

## Brain morphology according to age, sex, and handedness

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In this article, we review the differences of the brain morphology according to age, sex, and handedness. Age is a well-known factor affecting brain morphology. With aging, progressive reduction of brain volume is driven. Sex also has great effects on brain morphology. Although there are some reports that the differences of brain morphology may originate from the differences of weight between the 2 sexes, studies have demonstrated that there are regional differences even after the correction for weight. Handedness has long been regarded as a behavioral marker of functional asymmetry. Although there have been debates about the effect of handedness on brain morphology, previous well-established studies suggest there are differences in some regions according to handedness. Even with the studies done so far, normal brain morphology is not fully understood. Therefore, studies specific for the each ethnic group and standardized methods are needed to establish a more reliable database of healthy subjects' brain morphology.

**Key words:** Brain; Magnetic resonance imaging; Demography

## INTRODUCTION

Brain magnetic resonance imaging (MRI) has been an important visual analysis tool to diagnose various neurologic disorders such as ischemic stroke, hemorrhage, or brain tumors. With the development of modern neuroimaging technology and processing analysis, the expectations of its application have grown widely. MRI not only helps diagnose diseases by visual analysis, but also can be used to understand pathogenesis by quantification analysis in variable diseases such as autism<sup>1,2</sup> or schizophrenia<sup>3,4</sup> which usually have normal MRI. There are several commonly used techniques in studies using MRI as a tool for quantitative analysis. With gray matter (GM), many studies have used voxel-based morphometry (VBM),<sup>5</sup> which is a fully automated whole-brain technique that registers high-resolution MRIs into

a common stereotactic space and allows for comparison at every voxel.<sup>6</sup> With white matter (WM), many studies have used diffusion tensor imaging (DTI), which can measure the displacement of water molecules across tissue components, thus providing information regarding the microstructure of cerebral WM.<sup>7,8</sup> Mean diffusivity (MD) and fractional anisotropy (FA) are the measures commonly used in DTI. MD is the net degree of displacement of the water molecules<sup>9</sup> and is related to cell density.<sup>10</sup> FA ranges between 0 and 1.<sup>9</sup> A value of 0 means that diffusion is unrestricted in all directions while a value of 1 means that diffusion is oriented and coherent.

Increased use of these MRI techniques in neurologic and psychiatric diseases has resulted in increased necessity of understanding the brain morphology in normal subjects. In this study, we reviewed the most important articles to reveal the differences of brain morphology using MRI according to age, sex, and handedness in normal subjects.

## RELATIONSHIP BETWEEN AGE AND BRAIN MORPHOLOGY

There have been studies regarding the relationship between aging and brain morphology (Table 1). It is well-known that there is an inversely proportional relationship between age and overall brain volume.<sup>11</sup> Specifically, there are studies

about exactly which part of the brain volume changes most significantly with the aging process.<sup>11</sup> These studies are classified by each separate brain structure.

## OVERALL GRAY MATTER AND WHITE MATTER

Resnick et al. quantified longitudinal MRI scans of 92 healthy adults aged 59 to 85 to determine the rates and regional distributions of GM and WM tissue loss in older adults.<sup>12</sup> Annual rates of tissue loss were 5.4, 2.4, and 3.1 cm<sup>3</sup> per year for total brain, GM, and WM volumes, respectively.<sup>12</sup> The frontal and parietal lobes showed greater decline compared to the temporal and occipital lobes.<sup>12</sup>

## CEREBRAL CORTEX

Curiati et al. used VBM to conduct a voxel-wise search for correlations between GM volume and age and found that the temporal neocortex, prefrontal cortex, and medial temporal regions showed especially greater GM decline rates.<sup>13</sup> Grieve et al. also found that there was an accelerated loss in focal regions of the frontal and parietal cortices, including the dorsolateral frontal cortex, pre- and post-central gyrus,

**Table 1.** Studies about the relationship between aging and brain morphology

Authors	Brain region	Age related results
Jernigan et al. (1991) <sup>11</sup>	Anterior cingulate cortex	No significant associations to age
Resnick et al. (2003) <sup>12</sup>	GM, WM, total brain	GM: 3.1 cm <sup>3</sup> decline annually WM: 2.4 cm <sup>3</sup> decline annually Total brain: 5.4 cm <sup>3</sup> decline annually
Grieve et al. (2005) <sup>14</sup>	Cerebral cortex Limbic structure Paralimbic structure	Accelerated loss in dorsolateral frontal cortex, pre- and post-central gyrus, and inferior and superior parietal lobes No significant associations to age in limbic and paralimbic structures
Abe et al. (2008) <sup>17</sup>	Globus pallidus	No significant associations to age
Cherubini et al. (2009) <sup>47</sup>	Basal ganglia	Decreased volume of putamen and caudate nucleus
Hughes et al. (2012) <sup>16</sup>	Thalamus	Decreased, with anterior regions generally more compromised than posterior regions

GM, gray matter; WM, white matter.

and the inferior and superior parietal lobes.<sup>14</sup> Jernigan et al. studied GM volume loss in 8 separate cortical regions (inferior anterior, inferior posterior, superior anterior, and superior posterior peripheral cortex, and mesial cortex) and confirmed that only the volume of the superior anterior mesial cortex, which mainly includes the anterior cingulate cortex, was unchanged with aging.<sup>11</sup>

## THALAMUS

As with the aging process, structural MRI and DTI demonstrated regional thalamic volume shrinkage and microstructural degradation. The anterior regions were generally more compromised than the posterior regions.<sup>15,16</sup>

## LIMBIC AND PARALIMBIC STRUCTURE

Per Grieve et al., GM was relatively preserved in limbic and paralimbic structures, including the amygdala, hippocampus, and cingulate gyrus.<sup>14</sup> In these clusters, GM loss was significantly attenuated relative to the global rate of shrinkage of the overall volume.<sup>14</sup> Furthermore, they found that the preservation of these structures was consistent with the functional importance of the thalamo-limbic circuits in sensory integration, arousal, emotion, and memory.<sup>14</sup> Therefore,

it can be inferred that these early maturing subcortical limbic regions are relatively intact to age-related morphologic changes.<sup>14</sup>

## BASAL GANGLIA

Even within the basal ganglia, there was a big difference in the degree of the changes between each structure. Large age-related variations were observed in the putamen and caudate nucleus. However, no significant correlation with age was observed in the globus pallidus.<sup>17</sup>

## RELATIONSHIP BETWEEN SEX AND BRAIN MORPHOLOGY

There have been studies regarding the relationship between sex and brain morphology (Table 2). Sex also has great effects on human brain morphology. While the average volume of the total brain is larger in males than in females, there are differences of brain morphology in specific brain regions according to sex.<sup>18</sup> There are also controversies whether the body size difference between the 2 sexes was considered.<sup>19</sup> There are several studies about brain morphology differences according to sex.

**Table 2.** Studies about the relationship between sex and brain morphology

Authors	Brain region	Sex related results
DeLacoste-Utamsing et al. (1982) <sup>24</sup>	Corpus callosum	Longer in females
Good et al. (2001) <sup>6</sup>	GM	Bigger GM volume and GM volume/ICV in males
Abe et al. (2010) <sup>22</sup>	WM	Bigger WM volume in males Bigger WM volume/ICV in females
Xie et al. (2012) <sup>28</sup>	Brainstem Thalamus	Bigger brainstem volume in males, no significant difference in brainstem volume/ICV Bigger thalamus in males, bigger thalamus volume/GM volume in females, rightward asymmetry more prominent in females
Sacher et al. (2013) <sup>21</sup>	Total brain	Bigger total brain volume in males after correction for body volume
Ardekani et al. (2013) <sup>19</sup>	Corpus callosum	Bigger CCA in females after correction for brain volume and age
Luders et al. (2014) <sup>25</sup>	Corpus callosum	No significant associations to sex
Perlaki et al. (2014) <sup>26</sup>	Hippocampus	No significant associations to sex after correction for brain volume
Tan et al. (2016) <sup>27</sup>	Hippocampus	Bigger hippocampus volume in males

GM, gray matter; ICV, intracranial volume; WM, white matter; CCA, corpus callosum cross-sectional area.

## OVERALL GRAY MATTER AND WHITE MATTER

Average total brain volume is greater in males even after correction for body volume.<sup>20,21</sup> GM volume, GM volume/intracranial volume (ICV), and the WM volume of males were bigger than females, except for WM volume/ICV, which was bigger in females.<sup>6,21,22</sup> There was no difference in global MD, but males had bigger global FA than females.<sup>22</sup>

## GRAY MATTER

There were more regional differences. The surface expansion of the frontal lobe of the right hemisphere was more significant in the male brain than in the female.<sup>23</sup> Radial surface expansion in the posterior-occipital region of the left hemisphere was more prominent in males than in females.<sup>6</sup> Males had a bigger perirhinal cortex and left anterior superior temporal gyrus than females.<sup>6</sup> Females had a bigger right middle temporal, right transverse temporal, right inferior parietal, left parahippocampal, lateral orbital, cingulate gyri, and right planum temporale than males.<sup>6</sup> Also, female cortical depth was deeper than male.<sup>21</sup>

## CORPUS CALLOSUM

There are debates about the corpus callosum. In research in 1982, De Lacoste-Utamsing and Holloway first found that females had a larger mid-sagittal corpus callosum cross-sectional area.<sup>24</sup> Although the lengths of the corpus callosum of the 2 sexes had no significant difference, it was larger in females than in males, considering brain volume.<sup>24</sup> However, the correction of total brain volume was not carried out precisely. Relatively recent research in 2013 provided evidence that females had a bigger corpus callosum cross-sectional area than males, even after correcting for brain volume and age.<sup>19</sup>

On the other hand, another study in 2014 demonstrated that the callosal difference between the 2 sexes resulted from brain volume difference and that there was no actual callosal difference between the 2 sexes.<sup>25</sup>

## HIPPOCAMPUS

When comparing only absolute hippocampus volumes, males were larger.<sup>26,27</sup> Meta-analysis demonstrated reduced hippocampus volume in many neuropsychiatric disorders commonly found in women.<sup>27</sup> Therefore, researchers assumed that the smaller hippocampus volume of women contributed to increased vulnerability of neuropsychiatric disorders.<sup>27</sup> However, there are conflicting results about the hippocampus volume after correction for brain size.<sup>27</sup> Hippocampus volume/ICV was bigger in females than in males, but when comparing the hippocampus volume of samples matched for brain volume, there was no significant difference.<sup>27</sup> This study suggested that there is no sexual difference in hippocampus volume and the difference in hippocampus volume/ICV came from the ICV difference of the 2 sexes.<sup>26,27</sup>

## BRAINSTEM AND THALAMUS

Males had greater brainstem volume than females, but brainstem volume/ICV difference was not significant.<sup>28</sup> Thalamus volume of males was larger than females, but thalamus volume/GM volume was bigger in females.<sup>6,28</sup> Rightward thalamus asymmetry, which means a larger thalamus in the right side, was more prominent in females than in males.<sup>28</sup>

## WHITE MATTER

In regional differences, males had larger anterior temporal WM that extends into the internal capsule than females.<sup>6</sup> WM concentration in the anterior temporal and posterior frontal lobes of males was increased more than in females.<sup>6</sup> Females had larger volume in the posterior frontal lobes, left temporal stem/optic radiation than males.<sup>6</sup> The concentration in internal and external capsules and optic radiation of WM of females was increased more than in males.<sup>6</sup>

## RELATIONSHIP BETWEEN HANDEDNESS AND BRAIN MORPHOLOGY

There have been studies regarding the relationship between

handedness and brain morphology (Table 3). Handedness has long been regarded as a behavioral marker of functional asymmetry. Many researchers have demonstrated differences in brain morphology that might underlie handedness.<sup>18,29</sup> However, the effect of handedness on brain morphology is controversial as there are some recent studies suggesting that there might be no difference in brain volume as well as in brain asymmetry related to handedness.<sup>6,30,31</sup> A study involving 398 right-handed and 67 left-handed subjects using VBM found no global, regional difference in GM and WM volume between right-handers and left-handers.<sup>6</sup> It also found no difference in brain asymmetry.<sup>6</sup> A larger study involving 1960 right-handed subjects and 106 left-handed subjects found no structural differences in the cerebral cortex regarding handedness.<sup>30</sup> However, as Good et al. stated, while many of the reported handedness effects are related to sulcal topography, it is possible that VBM is not yet sensitive enough to detect

subtle sulcal differences.<sup>6</sup> There are also well-established studies showing the relationship between handedness and brain morphology in specific regions.

## MEASUREMENT SCALES OF HANDEDNESS

To study the relationship between handedness and brain morphology, researchers need an appropriate means to measure subjects' handedness. There are 2 types of tests that can be done simply. One is a questionnaire type such as the Edinburgh Handedness Inventory and the Annett Hand Preference Questionnaire.<sup>32,33</sup> Among these, the Edinburgh Handedness Inventory is the most widely used handedness inventory; it was devised by Oldfield in 1971.<sup>34</sup> A search of the Web of Science Cited Reference conducted on June 15, 2014, revealed that the Edinburgh Handedness Inventory

**Table 3.** Studies about the relationship between handedness and brain morphology

Authors	Brain region	Handedness related results
Habib et al. (1991) <sup>29</sup>	Corpus callosum	Smaller in right-handers especially in its anterior half than in left-handers
Peterson et al. (1993) <sup>42</sup>	Basal ganglia	Bigger total basal ganglia volume in left hemisphere than right in right-handers; bigger globus pallidus, putamen on the left, bigger caudate nuclei on the right No asymmetries in left-handers
Foundas et al. (1995) <sup>39</sup>	Pars triangularis Planum temporale	Leftward asymmetry of pars triangularis and planum temporale in right-handers No asymmetries in left-handers
Amunts et al. (2000) <sup>18</sup>	Central sulcus	Deeper central sulcus on left hemisphere than on right in male right-handers
Ifthikharuddin et al. (2000) <sup>41</sup>	Basal ganglia	Bigger caudate nucleus in right hemisphere than in left in both right-handers and left-handers Bigger putamen in right hemisphere than left in left-handers
Good et al. (2001) <sup>6</sup>	GM, WM	No significant associations to handedness
Büchel et al. (2004) <sup>45</sup>	WM	Higher FA in WM underneath precentral gyrus in right hemisphere than in left in left-handers, while higher FA in left hemisphere in right-handers
Anstey et al. (2004) <sup>40</sup>	Hippocampus Amygdala	Bigger hippocampus in female left-handers than in female right-handers No significant associations to handedness in amygdala
Hervé et al. (2006) <sup>38</sup>	Inferior frontal sulcus Precentral sulcus Planum temporale	Leftward asymmetry of inferior frontal sulcus and precentral sulcus in right-handers, and no asymmetry or rightward asymmetry in left-handers Leftward asymmetry of planum temporale in right-handers while no asymmetry in left-handers
Mckay et al. (2017) <sup>46</sup>	WM	Higher FA in anterior corpus callosum and frontal cortex in left-handers than in right-handers
Kavaklioglu et al. (2017) <sup>44</sup>	Cerebellum	No significant associations to handedness
Ocklenburg et al. (2016) <sup>31</sup>	GM	No significant associations to handedness

GM, gray matter; WM, white matter; FA, fractional anisotropy.

had been cited 15,117 times.<sup>35</sup> Putting this number in perspective, another well-known handedness inventory, Annett's Hand Preference Questionnaire, had been cited only 1,536 times.<sup>35</sup> The other type is a test of manual dexterity, the Purdue Pegboard test, which assesses the motor performance of each hand.<sup>36</sup> Both types are useful, but the questionnaire type invariably has the advantage of being faster and easier to administer.<sup>35</sup> Furthermore, inventory scores correlate sensibly with performance measures as well as with differential activity in the motor cortex regions, which supports their validity.<sup>35</sup>

## CEREBRAL CORTEX

There are reported differences in cortical areas such as the central sulcus, inferior frontal sulcus, precentral sulcus, pars triangularis, and planum temporale.

Amunts et al. in 1996 suggested that right-handers had a deeper central sulcus in the left than in the right hemisphere while left-handers had a deeper central sulcus in the right hemisphere at more dorsal levels.<sup>37</sup> The study included only male subjects to exclude possible sex influences. In 2000, Amunts et al. included female subjects (51 males and 52 females) and showed that only male right-handers had a significant deeper central sulcus on the left hemisphere than on the right.<sup>18</sup> No interhemispheric asymmetry was found in females.<sup>18</sup> Thus, they found that central sulcus anatomical asymmetry was associated with handedness only in males, but not in females.<sup>18</sup>

The inferior frontal sulcus and precentral sulcus, which are the 2 small regions bordering the inferior frontal gyrus, displayed leftward asymmetry (more volume in the left) in right-handers and no asymmetry or rightward asymmetry in left-handers.<sup>38</sup> The pars triangularis and planum temporale also displayed significant leftward asymmetry in right-handers and no asymmetry in left-handers.<sup>38,39</sup>

## CORPUS CALLOSUM

The callosum was found to be significantly smaller in right-handers especially in its anterior half than in left-handers.<sup>29</sup>

## HIPPOCAMPUS AND AMYGDALA

Hippocampal volume was larger in female left-handers than in female right-handers.<sup>40</sup> Hippocampal volume was not associated with handedness in males, and amygdalar volume was not associated with handedness in both males and females.<sup>40</sup> This study has a limitation as the participants were ages 60 to 64.<sup>40</sup>

## BASAL GANGLIA

The basal ganglia is one of the most ambiguous regions to determine the relationship between handedness and its morphology. Regardless of handedness, there are already conflicting studies about basal ganglia asymmetry. Ifthikharuddin et al.<sup>41</sup> and Peterson et al.<sup>42</sup> found rightward asymmetry of the caudate nucleus, while Gunning-Dixon et al.<sup>43</sup> found leftward asymmetry of the caudate nucleus. In regard of handedness, Peterson et al.<sup>42</sup> found that right-handers had a larger globus pallidus and putamen on the left, but a larger caudate nuclei on the right, and left-handers did not show any basal ganglia asymmetries. Meanwhile, Ifthikharuddin et al.<sup>41</sup> found that the right caudate nucleus was larger in both right-handers and left-handers and the right putamen was significantly larger than the left putamen in left-handers.

## CEREBELLUM

There was no evidence for relationships between individual differences in cerebellar asymmetry and handedness.<sup>44</sup>

## WHITE MATTER

In the WM underneath the precentral gyrus, left-handers showed higher FA in the right hemisphere compared to the left hemisphere while right-handers showed higher FA in the left hemisphere.<sup>45</sup> Regions such as the anterior corpus callosum and frontal cortex also showed increased FA in male left-handers compared to male right-handers.<sup>46,47</sup>

## CONCLUSION

Thus far, we have had a thorough review of the many interesting studies about the relationships between brain morphology and objective factors such as age, sex, and handedness. However, there have been many conflicting results even in studies of each factor. These different results may be attributed to a wide range of ethnic groups included in each studies and different methods of analysis. Therefore, more studies specific for the each ethnic group and standardized methods are needed to establish a more reliable database of healthy subjects' brain morphologies. With accumulated data, it will be possible to deeply understand the pathogenesis of neurologic or psychiatric diseases by comparing the brain morphologies of healthy subjects.

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