# Brief International Cognitive Assessment for Multiple Sclerosis scores are associated with the cortical thickness of specific cortical areas in relapsing-remitting patients.

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# Abstract (205 words)

**BACKGROUND:** Cognitive impairment is frequent and disabling in multiple sclerosis (MS). The Brief International Cognitive Assessment in MS (BICAMS) is a recent short battery usable in clinical practice for cognitive evaluation of MS patients.

**OBJECTIVE:** To find cortical areas or brain volumes on magnetic resonance imaging (MRI) structural sequences associated with BICAMS scores in MS.

**METHODS:** In this cross-sectional single-center study (NCT 03656055, September 4, 2018), 96 relapsing remitting-MS patients under natalizumab and without recent clinical or radiological inflammation were included. Patients underwent brain MRI and the three BICAMS tests, evaluating information processing speed (SDMT), visuo-spatial memory (BVMT-R), and verbal memory (FVLT).

**RESULTS:** Cortical thickness in the left frontal superior and the right precentral gyri was associated with BVMT-R scores whereas cortical thickness in the left Broca's area and the right superior temporal gyrus was associated with FVLT scores. We observed associations between white matter inflammatory lesions connected to these cortical regions and BICAMS subscores.

**CONCLUSIONS:** BICAMS scores are associated with specific cortical areas, the cognitive domain matching the known functions of the cortical area. Specific cognitive impairments in MS may be associated with specific cortical regions, themselves influenced by white matter inflammatory lesions and demographical parameters (age, sex, education level).

## Declarations

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**Disclosures:** Jean-Baptiste Davion, Renaud Lopes, Caroline Jougleux, Romain Viard, Julien Dumont, and Xavier Leclerc have nothing to report. Olivier Outteryck reports grants, personal fees and non-financial support from BIOGEN, personal fees and non-financial support from SANOFI, non-financial support from MERCK, personal fees and non-financial support from TEVA, non-financial support from ROCHE, outside the submitted work.

**Ethics approval**: Study was approved by the ethic committee of Dijon, France, after national randomization, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Consent to participate**: All patients were informed and gave their written consent to participate to the study.

**Availability of data and material** (data transparency)

**Code availability**: The complete pipeline for tractography can be sent upon request.

**Authors' contributions**: Jean-Baptiste Davion and Olivier Outteryck contributed to the study plan, patient selection, clinical examination, cognitive assessment, statistics and redaction of the manuscript. Caroline Jougleux contributed to the study plan, cognitive assessment, and redaction of the manuscript. Renaud Lopes, Romain Viard, Julien Dumont, and Xavier Leclerc contributed to the study plan, MRI evaluation, statistics and redaction of the manuscript.

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## Introduction

Cognitive impairment is observed in 40 to 70% of multiple sclerosis (MS) patients, independently of disease duration and physical impairment. Various domains are impaired, mainly information processing speed, working memory, attention, executive functions, verbal fluency, but also episodic verbal and non-verbal memory. This cognitive impairment impacts quality of life, and is associated with a higher risk of depression, sleep disorders, unemployment and therapeutic non-compliance [1].

In routine clinical practice, cognitive impairment can be underestimated in MS patients because complaints are not a reliable reflection of the real situation [2] and frequently used scores such as the Expanded Disability Status Scale (EDSS) [3] do not give a precise evaluation of cognition. As complete cognitive evaluations can be time-consuming and require qualified staff, the Brief International Cognitive Assessment for MS (BICAMS), a short MS-specific cognitive battery, was introduced in 2012. An BICAMS assessment takes around 15 minutes and can be performed by a non-specialist after a short training period [4]. As it is easily usable in routine clinical practice, BICAMS will probably become increasingly used for systematic evaluation of MS patients.

Many studies tried to link magnetic resonance imaging (MRI) structural parameters with cognition in MS, and have found significant associations with white or grey matter modifications.

Regarding white matter modifications, some cognitive scores are significantly associated with the overall inflammatory lesion volume, or with the white matter volume [5]. Being more focal, some studies highlighted a link between the location of some white matter lesions and some cognitive tests [6, 7]. An association between

cognitive functions (such as information processing speed) and normal appearing white matter impairment has also been proven with diffusion-tensor imaging (DTI) or magnetizing transfer ratio (MTR) [8–10]. The main hypothesis to explain this impact of white matter lesions is a disconnection between grey matter regions, leading to cognitive impairment [8].

Regarding grey matter modifications, significant associations have been found between some cognitive scores and the overall grey matter volume, cortical thickness, inflammatory cortical lesions, and deep grey matter volume including different basal ganglia such as the thalamus, putamen and caudate [5]. Some cortical regions have been linked to precise cognitive functions [9, 11].

However, the relative contribution of white and grey matter involvement to cognitive impairment remains debated. Studies combining those different parameters have heterogeneous results: some concluding to the predominant importance of inflammatory lesions and white matter involvement [11, 12], while others put forward the grey matter involvement especially for the cortex [13, 14]. This discrepancy may be explained by methodological differences. Studied populations sometimes mixed relapsing-remitting (RR-MS) and progressive forms, however different regarding pathophysiology and cognitive impairment [5]. Some studies compared cognitively *impaired* versus cognitively *respected* groups, whereas there is a continuum. Other studies used a cognitive global score, calculated from many cognitive tests evaluating different functions with different neuronal basis; gathering these scores may therefore be irrelevant.

Our main objective was to find associations between BICAMS scores and MRI structural parameters such as brain volumes and cortical thickness in a population of relapsing-remitting MS (RR-MS) patients considering separately each score and

using mainly associations rather than group comparison, to avoid the issues described in the previous paragraph. We hypothesise that the impairment of a specific cognitive domain in RR-MS can be related to structural changes in specific cortical areas, themselves partly secondary to white matter inflammatory lesions.

## Patients and Methods

*Population*

We used data from the VWIMS (Visual Ways In MS) prospective single-centre cross-sectional study (NCT 03656055) [15]. This study included patients with RR-MS fulfilling McDonald 2017 revised criteria [16], aged from 18 to 65 years old, treated by natalizumab since at least six months at the Lille University Hospital, France. Patients were not included if they had signs of MS activity in the last six months (relapse, gadolinium-enhancing lesion on MRI). Our population was thus composed of MS patients without recent inflammation, but with a disease that has been active enough to develop a moderate-to-marked lesion burden. All patients were informed and gave their written consent to participate in the study. The study was approved by the ethics committee of Dijon, France, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Patients underwent physical examination, cognitive evaluation, and brain MRI. Each evaluation was done in a blinded fashion for any other clinical or paraclinical data, within two months at maximum.

Clinical parameters were recorded by interrogation and a complete reading of the medical records: age, sex, education level (classified as under high school graduation, high school graduation or associate's degree, bachelor's degree, master's degree or higher).

*Cognitive evaluation*

In our MS centre, BICAMS cognitive evaluation, performed by trained team members (JBD, OO, CJ) is part of routine clinical follow-up for MS patients. BICAMS is composed of three cognitive tests evaluating frequently impaired cognitive domains in MS: the Symbol Digit Modalities Test (SDMT) oral version; the three first recalls of the Brief Visuospatial Memory Test Revised (BVMT-R); and the five first recalls of the California Verbal Learning Test-II. Regarding this latter, we used its French version named French Verbal Learning Test (FVLT).

The SDMT basically quantifies speed of information processing, by asking the patient to associate as quickly as possible symbols and numbers. The patient's score is the number of correct associations produced in 90 seconds. The BVMT-R quantifies visuospatial memory, by asking the patient to remember geometric figures. The patient's score was calculated by a neuropsychologist (CJ) on objective and validated criteria [17] over 36 points. The FVLT quantifies the episodic verbal memory by asking the patient to remember a list of 15 words. The patient's score was the sum of the total number of recalled words after five trials over 80 points. Handedness was evaluated with the Edinburgh test.

To account for the effects of age, sex and education, we calculated a Z-score for each BICAMS score with the method proposed by Maubeuge et al. using a French control population [18]. The tests results indicated impairment when the Z-score was ≤ 1.5 [18].

*Brain MRI*

Complete description of MRI acquisition and processing is available in appendix 1. Briefly, MRI images were acquired on a 3T MRI (Achieva; Philips Medical Systems; Best, The Netherlands) using a 32-channel array head coil. The MRI protocol

included 3DT1 gradient-echo, 3D fluid-attenuated inversion recovery (FLAIR), 3D double inversion recovery (DIR) and diffusion tensor imaging (DTI) sequences. FreeSurfer software (v5.3.0, http://surfer.nmr.mgh.harvard.edu/) was used to segment and measure different brain volumes and cortical thickness from 3D-T1 images. ITK-SNAP® software [19] (v3.6.0, www.itksnap.org) was used to measure semi-automatically inflammatory lesions volumes from 3D-FLAIR images. An MS-specialized neuroradiologist (OO) looked for purely intracortical hyperintensities on the 3D-DIR sequence, to evaluate cortical pathology.

We developed a method to estimate the white matter pathology anatomically connected to a defined cortical region, using tractography from DTI images with the MRtrix3 package (http://www.mrtrix.org/) [20] (Fig. 1), to obtain the FLAIR-hyperintensity volume in the track. We normalized this volume by dividing it by the volume of the track itself.

*Statistical analysis*

Each cognitive score (SDMT, BVMT-R, FVLT) was separately associated with brain volumes normalized on the intracranial volume (FLAIR-hyperintensity, brain volume, white matter, grey matter, cortex, deep grey matter) using linear models. We also conducted these analyses with each of the cognitive Z-scores to account for the effects of age, sex and education level, which are potential confusing factors associated with both cognitive scores and cerebral volumes [21–23].

To link the cognitive scores with some precise cortical regions, we associated the cortical thickness maps and each cognitive score and Z-score using generalized linear models to find significant cortical clusters. We used the mri_glmfit-sim function

from FreeSurfer, applying a clusterwise correction for multiple comparison [24] (significance level 0.05).

Finally, we studied the link between the cognitive scores and the white matter pathology connected to the cortical clusters. We associated the normalized FLAIR-hyperintensity volume in the track with the cognitive Z-score, and then with the mean cortical thickness of the cluster, using linear models.

For each linear model, normality of variables was checked with the Kolmogorov-Smirnov test. We used a bilateral test with a significance level of 0.05. Statistical analysis was done using R software (v4.0.2).

## Results

*Population*

Between March and December 2017, we included 98 patients. For this current work, we excluded two patients who stopped natalizumab treatment before the BICAMS evaluation (one because of pregnancy, the other refused for personal reasons). Over the 96 patients, the sex ratio was 2.69 (70 women, 26 men), median age at inclusion was 40.7 ± 11.7 years (extremes: 19.5 – 65.0 years), median MS duration was 11.6 ± 9.6 years (extremes: 0.8 – 28.0 years), and median natalizumab duration without interruption was 5.4 ± 6.4 years (extremes: 6 months – 10.4 years). No patient developed progressive multifocal leukoencephalopathy during follow-up. Regarding education level, 36 patients had a level under high school graduation (37.5%), 17 patients a high school graduation or associate's degree (17.7%), 31 a bachelor's degree (32.2%) and 12 a master's degree or higher (12.5%). Regarding BICAMS scores (Table 1), 31 patients had an impaired SDMT test (32.3%), 30 patients an impaired BVMT-R test (31.2%) and 31 patients an impaired FVLT test (32.3%). Overall, 51 patients (53.1%) had at least one test impaired: 22 exactly one test impaired (22.9%), 17 exactly two tests impaired (17.7%) and 12 exactly three tests impaired (12.5%). The normalized volumes of inflammatory lesions and of different cerebral parts are also described in Table 1. We observed purely intracortical hyperintensities on the 3D-DIR sequence in only 19 patients (19.8%), being unique in 16 patients and located in different lobes (Fig. 2). As 3T MRI only highlights a minor part of the cortical pathology, these purely intracortical lesions were not included in the T2 lesion burden which was measured on 3D-FLAIR sequence. However, all juxtacortical lesions observed on the 3D-DIR sequence were easily detected on the 3D-FLAIR sequence and included in the total T2 lesion burden.

*Overall measures and cognitive scores*

Except for FVLT score and white matter volume normalized volume, we found significant associations between each cognitive score and each brain compartment volume (Table 2). Then we accounted for the effects of age, sex and education by considering cognitive Z-scores. The SDMT and BVMT Z-scores were significantly associated with each brain compartment volume, but the FVLT Z-score was only associated with the FLAIR-hyperintensity normalized volume. The highest R-squared were observed with the FLAIR-hyperintensity normalized volume for all three cognitive Z-scores.

*Local cortical thickness and cognitive scores*

We studied the association between cognitive score and cortical thickness maps, to look for precise cortical regions which may be more specifically involved.

For the SDMT score (Fig. 3), we found a positive association with many cortical clusters: in the left (superior frontal and lateral orbito-frontal gyri) and right frontal cortex (caudal middle frontal gyrus), left (superior temporal and fusiform cortex) and right temporal cortex (superior temporal gyrus), left (inferior parietal cortex) and right parietal cortex (inferior parietal, post-central, supramarginal, precuneus gyri), right occipital cortex (lateral occipital gyrus) and left insula.

For the BVMT-R, we found a positive association with two clusters in the left superior frontal gyrus and one cluster in the right precentral gyrus (Fig. 4). For the FVLT, we found a positive association with two clusters in the left pars opercularis which is a part of Broca's area in right-handed persons and 70% of the left-handed persons

[25], and three clusters in the right superior temporal gyrus (Fig. 5). The same analysis restricted to right-handed subjects (n = 82) gave the same results (not shown).

Conducting the same analysis with Z-scores to account for the effects of age, sex and education, we found only some of the same clusters: in the left superior frontal gyrus and right precuneus gyrus for the SDMT Z-score, in the left superior frontal gyrus for the BVMT-R Z-score and no significant cluster for the CVLT Z-score (Appendix 1, Fig. 6 and 7). Nevertheless, we observed a significant association between the mean cortical thickness in each cluster and its corresponding cognitive Z-score (Table 3), these models being even more predictive than models using the overall volumes for the BVMT-R and FVLT Z-scores (higher adjusted R-squared values than in Table 2).

*Cognitive scores and local white matter lesions*

We studied the white matter pathology anatomically connected with these cortical clusters. The normalized FLAIR-hyperintensity volumes within the connected track were significantly associated with all cognitive Z-scores (Table 4), and also significantly associated with the cortical thickness within each cluster, except for the right superior temporal cluster (related to SDMT), and for the left pars opercularis cluster (related to CVLT) (Table 5).

## Discussion

We demonstrated significant associations between the BICAMS cognitive scores and several MRI parameters in RR-MS: total FLAIR-hyperintensity volume; some precise cortical regions different for each test; and white matter pathology anatomically-connected to these cortical regions.

Our study has several strengths. First, we studied separately each BICAMS score, which seems more relevant than using only one cognitive global score gathering many cognitive tests, as different cognitive functions may rely on different neuronal basis and different structures. Using of linear models better reflects the continuum which exists in the cognitive impairment in MS than comparing cognitively *impaired* and cognitively *respected* groups. Although including only a relatively homogeneous population of RR-MS patients does not allow an extrapolation to other MS forms, it allows an easier interpretation of our results as RR-MS and progressive forms are different in regards to pathophysiology and cognitive impairment [5]. Including patients taking natalizumab without evidence of recent inflammation gave a good assurance that the patient was in a stable state

On one hand, our results highlight the role of inflammatory lesions in cognitive dysfunction. Considering overall brain volumes, the total FLAIR-hyperintensity volume was the only one almost constantly associated with BICAMS scores and the more predictive one. On the other hand, we found even stronger associations with the thickness of precise cortical regions, emphasizing a contribution of grey matter involvement. Moreover, the cortical regions associated with each cognitive score was different for each test, and these associations were consistent with the functions of

the considered cortical regions. Thereby BVMT-R, testing the visuo-spatial memory, is associated with left superior frontal gyrus thickness implicated in spatial working memory [26], and with right prefrontal gyrus thickness, which may be implicated in spatial attention control [27]. FVLT, testing verbal memory, was associated with left pars opercularis gyrus thickness, a part of Broca's area in right handed persons, implicated in language and especially in verbal working memory [28]. FVLT was also associated with thickness of multiple areas in the right superior temporal gyrus, which includes the right associative auditory cortex and is implicated in verbal and non-verbal memory such as music [29]. SDMT was associated with a large number of cortical areas in several lobes, maybe because this test involves many cognitive functions such as information processing speed, attention, working memory, and mental flexibility. This may also explain why SDMT is well associated with total cortical volume but also deep grey matter, itself connected with all cortical areas. Mean cortical thickness within those regions better predicted BVMT-R and FVLT scores than overall volumes, and may therefore be an interesting biomarker. The different cortical regions found also illustrate the benefit of considering each cognitive test separately. These results are probably not specific to MS and may be found in other neurological conditions.

Then, we tried to link cognitive scores with some locations of white matter T2-hyperintensities. As there were few overlaps between subjects, we did not use a lesion-symptom mapping approach, but rather developed a method using tractography to identify the track from the cortical regions previously identified. We observed an association between FLAIR-hyperintensity volume in tracks connected with clusters and the corresponding cognitive scores, linking one more time white matter inflammatory lesions to cognitive scores. Nevertheless, the R-squared values were not higher than observed using the FLAIR-hyperintensity volume for the whole brain for BVMT-R and CVLT scores.

Our results generate hypotheses about the pathophysiology of cognitive impairment in RR-MS. The impairment of some cognitive functions (visuo-spatial memory, verbal memory) seems to be strongly related with the cortical thickness of specific cortical areas. The cortical thickness of these area may be influenced by factors independent of MS such as age, sex and education level which are known to be associated with modifications of cortical thickness [21–23], but also by white matter inflammatory lesions connected with this cortical region. A relation between white matter lesions and grey matter atrophy has already been showed in studies on MS [30], and can be explained biologically by axonal transection. Moreover, it has been suggested that white matter lesions in strategic area might better explain cognitive impairment than diffuse involvement of grey or white matter [31]. Finally, primary grey matter impairment independent of inflammatory lesions has been evoked in RR-MS [32], and might participate in focal cortical atrophy. This focal cortical atrophy might be a sign of the disconnection mechanism between two cortical areas [8].

Our work has several limitations. First, we used French norms for BICAMS [18] which were created on subjects from another French centre (Bordeaux) and not from ours. We had no control group of healthy subjects from our centre for the MRI data, therefore it is impossible to know whether the cortical areas found associated with cognitive scores had normal volumes or showed some atrophy. Then, we only considered relatively severe RR-MS patients, thus our results do not apply to clinically isolated syndromes, benign MS, nor to progressive forms. It would be interesting to make the same analysis in patients with a clinically isolated syndromes or primary progressive MS, which might produce further information on the cognitive differences between MS forms. The choice of BICAMS for cognitive assessment is questionable, as it is a screening and following tool, has no norms and is not yet validated in our population. Moreover, BICAMS does not specifically evaluate

executive functions, frequently impaired in MS. However, BICAMS will probably be increasingly used in routine clinical practice in the years to come. Moreover, our evaluation did not take into account all the pathologic processes in MS. We only considered the FLAIR-hyperintensity volume, whereas there is an association between cognitive impairment and normal appearing white matter involvement measured with MTR [10] or DTI [8], and with cortical inflammatory lesions which can be viewed as DIR hyperintensities [13]. This incomplete description of the lesions may explain the weak associations. We did not include purely intracortical 3D-DIR hyperintensities in our analysis because we found few of them in a restricted number of patients, and because our primary hypothesis focused on focal cortical atrophy, which don't overlap with grey matter lesions [33]. Cortical lesions should be considered in future studies if progress in MRI techniques allow better detection of them. We only used structural data, whereas a functional reorganization of the cortex exists from the beginning of MS, allowing a partial compensation of structural lesions [34]. Functional MRI might therefore be complementary of our structural data. Finally, we remind readers that we could not exclude false positive findings regarding multiple comparisons, and that associations cannot establish causality but only hypotheses.

Our work demonstrates the pertinence of brain structural parameters as biomarkers of cognitive impairment. The associations found also generated hypotheses about the mechanisms of cognitive impairment in MS. These associations need to be confirmed by further cross-sectional studies. Longitudinal studies might also study the dynamics of cognitive disorders according to the evolution of structural parameters.

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## Figure legends

**Fig. 1:** Example of the procedure to estimate white matter pathology anatomically connected to a defined cortical region, here two clusters in the pars opercularis **(A)**. These clusters were transformed to a volume in the T1-space, warped to the DTI space **(B),** and used as a seed for tractography **(C)**. The binary mask of the track was registered into the FLAIR-space (yellow), measured the hyperintensity volume within it (red) to measure a percentage of lesion within the track (percentage of red within the yellow volume).

**Fig. 2:** Brain MRI (Axial plane; DIR-sequence) of a patient presenting juxta-cortical (yellow arrows) and purely cortical lesions (red arrows)

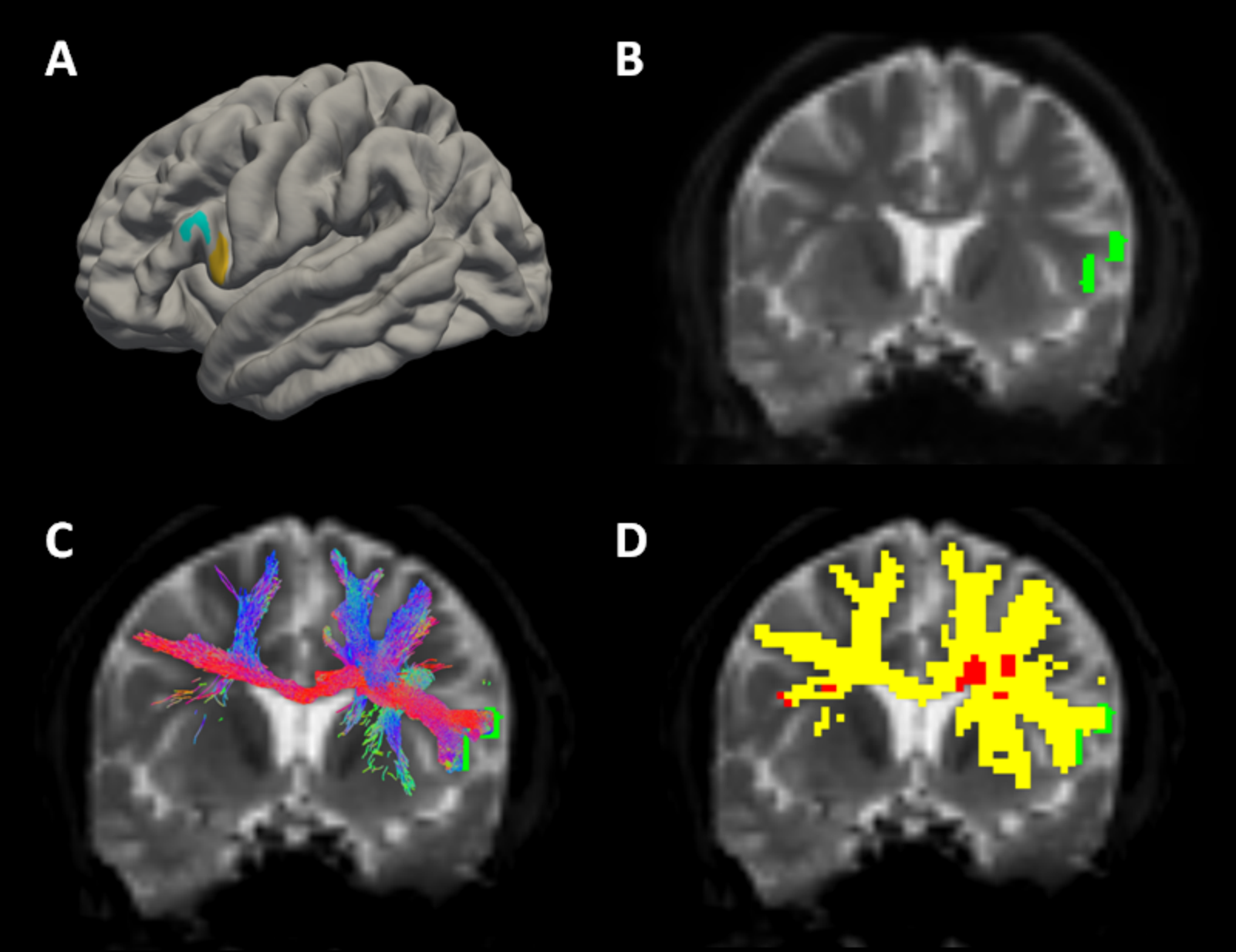
**Fig. 3:** Clusters where the cortical thickness was significantly associated with SDMT score.

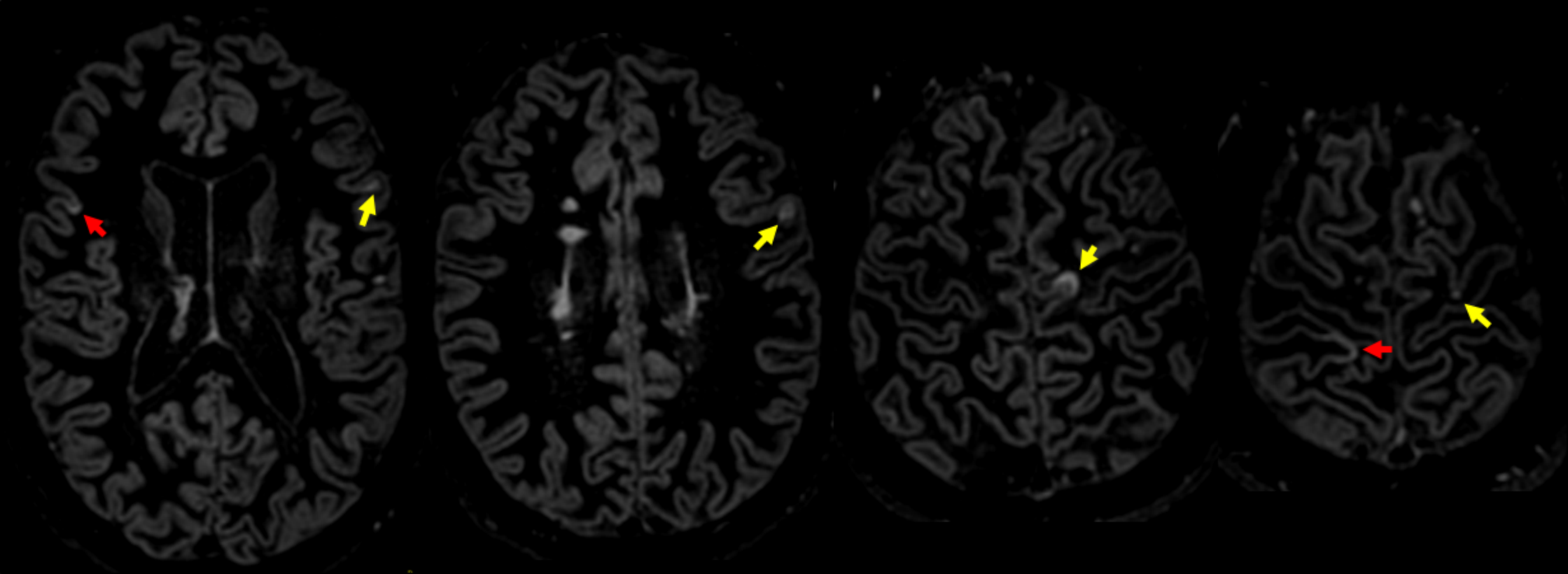
**Fig. 4:** Clusters where the cortical thickness was significantly associated with BVMT-R score.

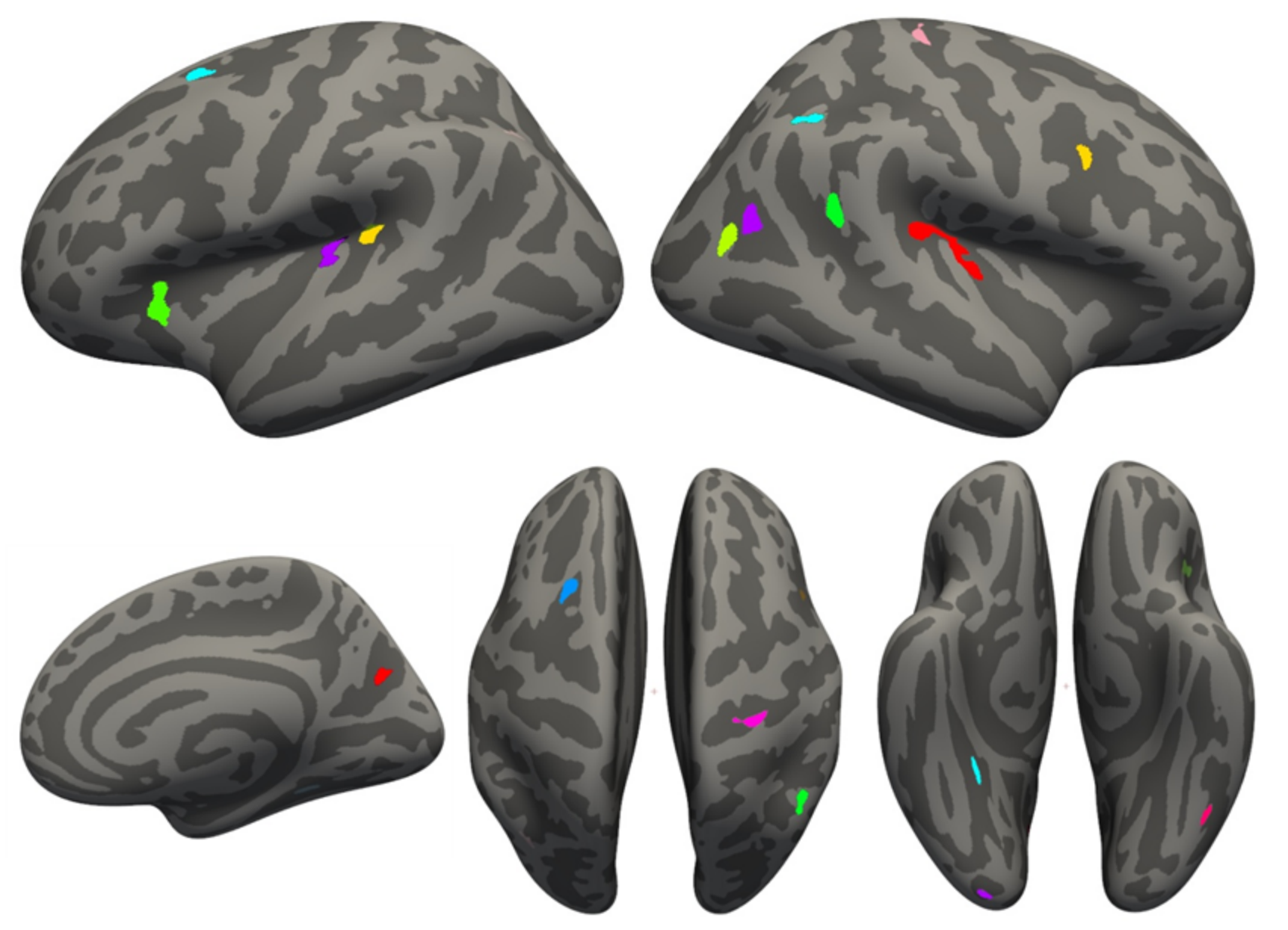
**Fig. 5:** Clusters where the cortical thickness was significantly associated with CVLT score.

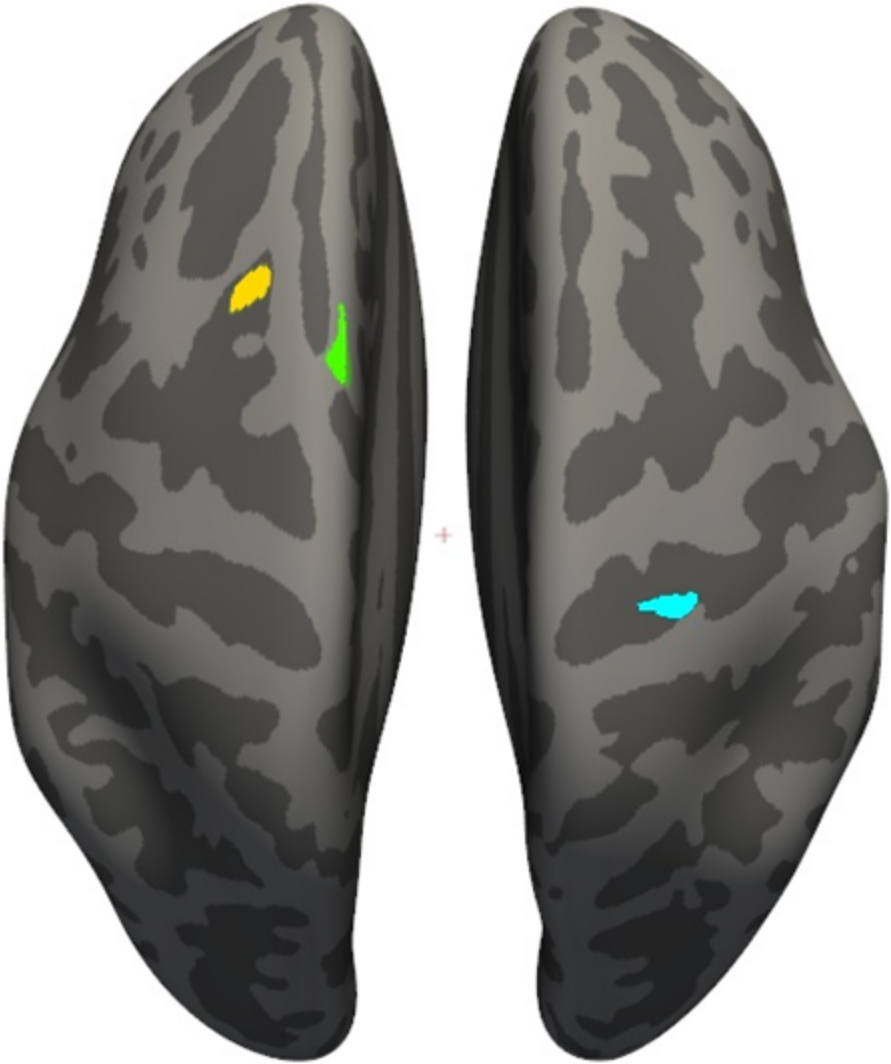
**Fig. 6.** Clusters where the cortical thickness was significantly associated with SDMT Z-score.

**Fig. 7.** Clusters where cortical thickness was significantly associated with the BVMT-R Z-score.


A
B
C
D







## Tables

| **Table 1: BICAMS scores and MRI volumes in our whole population.** | | | | |
|---|---|---|---|---|
| | **Mean** | **Standard deviation** | **Minimum** | **Maximum** |
| **BICAMS scores** | | | | |
| SDMT | 51.5 | 13.3 | 17 | 88 |
| BVMT-R (/36) | 21.9 | 8.3 | 1 | 34 |
| FVLT (/75) | 49.5 | 11.6 | 17 | 73 |
| **BICAMS Z-scores** | | | | |
| Z-score SDMT | -0.90 | 1.29 | -3.49 | 2.40 |
| Z-score BVMT | -0.81 | 1.19 | -3.03 | 1.93 |
| Z-score FVLT | -1.06 | 1.13 | -3.78 | 2.25 |
| **Raw cerebral volumes** | | | | |
| Estimated intracranial volume (cm3) | 1406.0 | 224.2 | 818.4 | 1938.0 |
| **Normalized cerebral volumes** | | | | |
| Normalised FLAIR hyperintensities (%) | 0.66 | 0.70 | 0.01 | 3.74 |
| Normalised brain (%) | 72.40 | 10.25 | 49.74 | 101.30 |
| Normalised white matter (%) | 29.86 | 4.85 | 18.45 | 46.54 |
| Normalised total grey matter (%) | 40.54 | 5.74 | 30.05 | 56.19 |
| Normalised cortex (%) | 30.28 | 4.29 | 22.57 | 42.49 |
| Normalised subcortical grey matter (%) | 3.70 | 0.63 | 2.62 | 5.52 |

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**Table 2: Linear models explicating cognitive scores and Z-scores as a function of different brain normalised volumes**

| | SDMT | | | BVMT-R | | | FVLT | | |
|---|---|---|---|---|---|---|---|---|---|
| | **β** | **p** | **adj. $R^2$** | **β** | **p** | **adj. $R^2$** | **β** | **p** | **adj. $R^2$** |
| FLAIR-hyperintensity (%) | -8.079 | **<0.001** | 0.175 | -3.364 | **0.005** | 0.071 | -5.000 | **0.003** | 0.082 |
| Total brain (%) | 0.600 | **<0.001** | 0.207 | 0.269 | **<0.001** | 0.100 | 0.279 | **0.006** | 0.050 |
| White matter (%) | 1.164 | **<0.001** | 0.172 | 0.482 | **0.003** | 0.069 | 0.461 | 0.07 | 0.027 |
| Grey matter (%) | 1.024 | **<0.001** | 0.188 | 0.481 | **<0.001** | 0.100 | 0.518 | **0.004** | 0.055 |
| Cortex (%) | 1.382 | **<0.001** | 0.192 | 0.624 | **<0.001** | 0.094 | 0.686 | **0.004** | 0.054 |
| Deep grey matter (%) | 8.968 | **<0.001** | 0.175 | 4.311 | **<0.001** | 0.098 | 4.368 | **0.007** | 0.047 |
| | **SDMT (Z-score)** | | | **BVMT-R (Z-score)** | | | **FVLT (Z-score)** | | |
| | **β** | **p** | **adj. $R^2$** | **β** | **p** | **adj. $R^2$** | **β** | **p** | **adj. $R^2$** |
| FLAIR-hyperintensity (%) | -0.731 | **<0.001** | 0.150 | -0.448 | **0.009** | 0.059 | -0.449 | **0.006** | 0.069 |
| Total brain (%) | 0.047 | **<0.001** | 0.128 | 0.029 | **0.014** | 0.053 | 0.008 | 0.46 | <0.001 |
| White matter (%) | 0.102 | **<0.001** | 0.136 | 0.060 | **0.017** | 0.049 | 0.013 | 0.59 | <0.001 |
| Grey matter (%) | 0.072 | **0.001** | 0.093 | 0.046 | **0.029** | 0.039 | 0.015 | 0.44 | <0.001 |
| Cortex (%) | 0.098 | **0.001** | 0.096 | 0.058 | **0.042** | 0.033 | 0.019 | 0.49 | <0.001 |
| Deep grey matter (%) | 0.635 | **0.002** | 0.088 | 0.443 | **0.020** | 0.045 | 0.121 | 0.51 | <0.001 |

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Significant p-values are indicated in bold
β = estimate of the model
adj. $R^2$ = adjusted R-squared

| **Table 3 : Linear models explicating a cognitive Z-score score as a function of the mean thickness in cortical cluster(s) in a given region** | | | |
|---|---|---|---|
| | **β** | **p-value** | **adj. $R^2$** |
| **SDMT** | | | |
| Right caudal middle frontal (1 cluster) | 1.463 | **0.002** | 0.085 |
| Right lingual (1 cluster) | 1.217 | **<0.001** | 0.151 |
| Left superior frontal (1 cluster) | 1.946 | **<0.001** | 0.196 |
| Left parietal inferior (1 cluster) | 1.266 | **<0.001** | 0.097 |
| Left fusiform (1 cluster) | 1.443 | **<0.001** | 0.147 |
| Right postcentral (1 cluster) | 3.121 | **<0.001** | 0.228 |
| Right inferior parietal (3 clusters) | 3.077 | **<0.001** | 0.272 |
| Right precuneus (1 cluster) | 2.539 | **<0.001** | 0.238 |
| Left insula (1 cluster) | 2.113 | **<0.001** | 0.150 |
| Right superior temporal (1 cluster) | 2.203 | **<0.001** | 0.159 |
| Right lateral occipital (1 cluster) | 1.382 | **<0.001** | 0.132 |
| Right supramarginal (1 cluster) | 1.547 | **<0.001** | 0.154 |
| Left lateral orbitofrontal (1 cluster) | 2.554 | **<0.001** | 0.260 |
| Left superior temporal (1 cluster) | 1.872 | **<0.001** | 0.170 |
| **BVMT-R** | | | |
| Left superior frontal (1 cluster) | 2.381 | **<0.001** | 0.290 |
| Right precentral (1 cluster) | 2.344 | **<0.001** | 0.165 |
| **CVLT** | | | |
| Left pars opercularis gyrus (2 clusters) | 1.743 | **<0.001** | 0.148 |
| Right superior temporal gyrus (3 clusters) | 2.401 | **<0.001** | 0.223 |

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| **Table 4: Linear models explicating a cognitive Z-score as a function of the FLAIR-hyperintensity volume in different tracks (normalised on the volume of the track)** | | | |
|---|---|---|---|
| | **β** | **p-value** | **adj. $R^2$** |
| **SDMT** | | | |
| Track from the right caudal middle frontal (%) | -0.230 | **<0.001** | 0.129 |
| Track from the right lingual (%) | -0.146 | **<0.001** | 0.141 |
| Track from the left superior frontal (%) | -0.244 | **<0.001** | 0.141 |
| Track from the left parietal inferior (%) | -0.175 | **<0.001** | 0.124 |
| Track from the left fusiform (%) | -0.170 | **<0.001** | 0.118 |
| Track from the right postcentral (%) | -0.217 | **<0.001** | 0.151 |
| Track from the right inferior parietal (%) | -0.220 | **<0.001** | 0.135 |
| Track from the right precuneus (%) | -0.163 | **<0.001** | 0.135 |
| Track from the left insula (%) | -0.212 | **<0.001** | 0.133 |
| Track from the right superior temporal (%) | -0.233 | **<0.001** | 0.149 |
| Track from the right lateral occipital (%) | -0.132 | **<0.001** | 0.121 |
| Track from the right supramarginal (%) | -0.193 | **<0.001** | 0.170 |
| Track from the left lateral orbitofrontal (%) | -0.269 | **<0.001** | 0.146 |
| Track from the left superior temporal (%) | -0.213 | **<0.001** | 0.131 |
| **BVMT-R** | | | |
| Track from the left superior frontal (%) | -0.159 | **0.011** | 0.057 |
| Track from the right precentral (%) | -0.117 | **0.026** | 0.042 |
| **FVLT** | | | |
| Track from left pars opercularis (%) | -0.147 | **0.007** | 0.064 |
| Track from right superior temporal (%) | -0.119 | **0.059** | 0.050 |

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β = estimate of the mode
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| **Table 5: Linear models explicating cluster cortical thicknesses as a function of the FLAIR-hyperintensity volume in different tracks (normalised on the volume of the track)** | | | |
|---|---|---|---|
| **Mean thickness in the clusters in a given region** | **β** | **p-value** | **adj. $R^2$** |
| **SDMT** | | | |
| Track from the right caudal middle frontal (%) | -0.044 | **0.001** | 0.099 |
| Track from the right lingual (%) | -0.047 | **<0.001** | 0.139 |
| Track from the left superior frontal (%) | -0.064 | **<0.001** | 0.179 |
| Track from the left parietal inferior (%) | -0.040 | **0.001** | 0.096 |
| Track from the left fusiform (%) | -0.036 | **0.005** | 0.069 |
| Track from the right postcentral (%) | -0.031 | **<0.001** | 0.126 |
| Track from the right inferior parietal (%) | -0.043 | **<0.001** | 0.179 |
| Track from the right precuneus (%) | -0.039 | **<0.001** | 0.200 |
| Track from the left insula (%) | -0.040 | **<0.001** | 0.137 |
| Track from the right superior temporal (%) | -0.063 | **<0.001** | 0.327 |
| Track from the right lateral occipital (%) | -0.017 | 0.098 | 0.019 |
| Track from the right supramarginal (%) | -0.049 | **<0.001** | 0.164 |
| Track from the left lateral orbitofrontal (%) | -0.046 | **0.001** | 0.099 |
| Track from the left superior temporal (%) | -0.061 | **<0.001** | 0.214 |
| **BVMT-R** | | | |
| Track from the left superior frontal (%) | -0.055 | **<0.001** | 0.141 |
| Track from the right precentral (%) | -0.031 | **<0.001** | 0.109 |
| **FVLT** | | | |
| Track from left pars opercularis (%) | -0.019 | 0.15 | 0.012 |
| Track from right superior temporal (%) | -0.041 | **<0.001** | 0.170 |

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