changes as in younger adults. For example, we might find more brain activations in the aging brain as compensation with VPL. As a result, we apply different brain-imaging observations, including both functional and structural imaging, to investigate the difference between older and younger brains with VPL.

1.3.3 How age-associated morphological changes affect VPL

Based on the first in, last out hypothesis, the occipital lobe including early visual areas should have less age-associated reduction; however, compared with other cortical areas, the brain structural studies focused on the effect of aging on

the occipital lobe still seem controversial (Fjell et al., 2009). In addition, some studies have indicated that the areal size in early visual area V1 is related to the visual function (Schwarzkopf and Rees, 2013). If VPL is related to the changes in the lower cortical area, it could suggest that the age-associated morphological changes will also relate to the performance in VPL rather than the higher cortical area. Thus, it is necessary to observe age-associated differences among the early visual areas and evaluate their relationships using VPL.

1.3.4 Effect of attention on VPL in older adults

The literature discussed thus far has indicated that the frontal area is subject to the largest aging effect. The frontal area influences human cognitive functions, like working memory, attention, inhibition, executive functions, and processing speed. As attention and inhibition functions largely decline with aging, inhibition from the attentional control system to the salient task-irrelevant feature around the suprathreshold might be weaker in older people. In younger adults, the TIPL from the suprathreshold exposure has been shown to be inhibited by the attention system. If attention declines due to aging, older adults should have a different performance in TIPL compared to younger adults. For example, TIPL should occur with suprathreshold as well as subthreshold feature signals in older people due to their impairment in the attention control system.

1.4 Research aims

Based on the literature reviewed and the problem statements, the current dissertation research aims to investigate and clarify the following two main questions: (1) Does perceptual learning in older adults enhance performance in a

visual task? (2) If older adults can obtain VPL like younger adults, what is the underlying neuronal mechanism in the perceptional learning in aging? In order to investigate the underlying mechanism of perceptual learning in aging, we will conduct a systematic observation of both functional and structural changes using standard VPL training. Finally, we will examine the effect of attention on older adults in VPL, applying the TIPL paradigm.

2. Chapter 2: Methodology

To address the identified questions, we will apply both structure and functional MRI to examine whether an aging-associated change occurs in the brain structure or brain function related to the performance of VPL. Here, we first review and evaluate different MRI tools in the field of cognitive neuroscience of aging field and its applied data analysis methods.

2.1 Magnetic resonance imaging (MRI)

MRI is a non-invasive imaging technique with a wide range of applications, like clinical diagnosis or medical treatment. MRI has recently become a common medical imaging technique used to visualize the structure and function of the brain (Logothetis, 2008). The idea of MRI was first presented by Herman Carr in 1952; at that time, it was mainly used for studying the chemical structure of substances. In 1972, Paul Lauterber expanded Carr's technique and successfully generated the first MRI images using different gradient techniques (Frackowiak et al., 2003). MRI uses the resonance of the protons to generate images. The basic idea is that the tissue of the brain consists of water molecules with hydrogen nuclei or protons. When the individual is inside the magnetic field of the scanner, each hydrogen proton in the brain is attracted by the strong magnetic field and aligned with the direction of the field. When the magnetic field is off, the protons relax and return to the thermodynamic equilibrium in random directions.

Different tissues have different relaxation rates. If we turned the magnetic field on and off using different radio-frequency (RF) pulses, we can measure the

variations in the electromagnetic field from different brain tissues to generate image contrast from the receiver coils (Frackowiak et al., 2003). In addition, the quality of the brain image is related to the magnetic field strength. Higher magnetic fields will increase the signal-to-noise ratio and provide a higher resolution of the brain image. There are many advantages of applying MR technology in brain structural and functional measures. First, MRI is a non-invasive technique. It is quite safe for people during operations and under observation compared with the other brain imaging tools like computed tomography (CT) or X-rays, which produce radiation. Another advantage of MRI is that it provides much greater contrast between the different soft tissues of the brain than the other brain-imaging tools (Gazzaniga et al., 2002).

2.2 MRI for brain structural measures

In an MRI study, mainly two different MR pulse sequences are used for the structural analysis: T1-weighted images and diffusion-weighted images. Basing the application on these two main MR sequences, we reviewed and summarize four methods of brain structural analysis: voxel-based morphometry (VBM), surface-based morphometry (SBM), fiber-tracking analysis (FT), and tract-based spatial statistics (TBSS). VBM and SBM are based on the images obtained from a T1-weighted MRI whereas FT and TBSS are based on the images obtained from diffusion-weighted MRI.

2.2.1 T1-weighted imaging and diffusion-weighted imaging

T1-weighted imaging is one of the most common MRI pulse sequences and demonstrates the differences in the T1 relaxation time of tissues (Frackowiak

et al., 2003; Gazzaniga et al., 2002). T1 longitudinal relaxation time is a constant time that refers protons back to the thermal-equilibrium status. Compared with another MRI pulse—namely, the T2-weighted image—T1-weighted images have short TE (the echo time) and TR (repetition time) times. Different brain tissues have their own physical characteristics related to the magnetic fields; thus, they demonstrate different levels of brightness in the T1-weighted image. For example, fat has a large longitudinal and transverse magnetization, so it will appear brighter on a T1-weighted image. On the other hand, water has less longitudinal magnetization; therefore, it will reflect a low signal and appear darker on the image. As a result, the cerebrospinal fluid appears darker in the T1-weighted brain images while white matter, which has more fat tissue, appears brighter in the brain images. Based on these differences, we can use brain morphological tools to measure and compare the differences of these images.

Meanwhile, diffusion-weighted imaging (DWI) is another magnetic resonance imaging technique that enables the measurement of the restricted diffusion of water in tissue to produce neural tract images measured by diffusion weighted tensor imaging (DTI). Compared with T1-weighted images, which have different contrasts for different brain tissues, in DWI, each voxel on the image reflects a single best measurement of the rate of water diffusion at that location (Lee et al., 2005). Ideally, free diffusion occurs equally in all directions, which is called “isotropic.” We know that the water diffusion inside the brain is “anisotropic” diffusion, which suggests that the brain’s neural axons of white matter have their own fibrous structure as the anisotropy structure. Thus, water

diffuses rapidly in the direction aligned with this fibrous structure. As result, if we can measure and estimate the most likely direction of water diffusion inside the brain, we can build up a statistical structure to represent white matter or the neural axons structure as neural tracts (Conturo et al., 1999). In DTI, each voxel has one or more pairs of parameters: a rate of diffusion or a preferred direction of diffusion with in a three-dimensional space. Anisotropy can be measured in several ways. One way involves calculating a diffusion ratio: FA. FA is a measure of the orientation coherence of water self-diffusion (Tuch et al., 2005) that can quantify the most possible directionality of water diffusion. An anisotropy with an FA value of “0” corresponds to a perfect sphere, whereas an FA value of “1” is an ideal linear diffusion. FA suggests reflecting anatomical features of white matter, like fiber density, axon caliber, and myelination, and is regarded as the most commonly studied parameter (Imfeld et al., 2009) in DWI.

2.2.2 Voxel-based morphometry (VBM)

Voxel-based morphometry (VBM) is one of the earliest developed tools for analyzing the brain structure based on the different contrast voxel-wise comparison of spatial normalized T1-weighted images (Ashburner and Friston, 2000). VBM is effective for identifying the differences in relative voxels of brain structures in whole-brain analyses to characterize volume and tissue differences in the specific region of interest. In general, the procedures of VBM analysis can be divided into two parts: T1-weighted imaging preprocessing and the voxel-based parametric statistical analysis. The procedures of the preprocessing involve spatial normalization, segmentation, and smoothing (Ashburner and

Friston, 2000; Greve, 2011; Mechelli et al., 2005). Finally, a voxel-wise statistical inference is applied to these preprocessed images.

During the processing, the T1-weighted images from individuals are spatially normalized to a group template (see Figure 5) to help the user establish a voxel-by-voxel correspondence matrix across all subjects. After normalization, the local areas for individuals are stretched and compressed with each other using non-linear registration processing. The VBM subsequently creates a deformation field to apply the individual T1-weighted images to register on the group template, so we can compare the individual differences in common group templates. In addition, VBM provide an optional step called modulation. In order to correct for the volume changes due to the registration, the volume is also calculated by multiplying the parameter of the modulation using Jacobian determinants of the deformations to register the brain to the template. For example, in Figure 5 (Greve, 2011), the volume is red/yellow in the area of the Jacobian map that needed to be compressed and blue in areas that needed to be stretched based on modulation. The value at a voxel in the modulated image is interpreted as the volume of gray matter at that location. After spatial normalization, the deformed image is segmented into different parts based on their intensity in the images or the tissue feature with their location to gray matter, white matter, and cerebrospinal fluid. Finally, every individual image is spatially smoothed using the Gaussian kernel. The goal of smoothing is to make the population in the images more normally distributed and reduce the registration

error. Usually, an 8 mm or 12 mm full width at half maximum (FWHM) smoothing kernel is used in the VBM method.

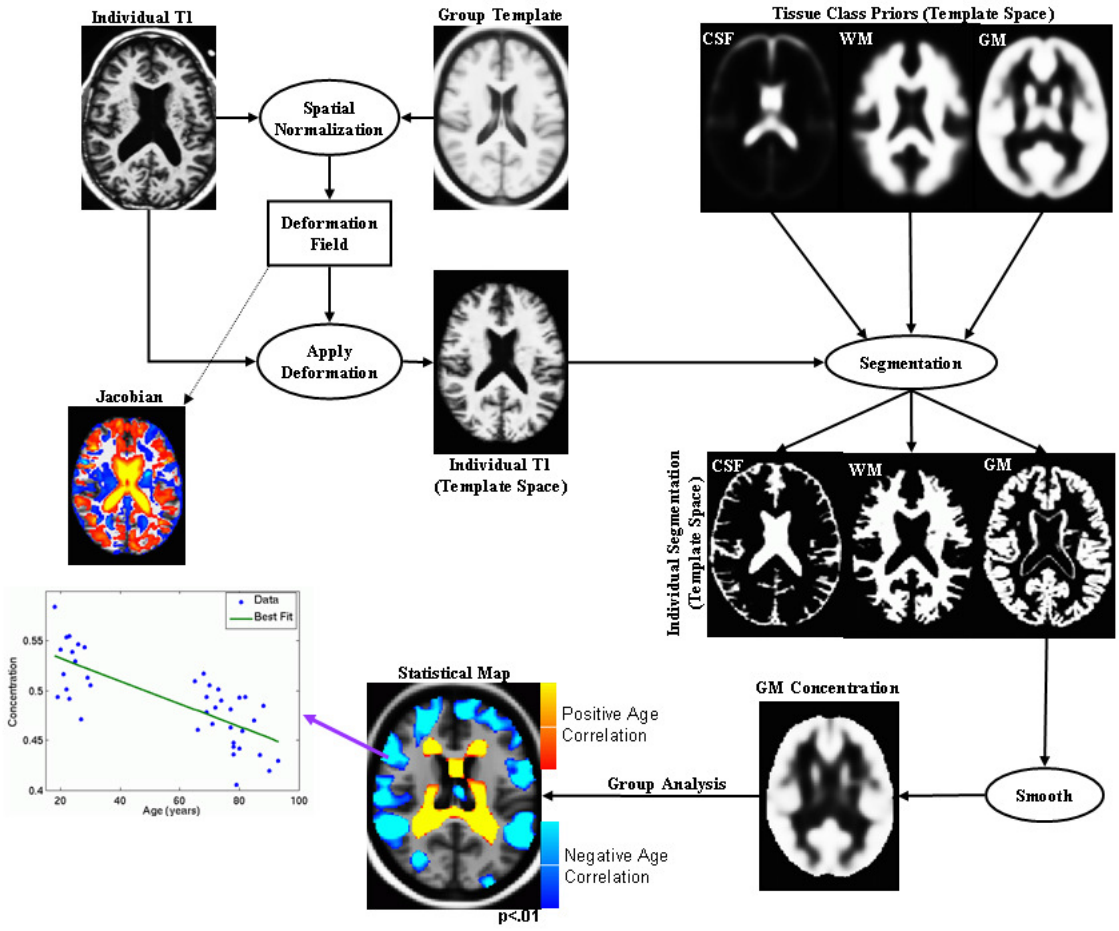

Figure 5. Processing stream of VBM analysis
(Greve, 2011)[5]

In voxel-based statistical analysis, the preprocessed images are characterized regionally between different groups. The analysis uses a two-sample *t*-test to calculate the significance between groups at every single voxel. The *t*-test map is projected on a normalized 3D-shape volume, and the

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dimension and size are the same with every MR image. Thus, we can interpret the statistical results based on group differences by voxels in the *t*-test map above the significance level. Overall, the VBM analysis is popular and dominant in brain structure studies in different fields. Currently, Statistical Parametric Mapping (SPM, www.fil.ion.ucl.ac.uk/spm) using the VBM toolbox (dbm.neuro.uni-jena.de/vbm) and FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl) provides users with VBM analysis.

2.2.3 Surface-based morphometry (SBM)

In addition to VBM, the T1-weighted images can be analyzed using surface-based morphometry (SBM). Currently, FreeSurfer (surfer.nmr.mgh.harvard.edu), Brain Visa (brainvisa.info), CARET (brainvis.wustl.edu/wiki/index.php/Main_Page), and Brain Voyager (brainvoyager.com) applying the SBM analysis. Here, we will discuss the process stream of FreeSurfer, which was developed by Massachusetts General Hospital NMR Center (Fischl, 2012; Greve, 2011).

FreeSurfer contains two main processing streams: volume-based stream and surface-based stream (Dale et al., 1999). The volume-based stream is designed to process MRI volumes and label the sub-cortical tissues whereas the surface-based stream can contract models of boundaries between white matter and cortical gray matter for morphological analysis. Unlike the preprocessing in VBM, SBM processes the T1-weighted image from the extraction of the cortical surface. First, the whole brain volume is registered with the Talairach atlas (Talairach and Tournoux, 1988), so FreeSurfer can compute each seed point at

later stages. In the second stage, the brain skull is removed applying a deformable template. The possible white matter points are chosen based on their locations in the Talairach space, comparing their intensity and the local neighborhood intensities. In addition, the brain is segmented into different hemispheres, and the cerebellum and brain stem are removed to cutting planes based on the Talairach location of the corpus callosum and pons. Rules-based algorithms encode the expected shape of the structures. During the third stage, an initial surface is generated for each hemisphere following the intensity gradients between the white and gray matter as the white surface. The white surface is then pulled to follow the intensity gradients between the gray matter and cerebrospinal fluid as the pial surface. The distance between the white and the pial surfaces represents the thickness at each location of the cortex (see Figure 6G; Greve, 2011).

In FreeSurfer, the surface model counts as a mesh of triangles like faces (see Figure 6D). The cross-point of each triangle is called a vertex. FreeSurfer calculates the coordinates (i.e., the X, Y, and Z) at each vertex and represents the brain space as a 3D shape (Figure 6C), inflation representation (Figure 6E), curvature representation (Figure 6F), or sphere (Figure 6I). Finally, the spatial information of these coordinates allows the users to calculate the morphometric measures. For instance, the surface area can be computed by summing up the areas of the triangles in the defined region of interest (ROI). In addition, the distance between the white and pial boundaries counts as cortical thickness (see Figure 6G). Few studies have compared the analysis of the same T1 images

analysis between VBM and SBM. It has been suggested that FreeSurfer is applying inter-subject registration, which will have better matching of the homologous cortical regions than volumetric techniques (Greve, 2011). FreeSurfer also allows users to measure two components of volume separately (like thickness and surface area) as these do not necessarily match one another (Lemaitre et al., 2012).

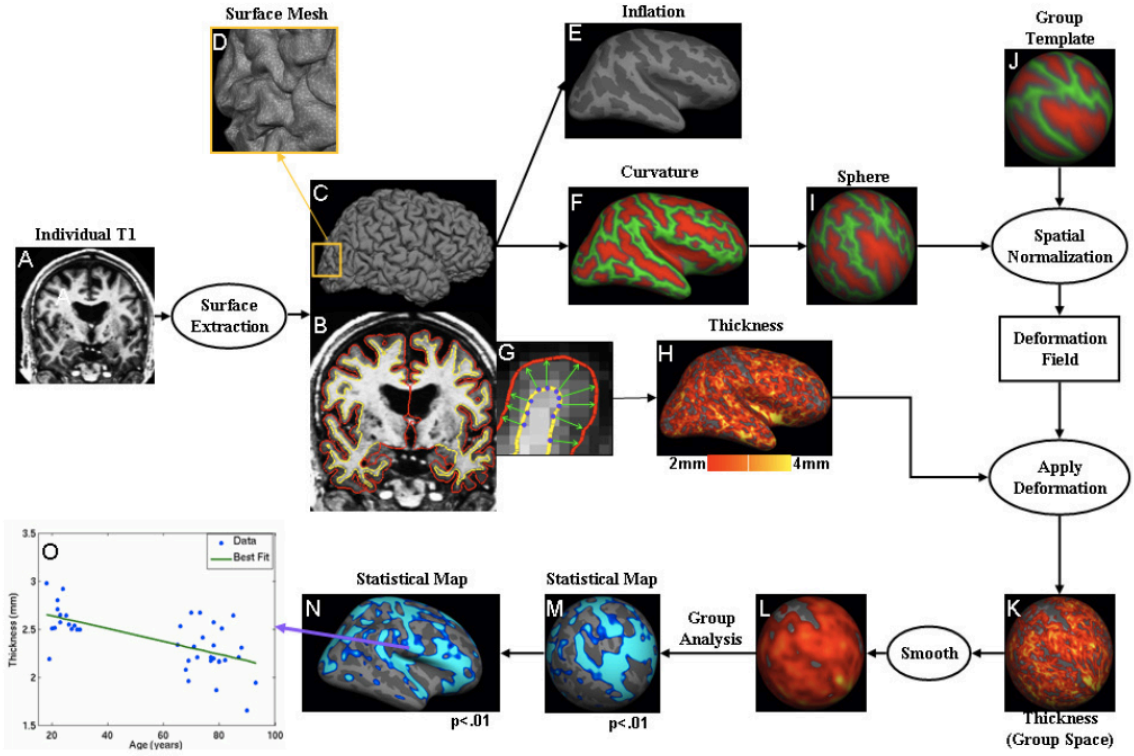

Figure 6. Processing stream of VBM analysis
(Greve, 2011) [6]

In conclusion, unlike VBM, which analyzes the image property voxel by voxel, SBM constructs and analyzes surfaces from geometric models of the

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cortical surface representing different structural boundaries of the brain. Thus, SBM might provide more information on the structural changes on the areal space among the cortex than VBM. In Chapter 4, we used SBM analysis-applied retinotopic method to examine the effect of aging on the areal space among the surface of the early visual cortex and discuss the relationship between the structural difference in the early visual area and visual plasticity in the older adults.

2.2.4 Fiber tracking (FT)

The DTI tractography technique (also called fiber tracking [FT]) reconstructs the 3D trajectories of white matter tracts, generally by following a continuous path of greatest diffusivity through the brain (Catani et al., 2002). The high information content of a DTI voxel makes it extremely sensitive to subtle pathology in the brain, and it can reveal the macroscopic anatomy of white matter tracts.

To preprocess the DWI, all diffusion-weight images are first aligned to a non-diffusion-weighted image using non-linear 2D registration (Jezzard et al., 1998) to reduce the distortions. Second, the 3D rigid registration to the non-diffusion-weighted target image is applied to corrected motion artifacts (Woods et al., 1998). Finally, using the tractography algorithms, we can include the strongest anisotropy in each pixel and compare the difference with the surrounding pixels' angles to find the most possible pathway for the fibers. One common algorithm is the deterministic algorithm, which traces the tract by

determining the best direction in each voxel and building up the best possible direction from the seed and target ROIs.

Yet how can we select the fibers we want and compare them with other subjects? The most common method is called two regions of interest (two ROIs; Catani et al., 2002). For example, we wanted to examine the main pathway between frontal area and temporal areas on the 3D white matter track map, like uncinate fasciculus. First, we defined one ROI on the frontal lobe and another ROI based on the anatomical T1-weight image. We subsequently kept only the fibers that passed through the two target ROIs to isolate the uncinate fasciculus. When we keep the fasciculus we need, how do we conduct the statistical analysis on it? One way to quantify the tractography is called track count, which calculates the number of streamlines comprising a particular tract and compares them quantitatively between subjects.

2.2.5 Tract-based spatial statistics (TBSS)

Tract-based spatial statistics (TBSS)—like VBM, which compares the image volume across the brains at every voxel using a statistical test from two groups in T1-weighted images—is another voxel-wise analysis comparing the FA values between groups in DWI. Unlike VBM, the TBSS stream does not include linear registration and smoothing to keep more detailed information from the image. Four steps are included in processing DWI (Smith et al., 2006). First, TBSS identifies a common registration target and aligns all subjects' FA images to this target using nonlinear registration. The common registration could be a group template or one specific brain model. Second, TBSS creates a mean of all

aligned FA images and applies a “thinning” skeleton-based mean FA image. The FA skeleton obtains a threshold to suppress the areas of low mean FA and/or high inter-subject variability. Third, TBSS projects each subject’s (aligned) FA image to the skeleton by filling the skeleton with FA values from the nearest relevant tract. Finally, we can conduct voxel-wise statistics to compare the FA value across subjects on the skeleton-space FA data. Compared with VBM, TBSS creates a group mean FA skeleton, which is suggested as the centers of fiber clusters generally common to the subjects involved in a study and has been regarded as a better solution for the alignment and smoothing issues in VBM (Smith et al., 2006).

In conclusion, for the white matter analysis, FT can avoid the registration confounding associated with voxel-based analyses of DTI data (Alexander et al., 2007), and it can process three-dimensional information of diffusion-weighted data to reveal the larger scale of the network connection between different cortical areas than the TBSS. In addition, TBSS still has limited information on the directional information in the two-dimensional space of the diffusion data; however, TBSS can assemble a shorter range of tracts and can focus more on the specific region in which we are interested, like the space underneath the early visual area. Thus, we applied TBSS rather than FT in white matter structure analysis to examine the effect of aging with PL training (see Chapter 3).

2.3 MRI for brain functional measures

What is the underlying brain mechanism for the specific cognitive function declination associated with aging? Although we can compare the longitudinal

brain structural information from the T1- and diffusion-weighted images, unfortunately, these cannot provide more instant information on brain activity during the cognitive process. In order to find the underlying brain mechanism for cognitive declination associated with aging, cognitive scientists started to apply new technologies involving more time-sensitive observations in cognitive neuroscience, including electroencephalography (EEG), PET, magnetoencephalography (MEG), TMS, and fMRI to build up more direct relationships between specific cognitive functions and brain activity (Frackowiak et al., 2003; Gazzaniga et al., 2002). Among these technologies, fMRI is widely used to investigate regional brain activity during cognitive tasks. Unlike traditional brain structural analyses applying T1- or diffusion-weighted image data, fMRI analyzes the BOLD signal, a change in the signal strength of brain water protons produced by magnetic effects of blood deoxygenated hemoglobin (dHb) in contrast to the T2-weighted images (Amaro and Barker, 2006). Thus, by comparing the oxygen-rich and oxygen-pool signal ratio in the T2-weighted brain image, the fMRI data can reveal the areas related to the cognitive functions that require more blood supply and change the MR signals as a hemodynamic response (HDR). fMRI has been found to provide an overall good spatial resolution (Bandettini, 2009) but relatively poor time resolutions (few seconds) compared to EEG or MEG (milliseconds).

2.3.1 Function MRI in aging study

Regarding fMRI studies with older adults, previous studies have concluded that the amplitude BOLD signal in the aging brain can be reduced,

which might be due to vasculature structural changes (Buckner et al., 2000). For example, Kannurpatti et al. (2010) found on average a lower BOLD signal response amplitude for older adults on motor tasks, cognitive task, and breath-holding control task than younger brains. However, the authors also concluded that the impact of aging on the BOLD signal is relatively small during cognitive tasks and encouraged the continued use of the fMRI technique on the cognitive neuroscience and aging. Thus, in Chapter 3, we compared the BOLD signal changes before and after the PL training among the early visual areas with both older and younger adults to examine the effect of aging.

3. Chapter 3: White matter in the older brain is more plastic than in the younger brain (joint effort with Yuko Yotsumoto)

3.1 Introduction

Human brain processing declines with aging (Brehmer et al., 2008). However, many age-related declines in function can be to some degree restored by practice. It has been generally thought that such restoration is mainly due to reorganization of cortical areas (de Villers-Sidani et al., 2010; Dinse, 2006).

Visual perceptual learning (VPL) is defined as performance improvement on visual tasks due to practice or exposure to visual features (Adini et al., 2004; Dosher and Lu, 1998; Fahle and Poggio, 2002; Karni and Sagi, 1993; Karni et al., 1994; Law and Gold, 2008; Sasaki et al., 2010; Schoups et al., 2001; Seitz and Watanabe, 2003; Watanabe et al., 2001; Yang and Maunsell, 2004; Yotsumoto et al., 2008). It has been shown that VPL is also possible with older individuals (age 65+) (Andersen and Enriquez, 2006; Andersen et al., 2010). The important question is what neural substrates correspond to VPL in older adults. Research has shown that, in younger human subjects, the functional brain activation changes in the early visual cortex are involved in VPL (Furmanski et al., 2004; Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008).

However, there are several age-related cortical differences that may limit VPL for older adults. First, the cortical gray matter volume declined with normal aging (Allen et al., 2005; Courchesne et al., 2000; Good et al., 2001; Lemaitre et al., 2012; Raz et al., 1997; Sherwood et al., 2011). Second, the cortical thickness

becomes thinner with normal aging (Fjell et al., 2009; Kochunov et al., 2011; Lemaitre et al., 2012). Third, lower cortical activations were seen on cognitive (Kannurpatti et al., 2010) and visual (Buckner et al., 2000) tasks in older as compared to younger adults.

In contrast to the cortical structure and function, there is evidence that the white matter for older individuals may be relatively preserved in the occipital region (Davis et al., 2009; Fjell et al., 2008). Thus, it may be possible that VPL in older individuals exploit white matter instead of gray matter. In the present study, we tested whether changes in neural processing due to VPL are similar for older and younger individuals. We used magnetic resonance imaging (MRI) to measure brain activation with functional MRI (fMRI) and white matter architectures with diffusion tensor imaging (DTI), in younger and older subjects.

3.2 Methods

3.2.1 Subjects

Eighteen older adults (11 females) aged 65-80 (mean = 72.2, SD = 5.4 years old), and 21 younger adults (7 females) aged 19-32 (mean = 22.9, SD = 2.9 years old) participated in this study. Diffusion tensor imaging (DTI) scan was not conducted with one of the older subjects due to a technical difficulty. Thus, a total number of 17 older subjects were used and DTI data were analyzed. All subjects had normal or corrected-to-normal vision. Older subjects were recruited through the Harvard Cooperative on Aging, and were screened for dementia using the Mini Mental Status Examination. All subjects were healthy and subjects were excluded if they had a dementia, a history of neurological of psychiatric

disorder, or serious cardiovascular disease. All subjects gave written informed consent for their participation in the experimental protocol approved by the Institutional Review Board at Massachusetts General Hospital, University of California Riverside, Keio University and Boston University, where experiments were carried out.

3.2.2 Experimental schedule

Two MRI sessions including fMRI and DTI were conducted approximately one week apart, and three training sessions were conducted between the two MRI sessions (Figure 7A). Each MRI session lasted about two hours, and each training session lasted about 45 minutes. All sessions were conducted on separate days, so that it took at least 5 days to complete the entire session. Additionally, older subjects took the Useful Field of View test (UFOV, Visual Awareness Research Group Inc) after each MRI session to test whether attentional capacity changed as a result of TDT training (Andersen et al., 2010) (see Figure 8 for the results). The UFOV results ruled out the possibility that the performance improvement with the older subjects was due to a change in attentional capacity, suggesting that the performance improvement in TDT involved the sensory level (Andersen et al., 2010), as has been found for younger individuals (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008).

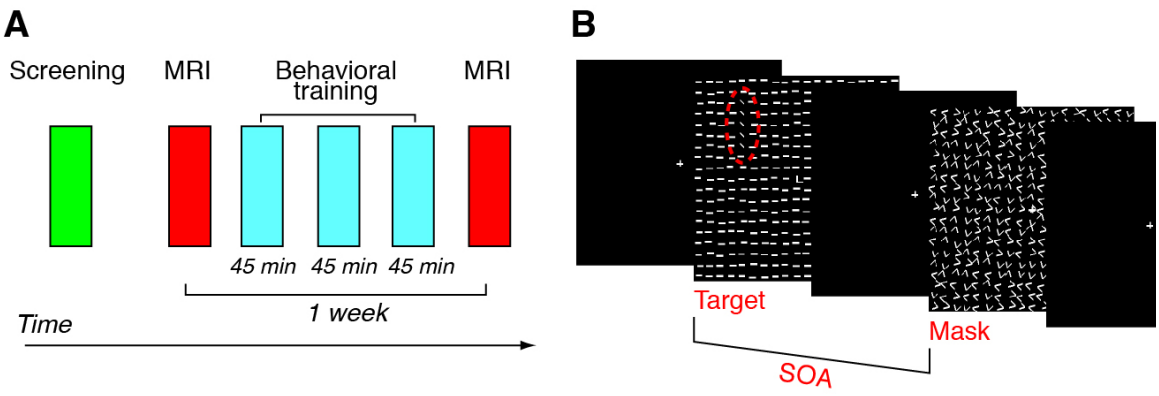

Figure 7. Experimental procedure

(A) The complete experimental procedure. (B) The procedure of each trial. The time interval between the onsets of a target display and a mask (SOA) was varied. The red dotted ellipse indicates the target location. It is for an illustrative purpose and did not appear in the experiment.

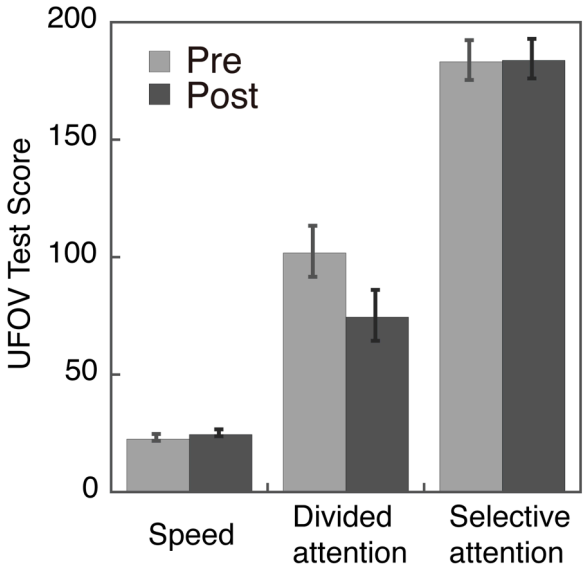

Figure 8. The results of the UFOV test with the older group

There was no significant difference in processing speed, divided attention or selective attention between the sessions before and after training (for processing speed, $t(17) = 0.46$, ns; for divided attention, $t(17) = 1.99$, ns; for selective attention, $t(17) = -0.77$, ns).

3.2.3 Task and stimuli

We employed TDT (Karni and Sagi, 1991), in which a test stimulus was briefly presented and followed by a blank screen and a mask stimulus (Figure 7B). The test stimulus consisted of a centrally located letter, either a 'T' or a 'L', and a peripherally positioned horizontal or vertical array of five diagonal bars on a background of horizontal bars. Each line segment was arranged within a 19-by-19 lattice in the area of an 18-by-18 visual angle. Viewing distance was 57 cm in the training sessions as well as in the MRI sessions. Subjects answered whether the central letter was either T or L, and whether the target array was either horizontal or vertical, by pressing buttons. The letter task was to ensure that subjects fixate at the center of display. The orientation task was the main task, which improves with training. The target array was presented at 3-7 degrees from the fixation in one of the visual quadrants. Task difficulty was determined by stimulus-to mask onset asynchrony (SOA). The task was easier with longer SOA.

3.2.4 Training sessions

Throughout the training, a target was constantly presented within the same quadrant, which was either in the left or right upper visual field. Assignment of the trained quadrant was counter-balanced across the subjects. A set of five SOAs was used in the training sessions. A set of [2000, 1000, 500, 250, 125 msec] or [500, 250, 200, 150, 125 msec] was used for older subjects. Which set to be used was predetermined by their performance in the screening session, in which 20 practice trials were conducted at the very beginning of the experiment. Subjects used the same SOA set during training. This arrangement was used to

control for individual differences in task difficulty for older subjects. The SOA set was [200, 150, 100, 75, 50 msec] for younger subjects. The duration for the target stimulus was 100 msec for older subjects, and 20 msec for younger subjects, respectively. Each training session consisted of 72 trials per SOA, resulting in a total of 360 trials per session. According to the original study (Karni and Sagi, 1991), the trials with the same SOA were blocked. The trials started with the longest SOA, which was gradually reduced in order. The 80% threshold SOA was estimated from a psychometric function where the percentage of correct responses were plotted against the various SOA, according to the previous study (Yotsumoto et al., 2008).

3.2.5 fMRI for TDT

A 3 Tesla scanner (Trio, Siemens, Erlangen, Germany) was used for all MRI sessions. The fMRI experiments tested two conditions for presentation of the target arrays. Target array was presented either in the upper left or at upper right visual quadrant; one of which was the trained quadrant as in the training session and the other was the control quadrant (untrained quadrant) that was not trained during the training session. Unlike the training session, only one SOA was used during the MRI session (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008). The length of SOA was chosen from the initial screening session so that the correct response would be about 50-60 % before the training for the older subjects. All younger subjects were tested with the SOA of 100 msec. The target durations were 100 msec for older subjects and 20 msec for younger subjects, respectively. There were a total of 96 trials for each of trained

and untrained conditions. A single trial lasted 2 sec, and each block lasted 18 sec. One fMRI scan lasted 224 sec, and was repeated 6 times. There were a total of 96 trials per condition per session.

3.2.6 fMRI for retinotopic mapping

We individually localized V1, V2, and V3 areas functionally using a standard flickering checkerboard pattern (Fize et al., 2003; Yotsumoto et al., 2009; Yotsumoto et al., 2008), to identify retinotopic representation of horizontal and vertical meridians of the visual fields, as well as the trained and untrained regions (3-7 degrees eccentric from the fixation, in the upper left and the upper right visual field for either the trained and untrained regions, respectively). In the localizer scans, a total of 5 types of visual stimuli were presented with a gray background: (1) horizontal checkerboards (two of 12-deg wedges centered on the horizontal meridian axis, and symmetric to the fixation point at the center of the display), (2) vertical checkerboards (2 of 24-deg wedges centered on the vertical meridian axis and symmetric to the fixation point), (3) checkerboards placed in trained and untrained visual fields, (4) a 168-deg wedge-shaped checkerboard placed in the upper visual field where the 2 parts that correspond to the trained and untrained regions were just in gray color, and (5) no checkerboard but a fixation. These stimuli were presented in counterbalanced orders in a blocked manner. Each block lasted 12 seconds. Each scan lasted 240 seconds, and was repeated twice.

All functional MR images were acquired using gradient echo EPI sequences (TR = 2 sec, TE = 30 ms, Flip Angle = 90 deg) for measurement of

BOLD contrast. Thirty-three contiguous slices (3 x 3 x 3.5 mm^3) oriented parallel to the AC-PC plane were acquired to cover the entire brain. The slices were positioned using an automatic slice positioning technique (van der Kouwe et al., 2005). Data were analyzed with the FS-FAST and FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/). All functional images were motion corrected (Cox and Jesmanowicz, 1999), spatially smoothed with a Gaussian kernel of 5.0 mm (FWHM), and normalized individually across scans.

3.2.7 DTI

Subjects received a high-resolution whole-head DTI scan (TR = 7.98sec, TE = 84ms, slice thickness = 2mm isotropic, 64 slices total, acquisition matrix 128 mm x 128 mm (FOV = 256mm x 256mm), 6/8 Phase partial Fourier, b-value = 700s/mm^2). The bandwidth was 1396Hz/Px. Images were collected parallel to AC-PC plane with total scan duration of 9 min 44 sec. DTI scan was not conducted with one of the older subjects due to a technical difficulty.

DTI pre-processing was conducted as described previously (Salat, 2005), using FreeSurfer. First, motion/eddy current distortion correction procedure was conducted on diffusion volumes, using FLIRT (Jenkinson et al., 2002). Then the diffusion volumes were registered to the anatomical volume (see below) using a boundary based registration procedure (Salat et al., 2009). Our primary measure acquired from the DTI data was FA, calculated by using the standard formula defined previously (Rosas et al., 2006).

3.2.8 MRI-anatomical scan

For the anatomical reconstruction (Dale et al., 1999; Fischl et al., 1999), three T1-weighted MR images (MPRAGE) were acquired (TR = 2.531 sec, TE = 3.28 msec, flip angle = 70, TI = 1100 msec, 256 slices, voxel size = 1.3 x 1.3 x 1.0 mm^3, resliced during analysis to 1 mm^3).

3.2.9 Definition of region of interest (ROI) and volume of interest (VOI)

We determined the cortical ROIs, beneath which the white matter VOIs were determined as follows (also see Figure 9A-D). First, cortical regions of 3-7 degrees of eccentricity in V1, V2, and V3 were determined by functional localizer scans as described above. The ROIs were mapped onto the surface of an inflated brain (Dale et al., 1999; Fischl et al., 1999). Next, the cortical surface of each ROI was converted into a volume ROI, by filling into voxels up to 4 mm underneath the white matter/gray matter boundary to construct the white matter VOI. Because cortical surfaces were curved, some VOIs could be both underneath 2 regions such as V1 and V2, or V2 and V3. We identified such possible overlapping white matter volumes located between the borders (V1/V2 and V2/V3 volumes) and combined V1 and V1/V2 volumes as V1, and V2 and V2/V3 volumes as V2 so that no volumes belong to two different volumes. Raw FA map obtained from the DTI scans were co-registered to the subject's anatomical volumes. So was the white matter VOI to calculate FAs within the white matter VOI. The FA values within the white matter VOI were averaged to represent the VOI, while only FA values larger than 0.2 were considered to correspond to white matter tissue, and included in the analysis.

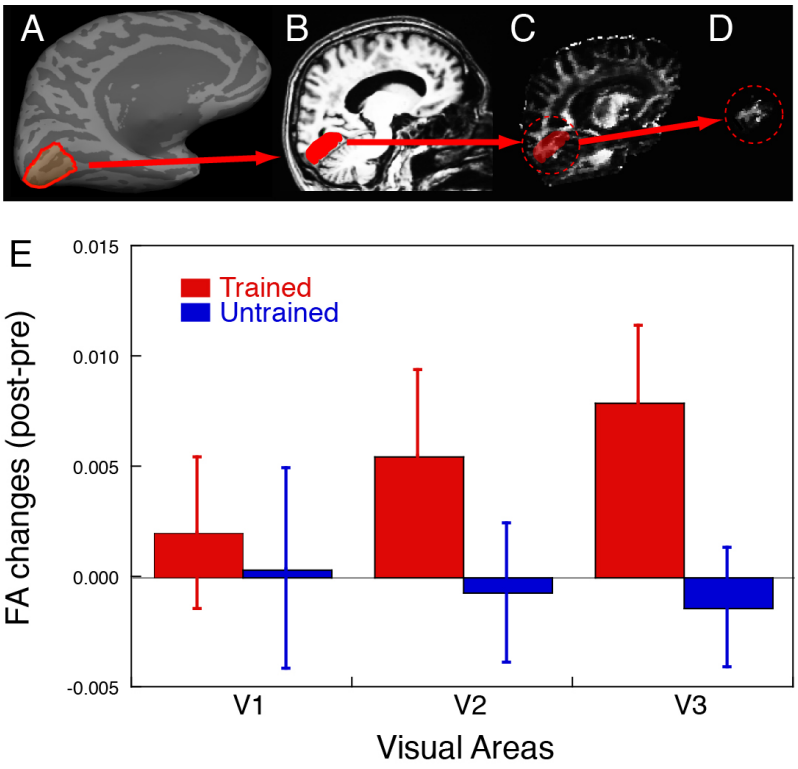

Figure 9. FA changes in the older subjects

(A) An inflated format of the left brain of a subject and an ROI. First, using an inflated format of the brain (Dale et al., 1999; Fischl et al., 1999; Fischl et al., 2004) and a standard retinotopic mapping technique (Fize et al., 2003), the visual borders of V1, V2, and V3 were determined to make cortical surface ROIs. The red line indicates one of the ROIs, the ventral cortical area, which retinotopically corresponds to a trained quadrant of visual field in V1. (B) Sagittal image of an anatomical MRI and the white matter VOI. The cortical ROI shown in (A) was converted into a folded format of the brain, and the white matter beneath the cortical ROI was selected as the white matter VOI (illustrated in red). (C) Raw FA map and white matter VOI. The rendered white matter VOI was applied to the raw FA map where FA value in each voxel is available. (D) Resultant FA volume within the white matter VOI. The FA value in voxels within the white matter VOI were averaged. Note the ROI and VOI oversimplified here for an illustrative purpose. (E) The mean subtraction (± s.e.) of FA obtained by DTI in the pre-test from that in the post-test for the trained region (red) and untrained region (blue) in V1, V2 and V3 for the older subjects.

3.3 Results

3.3.1 Behavioral evidence for VPL in older people

Older subjects (see **Methods** for more details) participated in two magnetic resonance imaging (MRI) sessions, between which there were three behavioral training sessions that occurred within a 7 day period (Figure 7A). During the behavioral training sessions, the subjects were trained with texture discrimination task (TDT; see **Methods** for more details), a task that is commonly used in VPL research (Yotsumoto et al., 2009; Yotsumoto et al., 2008), and is known to lead to VPL with a strong specificity in the trained visual location. On each trial, a texture display made of numerous line elements was presented (Figure 7B). The subject's main task was to report the orientation (vertical or horizontal) of the target, which consisted of 5 obliquely oriented lines, against the background, which consisted of horizontally oriented lines. The stimulus-to-mask onset asynchrony (SOA)--- the time interval between the onset of the target display and the onset of masking pattern--- was varied across blocks. The SOA that induced the 80% correct responses was defined as the threshold SOA, and was the primary behavioral measure.

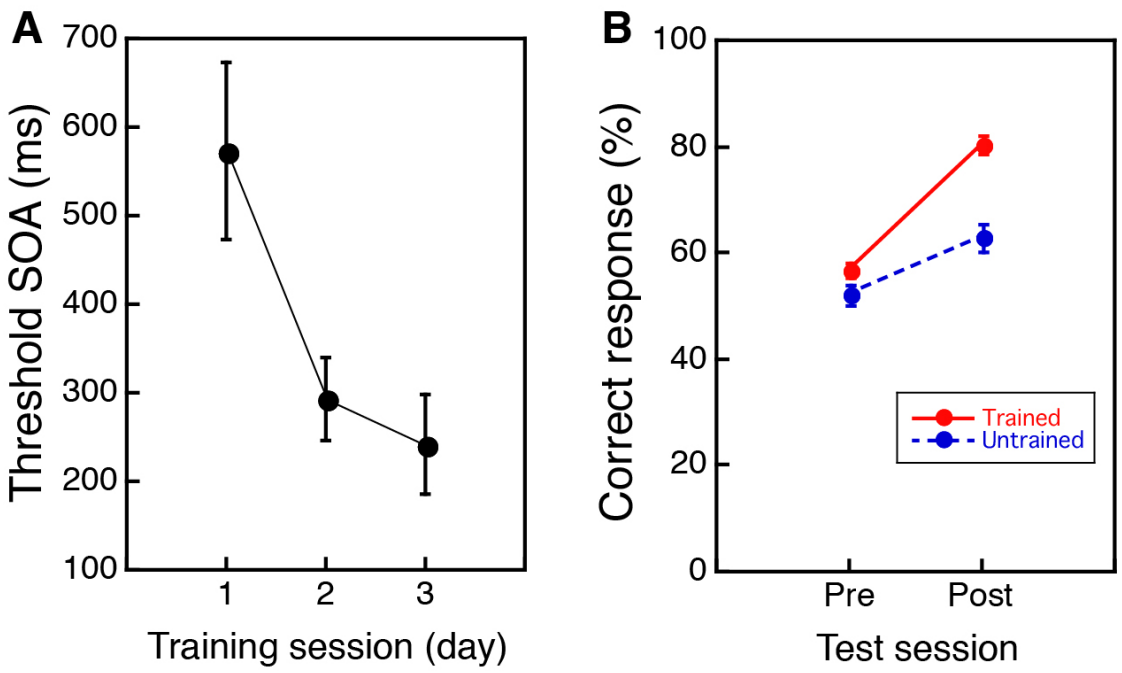

Figure 10. Behavioral improvement in the older people

(A) The mean threshold SOA (± s.e.) as a function of training session (day) for the older group. (B) TDT performance during the two MRI sessions that showed the specificity in the training location (mean ± s.e).

The mean threshold SOAs significantly decreased over the three-day training (one-way repeated measures ANOVA, the significant training effect, $F(2,34) = 4.135$, $p = 0.0247$, Figure 10A). Moreover, the present VPL for the older subjects showed the trained-location specificity (Figure 10B). While the behavioral training was conducted only in one visual field quadrant, in the pre- and post-training MRI scans, TDT targets were presented not only in the trained but also in an untrained quadrant of the visual field (untrained quadrant) as a control. A repeated measures ANOVA with 2 factors being time (pre/post) and location (trained/untrained) showed significant main effects of time ($F(1,17) = 43.62$, $p < 0.001$), location ($F(1,17) = 21.583$, $p < 0.001$) and a significant

interaction between these variables ($F(1,17) = 13.969$, $p = 0.001$). The results replicate previous research indicating that VPL occurs for older subjects with trained-location specificity in learning (Andersen et al., 2010).

3.3.2 White matter changes due to VPL in the older people

Previous research that investigated younger individuals has shown that cortical activation was significantly higher in the post-training scan, as compared to the pre-training scan in the region of V1 that retinotopically corresponds to the trained quadrant (trained region in V1)(Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008). Thus, we focused our investigation of the white matter underneath early visual cortex. To examine whether structural changes in the white matter occur in association with TDT, we measured the FA of the white matter volumes (volume of interest; VOI) beneath the trained and untrained regions in the early visual cortex, that retinotopically correspond to the trained and untrained visual fields (Figure 9A-D, for more detail, see **Methods**). If FA changes are associated with VPL then the FA change should be larger in the white matter volume that is beneath the trained cortical region than for the volume beneath the untrained cortical region---a finding consistent with trained location specificity for TDT.

Figure 9E shows the mean FA changes from the pre- to post-training MRI scans within each of the white matter VOIs, which are beneath the cortical regions retinotopically corresponding to the trained and untrained visual field quadrants in V1, V2, and V3 in the older subjects. The FA of trained regions of V1, V2 and V3 were increased, whereas the FA of the untrained regions was not,

in the post-training in comparison to the pre-training (Figure 9E). Furthermore, the increase of FA change was largest in V3. We tested whether the FA values of the visual areas were significantly changed due to TDT training by 3-way repeated measures ANOVA with factors being visual areas (V1/V2/V3), location (trained/untrained), and time (pre and post-training). The results of ANOVA showed a significant main effect of visual areas ($F(2,32) = 8.448$, $p = 0.0011$), no significant main effects of location and the time factors, but a significant interaction between the location and the time ($F(1,16) = 6.455$, $p = 0.0218$). The significant main effect of visual areas and the significant interaction between the location and the time suggest that the FA values were increased in the white matter volume beneath the trained regions compared to the white matter volume beneath the untrained region, especially beneath the early visual areas of V3 due to the TDT training for older subjects.

3.3.3 Larger FA changes in the early visual area in older people than younger people

Next, we tested whether the FA changes in the early visual areas are specific to older adults. Similar to the protocol for older adults, the younger subjects participated in two MRI sessions between which there were three behavioral training sessions that occurred over a 7 day period. As expected, the younger group showed learning during the training (Figure 11A, one-way repeated measures ANOVA, a significant main effect of day, $F(2,40) = 28.360$, $p < 0.001$) and the learning was location specific (Figure 11B), as indicated by comparing the pre- and post-training MRI sessions (two-way repeated measures

ANOVA, a significant main effect of time (pre/post), $F(1,20) = 84.538$, $p < 0.001$, a significant main effect of location (trained/untrained), $F(1,20) = 38.505$, $p < 0.001$, a significant interaction ($F(1,20) = 55{,}040$, $p < 0.001$). These results are in accord with previous work (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008).

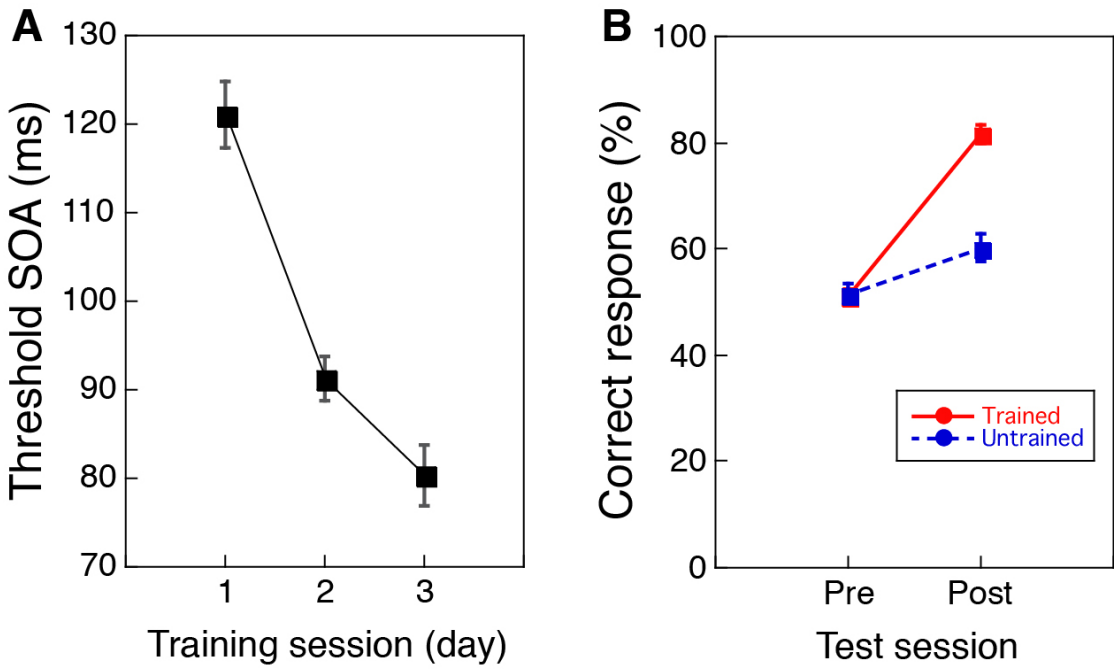

Figure 11. Behavioral improvement in the younger people

(A) The mean threshold SOA (± s.e.) as a function of training session (day) for the younger group. (B) TDT performance during the two MRI sessions that showed the specificity in the training location (mean ± s.e).

Importantly, the FA changes in white matter volumes beneath the early visual cortex for younger subjects were much smaller than that observed in older subjects (Figure 12). We tested whether the FA changes beneath the early visual cortex were significantly different between the older and younger subjects, by applying 4-way repeated measures ANOVA with factors being age

(older/younger), visual area (V1/V2/V3), location (trained/untrained) and time (pre/post). The results of the ANOVA showed a significant main effect of age ($F(1,36) = 14{,}810$, $p = 0.0005$), a significant main effect of visual area ($F(2,72) = 57.374$, $p = 0.0000$), and a significant location x time interaction ($F(1,36) = 6.367$, $p = 0.0162$). More importantly, the results showed a significant age x visual area interaction ($F(2,72) = 10.661$, $p = 0.0001$); furthermore, the simple main effect of age indicated that older adults experience significantly larger FA changes before and after the VPL training than younger adults in V2 ($F(1,36) = 10.418$, $p = 0.003$) and V3 ($F(1,36) = 26.012$, $p = 0.0000$). In addition, we found a significant age x location x time interaction ($F(1,36) = 5.245$, $p = 0.028$). The further simple interaction of location x time only showed significant interaction in younger adults ($F(1,16) = 6.445$, $p = 0.022$).

These results suggest that the FA changes of the white matter volume beneath the early visual areas due to perceptual learning were (1) significantly larger for older as compared to younger subjects, (2) significantly larger beneath the trained location than in the untrained location, and (3) significantly larger in the trained cortical region for older as compared to younger subjects.

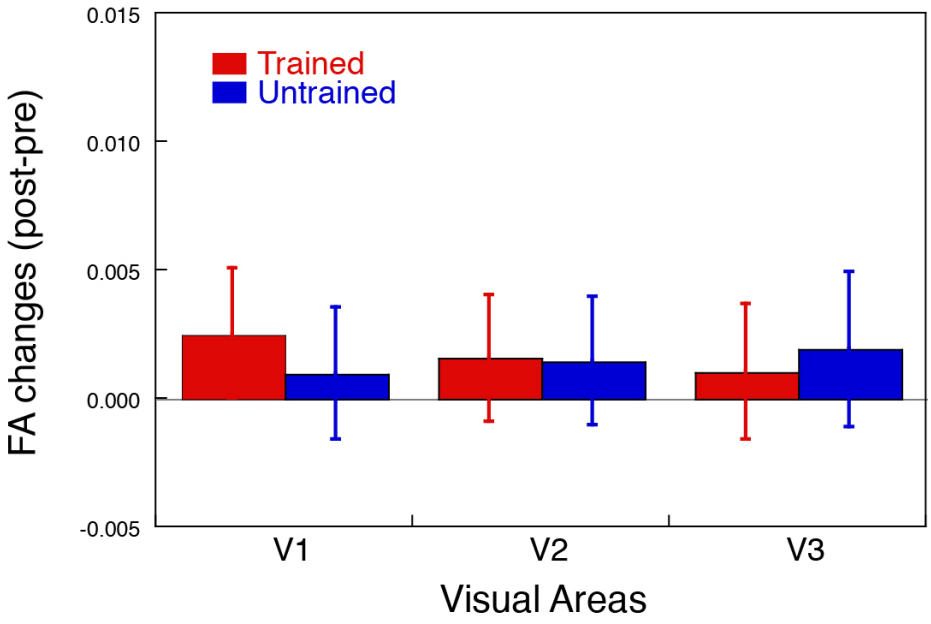

Figure 12. FA changes in the younger subjects

The mean subtraction (± s.e.) of FA obtained by DTI in the pre-test from that in the post-test for the trained region (red) and untrained region (blue) in V1, V2 and V3 for the younger subjects.

3.3.4 BOLD activation changes with VPL associated only with younger adults in the early visual areas

As previous research indicated that VPL was associated with functional activation changes in the early visual area V1 younger individuals (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008), we also measured BOLD signal on the trained and untrained regions in the early visual areas corresponding to the trained and untrained visual fields in the pre- and post-training MRI scans for both older and younger adults (for more details, see **Methods**). Our results indicated that the BOLD signals on trained location increased after the training in only the younger adults (especially V1 area, see

Figure 13), replicating previous research indicating that VPL is involved in the BOLD activation changes in the early visual areas in younger adults (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008). Moreover, we applied the same 4-way repeated measures ANOVA with factors being age (older/younger), visual area (V1/V2/V3), location (trained/untrained) and time (pre/post) to test whether any functional activation changes with PL training were associated with older and younger adults in the early visual areas. The results of the ANOVA showed a significant main effect of visual area ($F(2,72) = 112.416$, $p = 0.0000$) and a significant age x location x time interaction ($F(1,36) = 5.315$, $p = 0.027$). The further simple interaction of location x time only shows a clear tendency to significance ($F(1,20) = 4.035$, $p = 0.05$) in younger adults but not older adults ($F(1,16) = 1.681$, $p = 0.213$).

Our results clearly demonstrate that the BOLD changes in the early visual areas stemming from perceptual learning are only associated with younger subjects, and a similar tendency was not found in the BOLD activation changes in older adults.

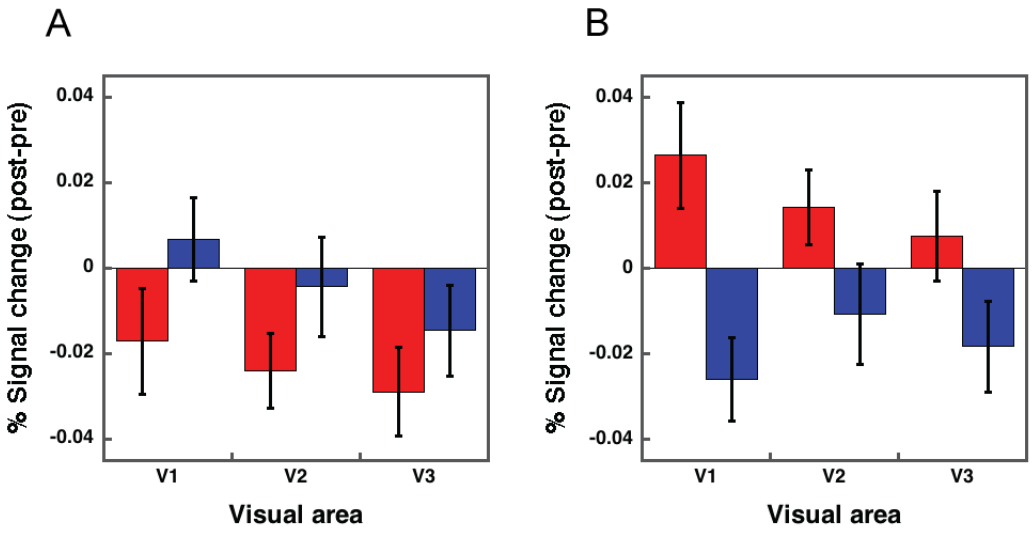

Figure 13. BOLD signal change

The mean subtraction (± s.e.) of BOLD signal in the pre-test from that in the post-test for the trained region (red) and untrained region (blue) in V1, V2 and V3, (A) for the older group and (B) for the younger group.

3.3.5 Head motion

Does a possible difference in head motions between the younger and older groups cause the differential results in FA values with the two groups? This is not likely for the following reasons. First, we calculated the FA values after motion correction procedures. Second, there was no significant difference in the overall sum of corrected head motions between the two groups. The sum of overall corrected motion was calculated as follows: square root of the sum of (displacement-in-the-slice-direction (mm)^2 + displacement-in-the-column-direction (mm)^2 + displacement-in-the-row-direction (mm)^2) based on the results of the motion correction procedure. We compared the sum of overall corrected motion between the younger and older groups, before and after the

training. In the younger group, the averaged overall corrected motion amount was 4.485 ± 1.97 mm before training, and 4.536 ± 2.36 mm after training, whereas in the older subjects, the amount was 3.31 ± 1.83 mm before training and 3.72 ± 2.61 mm after training. Two-way repeated measures ANOVA with factors being time (pre/post) and age (young/old) showed no main effects of time ($F(1,37) = 0.492$, $p = 0.49$) and age ($F(1,37) = 2.47$, $p = 0.12$) factors, and no interaction of factors ($F(1,37) = 0.30$, $p = 0.59$).

3.4 Discussion

Our results are unique and surprising. First, most previous evidence has shown that the brains of older adults are less plastic than that of younger individuals (Bloss et al., 2011). However, results of the present study indicate that changes in the white matter structure only occurred with older individuals. The results of the present study provide a strong case in which white matter beneath the early visual cortex is more readily changed with older as compared to younger individuals, although the lack of a significant white matter change with younger individuals due to VPL of TDT does not necessarily indicate that such changes never occur (Scholz et al., 2009). Second, the clear dissociation of the results for older and younger groups in terms of where the change takes place indicate that the mechanism for VPL are significantly different between the younger and older groups: While VPL in the younger brain is associated with functional changes (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008), VPL in the older brain is associated with structural changes in the white

matter. These results, considered together, suggest that at least two distinct mechanisms exist for brain plasticity for vision.

After training, FA in the white matter VOI increased beneath the trained region in older individuals (Figure 9E). How can this increased FA be interpreted? FA changes might reflect changes in myelination, axon caliber or crossing fibers in white matter (Fields, 2008; Salat, 2005). However, the exact underlying biological mechanism for FA changes is still under investigation, thus leaving the interpretation of the increase or decrease in FA values unspecified. One possible interpretation may be that a larger increase of FA reflects a larger amount of re-organization in the local structure of white matter (Fields, 2008; Salat, 2005). For target orientations (either vertical or horizontal) to be better recognized in TDT, an efficient approach would be to make target representation more structured in a way that a target would stand out and pop out. This could be accomplished by increasing the salience of the target while decreasing the salience of the background (Karni and Sagi, 1991). While such differential requirements on processing of the trained region as the target and the untrained regions as the background might be reflected in the differential amounts of BOLD activation in the trained and untrained regions of V1 for younger individuals (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008), for older individuals the differential requirements might be reflected in the differential degrees of FA values in the white matter VOI beneath the trained and untrained regions of the early visual areas.

Why did the white matter change occur only for older and not for younger individuals? Previous research suggests that TDT training induces changes in the neural circuits in the V1 corresponding to the background texture as well as the trained region with younger individuals (Karni and Sagi, 1991; Mednick et al., 2005; Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2009). One possibility is that V1 cortex of older individuals has become too rigid to change due to the gray matter volume reduction (Allen et al., 2005; Courchesne et al., 2000; Good et al., 2001; Lemaitre et al., 2012; Raz et al., 1997; Sherwood et al., 2011) and thinning (Fjell et al., 2009; Kochunov et al., 2011; Lemaitre et al., 2012; Salat et al., 2004) and thus that structural changes in white matter beneath the early visual cortex are used to compensate for the lack of V1 cortical change. A second possibility, which does not necessarily contradict the first, is that the white matter structure in the older individuals is less optimal for such a demanding sensory task as TDT as a result of normal aging. This may require white matter structure change to produce the optimal learning. As a result, the effects of VPL of TDT on plasticity may be more manifest in structural rather than functional changes with the older group. In contrast, the white matter structure of the younger may be nearly optimal for the task. Thus, changes due to VPL of TDT could occur at a cortical and functional level rather than at a structure level. It is important for future research to examine these hypotheses in further detail.

The present study also indicates the importance of examining structure changes in addition to functional activity/activation changes in the brain. While it has been indicated by many studies, including studies measuring BOLD signal,

that the brains of older individuals are significantly less plastic, the results of the current study clearly show a higher degree of plasticity in the white matter of older individuals as compared with that of younger individuals. We suggest that such a higher degree of plasticity in white matter occurs to compensate for the smaller degree of plasticity shown in functional processing of gray matter.

4. Chapter 4: Retinotopy reduction with normal aging

4.1 Introduction

During the last decade, the application of magnetic resonance imaging (MRI) techniques has enabled us to observe the brain structural changes with normal aging widely in vivo. This research has included the whole brain analysis that indicate that normal aging manifests itself as an overall cerebral atrophy that includes the shrinkage of gray matter volume (Allen et al., 2005; Courchesne et al., 2000; Fotenos et al., 2005; Good et al., 2001; Lemaitre et al., 2012; Raz et al., 1997; Resnick et al., 2003; Sherwood et al., 2011; Walhovd et al., 2005), cortical thickness (Fjell et al., 2009; Kochunov et al., 2011; Lemaitre et al., 2012), cortical areal size (Lemaitre et al., 2012), white matter volume or white matter integrity (Allen et al., 2005; Fotenos et al., 2005; Guttmann et al., 1998; Head et al., 2004; Kochunov et al., 2011; Raz et al., 1997; Resnick et al., 2003; Salat, 2005; Sherwood et al., 2011; Walhovd et al., 2005), as well as the enlargement of cerebrospinal fluid spaces (Courchesne et al., 2000).

On the other hand, studies focused on regional analysis have found that the brain structural reduction is not homogenous, and may be affected differently across different brain regions. For instance, aging effects are significantly stronger in frontal cortices (Allen et al., 2005; Brickman et al., 2007; Fjell et al., 2009; Lemaitre et al., 2012; Raz et al., 1997; Raz et al., 2004; Salat et al., 2004; Salat et al., 1999) but more moderate in the temporal (Cowell et al., 1994;

Lemaitre et al., 2012; Sullivan et al., 1995) and parietal areas (Abe et al., 2008; Brickman et al., 2007; Good et al., 2001; Resnick et al., 2000; Salat et al., 2004).

One controversy, however, is whether the occipital area is affected by aging (Fjell et al., 2009). Some studies suggest that the occipital area is largely preserved with normal aging, including cortical areal size (Lemaitre et al., 2012), gray matter volume (Lemaitre et al., 2012; Raz, 2001; Raz et al., 1997), cortical thickness (Lemaitre et al., 2012), white matter-gray matter intensity contrast (Davatzikos and Resnick, 2002), white matter volume and fractional anisotropy (Fjell et al., 2008; Good et al., 2001). However, other studies have found significant morphological declination on gray matter volume (Allen et al., 2005; Resnick et al., 2003), cortical thickness (Salat et al., 2004), and white matter volume or white matter integrity (Allen et al., 2005; Head et al., 2004; Madden et al., 2004; Nusbaum et al., 2001; Resnick et al., 2003) in the occipital area.

Although the occipital area can be defined by the anatomical landmarks including an automated parcellation technique used in previous studies (Fischl et al., 2002; Fischl et al., 2004), the occipital lobe can also be divided into several functional visual areas by retinotopic representation including V1, V2 and V3 (Tootell et al., 1982; Wandell and Winawer, 2011). While it is likely that some portions of the occipital lobe show atrophy, which may be less than other parts of the brain, it is unclear whether this is found in functionally distinct regions and how this might relate to visual plasticity. Here, we tested whether normal aging affects local structures of retinotopically defined early visual areas, and whether the aging effects differ on the retinotopically defined or anatomically defined

visual areas. We hypothesized that if aging affects visual functions in older individuals, then aging effects may be more clearly seen in the retinotopically defined visual areas. To examine this issue, we measured the areal size of the early visual areas, because it has been shown that the size of visual areas are involved in the visual function of younger subjects (Schwarzkopf and Rees, 2013). Thus, we investigated the effect of aging on areal sized of retinotopically defined early visual areas, by comparing these regions in older and younger adults.

Furthermore, we examined whether any morphological aging effects, for different visual areas, were associated with individual differences among older adults for visual perceptual learning. Perceptual learning is defined as long-term improvement on a visual task and is regarded as a manifestation of visual plasticity (Sasaki et al., 2010) that occurs due to repetitive and intensive practice (Sagi, 2010), that may result in changes in the activation of the early visual area (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008). In addition, recent studies have shown that perceptual learning is possible with older individuals with learning effects that are similar to younger adults (Andersen et al., 2010; Bower and Andersen, 2012). These results suggest that plasticity is preserved for visual training, which is in contrast to studies, which have found limited effects of training for cognitive tasks (Jones et al., 2006; Verhaeghen et al., 1992; Yesavage et al., 1990). We thus tested whether areal sizes of the early visual area were correlated with the magnitude of visual perceptual learning in the older individuals.

4.2 Methods

4.2.1 Subjects

Participants were recruited into 2 age groups: 18 older adults (6 male and 12 female, the average age 71.8 ± 5.13, mean ± SD, ranging between 65 to 86 years old), and 21 younger adults (14 male and 7 female, the average age 23.3 ± 3.5, mean ± SD, ranging between 19 to 32 years old). One older participant was dropped, because we could not collect retinotopic mapping for this individual. The older participants were recruited through the Harvard Cooperative on Aging and Brookline Senior Center. The younger participants were recruited from Keio University and Boston University. All participants had normal or corrected to normal vision. The older participants were evaluated by pre-experiment screen session (including WAIS sub-tests: digit span, digit symbol coding, Mini Mental Status Examination, and activity level) to ensure normal cognitive and memory function. All participants gave informed consent for their participation to the experiments. The experiment procedure was approved by the Institutional Review Board at Massachusetts General Hospital, Keio University, and Boston University where the experiments took place.

4.2.2 MRI

4.2.2.1 Anatomical image acquisition

All images were scanned by 3 Tesla scanners (Trio, Siemens, Erlangen, Germany) at Massachusetts General Hospital or Keio University. For anatomical images, two T1-weighted MR images (MPRAGE: TR = 2.531 sec, TE = 3.28

msec, flip angle = 70, TI = 1100 msec, 256 slices, voxel size = 1.3 x 1.3 x 1.0 mm^3, resliced during analysis to 1 mm^3) were acquired from each subject.

4.2.2.2 Functional Image acquisition for the retinotopic mapping scans

V1, V2 and V3 areas were localized functionally using a standard retinotopic mapping technique (Engel et al., 1994; Fize et al., 2003; Yotsumoto et al., 2008). All functional MR images were acquired using gradient echo EPI sequences (TR = 2 sec, TE = 30 ms, Flip Angle = 90 deg) with the standard 12-channel head coil. Thirty-three contiguous slices (3 x 3 x 3.5 mm^3) oriented parallel to the AC-PC plane were acquired to cover the entire brain by automatic slice alignment method (van der Kouwe et al., 2005). During the retinotopic mapping scans, five different visual stimuli were presented on a gray background: (1) horizontal condition (12 degree wedge-shaped checkerboards centered on the horizontal meridian axis), (2) vertical condition (24 degree wedge-shaped checkerboards centered on the vertical meridian axis), (3) foveal condition (a small 168 degree wedge-shaped checkerboard placed between 3-7 degree eccentricity from the fixation), (4) parafoveal condition (a large 168-deg wedge-shaped checkerboard where the area within 3-7 degree eccentricity was filled with gray color as background), and (5) fixation condition. All conditions were presented in the counterbalanced order by blocked design during 4 times of the retinotopic mapping scans (12 sec/block; 240 sec/scan).

The activation of the functional localizer was projected on individual flattened format of cortical surface to allow us to functionally define V1, V2 and V3 areas with varied eccentricity. By contrast of horizontal and vertical

checkerboard conditions, we defined the boundary of V1, V2 and V3 from the meridian of the activations (Engel et al., 1994; Fize et al., 2003; Yotsumoto et al., 2008). The foveal region was defined as the cortical part from the fovea to 3 deg eccentricity and the parafoveal as 3-7 deg eccentricity.

4.2.2.3 Image Processing

All imaging data were analyzed by FreeSurfer 4.5 version (http://surfer.nmr.mgh.harvard.edu/). The T1-weighted images were processed to reconstruct cortical surface (Dale et al., 1999; Fischl et al., 1999) and segmented into gray and white matter. The cortical surface information will be processed by Freesurfer surface-based stream for the morphological analysis (Dale et al., 1999). The functional images were analyzed by Freesurfer Functional Analysis Stream (FSFAST) package for pre-processing motion correction (Cox and Jesmanowicz, 1999), spatial smoothing (a Gaussian kernel of 5.0 mm (FWHM)), and normalization across the scans.

4.2.2.4 Computation of the areal size

ROIs were determined by the retinotopic mapping as described above. ROIs were V1, V2, and V3 in the left and right hemispheres, and their fovea and parafoveal regions of each V1, V2 and V3. Then, we extracted the cortical areal size in these ROIs in each hemisphere by a FreeSurfer MRI SegStats function.

4.2.3 Texture discrimination task

We conducted three sessions of TDT training on separate days for older subjects. In the TDT task, subjects were asked to fix their eyes at the center. In

each trial, the task stimulus (100 ms) was presented shortly and followed by a blank screen and mask stimulus (100 ms). The stimuli were composed of a central target (either letter “L” or “T”) surrounding with horizontal bars as a background. Besides the central target, the peripheral target (five array of “horizontal” or “vertical” diagonal bars) was also presented in the assigned targeted visual quadrants on the peripheral regions. Subjects were asked to report both central target ("L" or "T") and peripheral target (“horizontal” or “vertical”) by pressing buttons. The task difficulty was determined by stimulus-to-mask onset asynchrony (SOA), which is the time interval between the target stimulus presentation and the mask stimulus (the longer the SOA, the easier the task). If the SOA is longer, the task becomes easier. In each session, five different SOAs were presented from easier to harder SOA in order. Seventy-two trials were presented for each SOA (360 trials for a session in total).

4.3 Results

To examine age-related effects we measured the areal size of the early visual cortex defined by a standard retinotopic mapping (see **Method**) in older and younger adults. The region of interests (ROIs) were defined by early visual cortex (V1, V2, and V3), which were further subdivided by eccentricity (foveal and parafoveal), and hemispheres (left and right). We conducted four-way repeated measures mix-design ANOVA with the main factors of Age (old and young), Visual area (V1, V2 and V3), Eccentricity (foveal and parafoveal), and Hemisphere (left and right), to test whether there is any significant difference in the areal size of early visual cortex.

4.3.1 Effect of aging on the areal size in the early visual areas

The four-way ANOVA results of the areal sizes showed significant main effects of Age ($F(1,36) = 18.138$, $p < 0.001$), Visual area ($F(2,72) = 32.789$, $p < 0.001$), and Eccentricity ($F(1,36) = 120.820$, $p < 0.001$), but no significant main effect of Hemisphere ($F(1,36) = 3.575$, $p = 0.067$). The significant main effect of Age indicated that the areal sizes of early visual cortex in older adults were significantly smaller than those of younger adults.

In addition to the significant main effect of Age in the areal size, we found a significant interaction between Age and Visual area ($F(2,72) = 4.684$, $p = 0.012$). The simple main effect of Age on this interaction (Figure 14A) was significant in all of the early visual areas; V1 ($F(1, 36) = 21.048$, $p < 0.001$), V2 ($F(1, 36) = 16.737$, $p < 0.001$) and V3 ($F(1, 36) = 7.212$, $p = 0.011$) and the simple main effect of Visual area on this interaction was also significant for both older ($F(2,32) = 7.364$, $p = 0.002$) and younger ($F(2,40) = 31.863$, $p < 0.001$) subjects. The significant simple main effects of Age on all early visual areas suggest that the areal size of all of the early visual areas were significantly different between the older and younger, and smaller with the older individuals. See Figure 15, which is a scatter plot version of data.

We found no significant interactions between Eccentricity and Age ($F(1,36) = 1.894$, $p = 0.177$, Figure 14B) or Hemisphere and Age ($F(1,36) = 0.201$, $p = 0.657$,Figure 14C). In addition, we found no significant 3-way or 4-way interactions.

These results demonstrate clear age-associated reductions in areal sizes in V1, V2 and V3. Next we asked how much age-associated reduction took place for each of visual areas and computed the overall an older/younger ratio (Figure 14D). The older/younger ratio was obtained by the average areal size with the older subjects divided by the average areal size with the younger subjects for each visual area. The older/younger ratio was 73-76% for V1 and V2, whereas it was 83% for V3, suggesting that the age-associated size reduction for V3 is smaller than V1 and V2.

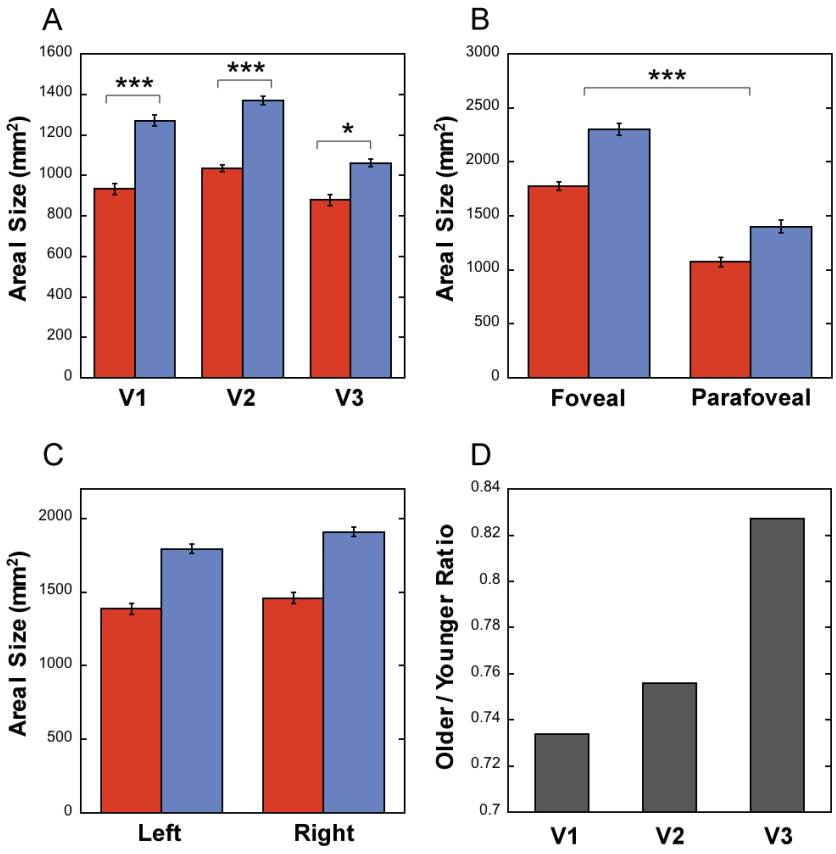

Figure 14. The mean areal size (± S.E.M) in the early visual cortex of older (red) and younger (blue) people.

(A) The areal size by the visual areas. The size is the sum of foveal and parafoveal areas in both left and right hemispheres. Asterisks indicate the statistical significance of the simple main effect of age on the age x visual area interaction. *$p < 0.05$, ***$p < 0.001$. (B) The areal size by the eccentricity. The size is the sum of V1, V2 and V3 of both hemispheres. Asterisks indicate the significant main effect of Eccentricity (see text, ***$p < 0.001$). (C) The areal size for each of the hemispheres. The size is the sum of the foveal and parafoveal areas of V1, V2 and V3. (D) An older/younger ratio. The age-associated size reduction may be the smallest in V3.

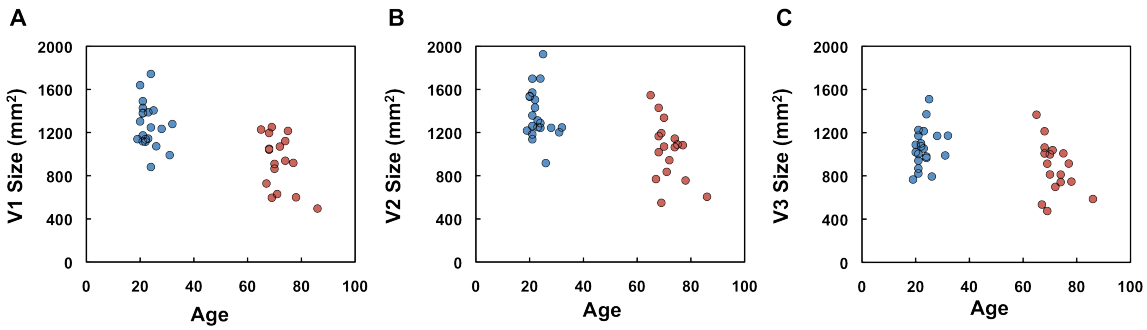

Figure 15. The correlation between age and the areal size in each of early visual areas in older (red) and younger (blue) subjects.

The size includes foveal and parafoveal regions of V1 (A), V2 (B), and V3 (C) in the both hemispheres. The correlation coefficients for each panel are shown in Table 1.

Table 1.

The correlation between age and the areal size of V1 (A), V2 (B), and V3 (C) in Figure 15 are as follows:

	V1	V2	V3
Younger	-0.253	-0.232	0.236
Older	-0.464	-0.482	-0.418
Including both the younger and older	-0.649***	-0.608***	-0.427**

4.3.2 Correlations between visual perceptual learning and morphological measures

The subjects were trained with a texture discrimination task (TDT), one of the standard visual perceptual learning tasks (Karni and Sagi, 1993) for 3 training sessions, with one training session per day over a week period (see **Methods**). In this task, a target stimulus is masked with a noise pattern and the task difficulty is increased with shorter stimulus-to-mask onset asynchrony (SOA). We calculated the individual threshold SOA (ms), at which subjects were 80% correct to indicate daily performance (see **Methods**). For older subjects, the one-way

ANOVA with repeated measures showed a significant main effect of training ($F(2,34) = 4.135$, $p = 0.025$), indicating that the 80% threshold SOA significantly decreased during 3 days of training. Because shorter SOAs indicate greater task difficulty, the decrease in the threshold SOA indicates that subjects could correctly respond to more difficult conditions as a result of training. Here we replicate previous research indicating that perceptual learning can occur with older individuals (Andersen, 2012).

Next, the Pearson correlation coefficients were computed for each of the areal size of V1, V2 and V3, to test whether the size of each early visual area was correlated with visual perceptual learning (Figure 16). To represent the individual performance improvement ratio, the threshold SOA change index was computed by subtracting the threshold SOA for the first day from the last day and divided by the first day SOA threshold. A more negative threshold SOA index indicates a greater improvement. The average threshold SOA change index was -0.28 ± 0.35 (mean ± SD), indicating that the magnitude of improvement for older adults was approximately 28% over the 3 training sessions. We only found the areal size of V3 was significantly correlated with the magnitude of improvement ($r = -0.638$, $p = 0.006$, Figure 16C). The larger size of V3 was correlated with higher improvement in perceptual learning. Importantly, the Grubbs' test showed no outliers for the older subjects (Figure 16C).

Importantly, such correlation was not found for the younger subjects. For younger subjects, the one-way ANOVA with repeated measures showed a significant main effect of training ($F(2,40) = 28.36$, $p < 0.0001$), indicating that the

80% threshold SOA also significantly decreased during 3 days of training as expected from previous research (Karni and Sagi, 1991, 1993; Yotsumoto et al., 2008), with the mean threshold SOA change index being -0.31 ± 0.17 (mean ± SD). However, none of the areal size was significantly correlated with the threshold SOA change index for the younger adults (Figure 16D-F).

One may wonder whether the size of a frontal region is correlated with performance improvement. However, we find it unlikely, based on an additional analysis (see Figure 17). We measured the areal size of the middle frontal gyrus, a part of the frontal lobe and computed the correlation coefficients with performance improvement for the older and the younger subjects (Figure 17). The analysis showed only small correlations between the frontal region size and the performance improvement both in the older and younger subjects.

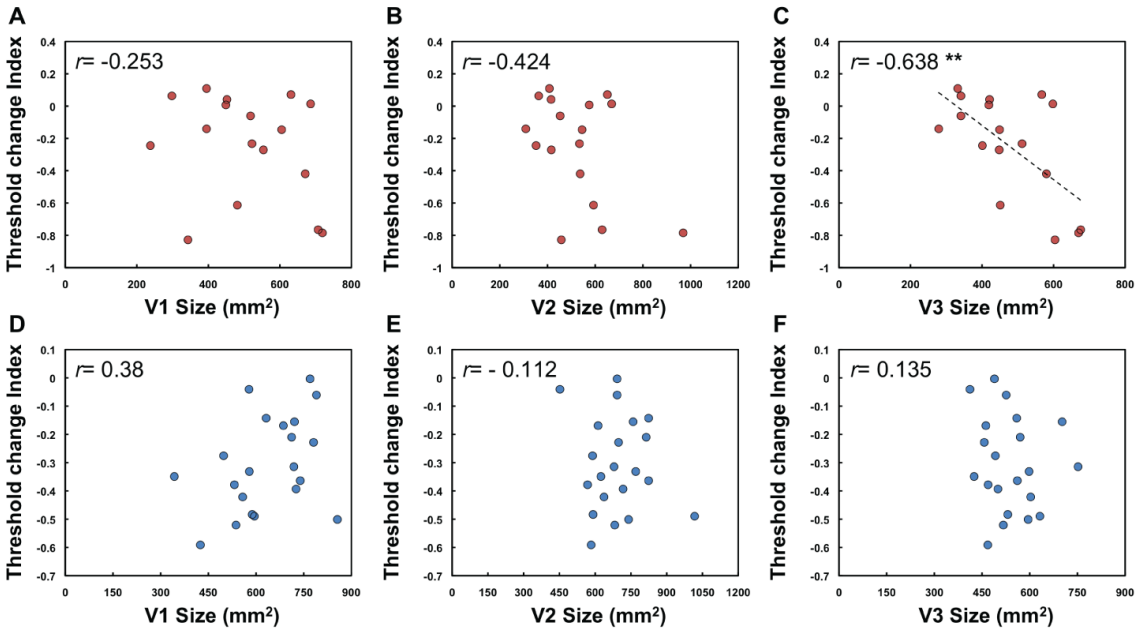

Figure 16. The correlation between performance improvement and the areal size in each of early visual areas for older (red, A-C) and younger (blue, D-F) adults

The performance improvement is shown as the threshold change index. A more negative threshold change index indicates a larger amount of performance improvement. The areal sizes of V1, V2, and V3 here are confined to the sum of foveal and parafoveal areas in the trained hemisphere. The results indicate that only the areal size of V3 in older adults was significantly correlated ($p = 0.006$) with the amount of performance improvement of TDT.

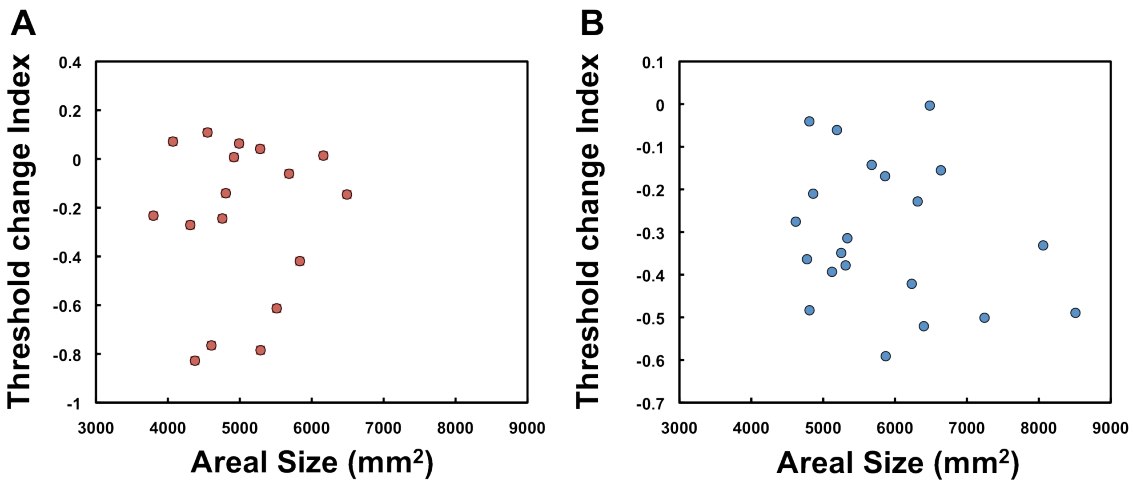

Figure 17. The correlation between performance improvement and the areal size in the middle frontal gyrus (MFG) in the trained hemisphere for the older (A) and younger (B) people.

The correlation coefficients for the MFG size and the performance change are shown in Table 2.

Table 2.

Correlation coefficients between the MFG size and the performance improvement (Figure 17) for the older and younger adults.

	Older	Younger
Correlation coefficient	0.063	-0.235

4.3.3 The proportion of the occipital lobe size relative to the whole brain size

While our results discussed above revealed a significant reduction by age in the areal size of V1, V2, and V3, the age-associated changes may be due to the overall shrinkage of the whole brain in older people. To test this possibility, we measured the areal sizes of the occipital lobe in both older and young groups. The occipital lobe was defined anatomically according to a previous study

(Desikan et al., 2006). In the Desikan et al. study, the occipital lobe was defined as a combination of the lateral occipital cortex, lingual gyrus, cuneus cortex and pericalcarine cortex. We followed the same procedure and these occipital areas were identified by the automated parcellation technique (Desikan et al., 2006; Fischl et al., 2004). Notably, the occipital lobe size itself was not significantly different between the older and younger groups ($t(36) = 1.398$, $p = 0.171$, see Figure 18). This is consistent with previous study comparing both global and regional analysis on the occipital lobe (Lemaitre et al., 2012).

Thus, the present results indicate an interesting dissociation: although the areal size of the anatomically defined occipital lobe were comparable between the older and younger, the areal size of the functionally defined early visual cortex was significantly smaller in older as compared to younger individuals.

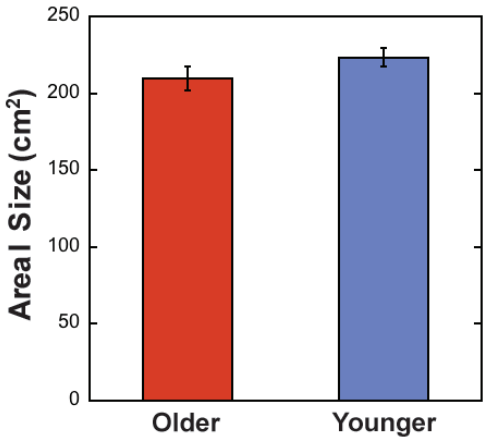

Figure 18. The areal size of the anatomically defined occipital lobe

The areal sizes of the occipital lobe with the red bar for the older and the blue bar for the younger participants, respectively. The size is the sum of the left and right hemispheres.

4.3.4 The comparison of BOLD signals amplitude between the older and younger groups

The early visual cortex in the present study was defined by retinotopic representation, which was obtained by a standard retinotopic mapping with functional MRI. It has been shown that older individuals, as compared to younger individuals, show smaller amplitude of BOLD signal (Buckner et al., 2000; D'Esposito et al., 2003; Kannurpatti et al., 2010). An important question is whether the smaller BOLD signal is associated with the smaller areal size in older adults. Although the retinotopic mapping utilizes the location of the functionally activated region, not the amplitude itself, we tested whether the BOLD signal for older individuals for retinotopically mapped regions was smaller

than younger adults. We found no significant difference between the older and younger adults for the BOLD signal amplitudes in early visual cortex (Figure 19**,** $t(36) = 0.56$, $p = 0.579$, NS). These results suggest that there is no clear evidence of a difference in the BOLD signal amplitude between the older and younger subjects.

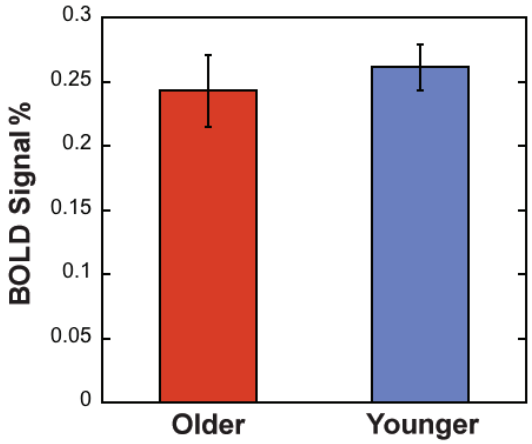

Figure 19. The BOLD signal amplitude

The mean BOLD amplitude ± S.D. averaged across in the early visual area including V1, V2 and V3 for older and younger participants.

4.4 Discussion

In the current study, we found the age-associated reduction of areal size in the functionally defined early visual cortex (Figure 14). In addition, we found that visual perceptual learning was highly correlated with the cortical size of V3 (Figure 16), suggesting that the structure of early visual cortex is indicative of visual plasticity in older adults. The latter finding is consistent with previous research (Schwarzkopf and Rees, 2013) in which the size of early visual area of

the younger subjects was highly associated with visual perception. The previous and present studies, considered together, suggest that the morphological difference of cortical areal size may be of critical importance in accounting for individual differences of visual processing that include learning and perception.

The present results suggest that the effect of aging on visual processing may manifest in functionally distinct regions such as retinotopically defined visual areas. Previous research found inconsistent results regarding whether age-associated reductions exist in the occipital lobe of older adults based on anatomically defined areas (Allen et al., 2005; Resnick et al., 2003; Salat et al., 2004). However, the present study found that examination of areal size by retinotopically defined visual areas indicates a significant areal size reduction for older individuals. This might indicate that the morphological changes are associated with modification in functional processing, which requires further validations. In contrast to the retinotopically defined size, the areal size of the anatomically defined occipital lobes was comparable for both older and younger adults (Figure 18). This finding suggests that age-associated shrinkage is smaller in the occipital lobe as compared to the anterior part of brain. This is consistent with previous research that found that the occipital lobe shows less age-related decline as compared to other cortical areas (Lemaitre et al., 2012).

It is important to note that although some MRI studies found that older adults have overall lower amplitude of the BOLD activation among different tasks (Buckner et al., 2000; D'Esposito et al., 2003; Huettel et al., 2001; Kannurpatti et al., 2010), it is unlikely that this factor was a co-varying variable in the present

study. First, our computation of the size of early visual areas does not depend on the *amplitude* of BOLD signals per se, because the identification and demarcation of early visual cortex does not depend on the BOLD amplitude. As described in the **Methods**, we identified the cortical regions that retinotopically corresponds to the horizontal and vertical meridians of the visual fields, because these regions would correspond to the boundaries between the early visual areas (Engel et al., 1994; Fize et al., 2003; Tootell et al., 1998). After we identified these visual boundaries, we calculated the areal size of sub-regions (V1, V2 and V3) of early visual cortex, which were enclosed by these meridian borders. We did not simply measure sizes of regions functionally activated by a visual stimulus. It is true that the size of the activated region may become smaller due to the lower signal to noise ratio of BOLD signal in the perimeter of activated regions (Huettel et al., 2001). However, the central locus of the activated regions may not be shifted due to the smaller BOLD amplitude. Moreover, the BOLD amplitude analysis among the early visual areas, during the retinotopic mapping scanning, showed no significant difference between the older and younger adults (Figure 19). This suggests that the effect of aging on the morphological measures in the early visual area cannot be accounted for by the difference of BOLD signal amplitude between older and younger adults.

To conclude, the present study demonstrated age-associated areal size changes in retinotopically defined early visual areas. Moreover, the areal size of V3 in older adults was highly correlated with the magnitude of visual perceptual learning. These results indicate the importance of functionally defined regions of

interest for understanding age-related differences in visual processing. Further, these low level changes in sensory processing may also contribute to declines in higher order cognition, which should be a topic of study.

5. Chapter 5: Is the older brain always think less plastic?

5.1 Introduction

One of the biggest questions in learning is how a system can learn new items while retaining old items. If the system is too plastic and malleable, it runs the risk of replacing important items as well as core processing already stored or in place with newly learned items. For the system to work most efficiently, it should have a high capability of learning new items, but also have a high stability by retaining important items or processing in the system by not retaining insignificant information. This so-called stability and plasticity dilemma (Abraham and Robins, 2005; Nere et al., 2013) should hold true for visual perceptual learning (VPL), which is defined as an increase in long-term performance on a visual task as a result of visual experience (Sasaki et al., 2010).

A considerable number of studies have reported that older adults have a degraded capability of learning new items (Burke and Barnes, 2006). However, the question of how stable the older brain remains unclear. It has been found that mere exposure to a visual feature that is not relevant to a given task or goal with younger individuals does not lead to learning of the feature if it is suprathreshold (Seitz and Watanabe, 2003; Watanabe et al., 2002; Watanabe et al., 2001). This suggests that if an exposed task-irrelevant feature is detected, the system should inhibit the feature to avoid replacing existing important information or processing with insignificant or trivial information. If older individuals have less plasticity than younger individuals, as the conventional view indicates, then a smaller

magnitude of task-irrelevant perceptual learning (TIPL) should occur with older as compared to younger adults. Here, we found that older adults learned a highly conspicuous task-irrelevant feature that younger adults do not learn, indicating that older adults have a decreased capability of stability as well as plasticity.

Two groups of 10 older (ages between 67 and 79 years old) and 10 younger adults (ages between 19 and 30 years old) participated in the experiment with the same procedure used for both groups. The experiment consisted of 8 days of training sessions and 2 days' pre- and post test stages (Figure 20A). On each trial of the training sessions, subjects were presented with a sequence of 6 letters and 2 digits at the center of the display. After the offset of the sequence, subjects were asked to report the 2 digits as targets in the sequence of otherwise letters. During the presentations of the letters and digits, a motion display was exposed in the background as a task-irrelevant feature. The display consisted of a certain ratio of dots moving coherently from frame to frame and the other dots moving randomly. The coherent motion ratio (signal strength) was varied from trial to trial in 4 steps (0.3, 0.6, 1.0 and 4.0 x the individual 80% coherent motion detection threshold). The multiplicative values of the individual threshold were used to control individual differences on perception of coherent motion, particularly between older and younger subjects (Gilmore et al., 1992). Coherent motion with each coherent ratio moved in a different direction (see **Methods** for detail).

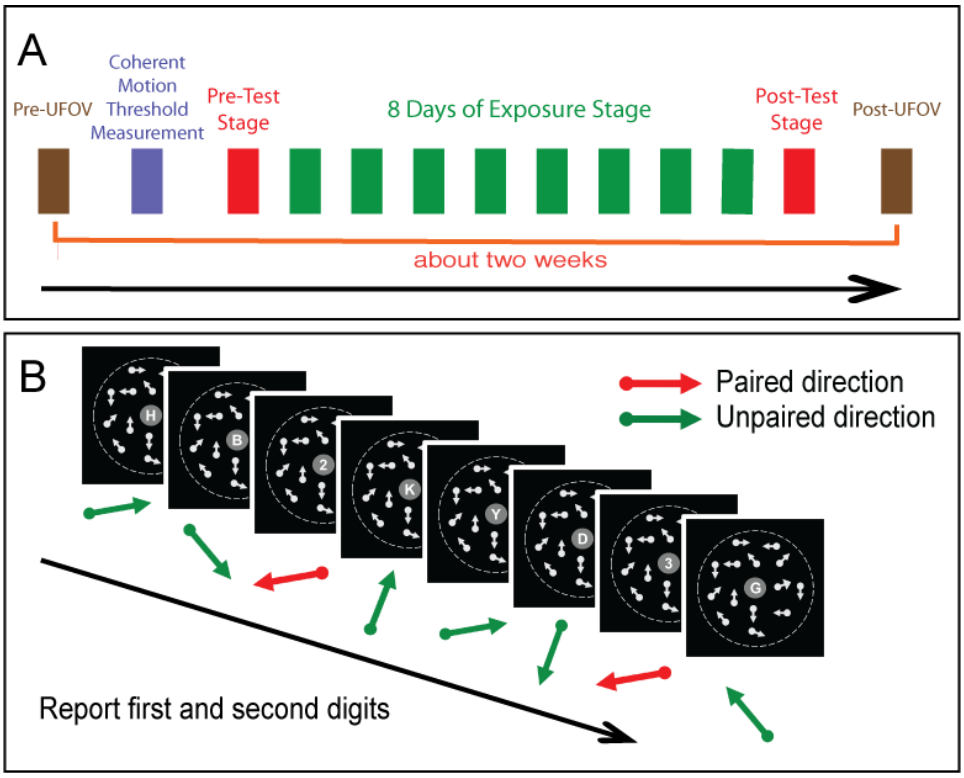

Figure 20. Procedure and stimulus

(A). The complete experimental procedure. It consisted of pre-UFOV, coherent motion threshold measurement, pre-test, exposure, post-test and post-UFOV stages conducted in that order. (B). The procedure of a trial in the exposure stage. Red arrows represent coherent motion direction that was paired with digits as targets (paired direction). Green arrows represent coherent motion directions that were not paired with digits (unpaired directions).

5.2 Methods

5.2.1 Subjects

We recruited 10 older adults (mean of age ± SD: 71.78 ± 4.02, range of age: 67-79) and 10 younger adults (mean of age ± SD: 25.9± 4.04, range of age: 19-30) with normal or corrected to normal vision. The older participants were recruited from the Brookline Senior Center. Younger participants were

undergraduate students from Boston University and Brown University. In order to make sure that older subjects had normal cognitive and memory functions, we conducted a screening session that consisted of the Mini Mental Status Examination, WAIS sub-tests: digit span, digit symbol coding, and activity level evaluation. Participants were given the informed consent reviewed and approved by the Institutional Review Board at Boston University or Brown University, and by the Elder Rights Review Committee (ERRC), Executive Office of Elder Affairs, Massachusetts Councils on Aging with the experiment site approval in local senior centers in the Commonwealth of Massachusetts.

5.2.2 Useful Field of View (UFOV)

In order to evaluate whether subject's attention ability is affected by TIPL, subjects were asked to perform the same Useful Field of View test (UFOV) before and after the experiments. The UFOV test is a computer-based test that assesses parallel attention processing and visuospatial attention (Visual Awareness Research Group Inc, http://www.visualawareness.com). The test consisted of three sub-tasks for processing speed, divided attention, and selective attention, each of which measures the ability to perform a central visual identification task, the ability to divide attention on both central and peripheral stimuli, and the ability to select peripheral stimuli from among distracters, respectively.

5.2.3 Coherent motion stimuli

A coherent motion display used in the present study was a standard display used in research on motion perception. It contained approximately 70

dots per frame. Each frame is displayed for approximately 16.7 ms. In the 10% coherent motion display, for example, 10% of the dots presented moved in a uniform direction and speed from their previous locations (10% coherent motion), while the remaining 90% of the dots move in pseudo-random directions. Coherent dots moved at a speed of approximately 24 deg/sec. On the next frame, another 10% of the dots were selected for coherent motion and so on. Dots not selected for coherence on a given frame were replotted to random locations. The luminance of the background and dots are 0.5 cd/m^2 and 178 cd/m^2, respectively.

5.2.4 Coherent motion threshold measurement

The threshold of coherent motion for each subject was measured before the pre-exposure task (see below) by a standard motion detection task. On half of 600 trials a coherent motion display was presented for 500 msec and in the other half a display consisting of randomly moving dots were presented. Which display was presented was pseudo-randomly determined from trial to trial. After the disappearance of the display, subjects were asked to press key “1” if they perceive coherent motion and key “2” if not. The measurement stage consisted of 600 trials. Throughout a trial, a light-grey bulls eye was presented at the center of the display (0.5 deg in radius) for 300 ms to maintain subjects’ fixation. The coherent motion percentage was varied in 5 steps (3, 13, 23, 33 and 53%) and pseudo-randomly assigned from trial to trial. This stage lasted approximately 40 min. The 80% threshold was determined for each subject from a psychometric function made based on the mean performance for each of the 5 coherent motion percentages.

5.2.5 Pre- and post- test stages

Before and after the motion exposure stage (see below), we measured performance (percentage of correct responses) for coherent motion direction discrimination. Each of the pre- and post- test stages consisted of 720 trials. On each trial, a light-grey bulls eye was presented at the center of the display (0.5 deg in radius) for 300 ms to maintain subjects' fixation. Then, a coherent motion display (6.5 deg in radius) was presented with the fixation point present. The direction and percentage of coherent motion were pseudo-randomly chosen from six motion directions (10, 70, 130, 190, 250, 310 deg) and three levels of the coherent motion display. The levels of coherent motion were multiplications of each subject's individual motion threshold obtained by the aforementioned coherent motion threshold measurement (threshold x 0.3, threshold x 0.6, threshold x 1.0). After the disappearance of the coherent motion display, six arrows were presented. Within 3000ms from the onset of the arrows, subjects were asked to click on the arrow that represented the perceived coherent motion direction. No feedback regarding response accuracy was given to subjects. This was followed by a 500 ms blank inter-trial interval before the onset of the next trial.

5.2.6 Exposure stage

On each trial of the exposure stage, subjects were presented with a sequence of eight items (two digits out of "1", "2", "3" and "4" and six letters such as "A", "B", "C", "D", "E", "F", "G", "H", "J", "K", "L", "M", "N", "P", "Q", "R", "S", "U", "V", "W", "X", and "Y") in a light-grey disk (0.5deg in radius) at the center of the

display. Each item was presented 75msec after the onset of the coherent motion display and disappeared 75msec before the offset of the coherent motion display, which was presented for 500 msec. Subjects were asked to press the corresponding number keys to report first and second digits with the respective order of presentations (RSVP task). No feedback as to response accuracy was provided to subjects.

In the background annulus (0.5 to 6.5 deg in eccentricity), a coherent motion display was presented and, because it was not required to perform the RSVP task, was considered to be task-irrelevant. Each subject was assigned to one of 4 groups. On each trial, each group was exposed to a coherent motion display with one of the two levels that were a combination of one of two higher levels (1.0 x threshold or 4.0 x individual threshold) and one of the two lower levels (0.3 x threshold or 0.6 x individual threshold). For each subject, two coherent motion directions were pseudo-randomly selected from six directions (10, 70, 130, 190, 250, 310 deg) and were consistently paired with two digits as targets presented at the center for the RSVP task. The other four directions were pseudo-randomly chosen and paired with letters as distractors.

5.3 Results

We measured subjects' performance on a coherent motion discrimination task in the pre- and post- test stages. Since coherent motion was irrelevant to the given task, the amount of performance increase in the post-test stages as compared to the pre-test stage, if any, is regarded as the magnitude of task-irrelevant perceptual learning. As shown in Figure 21A, for the younger group the

amplitude of task-irrelevant learning was the highest around the threshold and no learning was observed when the coherent motion ratio was threshold x 4. However, the results with the older group were different than the results of the younger group. With the increasing coherent motion ratio, the amplitude of learning did not decline with an increase in the coherent motion ratio. A significant magnitude of task-irrelevant perceptual learning with the older group was observed even with threshold x 4 motion coherence. In contrast, no increase was observed for younger adults.

In order to compare the overall learning amplitudes with the suprathreshold and subthreshold coherent motions, we averaged the magnitudes of task-irrelevant learning across 0.3, 0.6, 1.0 x threshold coherence ratios for parathreshold condition and compared performance with the magnitude of the suprathreshold coherent ratio (4.0 x threshold, see Figure 21B). The ANOVA results showed a significant interaction between age (old vs. young) and threshold (para vs. supra) condition ($F(1,36) = 5.026$, $p = 0.031 < 0.05$). The following simple main effect analysis indicated that the performance improvements for older adults in the suprathrehold condition were significantly larger than that observed with younger adults ($F(1,10) = 12.712$, $p = 0.005$, Bonferroni adjusted alpha level = 0.0125). However, no significant difference was obtained between the older and younger adults in the parathreshold condition ($F(1,26) = 0.061$ $p = 0.807$). These results indicate that although TIPL for the younger group only occurred for the parathreshold condition, for the older group TILP occurred for both the para- and supra-threshold conditions.

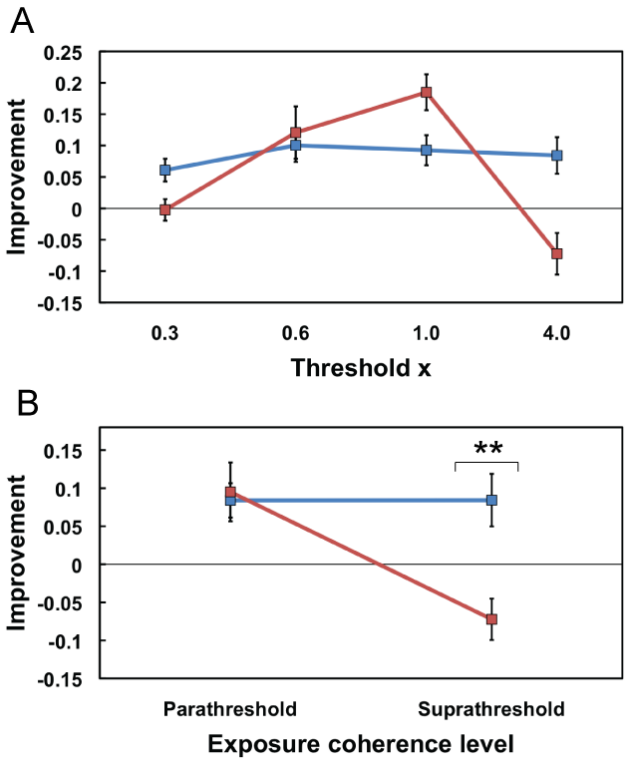

Figure 21. Performance improvement

Mean (± s.e.m) performance improvement in motion discrimination (mean percent correct in the pre-test stage subtracted from that in the post-test stage for four levels of coherent motion (A) and for parathreshold vs. suprathreshold coherent motion levels (B), for the older (blue) and younger (red) participants. $^{**}p < 0.01$.

Why did TIPL occur for older participants at such a high signal (4 x the threshold coherent motion) whereas TIPL did not occur with younger participants? A series of studies with younger individuals has suggested that when a task-irrelevant feature is above threshold or conspicuous, it is detected and suppressed by the attentional system. On the other hand, when it is below threshold, it fails to be detected and therefore to be suppressed by the attentional system (Tsushima et al., 2006). As a result, TIPL of a suprathreshold feature is less likely to occur (Tsushima et al., 2008). This finding is consistent with

previous research that indicates less inhibitory control for older as compared to younger adults (Betts et al., 2005; Healey et al., 2008).

One possibility for the occurrence of TIPL of suprathreshold motion in the present study with the older group is that the degree of suppression on a task-irrelevant signal is smaller with older individuals if it is suprathreshold and thus detected. This would allow for TIPL of the suprathreshold feature to occur. That is, TIPL of a suprathreshold motion may have occurred with older adults because older individuals have a decreased capacity to filter out irrelevant signals.

To test whether this is the case, we measured the useful field of view (UFOV) task---a standard measure of attentional processing of older adults (Ball et al., 1988)---before and after the experiment for both age groups. UFOV can be divided by three different attentional abilities: processing speed (Figure 22A), divided attention (Figure 22B) and selective attention (Figure 22C), and the lower scores represent higher performance. The selective attention measure has been proposed to assess the ability to filter out task irrelevant information. The ANOVA results found no significant difference between pre and post tests ($F(1,18) = 1.793$, $p = 0.197$) suggests that the performance changes between pre and post exposure tasks was not due to changes in attention. Furthermore, we found significant interaction ($F(2,36) = 21.884$, $p = 0.0001$) between age (old vs. young) and UFOV sub tests (sub test 1, 2 and 3). The following simple main effect analysis indicated that younger participants only have significantly better performance than older participants on UFOV sub test 3 ($F(1,18) = 30.634$, $p = 0.0003 < 0.01$). These results indicate that older participants have significantly

lower ability for filtering task-irrelevant signals. If TIPL of a suprathreshold motion occurred with older adults because they have lower ability to filter out irrelevant signals, then one can predict that for older individuals the lower the ability to filter out task-irrelevant signals should result in a greater amplitude of TIPL of suprathreshold motion. Figure 22D, shows that the correlation between these two factors is significant ($r = 0.735$, $p = 0.048 < 0.05$). These results are in accord with the hypothesis that TIPL of a suprathreshold motion may have occurred with older individuals because older adults have a decreased ability to filter out irrelevant signals.

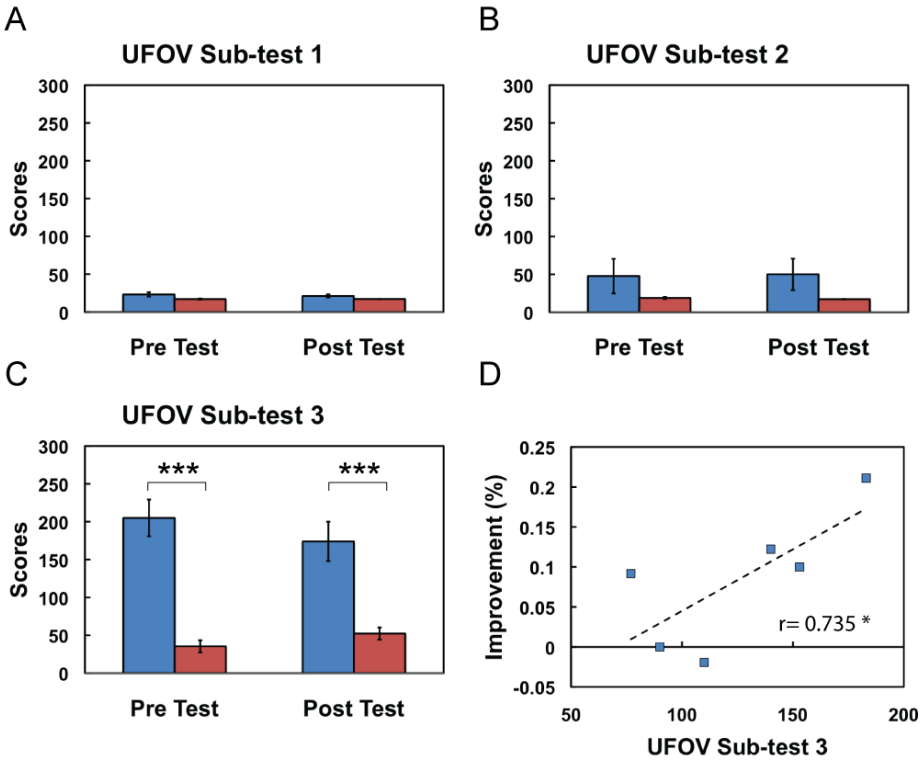

Figure 22. The correlation between UFOV and TIPL improvement under suprathreshold exposure

(A-C) Mean (± s.e.m) results of the pre- and post- UFOV tests, for both older (blue) and younger (red) participants. (A) For sub-test 1 for processing speed, (B) For sub-test 2 for divided attention and (C) For sub-test 3 for selective attention. A lower UFOV score indicates higher attention ability. (D) Correlation between Post UFOV sub test 3 and improvement in performance as a result of exposure to supra-threshold (4 x threshold) coherent motion across older subjects. These results suggests that a better ability to filter out of task irrelevant information is associated with a smaller magnitude of task-irrelevant perceptual learning of suprathreshold coherent motion. *$p < 0.05$, ***$p < 0.001$

The overall results of the present study suggest an important conclusion. While it has been pointed out that cortical function of older adults is generally less plastic or capable of learning than that of younger adults, the function of older adults does not filter information that is not important and should not be learned, resulting in cortical function that is less stable.

6. Chapter 6: Conclusion

First, the current dissertation work demonstrates the evidence of visual plasticity in the aging brain through VPL training. The traditional perspective of the human neural system is that the human brain is developed in the early stages of life: after a certain period of time, we experience age-related declines. The current dissertation work explores another possibility by applying VPL training to older adults. The behavior results from Chapters 3 and 5, which demonstrated the constant and significant performance improvement from VPL training for older adults, indicated that—after extensive training—VPL might be able to enhance older adults' performance on visual tasks to levels similar to when they were young.

Second, the current study also reveals the significance of the relationship between the brain structure and visual plasticity in aging studies. In Chapter 3, we examined the neural mechanism of the brain plasticity in the early visual area, applying both functional and structural MRI with VPL training. We used voxel-wised FA analysis from DTI to highlight significant changes in the microstructure of white matter that occur in older individuals after three days of intensive perceptual training; however, the similar changes were not observed in younger individuals. These results indicate that perceptual learning in older individuals might be associated with changes in microstructures in white matter, but not in younger individuals. The FA changes in the older brain might compensate for the limited capacity of functional plasticity. This is the first study to show that the structure of the human brain readily revealed changes in older people, but not

younger people, due to learning.

Furthermore, our study not only demonstrated that the structure of the aging brain might change with VPL, providing evidence of the plasticity, but we also found that the morphological difference of the brain structure in the aging brain can further predict the improvement of the VPL. In Chapter 4, by using standard retinotopic mapping and MRI-based morphological analyses, we demonstrated a significant association relationship between the human brain structure in the early visual area and VPL. Our results indicated a significant age-associated reduction in the areal size of V1, V2, and V3. In addition, the individual ability of VPL was significantly correlated with areal size in older people. These results clearly demonstrate age-associated changes in local structures of the early visual cortex; furthermore, the degree of the structural changes might be associated with individual visual plasticity.

Third, the current dissertation work demonstrates that the early visual area V3 might be critical in the aging brain associated with visual plasticity. Previous literature has indicated that VPL in the younger brain is involved in functional changes in the early visual area V1 (Schwartz et al., 2002; Walker et al., 2005; Yotsumoto et al., 2008); however, the same results were not observed in our study in the older adults (see Chapter 3). Although we did not find any BOLD activation changes associated with PL learning, we did find significant performance improvement after PL training. This suggests that the underlying neural mechanism of PL is different between older and younger adults. In Chapter 3, our results indicated that VPL is associated with microstructure

changes in the white matter underneath the early visual area V3 after VPL training. Interestingly, in Chapter 4, our results also showed that VPL improvement is only associated with the size of areal space among the early visual area V3. The same associations between the early visual area V3 and VPL were not found in younger adults. Based on the CRUNCH model (Reuter-Lorenz & Cappell, 2008), the lack of the function changes identified in Chapter 3 might be due to the inefficient functional compensation in the early visual area V1, because the V1 becomes too rigid and is unable to increase the cognitive loading by the function compensation. Thus, the structure compensation occurs with intensive VPL training to enhance the performance in older adults. Although the relationship between the areal space on the cortical surface and the underlying white matter volume structure is still not clear, our results might suggest that the larger V3 areal space on the cortical space could contribute to a large degree of plasticity on the microstructure changes in the white matter underneath the V3 area. Further study focused on the V3 area is necessary to test our hypothesis.

In addition, our finding on the early visual area V3 also goes against the previous reports from the anatomical regional analysis regarding the effect of aging followed by the linear relationship from anterior to posterior regions (Davis et al., 2009; Flood and Coleman, 1988; Head et al., 2004). If it is true that the effect of aging is stronger from the anterior to posterior brain, we should expect to observe more age-associated reduction from the V3 area (located on the more anterior side of the occipital lobe) to the V1 area (more the posterior side of

occipital lobe); however, our results seem to suggest an opposite tendency. In Chapter 3, our results showed that the VPL is mainly associated with the structural changes in the early visual area V3 rather than V1. In addition, in Chapter 4, we also observed that areal sizes of V1 and V2 have stronger aging-associated reduction than the areal size of V3. These studies imply the possibility that the effect of aging might have a bipolar gradient reduction from two ends of the brain to the central part of the brain rather than the linear relationship from anterior to posterior regions.

Fourth, the current study also investigated the relationship of the inhibition and visual plasticity in the aging brain. One important function of attention is the ability to filter out unnecessary information, which might affect learning. Research on task-irrelevant perceptual learning has found that younger adults' visual perception can be enhanced through weak but intensive task-irrelevant feature exposure as attention failed to filter the signal (Seitz and Watanabe, 2003; Watanabe et al., 2001); however, when the task-irrelevant visual feature became salient, no learning occurred as the task-irrelevant signal was detected and, therefore, inhibited by the attention system from higher cortical areas (Tsushima et al., 2006; Tsushima et al., 2008). However, inhibitory control largely declines with normal aging (Betts et al., 2005). In Chapter 6, our results on the TIPL in aging demonstrated that, unlike younger individuals, who only learned from weak signals, older individuals' motion perception was improved by both weak and salient task-irrelevant signals, suggesting that impaired inhibition from the higher cortical area might induce less stability than the younger adults in task-irrelevant

perceptual learning.

In conclusion, my dissertation has demonstrated that—after extensive visual training—VPL might be able to enhance older adults' performance to levels similar to when they were young. I investigated the performance improvement based on both intentional (TRPL) and unintentional (TIPL) learning, thereby providing more information for understanding humans' neural plasticity and the interaction between higher and lower neuron systems with aging. In addition, I investigated behavioral changes and the underlying neural mechanisms by using anatomical, functional MRI, and diffusion weight MRI. Unlike most previous perceptual learning studies, which have only examined either anatomical or functional changes of the brain, I measured both anatomical and functional MRI to demonstrate how structural changes of the brain influence the behavior performance of the older adults and provide more evidence to explain the relationship between brain plasticity and human behavior through VPL.

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