Cortical Grey Matter Ratio Differentiates Relapsing Remitting Multiple Sclerosis from Secondary Progressive Multiple Sclerosis

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INTRODUCTION AND SIGNIFICANCE

- To present date, MS phenotypes *Relapsing Remitting Multiple Sclerosis (RRMS)* and *Secondary Progressive Multiple Sclerosis (SPMS)* are differentiated retrospectively solely on clinical grounds by careful expert evaluation on routine follow up
- Patient management and prognosis vary considerably among phenotypes. Disease modifying therapy (DMT) regimens have considerable risk-benefit profiles and are of high financial burden to patient and society. Above all, effectiveness of DMT's is more or less limited to one phenotype and a therapy switch or stop is generally initiated when disease conversion is objectified
- **Earlier stage identification of phenotype conversion would presumably result in more accurate medical care and research**
- The neuropathological substrates inducing conversion from RRMS to SPMS remain unclear to date. Age is the most predictive factor for conversion known so far[1]
- Several other predictive factors have been proposed in recent years, among which quantitative Magnetic Resonance Imaging (MRI) modalities such as cerebral atrophy and lesion load. Most were unable to differentiate between phenotype or carried intrinsic limitations by default due to lack of correction for age- and sex related variability in healthy brains

OBJECTIVES

[I]

- **To cross-sectionally investigate differences in cerebral grey matter volumes between RRMS and SPMS patients**
- **More specifically;**
  - **Cortical Grey Matter volume (CGMv) and Deep Grey Matter volume (DGMv) will be investigated.**
  - **DGMv will comprise of Thalamus-, Caudate nucleus- and Putamen but not Globus pallidus**
  - **CGMv will comprise of supratentorial CGM only and thus exclude the cerebellum**
- **Patient volumes will be expressed as ratio of age- and sex corresponding healthy control (HC) volume to aid normalisation**

[II]

- **To test if any significant difference arising from aforementioned investigations can be applied in a binary logistic regression (BLR) model, to predict phenotype based on structure specific measured patient volume**

METHODS

Study design

- **Retrospective cross-sectional cohort study**

Data acquisition

- 108 RRMS and 30 SPMS patient MRI scans were selected from the *Antwerp University Hospital (UZA)* outpatient database and included in compliance with the following criteria:
  - MRI Scan acquired in previous 24 months at UZA
  - Expanded Disability Status Scale (EDSS) documented within 6 months from image acquisition
  - Age 18-65 years old with no documented history of neurological disease activity other than MS
- EDSS equal to or greater than 4.0 was applied as cut-off for SPMS based on methods used by Lavorgna[2] and Grothe[3]
- Anonymized patient MRI data were wire-transferred to *icoMetrix,* Leuven, Belgium, for further quantification of CGMv and DGMv
- Patient CGMv and DGMv were returned by *icoMetrix*, accompanied with patient age- and gender specific normalized volumes and 1st and 99th percentiles as reference for comparison (HC-CGMv and HC-CGMv respectively)
- SPSS 24 was used for further statistical analysis

Data expression

- Patient CGMv and DGMv were expressed as ratios of their respective HC-CGMv and HC-DGMv as denominators
- This resulted in
  - CGM ratio (CGMr = CGMv / HC-CGMv)
  - DGM ratio (DGMr = DGMv / HC-DGMv).

i.e. a value > 1,0 implies a measured volume greater than the population median of its respective age and gender matched cohort and vice-versa for a value <1,0)

RESULTS

[I] Group comparison

- **Mean CGMr differed significantly between phenotypes: [RRMS 1,0240 | SPMS 1,0016 | *P* = 0.006] (table 1)**
- **Mean DGMr did not differ significantly between phenotypes [RRMS 0,8767 | SPMS 0,8533 | *P* = 0.209] (table 1)**
- **CGMr correlated with DGMr in RRMS, however not in SPMS [RRMS: r = 0.308, *P* =0.001 | SPMS: r = 0.324, *P* = 0.080]**
- **34 patients (24,6 %) were not receiving disease modifying therapy (DMT) in the previous 6 months of image acquisition**
- **When comparing CGMr and DGMr in treated - versus untreated patients, no significant differences were found in total cohort, nor in subgroups, with the exception of DGMr in SPMS patients; SPMS patients receiving active therapy had significanly lower DGMr**

[II] Phenotype prediction

- **Log-transformed CGMr (logCGMr) and disease duration emerged as predictors of phenotype (P=.038, P=.002 respectively)**
- **Disease duration predicted RRMS and SPMS correct in 98,1% and 16,7% of cases respectively**
- **Addition of logCGMr increased overall predictive accuracy to 99,1% for RRMS and to 26,7% for SPMS**

DISCLOSURES
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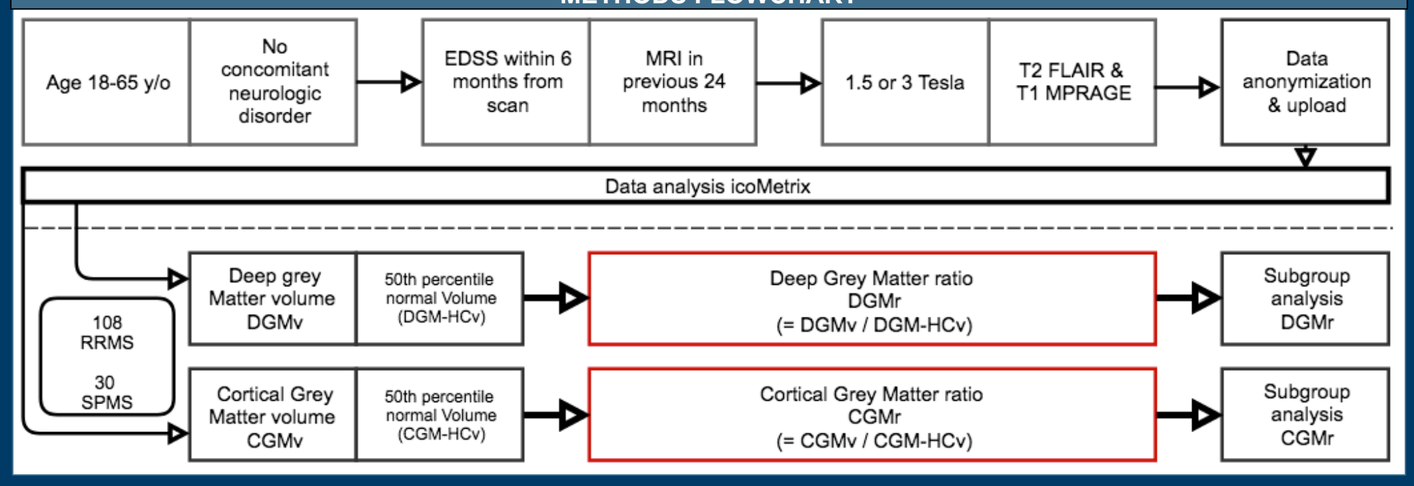
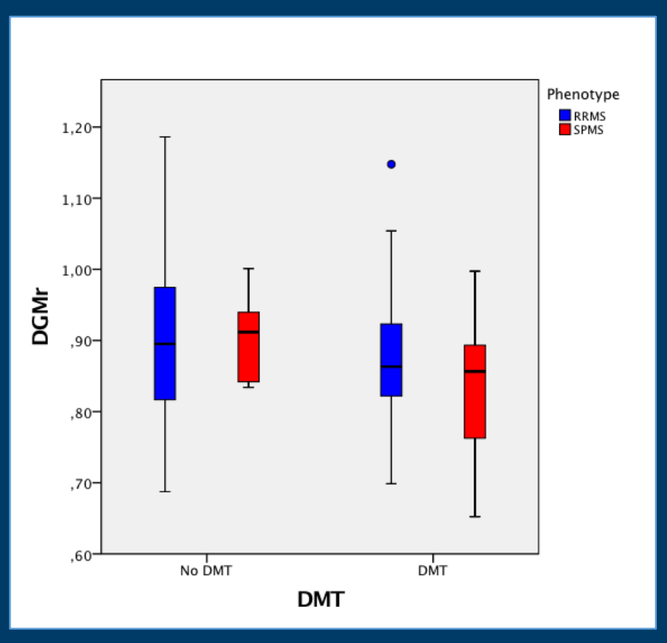
METHODS FLOWCHART

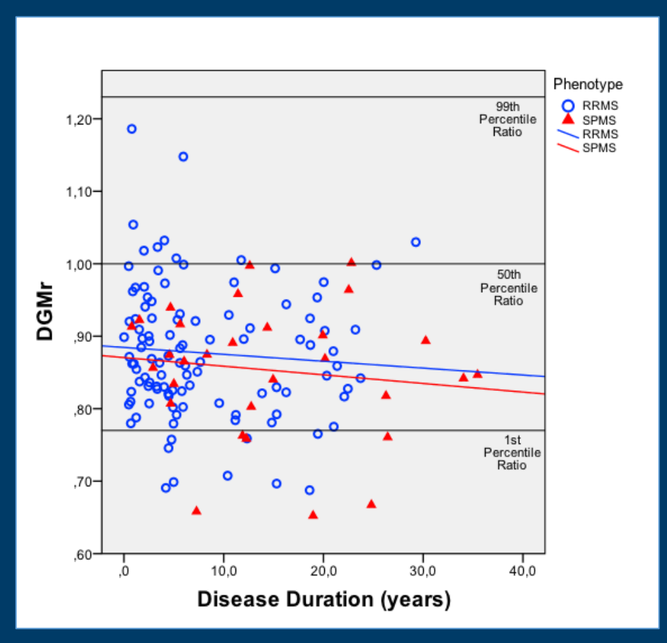


RESULTS *Table 1* - Group characteristics- and comparison: means and standard deviations

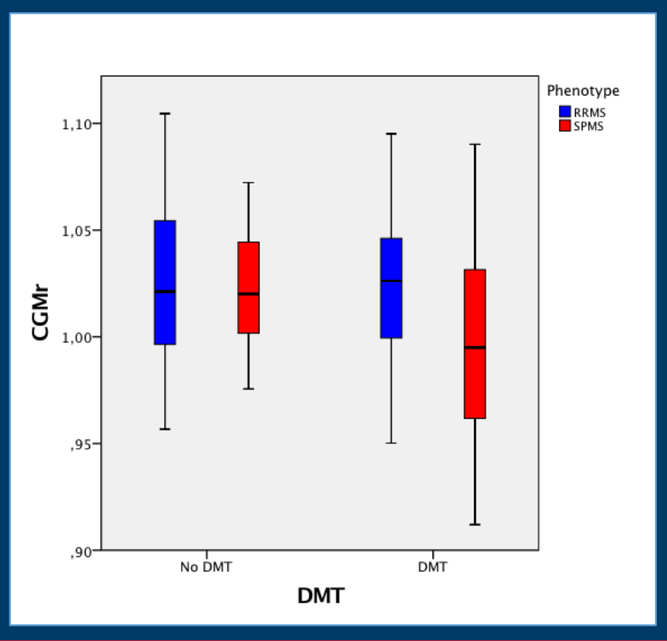
	All patients (n = 138)	RRMS (n = 108)	SPMS (n = 30)	P value
Age (years, SD)	40,15 (10,44)	38,87 (9,84)	44,78 (11,37)	0,006
Range (years)	22,1 - 63,7	22,1 - 62,6	27,0 - 63,7	
Gender (n, %)				
Males	58 (42,0)	41 (38,0)	17 (56,7)	
Females	80 (58,0)	67 (62,0)	13 (43,3)	
Disease duration (SD)	9,41 (8,31)	8,00 (7,27)	14,47 (9,87)	0,000
EDSS score				
Mean (SD)	2,46 (1,70)	1,77 (1,01)	4,95 (1,30)	0,000
Median	2	2	4,5	
Range	0 to 8	0 to 3,5	2,5 to 8	
Treatment				
DMT (%)	104 (75,4)	83 (76,9)	21 (70)	
No DMT (%)	34 (24,6)	25 (23,1)	9 (30)	
Therapy duration (years, SD)	4,30 (5,68)	3,82 (5,27)	6,01 (6,81)	0,150
MRI characteristics				
DGM volume (SD)	40,21 (4,26)	40,55 (4,19)	38,96 (4,34)	0,080
CGM volume (SD)	869,26 (47,56)	877,21 (43,22)	840,64 (52,07)	0,000
DGM ratio (SD)	0,8718 (0,0909)	0,8769 (0,0905)	0,8533 (0,0912)	0,209
CGM ratio (SD)	1,0191 (0,0397)	1,0240 (0,0368)	1,0016 (0,0449)	0,006

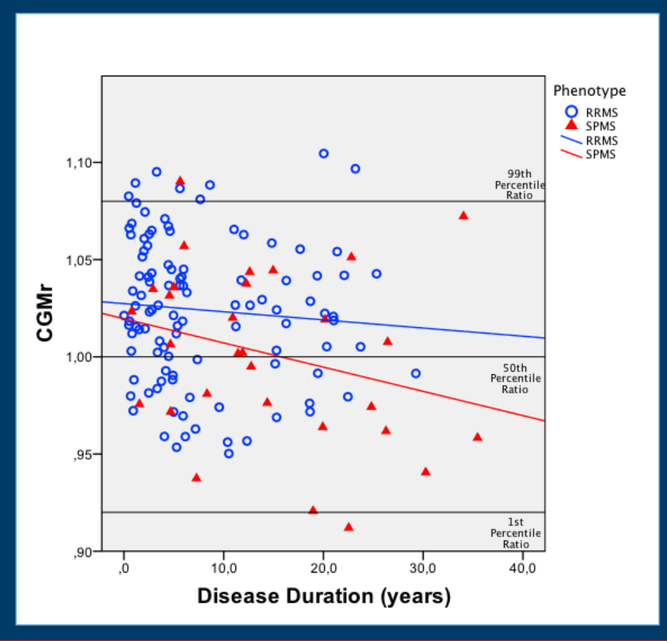
RESULTS: DEEP GREY MATTER RATIO (DGMr)





RESULTS: CORTICAL GREY MATTER RATIO (CGMr)





CONCLUSIONS

- **[I] Cortical Grey Matter normalized ratio's (CGMr) are significantly higher in RRMS compared to SPMS and means are > 1**
- **Deep Grey Matter normalized ratio's (DGMr), do not differ considerably across phenotypes and means are < 1**
- **It is unlikely that differences in CGMr are attributable to active therapy, however, effect of therapy cannot be fully excluded based on these results. It can be argued that active therapy implies more active disease with secondary volumetric effects in its own right**
- **[II] Addition of logCGMr to a predictive model as second covariate to disease duration, significantly increased its accuracy by 30,1% from default**
- **[I] [II] This indicates the potential of cortical volumes to support differentiation of RRMS from SPMS in clinical practice. Future analysis of regional cortical measurements could improve predictive accuracy**

ACCIDENTAL FINDING

- **Mean CGMr's are > 1 in both phenotypes, indicating measured volumes higher than controls. These results could suggest a conceivable pseudo-hypertrophy effect, secondary to cortical inflammation and structural remodelling. This is in sharp contrast to current knowledge of cortical pathology in MS. Repeated quality control of automated segmentations revealed no errors accountable for these findings**

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