**Supplementary Materials:**



**Figure S1.** (**a**) T1-weighted MR images show conventional axial images at the basal ganglia level; (**b**) color-coded images of NeuroQuant®; and (**c**) those of Aqua®.

**Appendix**

*Appendix E1. Calculation of Sample Size*

The sample size for the two-tailed Student's t-test was calculated using the common formula for calculating sample sizes for proportions. Based on a statistical power level of 0.80 and a statistical significance level of 0.05, we estimated the sample size. Similarly, based on previous studies, the impact size was conservatively established at 0.5 [1]. The sample size for this study was calculated to be 128.

*Appendix E2. Volumetry Process Steps of NeuroQuant® and Aqua®*

NeuroQuant® is a spin-off of FreeSurfer, a software with a research focus used for volumetry. The steps in the NeuroQuant® process were as follows: the process involves removing the scalp, skull, and meninges, expanding the brain into a sphere, mapping that sphere to a shared space using the Talairach atlas coordinates, identifying the segmented brain areas, and contracting the brain back to its original shape [1].

Similarly, Aqua® is built on FreeSurfer using Split-Attention U-Net, a convolutional neural network with skip routes and a split-attention module that separates brain MRI images. Two open sources and three research sites provided a wide variety of cognitively normal East Asian populations' normative MRI data (age, 18–96 years). The 97 different regions of the brain are divided using Aqua®, which is used to examine structural details, such as atrophy, structural alterations, anatomical asymmetry, and white matter abnormalities associated with degenerative brain illnesses. The segmentation of the central nuclei, hippocampus, brainstem, and ventricles; lobar parcellation; and the detection of white matter abnormality. The process steps of Aqua® included skull stripping, a tissue classification to extract brain tissue compartments, such as the white matter, gray matter, and intra/extra ventricular cerebrospinal fluid [2,3].

*Appendix E3. Mean Volume Comparison and Inter-method Reliability*

We categorized study samples into three groups according to clinical diagnoses by two clinicians: subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and Alzheimer's disease (AD) groups. We compared the mean volume of brain substructures between the two software using the paired t-test. Considering clinical diagnosis, most brain regions showed significant differences in mean volume except for the parietal lobe in the AD group and the frontal lobe and caudate nucleus in the SCI group, the white matter, parietal lobe, caudate nucleus, and cingulate gyrus in the MCI group. Intracranial volume, cortical gray matter, white matter of AD group, parietal lobe, hippocampus, amygdala, caudate nucleus, globus pallidum, and cerebellum were larger in Aqua® than NeuroQuant®. The other regions exhibited the reverse results.

Furthermore, we assessed the inter-method reliability between the two software using Pearson's correlation coefficient (r) and intra-class correlation coefficient (ICC). Pearson's correlation coefficient and ICC with a 95% confidence interval were defined thus: weak, <0.3; moderate, 0.3 ≤ and < 0.7; strong, ≥0.7. Most brain regions exhibited statistically significant values regardless of the clinical diagnosis, except for the caudate nucleus and accumbens of the SCI group and the cingulate gyrus and globus pallidum of the MCI group. These significant regions showed moderate to strong linear correlations across all groups (r=0.35–0.98). Most brain regions without group classification demonstrated moderate to strong inter-method agreement (ICC=0.45–0.96). Considering clinical diagnosis, the accumbens and globus pallidum of the SCI group and the cingulate gyrus and globus pallidum of the MCI group showed statistically insignificant values. On excluding these data, most brain regions showed moderate to strong inter-method agreement (ICC=0.37–0.97). These results of the mean volume comparison and inter-method reliability between the two software are summarized in Table E1.

**Table E1.** Mean volume, and inter-method reliability of brain regions

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mena volume ± Standard deviation | r | ICC (95 % CI) |
| Brain region (ml) | NeuroQuant® | Aqua® |
| Intracranial volume | 1344.32 ± 150.82 | 1466.32 ± 123.54 | 0.84 | 0.87 (0.82-0.90) |
| SCI | 1359.52 ± 125.60 | 1453.16 ± 118.70 | 0.97 | 0.86 (0.82-0.89) |
| MCI | 1389.78 ± 107.14 | 1479.89 ± 108.85 | 0.98 | 0.84 (0.69-0.92) |
| AD | 1366.28 ± 122.14 | 1461.43 ± 129.40 | 0.63 | 0.89 (0.83-0.93) |
| Cortical gray matter | 408.76 ± 45.81 | 577.58 ± 49.75 | 0.82 | 0.90 (0.87-0.93) |
| SCI | 392.83 ± 54.02 | 576.32 ± 49.59 | 0.71 | 0.83 (0.65-0.92) |
| MCI | 432.61 ± 43.49 | 598.05 ± 49.29 | 0.89 | 0.94 (0.88-0.97) |
| AD | 403.97 ± 40.07 | 568.95 ± 47.89 | 0.84 | 0.91 (0.87-0.94) |
| White matter | 393.77 ± 52.04 | 397.68 ± 41.80 | 0.84 | 0.90 (0.87-0.93) |
| SCI | 425.16 ± 68.81 | 402.75 ± 43.21 | 0.80 | 0.84 (0.66-0.92) |
| MCI † | 396.60 ± 39.02 | 400.52 ± 35.67 | 0.89 | 0.94 (0.88-0.97) |
| AD | 381.36 ± 44.98 | 394.90 ± 42.82 | 0.89 | 0.95 (0.93-0.97) |
| Frontal lobe | 146.45 ± 17.03 | 144.49 ± 13.69 | 0.88 | 0.93 (0.90-0.95) |
| SCI † | 140.67 ± 21.58 | 142.41 ± 14.50 | 0.81 | 0.86 (0.71-0.93) |
| MCI | 154.76 ± 15.11 | 150.65 ± 13.20 | 0.94 | 0.96 (0.93-0.98) |
| AD | 144.54 ± 14.94 | 142.27 ± 12.94 | 0.91 | 0.94 (0.92-0.96) |
| Temporal lobe | 104.59 ± 13.45 | 96.14 ± 10.96 | 0.86 | 0.91 (0.88-0.94) |
| SCI | 102.41 ± 14.32 | 97.51 ± 10.80 | 0.71 | 0.81 (0.61-0.91) |
| MCI | 111.97 ± 13.48 | 101.03 ± 10.59 | 0.92 | 0.94 (0.89-0.97) |
| AD | 102.62 ± 11.96 | 93.97 ± 10.26 | 0.87 | 0.93 (0.90-0.95) |
| Parietal lobe | 98.44 ± 12.00 | 99.94 ± 10.57 | 0.73 | 0.84 (0.78-0.88) |
| SCI | 94.19 ± 15.17 | 101.08 ± 9.90 | 0.64 | 0.74 (0.46-0.87) |
| MCI † | 103.93 ± 11.93 | 103.76 ± 10.19 | 0.80 | 0.88 (0.78-0.94) |
| AD | 97.64 ± 9.96\* | 98.10 ± 10.38\* | 0.75 | 0.87 (0.81-0.92) |
| Occipital lobe | 45.26 ± 6.24 | 41.65 ± 4.90 | 0.75 | 0.84 (0.78-0.88) |
| SCI | 43.20 ± 6.40 | 41.30 ± 4.52 | 0.62 | 0.74 (0.47-0.87) |
| MCI | 47.84 ± 6.01 | 43.06 ± 5.30 | 0.77 | 0.87 (0.74-0.93) |
| AD | 45.12 ± 5.98 | 41.25 ± 4.73 | 0.77 | 0.86 (0.79-0.91) |
| Hippocampus | 5.43 ± 0.96 | 8.09 ± 0.81 | 0.66 | 0.79 (0.71-0.84) |
| SCI | 5.92 ± 1.11 | 8.24 ± 0.84 | 0.74 | 0.83 (0.66-0.92) |
| MCI | 5.75 ± 0.88 | 8.15 ± 0.72 | 0.72 | 0.83 (0.67-0.91) |
| AD | 5.15 ± 0.82 | 8.01 ± 0.83 | 0.61 | 0.77 (0.65-0.85) |
| Amygdala | 2.46 ± 0.45 | 3.25 ± 0.53 | 0.87 | 0.92 (0.90-0.94) |
| SCI | 2.60 ± 0.26 | 3.30 ± 0.50 | 0.81 | 0.90 (0.78-0.95) |
| MCI | 2.51 ± 0.27 | 3.35 ± 0.54 | 0.88 | 0.93 (0.86-0.96) |
| AD | 2.38 ± 0.23 | 3.19 ± 0.52 | 0.88 | 0.93 (0.90-0.95) |
| Caudate nucleus | 5.94 ± 1.43 | 6.38 ± 0.89 | 0.37 | 0.50 (0.32-0.63) |
| SCI \* | 5.87 ± 1.31 | 6.55 ± 1.09 | 0.25 | 0.39 (0.27-0.71) |
| MCI † | 6.21 ± 1.42 | 6.57 ± 0.94 | 0.39 | 0.53 (0.10-0.76) |
| AD | 5.86 ± 1.45 | 6.26 ± 0.81 | 0.37 | 0.50 (0.25-0.67) |
| Thalamus | 13.78 ± 1.57 | 12.85 ± 1.16 | 0.85 | 0.90 (0.86-0.92) |
| SCI | 14.15 ± 1.84 | 13.01 ± 1.28 | 0.87 | 0.90 (0.79-0.95) |
| MCI | 14.14 ± 1.46 | 13.16 ± 1.64 | 0.77 | 0.84 (0.71-0.92) |
| AD | 13.50 ± 1.54 | 12.59 ± 1.17 | 0.87 | 0.91 (0.86-0.94) |
| Accumbens | 1.15 ± 0.16 | 0.78 ± 0.12 | 0.41 | 0.57 (0.41-0.68) |
| SCI \*, ‡ | 1.14 ± 0.15 | 0.80 ± 0.05 | 0.24 | 0.38 (-0.29-0.70) |
| MCI | 1.16 ± 0.17 | 0.81 ± 0.06 | 0.62 | 0.73 (0.47-0.86) |
| AD | 1.15 ± 0.17 | 0.76 ± 0.07 | 0.38 | 0.55 (0.33-0.70) |
| Cingulate gyrus | 16.28 ± 2.13 | 15.70 ± 2.04 | 0.49 | 0.66 (0.53-0.74) |
| SCI † | 15.68 ± 1.67 | 15.63 ± 1.97 | 0.57 | 0.72 (0.42-0.87) |
| MCI †, ‡ | 16.85 ± 2.57 | 16.30 ± 1.93 | 0.21 | 0.33 (0.29-0.65) |
| AD | 16.29 ± 2.07 | 15.47 ± 2.02 | 0.59 | 0.74 (0.61-0.83) |
| Globus pallidum | 0.81 ± 0.23 | 4.05 ± 0.44 | 0.35 | 0.45 (0.26-0.60) |
| SCI ‡ | 0.81 ± 0.30 | 4.16 ± 0.44 | 0.44 | 0.58 (0.13-0.80) |
| MCI \*, ‡ | 0.87 ± 0.21 | 4.11 ± 0.47 | 0.30 | 0.36 (-0.23-0.67) |
| AD | 0.79 ± 0.21 | 4.00 ± 0.44 | 0.40 | 0.41 (0.12-0.61) |
| Putamen | 9.86 ± 1.51 | 8.79 ± 1.18 | 0.66 | 0.78 (0.70-0.84) |
| SCI | 10.57 ± 1.80 | 8.78 ± 1.29 | 0.63 | 0.75 (0.48-0.88) |
| MCI | 10.20 ± 1.60 | 9.06 ± 1.25 | 0.84 | 0.90 (0.81-0.95) |
| AD | 9.50 ± 1.32 | 8.68 ± 1.14 | 0.64 | 0.74 (0.62-0.83) |
| Cerebellum | 114.49 ± 12.30 | 123.19 ± 12.16 | 0.93 | 0.96 (0.95-0.97) |
| SCI | 112.84 ± 13.78 | 121.37 ± 12.40 | 0.93 | 0.96 (0.92-0.98) |
| MCI | 117.45 ± 11.44 | 125.33 ± 11.98 | 0.92 | 0.96 (0.92-0.98) |
| AD | 113.27 ± 12.39 | 122.41 ± 12.53 | 0.93 | 0.97 (0.95-0.98) |

\* = p-value >0.05, values were not statistically significant. Pearson’s correlation test was used.

† = p-value >0.05, no significant difference between NeuroQuant® and Aqua®. Paired t-test was used.

‡ = p-value >0.05, values were not statistically significant. Intra-class correlation test was used.

SCI, subjective cognitive impairment; MCI, mild cognitive impairment; AD, Alzheimer’s disease; r, Pearson’s correlation coefficient; ICC, intra-class correlation coefficient; CI, confidence interval

Supplemental References

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