The molecular fingerprint of the CEST signal

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INTRODUCTION:

Chemical exchange saturation transfer (CEST) MRI allows non-invasive imaging of low-concentrated metabolites in the brain. Although these metabolites have been associated with broad brain molecular sources, e.g., peptides or proteins, further molecular characterization is still missing, especially in healthy subjects. Here, we characterized the cortical distribution of six CEST contrast maps with various microscopic and macroscopic aspects of brain organization.

METHODS:

Fourteen healthy participants (6 female; age range: 21 – 46 y) underwent a comprehensive 7 T CEST protocol (1-3) on a Siemens MAGNETOM Terra.X 7 T scanner using a Nova Medical 32Rx/8Tx-channel head coil. Additionally, an anatomical MP2RAGE T1 and a 10-minute functional resting MRI data were acquired. The comprehensive CEST maps were derived analytically, except for the slow-exchanging metabolites, which were predicted as Lorentzian amplitude maps by the deepCEST network (4). The six CEST contrast maps and the degree of functional connectivity (dFC) were gray-matter masked, converted to Z-scores, and parcellated using the Glasser brain atlas (5) using as reference the Yeo brain functional networks (6), a normative brain atlas widely used in neuroimaging. We modeled each average CEST contrast map as a function of 26 molecular markers related to cortical lamination, cellular types, and subcellular compartments, derived from cortical expression maps using a multiple linear model. The relative contribution of each molecular marker to the modeled CEST map was assessed using a dominance analysis (7), identifying the markers that contribute most to the linear fit. The cortical expression maps were derived from the Allen Human Brain Atlas (AHBA)(8) and the multiscale atlas of gene expression for integrative cortical cartography (MAGICC)(9).

RESULTS:

We derived a unique average map across participants for each CEST contrast map (Fig 1A, brain surface maps), which were significantly different between them ($p < 0.01$ Wilcoxon rank-sum test, FDR-corrected; Fig. 1A, polar plots). Interestingly, the control and visual networks show the lowest ranks in almost all CEST maps. As a reference, the fMRI map shows its typical distribution, with the sensory-motor networks (Vis & SomMot) having lower ranks than the higher cognitive ones. The molecular markers distributions explain a statistically significant amount of variance across the CEST contrast maps ($p < 0.05$; $21\% \leq$ adjusted variance $\leq 38\%$). The dominance analysis in Fig. 1B shows that for neuron type markers, excitatory (Ex) contributes more to the guanidine and amine maps, whereas the inhibitory (In) contributes more to the remaining maps. The endothelial cells (End) contribute largely to the fit across all CEST contrast maps for cell type markers, whereas the microglia (Mic) do it for amine, OH and ssMT. For subcellular compartments, the intracellular compartments (cytoskeleton, cytosol, nucleus) contribute to all CEST contrast maps. Furthermore, the amine also has a large contribution from the extracellular compartment. Finally, the markers for protein-protein interactions (PPIs) contributed similarly to all CEST maps, especially the ssMT map (2x).

DISCUSSION:

We observe a unique cortical distribution for each CEST contrast map in healthy participants with different associations across functional brain networks and different micro- and macro-molecular fingerprints. These fingerprints could highlight molecular differences between subcellular compartments, e.g., intra- vs. extra-cellular, neuron type, inhibitory vs. excitatory or cellular types, endothelial vs. microglia, the latter altered in different neurodegenerative diseases (10).

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