# 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 including R1 and MT saturation (MTsat), markers of macromolecular content, and R2*, a marker for iron and macromolecular content[1]. These parameters allow microstructural inferences to be made about the brain in vivo[1,2,3]. This project investigated the relationship of MPM parameters to regional expression of cell-specific genes in human neocortex, enhanced by exploring the spatial distribution of the residuals of a linear model of these parameters.

## Methods:

800 µm isotropic data recorded at 3T following a similar multiparameter mapping protocol to [1,2] from 17 healthy subjects, acquired as part of the MEG UK database (https://meguk.ac.uk /database), were converted to MPM maps of R1, R2* 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 mm FWHM kernel.

Surface-mapped parameters were fit to the biologically informed linear model of [1], R1 = a + b.MTsat + c.R2* + ε, with fit residual ε, in each subject and hemisphere. If the model parameters are universal in cortex, ε would be randomly distributed; ε otherwise gives 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. Cell-specific gene sets were obtained from [7].

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. Statistical significance for each comparison was set at false-discovery-rate (FDR) corrected $p < 0.05$.

## Results:

Cell-specific gene expression analysis (Table 1) showed the distribution of R1, R2* and MTsat (Figure 1) corresponded to astrocyte and CA1-pyramidal neuron (a marker of neuronal plasticity[9]) gene expression. Several studies have shown that in primary areas R1 and R2* correlate with myelination[3]; oligodendrocyte correlation might thus be expected. The observed correlations however support the hypothesis of [8] that quantitative parameters are more sensitive to dendritic proliferation over the cortex. R2* correlated with microglia as well, supporting its iron-proxy interpretation, as microglia are iron rich[3].

Fitted linear model parameters over the cortical surface were similar but not identical to those found in [1] over the whole brain (Table 1). ε showed spatial coherence (Figure 1): large positive ε corresponded to motor and sensory regions, while large negative ε largely corresponded to regions afflicted with physiological artefacts/low signal. Figure 1 also shows ε did not simply scale with the parameter magnitudes. The ε distribution also corresponded to the distribution of genes associated with astrocytes and CA1-pyramidal neurons (Table 1). 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/dendritic proliferation differences in those early developing cortical regions[3].

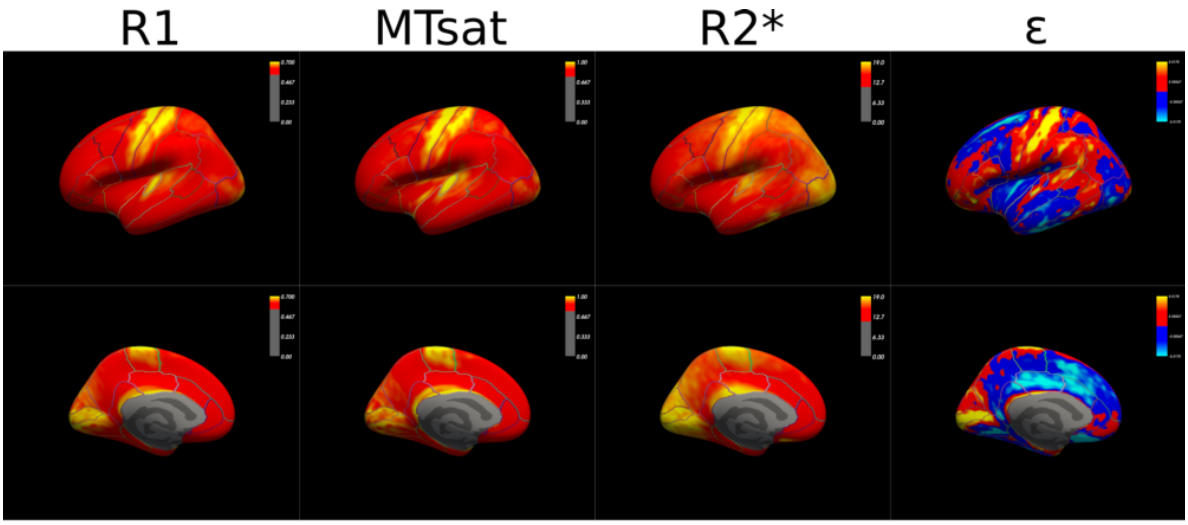


Figure 1: Spatial distribution of quantitative parameters and linear model residuals (ε) in the left hemisphere averaged over all subjects. Overlaid lines show the boundaries of the Desikan–Killiany atlas.

**A**

| cell type | number of genes | R1 avgr | R1 p | R1 fdr.p | MT avgr | MT p | MT fdr.p | R2* avgr | R2* p | R2* fdr.p | ε avgr | ε p | ε fdr.p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Astrocyte | 54 | -0.32 | 0.0003 | ***0.0013*** | -0.25 | 0.0005 | ***0.0022*** | -0.32 | 0.0006 | ***0.0027*** | -0.21 | 0.0001 | ***0.0004*** |
| CA1.Pyramidal | 103 | -0.28 | 0.0001 | ***0.0009*** | -0.22 | 0.0001 | ***0.0009*** | -0.28 | 0.0001 | ***0.0009*** | -0.20 | 0.0001 | ***0.0004*** |
| Endothelial | 57 | 0.11 | 0.1890 | 0.2940 | 0.10 | 0.1293 | 0.2327 | 0.12 | 0.1850 | 0.2405 | 0.03 | 0.5342 | 0.7578 |
| Ependymal | 84 | -0.09 | 0.1960 | 0.2940 | -0.06 | 0.2441 | 0.3661 | -0.10 | 0.1871 | 0.2405 | -0.06 | 0.1811 | 0.4074 |
| Interneuron | 100 | -0.02 | 0.6979 | 0.6979 | -0.03 | 0.5826 | 0.5826 | -0.02 | 0.8029 | 0.8029 | -0.02 | 0.6736 | 0.7578 |
| Microglia | 48 | -0.20 | 0.0270 | 0.0810 | -0.14 | 0.0615 | 0.1845 | -0.25 | 0.0089 | ***0.0267*** | -0.09 | 0.1081 | 0.3243 |
| Mural | 25 | -0.10 | 0.4481 | 0.5041 | -0.06 | 0.5533 | 0.5826 | -0.11 | 0.4310 | 0.4848 | -0.08 | 0.2938 | 0.5288 |
| Oligodendrocyte | 60 | 0.12 | 0.1380 | 0.2940 | 0.11 | 0.0874 | 0.1966 | 0.14 | 0.1032 | 0.2322 | 0.02 | 0.6616 | 0.7578 |
| S1.Pyramidal | 73 | 0.08 | 0.2716 | 0.3492 | 0.05 | 0.3703 | 0.4761 | 0.11 | 0.1363 | 0.2405 | 0.01 | 0.8357 | 0.8357 |

**B**

| parameter | mean | standard deviation |
|---|---|---|
| a | 0.2396 | 0.0388 |
| b | 0.2954 | 0.0396 |
| c | 0.0079 | 0.0017 |

**Table 1: A.** Correlation coefficients (avgr), p values (p), and FDR-corrected p-values (fdr.p) from the correlation of the MPM maps and linear model residuals (ε) with non-overlapping gene sets associated with different cell types in the brain. Statistically significant correlations (where fdr.p < 0.05) are bold and underlined. **B.** Fitted parameters of the linear model R1 = a.MT + b.R2* + c. They are similar but not identical to those found in Callaghan, et al. (2015) over the whole brain.

## Conclusions:

The correlations between gene markers of cell types and MPM parameters 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.

## Genetics:

Genetic Association Studies [2]

## Imaging Methods:

Anatomical MRI
Multi-Modal Imaging

## Neuroanatomy:

Cortical Anatomy and Brain Mapping [1]
Cortical Cyto- and Myeloarchitecture

**Keywords:**

Astrocyte
Cellular
Cortex
Data analysis
Glia
Modeling
Myelin
Neuron
Plasticity
STRUCTURAL MRI

[1|2]Indicates the priority used for review

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