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Reduction in the retinotopic early visual cortex with normal aging and magnitude of perceptual learning

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Abstract

While normal aging is known to reduce cortical structures globally, the effects of aging on local structures and functions of early visual cortex are less understood. Here, using standard retinotopic mapping and magnetic resonance imaging (MRI) morphological analyses, we investigated whether aging affects areal size of the early visual cortex, which were retinotopically localized, and whether those morphological measures were associated with individual performance on visual perceptual learning. First, significant age-associated reduction was found in the areal size of V1, V2, and V3. Second, individual ability of visual perceptual learning was significantly correlated with areal size of V3 in older adults. These results demonstrate that aging changes local structures

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of the early visual cortex and the degree of change may be associated with individual visual plasticity.

Keywords

Cortical surface size; aging; early visual area; perceptual learning; retinotopic mapping

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 in vivo. Whole brain analyses using these techniques has revealed 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, Guttman, et al., 1998, Head, et al., 2004, Kochunov, et al., 2011, Raz, et al., 1997, Resnick, et al., 2003, Salat, et al., 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 analyses have shown that the brain structural reduction is not homogenous, and may be affected differently across different brain regions (Sowell, et al., 2003). 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), 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 lobe.

To our knowledge, all the studies that examined effects of aging on the occipital lobe have defined the brain region by the anatomical landmarks including an automated parcellation technique (Fischl, et al., 2002, Fischl, et al., 2004). However, the occipital lobe is functionally divided into several visual areas, each of which can be clearly defined by

retinotopic representation including V1, V2 and V3 (Tootell, et al., 1982, Wandell and Winawer, 2011, Whitney, et al., 2003), where, V1 denotes the primary visual cortex and V1, V2, and V3 are considered the early visual areas. Each of these areas has different functional properties including plasticity. Nevertheless, the effect of aging on each of these areas in the occipital lobe has, to our knowledge, never been examined. This raises the possibility that non-significant effects of aging on the anatomically defined occipital lobe does not necessarily indicate that there are significant morphological changes in functionally defined divisions of the occipital lobe. If it is the case that there are indeed morphological changes, this would raise the possibility that some functional changes with aging are related to possible morphological changes. To examine this possibility, we first measured the areal size of the early visual areas, because it has been shown that the size of visual areas is related to visual functions of younger subjects (Duncan and Boynton, 2003, Schwarzkopf and Rees, 2013, Schwarzkopf, et al., 2011). Thus, we investigated the effect of aging on areal size of retinotopically defined early visual areas (morphological aging effects), by comparing these regions in older and younger adults.

Next, we examined whether observed changes in areal size retinotopically defined as early visual areas in the occipital lobe, if any, were associated with individual differences among older adults for visual perceptual learning, as one of possible functions of the visual cortex. Perceptual learning is defined as long-term improvement on a visual task and is regarded as a manifestation of visual plasticity (Doshier, et al., 2013, Ooi, et al., 2013, Sagi, 2010, Sasaki, et al., 2010, Seitz and Watanabe, 2003, Shibata, et al., 2011, Watanabe, et al., 2002, Watanabe, et al., 2001). 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). This finding suggests that visual plasticity is preserved for visual training in older adults, which is in contrast to studies that found limited effects of training for cognitive tasks (Jones, et al., 2006, Lustig, et al., 2009, Owen, et al., 2010, Verhaeghen, et al., 1992, Yesavage, et al., 1990). However, it remains unclear whether the underlying mechanism of perceptual learning in older adults is the same as that in younger adults. We thus tested whether areal sizes of the early visual area were correlated with the magnitude of visual perceptual learning in the older and younger individuals.

2. MATERIAL AND METHODS

2.1. Subjects

Subjects were recruited into 2 age groups: 18 older adults (6 male and 12 female, the average age 71.8 ± 5.13 , mean $\pm$ 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 $\pm$ SD, ranging between 19 to 32 years old). One older subject was dropped, because we could not collect retinotopic mapping for this individual. The older subjects were recruited through the Harvard Cooperative on Aging and Brookline Senior Center. The younger subjects were recruited from Keio University and Boston University. All subjects had normal or corrected to normal vision (see Supplementary Note 1, Table S1 and S2). The older subjects 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 (Andersen, et al., 2010). All subjects gave informed consent for their participation to the experiments. The experiment procedure was approved by the Institutional Review Board at Brown University, Massachusetts General Hospital, Keio University, and Boston University where the experiments took place.

2.2. MRI

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 ms, flip angle = 70, TI = 1100 ms, 256 slices, voxel size = $1.3 \times 1.3 \times 1.0 \text{ mm}^3$, resliced during analysis to 1 mm^3) were acquired from each subject.

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 ($3 \times 3 \times 3.5 \text{ mm}^3$) 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 0–3 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 region as 3–7 deg eccentricity for each of V1, V2 and V3.

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.

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.

2.3. Texture discrimination task (TDT)

TDT is one of the most standard visual perceptual learning tasks (Karni and Sagi, 1991, Karni and Sagi, 1993, Sagi, 2010, Schwartz, et al., 2002, Walker, et al., 2005, Yotsumoto, et al., 2009, Yotsumoto, et al., 2008). We conducted three sessions of TDT training on separate days for older subjects. In the TDT task, subjects were asked to fixate their eyes at the center. On 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. The size of the display was $18^\circ \times 18^\circ$ in visual angle, where each line segment was arranged within 19-by-19 lattice. Besides the central target, the peripheral target (five array of “horizontal” or “vertical” diagonal bars) was also presented in the assigned targeted visual field quadrant on the peripheral regions (Andersen, et al., 2010). Subjects were asked to report both central target (“L” or “T”) and peripheral target (“horizontal” or “vertical”) by pressing buttons. The visual field quadrant in which a target was presented was counter-balanced across the subjects. 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, 5 different SOAs were presented from easier (longer) to harder (shorter) SOA in order. Based on the original TDT study (Karni and Sagi, 1991, Karni and Sagi, 1993) the trials with the same SOA were blocked. Seventy-two trials were presented for each SOA (360 trials for a session in total). In general, longer SOAs were used for the older than the younger subjects, so that the degrees of task difficulty between the groups was equated. The SOA set [200, 150, 100, 75, 50 ms] was used for younger subjects. For older subjects, depending on their performance in the 20 initial practice trials, one of 2 sets [2000, 1000, 500, 250, 125 ms] and [500, 250, 200, 150, 125 ms] was selected.

3. RESULTS

To examine age-related effects we measured the areal size of the early visual cortex defined by the standard retinotopic mapping in older and younger adults (Engel, et al., 1994, Fize, et al., 2003, Yotsumoto, et al., 2008). The regions of interest (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.

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 ($F(2,72) = 4.684, p = 0.012$). Thus, we further tested whether the aging effect was present in each visual area: The simple main effect of Age on this interaction (Fig. 1A) was significant for 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 ($F(1, 36) = 7.212, p = 0.011$). 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 Fig. S1, which is a scatter plot version of data. In addition, see Table S3 for correlation coefficients between age and areal size.

We found no significant interactions between Eccentricity and Age ($F(1,36) = 1.894, p = 0.177$, Fig. 1B) or Hemisphere and Age ($F(1,36) = 0.201, p = 0.657$, Fig. 1C). In addition, we found no significant 3-way or 4-way interactions. See Supplementary Result 1 for more details of the ANOVA results.

These results clearly demonstrate significant age-associated reductions in areal sizes in V1, V2 and V3. Next we calculated the overall an older/younger ratio in V1, V2 and V3 (Fig. 1D). The older/younger ratio (mean areal size with the older subjects divided by that with the younger subjects) was obtained for each visual area. The ratio was 73–76% in V1 and V2 and was 83% in V3, suggesting that the amount of age-associated size reduction is smaller in V3 than in V1 and V2.

3.2. Correlations between visual perceptual learning and morphological measures

To examine whether there is any relationship between perceptual learning and areal sizes of early visual cortical areas in older and younger individuals, the same subjects as in the first experiment were trained on TDT, for 3 training sessions, with one training session per day over a week period. We calculated the individual threshold SOA (ms), at which subjects were 80% correct to indicate the orientation of the target daily performance. 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, et al., 2010).

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 (Fig. 2A–C for older adults). 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 threshold SOA. A more negative threshold SOA index indicates a greater improvement. The average threshold SOA change index was -0.28 ± 0.35 (mean $\pm$ SD), indicating that the magnitude

of improvement for older adults was approximately 28% over the 3 training sessions. We only found that the areal size of V3 was significantly correlated with the magnitude of improvement ($r = -0.628$, $p < 0.05$, after Bonferroni correction, Fig. 2C). The larger size of V3 was correlated with higher improvement in perceptual learning for older adults. The Grubbs' test showed no outliers for the older subjects (Fig. 2C).

Importantly, this relationship was not found for 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, Karni and Sagi, 1993, Yotsumoto, et al., 2008), with the mean threshold SOA change index of -0.31 ± 0.17 (mean $\pm$ SD), which is comparable to that obtained for older adults. However, none of the areal size values was significantly correlated with the threshold SOA change index for the younger adults (Fig. 2D–F).

One may wonder whether the size of a frontal region is correlated with performance improvement. It has been shown that the reduction in size and volume in a frontal region occurs with aging, which influences cognitive functions (Lemaitre, et al., 2012). However, we did not find evidence of this relationship. We measured the areal size of the middle frontal gyrus (MFG), a part of the frontal lobe, and computed correlation coefficients with performance improvement for the older and the younger subjects. Only small degrees of correlations were found between the frontal region size and the performance improvement for both older and younger subjects (Fig. S2 and Table S4). The lack of a correlation suggests that threshold changes due to training are not associated with the size of cortical regions known to decline with age (Lemaitre, et al., 2012) and have an impact on cognition.

3.3. The occipital lobe size

While the results shown above revealed a significant reduction by age in the areal size of V1, V2, and V3, the age-associated differences might have been merely due to the overall shrinkage of the whole brain in older adults. 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 (2006), 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 (Fig. 3, $t(36) = 1.398$, $p = 0.171$). This is consistent with previous research 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.

Do the current results indicate that the size of some other regions in the occipital lobe increase with aging? We did not functionally map visual areas higher than V3. Thus, we do not have data that directly address whether other functionally defined visual areas beyond V3 change by aging. However, two observations suggest that it is not likely that other regions in the occipital lobe increase with aging. First, although the statistical result of the comparison of occipital sizes between the younger and older groups was not significant, there was a tendency for the occipital size to be smaller for older as compared to younger individuals (Fig. 3). Second, there was no significant difference between the sizes of remaining occipital area (the whole occipital minus V1, V2, and V3) for younger and older subjects ($t(36) = 0.578$, $p = 0.567$).

3.4. BOLD signals amplitude and the areal size of early visual cortex

The early visual cortex in the present study was defined by retinotopic representation, which was obtained by the 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.

First, we tested whether the BOLD signal for older individuals for retinotopically mapped regions was smaller than that for younger adults. We found no significant difference between the older and younger adults for the BOLD signal amplitudes in the early visual cortex (Fig. 4, $t(36) = 0.56$, $p = 0.579$, NS). These results suggest that there is no clear evidence of a difference in the BOLD signal amplitude in the early visual cortex between the older and younger subjects.

Next, we tested whether the areal size in older adults is associated with the magnitude of BOLD signal activation. It might be the case that areal size of early visual cortex is related to the magnitude of BOLD activation. Thus, we investigated whether the magnitude of BOLD activation during the retinotopic mapping was correlated with the areal size of V1, V2 and V3 in older adults. The results (Table S5) indicated only weak correlations, suggesting that the magnitude of BOLD activation and the areal size of early visual cortex are primarily independent in older adults.

3.5. Visual performance and the areal size

Here we have shown that the areal size of V3 in older adults was significantly correlated with the magnitude of performance improvement in perceptual learning. However, one may wonder whether the visual performance is associated with the areal size of the early visual cortex in the first place. Thus, we tested whether the initial threshold in the TDT before training (Table S6), visual acuity (Table S7), and contrast sensitivity (Table S8) were correlated with areal sizes in the early visual cortex of older adults, as well as younger adults. As shown in the Tables S6–S8, initial threshold of TDT, visual acuity, or contrast sensitivity were not significantly correlated with the areal size of V1, V2, or V3. The results suggest that these measures for visual performance are not significantly related with the areal size of the early visual cortex.

4. DISCUSSION

In the current study, we found an age-associated reduction of areal size in the functionally defined early visual cortical areas such as V1, V2 and V3 (Fig. 1). In addition, we found that the amount of visual perceptual learning was highly correlated with the cortical size of only V3 in older adults and not significantly correlated with the cortical size of V1, V2 and V3 in younger adults (Fig. 2).

At a glance, it may appear that our results contradict the results indicating no significant age-associated reductions in the occipital lobe of older adults based on anatomically defined areas found by previous studies (Allen, et al., 2005, Resnick, et al., 2003, Salat, et al., 2004). However, this is not the case. It is worth noting that the technique and measures used in the present study were different than that used in previous studies. While we found areal size reductions in V1, V2, and V3 in older subjects that were retinotopically defined, the previous results indicating no significant size reduction in anatomically defined occipital lobe of the same older subjects was replicated in our study. Thus, we conclude that reduction in areal size in the early visual cortex with aging can be observed when these areas are retinotopically, therefore, functionally defined, whereas reduction could not be revealed clearly in the size of the anatomically-defined occipital lobe.

It is important to note that although some MRI studies found that older adults have overall lower amplitudes 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 **Material and Methods**, we identified the cortical regions that retinotopically correspond to the horizontal and vertical meridians of the visual fields, because these regions 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 single 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, used for retinotopic mapping, is unlikely to be shifted due to the smaller BOLD amplitude. Second, the BOLD amplitude analysis among the early visual areas, during the retinotopic mapping scanning, showed no significant difference between the older and younger adults (Fig. 4). While the lack of statistical significance does not necessarily indicate the lack of effect, the result 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. Moreover, the magnitude of BOLD signals during retinotopic mapping was not significantly correlated with areal size in V1, V2, or V3 (Table S5). This suggests that the age-related reduction of areal size and the magnitude of functional activations are likely to be independent in early visual cortex.

It has been found that morphological changes in the early visual cortex are related to visual abilities and perception for younger adults (Duncan and Boynton, 2003, Schwarzkopf and Rees, 2013, Schwarzkopf, et al., 2011). However, to our knowledge no study has reported relationships between the areal size of early visual cortex and visual functions in older adults. In the present study, individual visual acuity and contrast sensitivity were not correlated with the areal size of V1, V2 and V3, in older adults or in younger adults. Moreover, the initial performance of TDT was also not correlated with the areal size of the early visual cortex. However, we found that areal size in V3 is positively and strongly correlated with the magnitude of perceptual learning across older individuals. This may suggest that visual plasticity and baseline visual perception (as measured in the present study) are not governed by the same neural mechanisms.

A number of studies have found that visual perceptual learning in younger adults is associated with changes in the functional activation in the trained location of V1 (Furmanski, et al., 2004, Schwartz, et al., 2002, Walker, et al., 2005, Yotsumoto, et al., 2008). Why was the correlation found, for older adults, between V3 and perceptual learning in the present study, instead of between V1 and perceptual learning? One hypothesis is that functional plasticity of V3 cortex in older adults compensates for the reduced functional plasticity of V1 cortex, resulting in a shift in the responsive visual area for perceptual learning from V1 to V3 for older adults. It has been suggested that perceptual learning results from changes including a larger number of efficient neuronal connections in early visual cortex (Doshier and Lu, 1998, Piech, et al., 2013). Thus, one possibility is that reduced cortical size in V1 is associated with a decreased number of connectivity, which negatively influences capability of perceptual learning, which is a manifestation of functional plasticity in vision. The degree of age-related areal reduction was the largest in V1 and the smallest in V3 (Fig. 1D). This result implies that functional plasticity that relies on neuronal connections is reduced largely in V1, while it is relatively better preserved in V3. As a result, neural circuits associated with V3 may have been recruited to compensate for the insufficient functional plasticity of V1 in older adults, allowing perceptual learning to occur. It has also been found that perceptual learning is associated with significant changes (fractional anisotropy) in the white matter microstructure just beneath V3 in older adults, not in any other white matter region in older adults nor in any white matter region in younger adults (Yotsumoto, et al., 2010). These results are in accord with the hypothesis that aging makes the neural circuits associated with V1 so compromised that V1 of older adults is not sufficiently plastic for perceptual learning to occur. As a result, neural circuits associated with V3, which manifest itself as structural changes during perceptual learning, compensate for the insufficient functional plasticity in V1.

An important question to consider is if V1 plays a role in perceptual learning in young adults then why was there no significant positive correlation between V1 areal size and the amount of perceptual learning for young individuals? One possible explanation is a ceiling effect. Specifically, since the function of V1 is optimized for visual plasticity for younger adults, even the smallest size of all the young subjects' V1 may be sufficient for functional plasticity and therefore individual size differences are not significantly correlated with the amount of perceptual learning.

On the other hand, although the degree of age-related areal shrinkage in V3 of older adults is smaller than in V1 or V2, this does not indicate that neural circuits associated with V3 is fully optimal for functional plasticity for perceptual learning to be possible. Some older adults may have significantly smaller V3, which may make V3 less plastic than other older individuals. This may be an explanation for the positive correlation between the amount of perceptual learning and the size of V3 for the older subjects. Future research is necessary to test the validity of these hypotheses.

To summarize, the present study demonstrated age-associated areal size changes in retinotopically defined early visual areas for the first time, which is not consistent with the findings of previous research that aging does not influence the size of early visual cortex. Moreover, the areal size of V3 in older adults was highly correlated with the magnitude of visual perceptual learning, indicating the importance of functionally defined early visual areas for better understanding age-related changes in visual functions and plasticity. Possible influences of such age-related changes in early visual processing on higher order cognitive functions are important issues for future research (Anguera, et al., 2013, Kalisch, et al., 2012).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

V1	Primary visual cortex
V2	Second visual cortex
V3	Third visual cortex

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HIGHLIGHTS

- Age-associated structural changes in visual cortex is controversial (69/85)
- Aging reduces the areal size of retinotopically identified V1, V2 and V3 (74/85)
- Magnitude of perceptual learning and V3 areal size were correlated for older adults (85/85)
- Aging reduces visual cortex size, which predicts the degree of plasticity (75/85)

Fig. 1. The mean areal size ($\pm$ S.E.M) in the early visual cortex of older (red) and younger (blue) adults

(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 $\times$ visual area interaction. $*p < 0.05$, $***p < 0.001$. See for Supplementary Results 1 for more details of the ANOVA results. (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) The ratio of the mean areal size of the older subjects divided by that of the younger subjects. The age-associated size reduction is the smallest in V3. See also Fig. S1.

Fig. 2. 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 results indicate that only the areal size of V3 in older adults was significantly correlated ($p = 0.006$, before Bonferroni correction) with the amount of performance improvement of TDT.

Fig. 3. 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 subjects, respectively. The size is the sum ($\pm$ S.D) of the occipital regions in the left and right hemispheres. Note the unit for the Y-axis is cm^2 , not mm^2 as in Figs. 1 and 2.

Fig. 4. The BOLD signal amplitude

The mean BOLD amplitude $\pm$ S.D. averaged across the early visual area including V1, V2 and V3 for older and younger subjects.