**Distinct Brain Regions in Physiological and**

**Pathological Brain Aging**

Jin San Lee,1-3 Yu Hyun Park,1,2 Seongbeom Park,1,2 Uicheul Yoon,4 Yeongsim Choe,1,2 Bo Kyoung Cheon,1,2 Alice Hahn,1,2 Soo Hyun Cho,5 Seung Joo Kim,6 Jun Pyo Kim,1,2 Young Hee Jung,1,2 Key-Chung Park,3 Hee Jin Kim,1,2 Hyemin Jang,1,2 Duk L. Na,1,2 and Sang Won Seo1,2,7,8\*

1Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

2Neuroscience Center, Samsung Medical Center, Seoul, South Korea

3Department of Neurology, Kyung Hee University Hospital, Seoul, South Korea

4Department of Biomedical Engineering, Daegu Catholic University, Gyeongsan, South Korea

5Department of Neurology, Chonnam National University Medical School, Gwangju, South Korea

6Department of Neurology, Gyeongsang National University School of Medicine and Gyeongsang National University Changwon Hospital, Changwon, South Korea

7Samsung Alzheimer Research Center, Center for Clinical Epidemiology, Samsung Medical Center, Seoul, South Korea

8Department of Health Sciences and Technology, Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea

**\*Correspondence:** Sang Won Seo, MD, PhD

Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Kangnam-ku, Seoul 06351, South Korea

Tel: +82-2-3410-1233, Fax: +82-2-3410-0052, E-mail address: sangwonseo@empal.com

**Running Title:** Physiological and pathological brain aging

**Supplementary data:** Supplementary Table 1 and 2

**Supplementary Table 1** Neuropsychological performance in AD continuum patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Neuropsychological tests** | **SMI** | **aMCI** | **AD dementia** |
| **Total** | **Early-stage** | **Late-stage** | **Total** | **Very mild** | **Mild** | **Moderate to severe** |
| **Digit span: Forward** | 0.4 ± 1.1 | -0.1 ± 1.1 | -0.1 ± 1.1 | -0.1 ± 1.1 | -0.5 ± 1.2 | -0.3 ± 1.1 | -0.5 ± 1.1 | -0.9 ± 1.5 |
| **Digit span: Backward** | 0.4 ± 1.3 | -0.3 ± 1.2 | -0.3 ± 1.3 | -0.3 ± 1.1 | -1.0 ± 1.6 | -0.7 ± 1.3 | -1.0 ± 1.5 | -1.9 ± 2.2 |
| **K-BNT** | 0.6 ± 4.8 | -0.6 ± 1.7 | -0.3 ± 1.1 | -0.7 ± 1.9 | -2.9 ± 5.3 | -1.7 ± 3.3 | -2.7 ± 5.7 | -5.9 ± 6.3 |
| **RCFT: Copy** | 0.7 ± 1.1 | -0.8 ± 1.1 | -0.3 ± 1.1 | -1.0 ± 1.1 | -1.8 ± 1.3 | -1.3 ± 1.2 | -1.8 ± 1.3 | -2.6 ± 1.4 |
| **SVLT: Immediate recall** | 0.5 ± 1.0 | -1.6 ± 1.4 | -0.7 ± 0.9 | -2.1 ± 1.4 | -2.6 ± 1.5 | -2.4 ± 1.5 | -2.6 ± 1.5 | -2.9 ± 1.7 |
| **SVLT: Delayed recall** | 0.4 ± 0.8 | -0.9 ± 1.2 | -0.3 ± 1.0 | -1.1 ± 1.3 | -2.1 ± 1.5 | -1.8 ± 1.5 | -2.2 ± 1.4 | -2.7 ± 1.6 |
| **SVLT: Recognition score** | 0.4 ± 0.9 | -1.3 ± 1.0 | -0.8 ± 0.8 | -1.5 ± 1.0 | -2.0 ± 0.9 | -1.8 ± 1.0 | -2.1 ± 0.9 | -2.3 ± 0.9 |
| **RCFT: Immediate recall** | 0.3 ± 0.8 | -1.3 ± 0.9 | -0.9 ± 0.7 | -1.6 ± 0.9 | -2.1 ± 0.8 | -1.9 ± 0.8 | -2.2 ± 0.7 | -2.3 ± 0.7 |
| **RCFT: Delayed recall** | 0.6 ± 1.2 | -0.6 ± 1.8 | -0.2 ± 1.3 | -0.8 ± 2.0 | -2.5 ± 2.6 | -1.9 ± 2.1 | -2.6 ± 2.5 | -3.7 ± 3.5 |
| **RCFT: Recognition score** | 0.2 ± 1.1 | -0.8 ± 1.1 | -0.6 ± 1.1 | -0.9 ± 1.1 | -1.8 ± 1.2 | -1.3 ± 1.0 | -1.9 ± 1.0 | -2.7 ± 1.3 |
| **COWAT: Animal** | 0.3 ± 1.0 | -0.6 ± 1.0 | -0.4 ± 1.0 | -0.7 ± 1.1 | -1.6 ± 1.0 | -1.1 ± 1.0 | -1.7 ± 0.8 | -2.3 ± 1.0 |
| **COWAT: Supermarket** | 0.5 ± 1.2 | -0.3 ± 1.1 | -0.2 ± 1.0 | -0.4 ± 1.1 | -1.0 ± 1.0 | -0.6 ± 1.0 | -1.0 ± 1.0 | -1.6 ± 0.9 |
| **COWAT: Phonemic total** | 0.3 ± 1.0 | -0.9 ± 2.8 | -0.4 ± 4.4 | -1.1 ± 1.4 | -2.3 ± 1.8 | -1.8 ± 1.6 | -2.5 ± 1.8 | -3.1 ± 1.8 |
| **Stroop color reading** | 0.4 ± 1.1 | -0.1 ± 1.1 | -0.1 ± 1.1 | -0.1 ± 1.1 | -0.5 ± 1.2 | -0.3 ± 1.1 | -0.5 ± 1.1 | -0.9 ± 1.5 |

Values (Z-scores) are mean ± SD.

Abbreviations: AD = Alzheimer’s disease; SMI = subjective memory impairment; aMCI = amnestic mild cognitive impairment; K-BNT = Korean version of the Boston Naming Test; RCFT = Rey-Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test; COWAT = Controlled Oral Word Association Test; SD = standard deviation.

**Supplementary Table 2** Number of the study participants (N = 5,498)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **CN** | **SMI** | **aMCI** | **AD dementia** |
|  | **Total** | **Early-stage** | **Late-stage** | **Total** | **Very mild** | **Mild** | **Moderate to severe** |
| **Total** | 2823 | 874 | 954 | 305 | 649 | 847 | 282 | 411 | 154 |
| **50s** | 694 | 224 | 97 | 35 | 62 | 98 | 35 | 43 | 20 |
| **60s** | 1509 | 348 | 289 | 96 | 193 | 167 | 56 | 82 | 29 |
| **70s** | 572 | 247 | 425 | 137 | 288 | 377 | 125 | 198 | 54 |
| **80s** | 47 | 55 | 135 | 37 | 98 | 196 | 63 | 84 | 49 |
| **90s** | 1 |  | 8 |  | 8 | 8 | 2 | 4 | 2 |
| **100s** |  |  |  |  |  | 1 | 1 |  |  |

Abbreviations: CN = cognitively normal; SMI = subjective memory impairment; aMCI = amnestic mild cognitive impairment; AD = Alzheimer’s disease.