Cortical thin-patch-fraction reflects disease burden in multiple sclerosis: the mosaic approach (MAP)

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Supplementary Material

Supplementary Methods

Data pre-processing

The metric of interest in this study was CTh, which we calculated as two-dimensional cortical surface maps using the fully-automated reconstruction pipeline *recon-all* from the software *FreeSurfer* [1–3]. To facilitate data handling and visualization, we converted these data to the CIFTI format using the *Ciftify* package [4], which is based on pre-processing strategies from the Human Connectome Project (HCP) [5,6]. The main output from this pre-processing strategy was a single file for each subject estimating CTh at each of 32k data points ("vertices") per hemisphere (Fig. 1A).

Parcellation-based estimation of individual atrophy

The idea of the here-proposed MAP method is to rate parcelled CTh data for single patients with respect to HC data to estimate signs of atrophy (and hypertrophy). Importantly, given we wanted to probe the utility of MAP using externally acquired reference data, we included HC data from the CamCAN data base into our investigations (see below). Fig. 1 shows the details of the procedure. In brief, we start by parcellating the CTh map for each individual patient (Fig. 1A) into 1000 roughly equally sized "patches" or "mosaics" using a published cortical atlas [7]

(Fig. 1B). Next, we calculated *z*-scores for each patch and subject with respect to age-/sex-matched control groups (see next section), which we then converted into statistical *p*-maps using non-parametric permutation testing such that the resulting *p*-maps were corrected for the family-wise error rate (FWER). Note that we repeated this procedure for both ends of the thickness spectrum, such that we had two p_{FWER} maps reflecting significant "thinning" (suggestive of atrophy) and "thickening" (suggestive of hypertrophy), which can be displayed in one single image (Fig. 1C). We set the alpha-level below which we considered patches significantly different to $p_{FWER} <= 0.05$. Permutation testing was performed within *Matlab R2022b* (The MathWorks, Natick, MA, USA), whereas the exact details have been published before [8–11]. MAP allows to estimate cortical disease burden as a single (normalized) scalar, which is simply the fraction of all "significantly thin (/thick) patches" with respect to all $N = 1000$ patches. This "thin-(/thick-)-patch-fraction" is the metric investigated in this study. Notice that unlike raw CTh values, the TPF is an estimate of the topographical expansion of cortical disease burden: This may be illustrated with an example: Let's take an imaginative patient with atrophy only at one localized "patch" – for simplicity, cortical thinning by exactly 1 mm. Let's also imagine another patient, with localized atrophy at two "patches", 0.5 mm at each patch. Overall mean CTh will be the same for these two patients. However, the TPF of patient 2 will be twice that of patient 1. Therefore, TPF – unlike raw CTh – is sensitive to topographical expansion. In contrast, let's imagine that for patient 1, at a potential follow up, atrophy at the affected patch will further decrease, e.g., by 2 mm. Overall CTh will decrease, the TPF however not, since it is a binary criterion. A higher TPF indicates that more of the cortical surface is affected, lower raw CTh can also indicate further atrophy at one and the same cortical location.

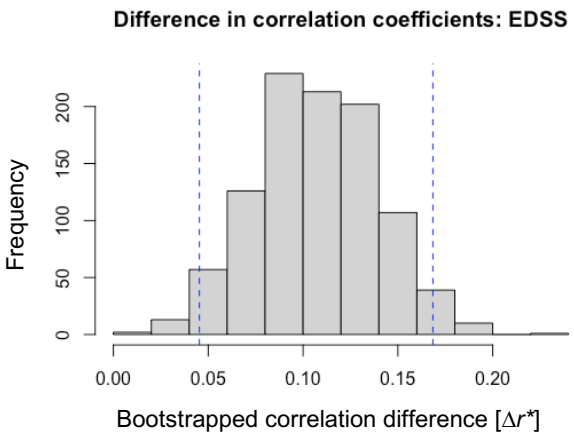
Definition of reference groups

The MAP method rates data patch-wise for individual subjects with respect to age-/sex matched HC groups. As suggested in the original paper [9], we combined HC data from our locally collected cohort in Munich and the CamCAN repository. For each given subject of age *X*, the reference group was selected individually and defined as all HCs from the combined Munich/CamCAN data set aged between $[X–2; X + 2]$, separately for males and females. For example, the reference group for a 40-year-old female MS patient comprises all females between 38 and 42 years from the collapsed Munich / CamCAN data set. This approach was shown to successfully correct for confounding effects of age and gender in the original publication.

Definition of super-ROIs

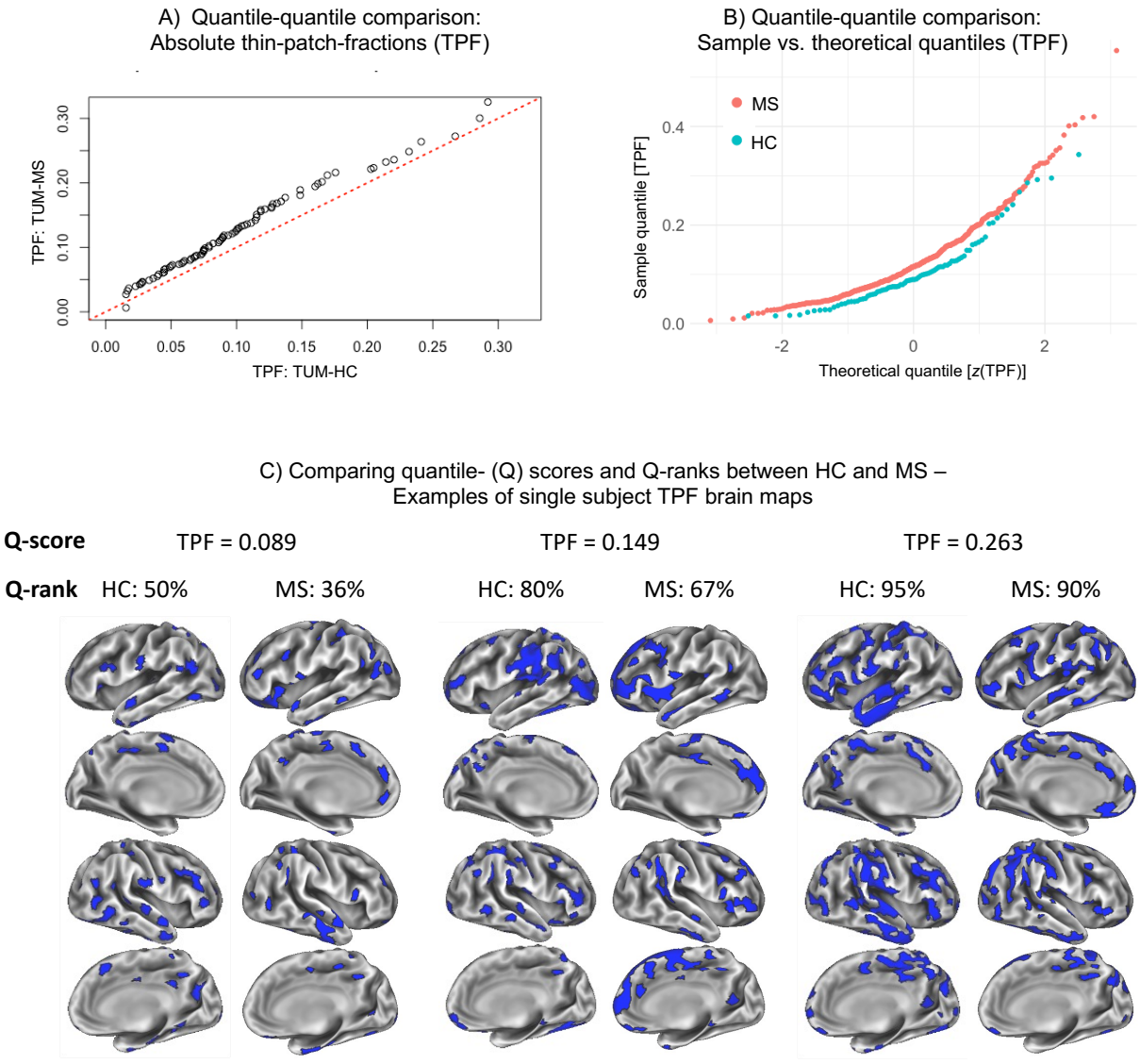
The primary outcome-measure of MAP is the TPF, which is an estimate of whole-brain cortical disease burden. However, it also allows for regional estimation of disease burden [10]. For example, instead of calculating the fraction of significantly thin patches across the entire cortex, one can only consider the TPF from a certain lobe or brain area (Fig. 5B), such as the motor (red), frontal (purple), parietal (yellow), insular (light blue), temporal (green) and visual (dark blue) cortices. One way to estimate such "super-ROIs" is by overlaying the here-used high-resolution parcellation scheme (N = 1000) on the Desikan-Killiany atlas [12], which provides a coarse but anatomically-labelled surface-based parcellation scheme of N = 34 parcels per hemisphere. With this information, estimates of atrophy (hypertrophy) can be individually and regionally displayed, e.g. using spider plots, such in Fig. 5C. Following this strategy, the total number of patches per super-ROI were as follows: 1) motor: N_{patches} = 140, 2) frontal: N_{patches} = 214), 3) parietal: N_{patches} = 187, 4) insular: N_{patches} = 54, 5) temporal: N_{patches} = 151), and 6) visual: N_{patches} = 140.

Supplementary Figure 1



SUPPLEMENTARY FIG. 1: We compared the differences in correlation coefficients between the EDSS score and the mosaic approach (MAP) vs. the EDSS and the standard approach using bootstrapping. This histogram shows the observed differences computed on 999 bootstrap replicates [Δr^*]. Dashed blue lines show the empirical 95% confidence interval (CI). Note that the CI does not include $\Delta r^* = 0.00$ which suggests a significant difference between the two approach's performances

Supplementary Figure 2



SUPPLEMENTARY FIG. 2. To estimate effects of the different origins of the healthy control groups (HC), we compared quantiles (Q) between TUM-HC and TUM-MS: TPF fractions were consistently higher in MS (notice deviation of observed Q-scores towards MS in (A) and elevation of MS Q-ranks vs. HC Q-ranks in QQ-plot in (B)). Moreover, we calculated the Q-scores for the 50%, 80% and 95% quantiles in the HC group and calculated the corresponding Q-ranks in the MS group (C). Additionally, we provide single-subject examples of TPF brain maps for each quantile.

Supplementary Table 1

Supplementary Table 1. Statistical details of the validation procedures for the here-proposed biomarker, the "mosaic approach" (parcelled CTh rated with respect to a control group), to for individual assessment of atrophy, and comparisons with the "standard approach", i.e. unparcelled CTh.

	One-way ANOVA (omnibus test, main effect: "*clinical variable*")					
Clinical associations						
	Standard approach: CTh		**Mosaic approach: Thin-patch-fraction**			
	Estimate	*t*-value	Estimate	*t*-value	Estimate	*t*-value
EDSS	-1.166	-1.510	0.132	2.10e-3	2.439	**0.0151***
Cognition (*MuSIC"*)	5.102	2.247	**0.025***	-5.36e-3	-2.114	**0.0350***
Fatigue (*MuSIC"*)	-5.804	-2.067	**0.039***	7.53e-3	2.399	**0.0168***
Lesion volume	-40.45	-8.953	**<.001****	0.0514	10.86	**<.001****

Differentiation between MS patients and controls									
	Standard approach			**Mosaic approach: Thin patches**			**Mosaic approach: Thick patches**		
	Estimate	*t*-value	*p*-value	Estimate	*t*-value	*p*-value	Estimate	*t*-value	*p*-value
	0.042	4.812	**<.001****	-21.92	-2.659	**0.008***	6.496	3.174	**0.002***

Differentiation between MS clinical phenotypes						
	Standard approach		**Mosaic approach: Thin patches**		**Mosaic approach: Thick patches**	
	F-value (DOF), *p*-value	Significant pairwise contrasts (post-hoc) [*p*-value]	*F*-value (DOF), *p*-value	Significant pairwise contrasts (post-hoc) [*p*-value]	*F*-value (DOF), *p*-value	Significant pairwise contrasts (post-hoc) [*p*-value]
	$F(4,564) = 35.24$, $p<.001$*	- RRMS – HC [$p_{adj} < .001$] - PMS – HC [$p_{adj} < .001$] - PMS – CIS [$p_{adj} < .001$] - PMS – RRMS [$p_{adj} < .001$] - RRMS – CIS [$p_{adj} = .002$]	$F(4,558) = 13.84$, $p<.001$*	- RRMS – HC [$p_{adj} < .001$] - PMS – HC [$p_{adj} < .001$] - PMS – CIS [$p_{adj} < .001$] - PMS – RRMS [$p_{adj} < .001$]	$F(4,558) = 7.663$, $p<.001$*	- RRMS – HC [$p_{adj} < .001$] - PMS – HC [$p_{adj} = .009$]

Statistics are provided for the main effect the respective independent variable between the MS patients / HC groups in a one-way ANOVA omnibus test, which was corrected for confounding effects of age, sex, and lesion volume (except for the association with "lesion volme"). When the overall ANOVA omnibus test was significant, we proceeded with post-hoc testing to identify significant pairwise contrasts using Tukey's HSD tests, which we provide in this table (we report only significant contrasts; notice that the resulting *p*-values in Tukey's HSD tests are corrected for family-wise error rate, which we indicate as "p_{adj}").

Abbreviations/Symbols: adj = adjusted, ANOVA = analysis of variance, CIS = clinically isolated syndrome, CTh = cortical thickness, DOF = degrees of freedom, EDSS = Expanded Disability Status Scale, HC = healthy control, HSD = honest significant difference, MAP = mosaic approach, MUSIC = MS Inventory of Cognition, MS = multiple sclerosis, PMS = progressive MS, RRMS = relapsing-remitting MS, " * " = significant at an alpha-level of $p <= 0.05$, " ** " at an alpha-level of $p <= .001$

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