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Age-related relative volume preservation of the dominant hand cortical region

Leonardo Bonilha^{a,*}, Mark A. Eckert^b, Julius Fridriksson^c, Victor A. Hirth^d, Dana Moser^c, Paul S. Morgan^e, and Chris Rorden^c

^aDivision of Neurology, Medical University of South Carolina, 96 Jonathan Lucas St, 3rd floor, Charleston, SC 29412, USA

^bDepartment of Otolaryngology, Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA

^cDepartment of Communication Sciences and Disorders, University of South Carolina, Charleston, SC, USA

^dDivision of Geriatrics, University of South Carolina, Charleston, SC, USA

^eDepartment of Radiology, Medical University of South Carolina, Charleston, SC, USA

Abstract

Aging is usually associated with a progressive difficulty in learning new skills. Similarly, the dexterity in the non-dominant hand is usually decreased with age, while the dominant hand maintains a relative preservation in agility. We investigated if age-related volume loss affects the hand areas asymmetrically by comparing structural measures of the dominant hand area versus the non-dominant area. We performed a region of interest analysis of T1-weighted images focusing on the sensorimotor cortex corresponding to the hand area. We evaluated images from young subjects (younger than 65 years of age, $n=38$, mean age= 24 ± 7 years) and senior subjects (65 years or older, $n=61$, mean age= 73 ± 6 years). We observed that older adults exhibited greater leftward gray matter asymmetry of sensorimotor cortex, due in large part to more pronounced age-related loss of gray matter in the right hemisphere. These results are consistent with evidence that disuse leads to atrophy and suggest that age-related declines in gray matter, and perhaps function, may be limited by increasing the use of the non-dominant hand.

Keywords

Motor cortex; Aging; Plasticity; Asymmetry; Cortical circuitry

1. Introduction

Aging is traditionally associated with a general reduction in cognitive and motor capabilities (Anstey and Low, 2004). Learning a foreign language or learning to play a new musical instrument is strikingly easier earlier in life, compared to more senior years. Similarly, successful recovery from a brain lesion is more likely when the lesion occurs earlier compared to later in life (Nakayama et al., 1994).

* Corresponding author. Fax: +1 843 792 8626. bonilha@musc.edu (L. Bonilha).

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A similar phenomenon is the age-related decline in dexterity for fine hand movements. The agility in the execution of complex hand movements is reduced in subjects older than 60 years of age compared to middle aged or young adults. However, the rate of decline of hand dexterity is significantly more pronounced for the non-dominant hand (Amirjani et al., 2007), even though peripheral factors such as age-related loss in muscle strength or reduced skin sensitivity affect all extremities (Stevens et al., 2003). Hence, the preservation of well-rehearsed motor function is a potential explanation for the asymmetrical loss in fine motor control, suggesting that a constantly used skill is relatively maintained.

Fine motor control of the hand is supported by regions within the “hand bump” region of the sensorimotor cortex (Yousry et al., 1997). Asymmetry of the sensorimotor region in younger adults is subtle (Zilles et al., 1996), with some earlier studies failing to detect robust differences between the dominant and non-dominant hemispheres. Recent improvements in equipment and methodology have helped identify that right-handers have a deeper central sulcus (Amunts et al., 1996) as well as a thicker sensorimotor region (Luders et al., 2006) in the left hemisphere compared to the right. Age-related changes in the structure of sensorimotor regions that support non-dominant hand control presumably underlie the loss of dexterity in older adults. We hypothesized that structural asymmetry of sensorimotor cortex is more pronounced in older adults due to exaggerated loss of tissue that supports the non-dominant hand and a relative preservation of tissue that supports fine motor control. In support of this hypothesis, in vivo high-resolution morphometrical MRI studies have demonstrated that preservation of cognitive functions often correlate with measures of structural brain integrity (Tisserand et al., 2004; Bonilha et al., 2007). To test our hypotheses, we examined the extent to which a large sample of older and younger adults exhibited group differences in gray matter asymmetry of sensorimotor cortex (Figs. 1 and 2).

2. Results

2.1. Voxel based morphometry

Voxel-wise comparisons between older and younger subjects demonstrated widespread age-related reductions in gray matter volume (Fig. 3), particularly in frontal, temporal, occipital areas, insula, basal nuclei and the diencephalon.

Whole brain analyses of asymmetry indices revealed a significant leftward asymmetry of the sensorimotor region, particularly involving the hand area (Fig. 4). Independently defined ROIs of this region were used to verify this finding, by demonstrating a significant positive correlation between leftward asymmetry and age (Fig. 4), and a significant difference between the mean asymmetry within the ROI between the young and the older groups ($t(97)=3.1$, $p=0.002$) (Fig. 5).

Finally, the mean gray matter volume within the left and right hand ROIs showed significantly less gray matter in older individuals compared to controls. Importantly, a lesser degree of decline was present for the left hemisphere hand area compared to the right hemisphere hand area ($F(1,1)=8.8$, $p=0.004$; Fig. 5).

3. Discussion

Age-related gray matter atrophy of the sensorimotor hand region was less pronounced for the dominant hand, compared to the non-dominant hand. We observed that, as a consequence of imbalanced gray matter atrophy, there is a progressive leftward structural hemispheric asymmetry of the sensorimotor hand cortex associated with aging. These findings provide indirect evidence that the hand area of the motor cortex (and perhaps other segments of the

primary motor and somatosensory cortex) is subjected to structural modifications across time, possibly as a reflection of its functional demands.

The age-related changes in brain structure observed in this study are consistent with findings from recent studies that have suggested that gray matter volume is influenced by functional usage. For example, skillful musicians tend to show more gray matter in motor, auditory, and visual-spatial brain regions (Gaser and Schlaug 2003). Certainly, structural differences in these populations could reflect cause, rather than a consequence. For example, anatomical differences could lead to the predisposition for music learning. However, subjects asked to perform a complex motor task, such as juggling balls, show transient enlargement of the occipital and parietal cortex (Draganski et al., 2004; Draganski et al., 2006), suggesting that motor training induces microscopic changes in the human cortex related to functional plasticity. These findings corroborate experimental studies of motor training that demonstrated a link between functional plasticity and structural changes in the motor cortex of rodents and monkeys (Kleim et al., 1998; Nudo et al., 1996). It is unclear, however, if structural changes of the human cortex represent a transient variation in architecture related to the acquisition of a motor skill, or the actual circuitry underlying the movement representation.

There is considerable evidence suggesting that motor cortex exhibits plastic adaptations in response to motor training. These adaptations are functional, as well as structural. Monfils et al. (2005) summarized the functional organization of motor cortex as a function of four different properties, namely multiplicity of representation of human movements, interconnectivity, larger cortical representation for movements requiring higher degrees of dexterity, and plasticity. In particular, the last of these four components, plasticity, relates to dynamic changes of the motor map topography in response to external pressures. Subsequent research demonstrated that functional changes of the motor cortex are related not to an increase in the frequency of the execution of the motor task, but it is rather dependent on the complexity of the task being trained. This was demonstrated by Kleim et al. (1998), working with rodents trained in a skilled and unskilled forelimb reaching task. An increase in the functional representation of forelimb movements was present only after training the skillful task. Functional motor cortex plasticity is also directly followed by structural plasticity. In fact, changes in synaptic strength or, similarly, potentiation and depression of synapses, is the structural substrate of functional changes in general (Monfils et al., 2005). Motor training causes an increase in the number of synapses per neuron in the motor cortex (Kleim et al., 1996), a change in the dynamics of the synaptic organization (Kleim et al., 2004; Kleim et al., 2002; Kleim et al., 2007) and, importantly, motor skill learning is directly dependent upon protein synthesis in the motor cortex (Luft et al., 2004; Kleim et al., 2003). Motor skill improvement is directly accompanied by, first, a surge in protein synthesis, followed by a rise in synaptogenesis, and ultimately by map re-organization (Adkins et al., 2006).

Our findings corroborate a dynamic asymmetry between dominant hand regions in humans. Older individuals appear to have a relative preservation of gray matter volume in the dominant region. This finding may suggest that the dominant hand region has inherent structural properties once brain maturation occurs, and these properties ensure structural integrity. Conversely, this finding may also suggest that a continuous demand for function (i.e., the daily life requirements for use of dominant hand dexterity) stimulate plasticity and confer protection against the age-related gray matter decline.

In conclusion, in this study we observed relative preservation of the gray matter volume in the dominant hemisphere hand region motor. This region showed a slower cross-sectional rate of atrophy compared with the non-dominant hemisphere. This result may suggest function is coupled with structural integrity and this may be a mechanism conferring protection against age-related brain atrophy. As a consequence, interventions or active lifestyles may limit the

rate of loss of cortex in the non-dominant hand, which may become increasingly important with the impact of age-related disease on systems that support dominant hand control such as dementia or vascular insults.

4. Experimental procedures

4.1. Subjects

Ninety-nine healthy right-handed (by self report, confirmed by the Edinburgh Handedness Inventory) individuals participated in this study. The participants belonged to two different age groups: (1) older than 65 years ($n=61$, mean age= 73 ± 6 years) and (2) younger than 65 years ($n=38$, mean age= 24 ± 7 years) (Fig. 1). The putative age threshold of 65 years was chosen, as this is the conventional upper limit of middle age (and the lower limit for senior age). All participants were recruited from the local community through newspaper and verbal advertisement, and all signed an informed consent. The demographics background of the studied populations was similar. The Institutional Review Board of the University of South Carolina approved this study.

4.2. Imaging protocol

All subjects were scanned in a Siemens Trio 3T scanner equipped with a 12 element head coil and parallel imaging located at the University of South Carolina. We collected a T1 weighted MRI scan (1 mm isotropic voxels, TR=2250 ms, TE=4.52 ms, matrix size=256×256, flip angle=9 °) from all subjects.

4.3. Voxel based morphometry

T1 images were transformed into analyze format using the software MRICro (Rorden and Brett, 2000). A symmetrical T1 template and symmetrical tissues priors were generated from all subjects. Initially, an asymmetrical template in MNI space was constructed from all T1 images from all participants involved in this study using modified routines of the software SPM2 (Ashburner and Friston, 2000). Then, a symmetrical template was obtained by averaging the original template and its left-right flipped image.

Images were then spatially normalized to the symmetrical template to ensure tissue alignment while preserving the amount of tissue, thus preserving the structural authenticity and minimizing registration-related distortion (Good et al., 2001). Images were then segmented with non-uniformity correction into gray matter probabilistic maps, and smoothed by a 10-mm full-width half maximum isotropic Gaussian kernel.

An independent sample *t*-test was applied to normalized, segmented and smoothed images in order to evaluate regional differences in gray matter volume between the older and the younger groups. This analysis was performed using SPM2. Results were corrected for multiple comparisons using a False Discovery Rate (FDR) corrected threshold of $q=0.05$. FDR balances the rate of hits to false alarms, so the 5% threshold we used means that 1/20th of the values that survive thresholding are false alarms. FDR is an alternative to traditional techniques that control Familywise Error (FWE), and it can be more sensitive in situations where a significant proportion of the samples exhibit an effect (Genovese et al., 2002).

Normalized and segmented gray matter images were then used to create asymmetry maps. Asymmetry maps were calculated on voxel-by-voxel basis using the function ImCalc included in SPM2, according to the formula: $2*[i-(f)i]/[i+(f)i]$; where *i* denotes the probabilistic map and gray matter and *(f)i* its left-right flipped version, over the *x* axis origin. The resulting asymmetry maps were submitted to an independent sample *t*-test comparing the two age groups (VBM analysis 2). We aimed to investigate brain areas where asymmetry would increase as a

function of age. The results of this type of analysis are difficult to interpret because they could reflect that the younger individuals started with a L>R asymmetry that diminishes with age, or that the older individuals have a R>L asymmetry that has increased with age. Therefore, to clarify the interpretation, we initially searched for voxels in older individuals that, compared to younger individuals, would exhibit an absolute Z score higher than 1.96, in the same direction of the mean asymmetry index for that voxel (positive or negative) in the older group. Once identified, these voxels were used to create a mask representing regions where asymmetry was more extreme (either positive or negative) in older individuals. This mask was then explicitly applied to an independent sample *t*-test comparing the smoothed asymmetry maps between the older and younger groups, i.e., only voxels contained in the mask were assessed. This parametric group analysis was performed using the software NPM. Results were then thresholded with a 5% False Discovery Rate (FDR).

Finally, we investigated changes in gray matter and asymmetry indexes in a region of interest (ROI) defined in the approximate sensorimotor region representing the hand (VBM analysis 3) (Fig. 2) (center of mass: $x=\pm 35$, $y=-26$, $z=58$, volume=4168 mm³, ranges: $-48 < x < -24$, $-40 < y < -14$, $52 < z < 66$), according to the BrainMap database library of ROIs (<http://brainmap.org>) available at (<http://hendrix.ei.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html>). This ROI was chosen based a review of functional and structural literature assessing hand area (Fox et al., 1994). It encompassed Brodmann areas 2, 3, 4, 6 and 40 (the number of 1 mm³ voxels in each areas being: BA 2=655; BA 3=3399; BA 4=3412; BA 6=2935; BA 40=185).

We investigated the correlation between the asymmetry index and age using a *t*-test for each voxel contained within the ROI. We also extracted the mean asymmetry index from the ROI and compared the values between the older and younger groups using an independent sample *t*-test. Finally, we extracted the gray matter volume from left and right hand areas and compared the values between younger and older subjects using a repeated measure ANOVA with 1 within subject factor (side: left or right) and 1 between subjects factor (group: older or younger). The test ANOVA was chosen so as to enable the discrimination of the effect size for each factor.

The mean gray matter volume or asymmetry data, described in second and third ROI analyses mentioned above were extracted using the software MarsBar (Brett et al., 2002). Statistical analyses involving mean gray matter or asymmetry indexes were performed with the software SPSS v12. The threshold for statistical significance was set as $p < 0.05$.

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Fig. 1.
We studied images from subjects pertaining to two distinct age groups, younger and older than 65 years.

Fig. 2.
Regions of interest located in the sensorimotor representation of the hand.

Fig. 3. Areas where gray matter volume is reduced in the older group compared to the younger group. The scale bar represents Z scores. Images are in neurological convention.

Fig. 4. Areas of progressive leftward (“hot”) and rightward (“cold”) asymmetry are shown in the left panel. The dashed contour represents the sensorimotor hand area. The right panel shows leftward asymmetry correlated with age, with the analysis focused in the hand area.

Fig. 5.

Left panel shows that the decline in gray matter volume is more intense in the right hemisphere hand area than in the left hemisphere. The right panel shows that the asymmetry index in the hand area is significantly smaller (therefore representing a leftward asymmetry) in older individuals, compared to younger individuals.