Quantitative MRI maps of human neocortex explored using cell-specific gene expression analysis

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Introduction

- Multiparameter mapping (MPM) protocols allow rapid acquisition of quantitative MR parameters sensitive to macromolecular content – R_1 and MT saturation (MTsat) – and R_2^*, a marker for iron and macromolecular content [1].
- Using these parameters, we can make in vivo microstructural inferences about the brain [1,2,3].
- We investigated the relationship of quantitative MPM parameters (MPMs) to regional expression of cell-specific genes in human neocortex.
- In addition, we explored the spatial distribution of the residuals of a linear model coupling these parameters to learn about their inter-relationships.

Methods

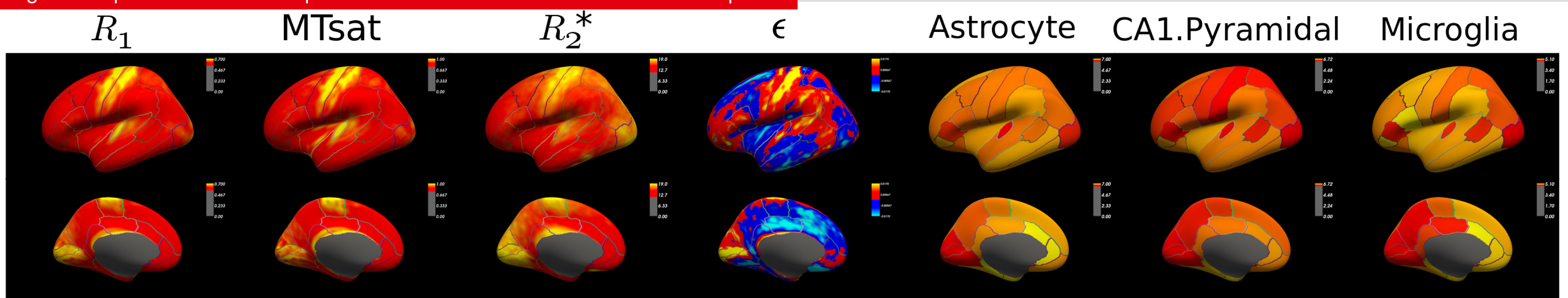
- $800\ \mu\text{m}$ isotropic MPM data [1,2] recorded at $3\ \text{T}$ from 17 healthy subjects, acquired as part of the MEG UK database (`https://meguk.ac.uk/database`), were converted to quantitative maps of R_1, R_2^* and MTsat using the hMRI toolbox (`hmri.info`).
- Cortical surfaces were reconstructed and registered to the average curvature template (fsaverage) using Freesurfer (`http://surfer.nmr.mgh.harvard.edu`); MPM values were mapped onto the surface using values at 50% of estimated vertexwise cortical depth and surface-smoothed with a $6\ \text{mm}$ full-width half-maximum (FWHM) kernel.
- Surface-mapped parameters were fit to the biologically informed linear model [1]

$$R_1 = \beta_0 + \beta_1 \text{MTsat} + \beta_2 R_2^* + \epsilon,$$

with fit residual ϵ, in each subject and hemisphere. A spatial dependence of ϵ could give further insight into the spatial dependence of parameters/cell types.
- Each parameter/ϵ was averaged over all subjects vertexwise, then averaged within each parcellation unit of the Desikan–Killiany (DK) atlas [4].
- The mapping of the Allen Institute of Brain Science (AIBS) transcriptome Atlas [5] into the DK atlas [6] was used.
- Only left hemisphere data are presented, as right hemisphere data are not available for all AIBS participants.
- Parameter–gene set association was assessed using a resampling approach [8,9]. This tested association with cell-specific genes relative to permutations of random gene sets of equal size from a reference gene panel, with statistical significance for each comparison set at a false-discovery-rate (FDR) corrected $p < 0.05$.
- Cell-specific gene sets were obtained from Zeisel, et al. [7].

Results

Figure 1: Spatial distribution of parameters and residuals over the left hemisphere



Spatial distribution of MPMs (R_1, R_2^*, and MTsat) and linear model residuals (ϵ) in the left hemisphere averaged over all subjects, alongside the spatial distribution of the mean of the significantly correlated gene expression sets (Table 1). Overlaid lines show the boundaries of the Desikan–Killiany atlas.

- Cell-specific gene expression analysis (Table 1) showed the distribution of R_1, R_2^*, and MTsat (Figure 1) corresponded to astrocyte and CA1-pyramidal neuron (a marker of neuronal plasticity [9]) gene expression.
- R_2^* is also correlated with microglia; because microglia are iron rich, this supports the interpretation of R_2^* as an iron-proxy [3].
- Fitted linear model parameters over the cortical surface were similar – but not identical – to those found by Callaghan, et al. [1] over the whole brain; mean fitted parameter $\pm$ standard deviation over all subjects:

$$\beta_0 = 0.2396 \pm 0.0388\ \text{s}^{-1}; \beta_1 = 0.2954 \pm 0.0396\ (\text{p.u.})^{-1}\text{s}^{-1};$$

$$\beta_2 = 0.0079 \pm 0.0017.$$

- The residuals, ϵ, showed spatial coherence (Figure 1) corresponding to the distribution of genes associated with astrocytes and CA1-pyramidal neurons (Table 1); Figure 1 shows that this correspondence is not due simply to the residuals scaling with the parameter magnitudes.

Table 1: Correlation parameters from correlation of MPMs and ϵ with gene sets

cell type	number of genes	R_1		MTsat		R_2^*		ϵ	
		r	p	r	p	r	p	r	p
Astrocyte	54	-0.32	0.0013	-0.25	0.0022	-0.32	0.0027	-0.21	0.0004
CA1.Pyramidal	103	-0.28	0.0009	-0.22	0.0009	-0.28	0.0009	-0.20	0.0004
Endothelial	57	0.11	0.2940	0.10	0.2327	0.12	0.2405	0.03	0.7578
Ependymal	84	-0.09	0.2940	-0.06	0.3661	-0.10	0.2405	-0.06	0.4074
Interneuron	100	-0.02	0.6979	-0.03	0.5826	-0.02	0.8029	-0.02	0.7578
Microglia	48	-0.20	0.0810	-0.14	0.1845	-0.25	0.0267	-0.09	0.3243
Mural	25	-0.10	0.5041	-0.06	0.5826	-0.11	0.4848	-0.08	0.5288
Oligodendrocyte	60	0.12	0.2940	0.11	0.1966	0.14	0.2322	0.02	0.7578
S1.Pyramidal	73	0.08	0.3492	0.05	0.4761	0.11	0.2405	0.01	0.8357

Correlation coefficients (r) and FDR-corrected p-values from the correlation of MPMs (R_1, R_2^*, and MTsat) and linear model residuals (ϵ) with non-overlapping gene sets associated with different cell types in the brain. Statistically significant correlations ($p < 0.05$) are in red.

Discussion and Conclusion

- The correlations between MPMs and gene expression presented above allow us to make several inferences.
- Several studies have shown that in primary areas R_1 and R_2^* correlate with myelination [3]; oligodendrocyte correlation might thus be expected. The observed correlations however support the hypothesis of Patel, et al. [8] that quantitative parameters are more sensitive to dendrite proliferation over the cortex.
- The preserved correlations in ϵ imply a difference in the relationship between astrocyte density and neuronal plasticity in motor and sensory regions as compared to elsewhere in cortex, perhaps due to vasculature, dendrite proliferation, or myelin regulation differences in those early developing cortical regions [3,10].
- The correlations between gene markers of cell types and MPMs in cortex, along with preservation of these relationships in a biologically informed linear model relating the parameters, allow greater insight into the origin of MR contrast and the interrelationship of different cell types in the cortex.

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