**Supplemental Material**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Patient 1 | Patient 2 | Patient 3 | Healthy controls |
| N | - | - | - | 33 |
| Age range | 70-75\* | 80-85\* | 75-80\* | 72.72 ± 5.01 |
| Sex | N/A\* | N/A\* | N/A\* | 19M (14F) |
| Education\*\* (years) | 11 | 5 | 11 | 8.71 ± 2.32 |

\*Due to the patient privacy policy; \*\*Considering from the secondary school.

Table S1. Demographic data of the three MCI patients and healthy controls matched against each patient.

|  |  |
| --- | --- |
| Grey matter volume | White matter volume |
|  | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 |
| Left amygdala | 33rd percentile | - | - | 33rd percentile | - | - |
| Right amygdala | - | - | - | - | - | - |
| Left hippocampus | 83rd percentile | - | - | 16th percentile | - | - |
| Right hippocampus | - | - | - | - | - | - |
| left superior parietal lobule (area 5) | 16th percentile  | 0th percentile  | 0th percentile | 91st percentile | 83rd percentile | 0th percentile |
| left superior parietal lobule (area 7) | - | 8th percentile | 0th percentile | 100th percentile | 83rd percentile | 0th percentile |
| right superior parietal lobule (area 5) | 25th percentile | 8th percentile | 0th percentile | 83rd percentile | 83rd percentile | 0th percentile |
| right superior parietal lobule (area 7) | 16th percentile  | 0th percentile | 0th percentile | 100th percentile | 83rd percentile | 0th percentile |

Table S2. Percentiles of grey and white matter volumes (defined as the value below/above which a given percentage of observations in a group of observations falls) considering the matched healthy control sample (N=12) for each patient.

**Inclusion and exclusion criteria for healthy adults and MCI patients**

MCI patients recruited from the Memory Clinic at Gasthuisberg University Hospital, Leuven, Belgium, followed the following inclusion criteria: between 70 and 85 years old, MMSE score ≥21, normal or corrected to normal vision, fluent in written and verbal Dutch, and in stable medical condition. Patients were ineligible if they had a history or current evidence of a neurological disorder that may contribute to the participant's cognitive impairment (such as large-vessel stroke, epilepsy, Parkinson’s disease, progressive supranuclear palsy, Huntington’s disease, amyotrophic lateral sclerosis, multiple sclerosis, Central Nervous System (CNS) infection, significant head trauma with loss of consciousness, normal pressure hydrocephalus), show evidence within 6 months prior to screening of a psychotic disorder or untreated depressive disorder, a history of malignancy in the last 5 years, a history or current evidence of any potentially known clinically significant condition, therapy, or lab abnormality that might confound the results of the study,

Patients were ineligible if they have a history or current evidence of a neurological disorder (such as large-vessel stroke, epilepsy, Parkinson’s disease, progressive supranuclear palsy, Huntington’s disease, amyotrophic lateral sclerosis, multiple sclerosis, Central Nervous System (CNS) infection, normal pressure hydrocephalus), show evidence within 6 months prior to screening of a psychotic disorder or untreated depressive disorder, a history of malignancy in the last 5 years, a history or current evidence of any potentially known clinically significant condition or lab abnormality that might confound the results of the study, currently using specific psychoactive medications (neuroleptics, chronic anxiolytics, tricyclic antidepressants, anti-epileptics, anticholinergics etc.) or anti-thrombotics with the exception of acetyl salicylic acid, a history of alcohol or substance abuse or dependence within the past 2 years (Diagnostic and Statistical Manual of Mental Disorders, DSM IV criteria), and currently participating or have been participating in a cognitive training study during the last 30 days.

Of the 33 healthy older adults, 14 were part of another study (Pergher et al., 2018). The selection criteria for the healthy older participants were as follows: MMSE score above 27, neuropsychological test scores (see Table 2) in a normal range based on their age ([MacPherson et al., 2002](https://www.sciencedirect.com/science/article/pii/S2213158219300476#bb0195)), fluency in written and verbal Dutch, normal or corrected to normal vision, and not on any medication that could interfere with cognitive functioning. Healthy subjects were excluded if they had already experienced subjective cognitive decline, had a medical condition that would predispose them to imminent functional decline or death (e.g., stroke within the past 12 months, certain cancers, or current chemotherapy or radiation treatment for cancer), a diagnosis of a neurological or psychiatric disorder, recently received cognitive training, and had severe losses in vision, hearing, or communicative ability that would sufficiently impair performance and preclude participation.

## Investigations

**Structural MRI**

MR imaging was performed using a 1.5 and 3.0 T scanner (Philips, The Netherlands) at the Radiology Department of Gasthuisberg University Hospital for patients and healthy controls respectively. All subjects were examined using a standard dementia MRI protocol: axial T2-weighted images, 3D fluid-attenuated inversion recovery (FLAIR), coronal T2-weighted images with perpendicular hippocampus orientation, axial diffusion weighted imaging, T2-weighted images, and gradient-echo T1-weighted 3D images. The imaging parameters of the 3D gradient-echo T1 weighted images were: TR/TE 2300/3 ms, flip angle 9°, field of view 256x240, slice thickness 1 mm and 160 slices. We segmented the MRI scans of each patient’s brain using Statistical Parametric Mapping (SPM) (<https://www.fil.ion.ucl.ac.uk/spm/>) and Voxel-based Morphometry (VBM) (https://www.fil.ion.ucl.ac.uk/~john/misc/) to obtain a normalized assessment (in percent) of the Total Intracranial Volume (TIV, mm3) of grey and white matter of the whole brain and specific brain regions (regions of interests (ROIs)), corrected within each patient and between patients and healthy adults.

**Visual rating scale evaluation**

The MR images were evaluated by an experienced neuroradiologist for Global Cortical Atrophy (GCA) (van de Pol et al., 2006), and Koedam (Koedam et al., 2011) using a 4-point rating scale (0-3), and for Medial Temporal Atrophy (MTA) (Scheltens et al., 2012; Duara et al., 2008) using a 5-point rating scale. Differently, the Fazekas scale quantifies the amount of white matter volume hyperintensities (WMH) and lesions of the entire brain (Fazekas et al., 1987). It uses a 4-point rating scale: grade 0 = absent or a single punctuate WMH, grade 1 = multiple punctuate lesions, grade 2 = beginning confluence lesions, grade 3 = large confluent lesions. Fazekas 1 is considered normal in the elderly, whereas Fazekas 2 and 3 are pathologic. Note that for these 4 rating scales, the scores obtained for the left and right hemispheres were averaged (for further information regarding the first three visual rating scales, see Pergher et al., 2019).

**Neuropsychological tests**

The battery of neuropsychological tests administered to participants was based on the tests used at Gasthuisberg University Hospital.

**MMSE**

The MMSE (Folstein et al., 1975 is a 30-point questionnaire used to measure cognitive impairment and its progression. It takes between 5 and 10 minutes and evaluates several cognitive functions, such as attention, [recall](https://en.wikipedia.org/wiki/Recollection), [language](https://en.wikipedia.org/wiki/Language) and the ability to follow simple commands.

**Digit Span**

This test is a subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955). It is commonly used to determine short-term memory capacities. During the test, participants are orally presented with a sequence of digits ranging from easy to more difficult. The test is divided into two sections, forward and backward. During the forward section, participants are required to repeat a sequence of digits in the same order as orally presented. In the backward version, participants are required to repeat a sequence of digits in reverse order. In this study, we considered only the Digit Span backward.

**Controlled Oral Word Association Test**

The Controlled Oral Word Association Test (COWAT) gauges verbal fluency and is part of the Halstead-Reitan Neuropsychological Test Battery (Reitan and Wolfson, 1986). During the test, participants are required to name as many words as possible that fit into a specific category during one minute. The categories used were professions (1), animals (2), letters ‘A’ (3), ‘K’ (4) and ‘N’ (5).

**Visual Association Test**

The Visual Association Test (VAT) is a test relying on short-term memory (Lindeboom, Schmand, Tulner, Walstra and Jonker, 2002). During the test, participants are presented with 12 pictures in total. During the first part of the test, participants are instructed to look at the first 6 pictures. After a certain amount of time, the pictures are removed, and the participants are presented with 6 pictures that are the same as the first ones but have one object added. Again, the pictures are removed, and the participants have to determine what object was added to the last 6 pictures compared to the first 6 ones.

**Stroop**

The Stroop task depends on the principle of inhibitory cognitive interference and attention (Stroop, 1935). The task consists of 3 variations of the same test. First, participants are presented with a sheet consisting of names of colors printed in black ink. During this part of the task, participants are required to simply read the names of all colors. During the second part of the task, participants are presented with a sheet consisting of squares printed in different colors. The goal of the task is to verbalize which colors are printed. During the third and final part of the task, participants are presented with a sheet consisting of names of colors printed in a different color than the name, called conflict words or interference (for example, the word ‘blue’ printed in green). The goal of this last task is to read the names that interfere in terms of the color in which they are printed. In our study, we considered only the third and last part of the task.

**Visual Search**

The Visual Search task is a cognitive test that gauges the efficiency of search, reflecting the distribution of attention from item to item (Wolfe, 1998). During some trials, a letter ‘T’ can be seen between the letters ‘L’. The goal of the task is to determine if a letter ‘T’ is presented among the letters ‘L’.

**CORSI**

The CORSI test is used to assess visuo-spatial short-term WM (Kessels et al., 2000). During the task, participants are perceived several identical spatially separated squares displayed on a computer screen. As the task commences, participants are presented with a sequence of blue squares turning yellow, while all the other blue squares remain blue. The goal of the task is to mimic the sequence of yellow squares as the task becomes more difficult.

**Raven Progressive Matrices Test**

The Raven test is a test for measuring abstract reasoning and fluid intelligence consisting of 60 multiple choice questions (Raven, 1938). All questions consist of a geometrical design with one piece missing. The goal of the task is to determine, out of 6 multiple choices, which one is the missing piece.

**N-Back**

We used the same N-Back task adopted in our previous study (Pergher et al., 2019). The N-Back is a task that measures working memory and working memory abilities (Kirchner, 1958). The goal of the task is to decide if the presented stimulus is the same as the one presented N-times before. The N is defined by the difficulty level of the task that here included three difficulty levels, named 1-Back, 2-Back and 3-Back.