Statistical modeling to assess the impact of cortical parameters on cognition in Multiple Sclerosis.

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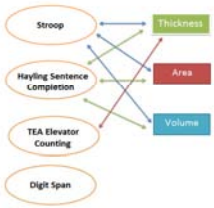
TARGET AUDIENCE: Clinicians, statisticians and researchers interested in modeling the effects of MRI-based cortical parameters on cognition.

BACKGROUND and PURPOSE: Brain atrophy as determined by quantitative magnetic resonance imaging (MRI) can be used to characterize disease progression in pathologies such as Multiple Sclerosis (MS). Focal thinning of the cerebral cortex in frontal regions has been reported in MS patients. Parameters like cortical volume, area and thickness may clarify the pathogenic mechanisms of cognitive problems in MS. We present a statistical model with several steps with increasing complexity, all within the General Linear Modeling (GLM) framework[1], to relate cognitive scores to MRI-based cortical parameters, using a cohort of patients with MS and healthy controls (HC). In particular the model aims to: 1) determine which cortical parameters and cognitive scores differ between MS patients and HCs; 2) determine whether cortical parameters are associated with cognitive scores, and if so, to which ones. Understanding these relationships could help improve prognosis and monitoring of the disease progression, and may be key for designing therapeutic interventions.

MATERIALS and METHODS: S*ubjects* - 86 patients with clinically definite MS (relapsing-remitting (RR), primary progressive (PP) and secondary progressive (SP) MS)) and 54 HC took part in this study. *MRI protocol* - Images were acquired on a 3 T Philips Achieva MRI scanner. *Cognitive tests* - All subjects underwent cognitive testing including tests of frontal function (the WAIS-III Digit Span for working memory, Hayling Sentence Completion and Stroop tests of executive function and the TEA Elevator Counting with distraction test of attention). The National Adult Reading Test was used as a test of premorbid IQ for matching groups. *Image analysis* - Thickness, area and volume of the frontal cortex were measured using a surface-based morphometry method (Freesurfer[2]). We implemented a scoring system to select subjects in which Freesurfer had an excellent performance and our sample was finally composed by 67 patients with MS (mean age 48.3±10.5 yrs, 46 F and 21 M) and 32 HC (mean age 39.0±13.0, 16 F and 16 M). Based on prior knowledge of cortical regions involved in cognitive processes, we limited the analysis to the Frontal Lobe, particularly to the following three areas (from Freesurfer Region Of Interest (ROI)): Orbitofrontal region (lateral orbitofrontal and medial orbitofrontal), Lateral region (rostral middle frontal, caudal middle frontal, pars triangularis, pars opercularis), Medial region (superior frontal and rostral cingulate). *Statistical models and analysis* – All the analysis was performed with Stata and using GLM. In the GLM framework[3] it is possible to include different types of random variables (continuous, discrete, Bernoulli 0-1) and different types of probability distributions (Gaussian, Poisson, Binomial). Here we used simple, multiple and multivariate linear regression for the continuous response variables and simple and multiple logistic regression for the Bernoulli response variable (see table 1). The following regression models were used for each cortical/cognitive parameter to explore which cortical and cognitive parameters differed between patient and control groups: $parameter = intercept + \beta * subject_{type} + \gamma * age + \delta * gender + \rho * Education + \sigma * prelQ$. First, we ran a simple linear regression, followed by multiple linear regressions. Second, we ran multivariate linear models for an advanced analyses of MS vs HC differences both in cognitive and in cortical parameters. Multivariate regression analysis attempts to determine an equation that can describe how elements in a vector of variables respond simultaneously to changes in others. We used SEM (structural equation modeling) in Stata to check all the parameters together. Advanced statistical analysis by constructing a logistic regression allows determining which parameter independently distinguish patients and controls, by considering cortical and cognitive measurements in the same model. Last, for each parameter we ran a multiple linear regression model with an interaction term ($cognitive = intercept + \beta * subjecty_{type} + \gamma * cortical + \delta * cortical\ x\ subject_{type}[+age\ and\ gender]$) to test whether there are associations between cortical and cognitive parameters and whether cognitive impairment in MS is best explained by a single cortical parameters or by non-specific changes in a combination of cortical parameters.

RESULTS: Cortical and cognitive parameters differed between MS patients and HC (see table 1). In particular the linear regression (simple and multiple) showed that MS and HC participants differed on the Stroop test (p=0.008) and on Thickness (p=0.003). Similar group differences were seen using SEM, with patients showing significantly worse performance on the Stroop and a significant loss of cortical thickness in the Right Medial parcellation. We found that the variables that best predict MS status were the Right Medial Thickness, Right and Left Lateral Area. The results of the association analysis using the linear regression with the interaction term are: Stroop with Right Medial Thickness and Left Lateral Area; Hayling Sentence Completion with Left Orbital Thickness and Left Lateral Area; Elevator Counting with Distraction with Right Orbital Thickness. However there is no evidence that pathology of MS has an effect on these associations, which hold independently of group (MS or HC).

Table 1: Summary of the questions, statistical models and results.

QUESTIONS	MODEL AND EQUATION	RESULTS
Are there DIFFERENCES in cortical structural parameters and neuropsychological scores between MS and HC?	LINEAR REGRESSION $par = \alpha + \beta * subject_{type} + \gamma * age + \delta * gender + \rho * education + \sigma * prelQ$	• THICKNESS (p=0.003) • STROOP (p=0.008)
	MULTIVARIATE LINEAR REGRESSION $par_i = \alpha + \beta * subject_{type_i} + \gamma * age_i + \delta * gender_i + \rho * education_i + \sigma * prelQ_i$	• THICKNESS • STROOP
	LOGISTIC REGRESSION $logit\left(E(subject_{type})\right) = \alpha + \beta * parameter$	• Right Medial THICKNESS and Lateral AREA • STROOP
Are there ASSOCIATIONS between cortical structural parameters and neuropsychological scores both in MS and HC?	LINEAR REGRESSION WITH INTERACTION TERM $cogn = \alpha + \beta * subject_{type} + \gamma * cortical + \delta * cortical\ x\ subject_{type}$	

DISCUSSION: Histopathology studies revealed reduced cortical thickness in people with MS compared to HC[4] [2.30 mm versus 2.48 mm]. Our results are in accordance with these findings. Focal cortical thinning in frontal brain regions was observed [2.37 mm versus 2.73 mm], even early in the course of the disease or in patients with mild disability. Regarding cognitive tests, previous studies have shown that the Stroop is associated with damage in the frontal lobe but not in the occipital lobe. Stroop interference effect is considered to be a measure of frontal lobe function: in traumatic brain injury studies, subjects with medial frontal lesions presented increased errors and slowness in response time[5]. Our results and conclusions are consistent with this role of the frontal lobe in Stroop performance and highlight the role of medial frontal regions in this task.

CONCLUSIONS: Statistical models of increasing complexity allowed us to thoroughly investigate cortical parameters and their associations with cognition in people with MS and HC. The models can be expanded to include other covariates such as total brain volume to account of atrophy or the expanded disability status scale indicative of disease progression.

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