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Whole-brain neuronal MCT2 lactate transporter expression links metabolism to human brain structure and function

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Brain activity is constrained by local availability of chemical energy, which is generated through compartmentalized metabolic processes. By analyzing data of whole human brain gene expression, we characterize the spatial distribution of seven glucose and monocarboxylate membrane transporters that mediate astrocyte–neuron lactate shuttle transfer of energy. We found that the gene coding for neuronal MCT2 is the only gene enriched in cerebral cortex where its abundance is inversely correlated with cortical thickness. Coexpression network analysis revealed that MCT2 was the only gene participating in an organized gene cluster enriched in K^+ dynamics. Indeed, the expression of K_{ATP} subunits, which mediate lactate increases with spiking activity, is spatially coupled to MCT2 distribution. Notably, MCT2 expression correlated with fluorodeoxyglucose positron emission tomography task-dependent glucose utilization. Finally, the MCT2 messenger RNA gradient closely overlaps with functional MRI brain regions associated with attention, arousal, and stress. Our results highlight neuronal MCT2 lactate transporter as a key component of the cross-talk between astrocytes and neurons and a link between metabolism, cortical structure, and state-dependent brain function.

ANLS | brain metabolism | gene expression | monocarboxylate transporters | cognition

Until recently, the prevailing wisdom was that glucose is the primary substrate for neuronal ATP production, while lactate was a waste product of fast ATP production through aerobic glycolysis. However, strong evidence supports that neuronal activity is fueled by activity-dependent lactate transfer from astrocytes, known as the astrocyte–neuron lactate shuttle (ANLS) hypothesis (1). This model proposes that the energetic requirements triggered by neuronal activity enhance astrocytic glucose uptake and glycolytic metabolism to ultimately produce and transfer lactate to the neuron for ATP production. ANLS-related transport requires glucose uptake by the astrocytes through GLUT1 transporter as well as astrocytic monocarboxylate transporters MCT1 and MCT4 to deliver lactate to the neuron, which in turn uptakes it through neuronal MCT2 (2). In contrast, the direct neuronal glucose uptake depends on GLUT2–4 transporters (3). The relative contribution of these different supply modes for brain structure and functional brain activity is still controversial.

Brain areas containing hundreds of millions of neurons differ from each other by their structural and functional attributes (4). Gene expression profiles underlie the configuration of local neural circuits and the local metabolic network, determining how signals are generated, transmitted, and integrated throughout the brain. Thus, the expression of genes—whose products are needed for the transfer of energy-relevant molecules between brain cells—might shape local energetic load into macroscale networks that could have a causal role in defining systems-level brain function.

We addressed these issues analyzing a dataset of human whole-brain gene expression, focusing on glucose and lactate transporters. Our main finding is that there is a strong correlation between the function and structure of the human brain and the expression of the neuronal MCT2 lactate transporter, but not with any of the glucose transporters or other MCTs.

Results

We mapped metabolic transporters gene expression by analyzing data from the Allen Human Brain Atlas (Fig. 1*A*). Expression data were segmented into cortical and subcortical areas for each analyzed transporter expression. Surprisingly, we found that only messenger RNA (mRNA) expression for the neuronal MCT2 transporter is enriched in the cortex, while the rest of the genes show no or even negative enrichment (Fig. 1*B*).

Genes tends to follow organized patterns of coexpression modules. We identified modules by analyzing the similarity of expression between pairs of genes across a set of

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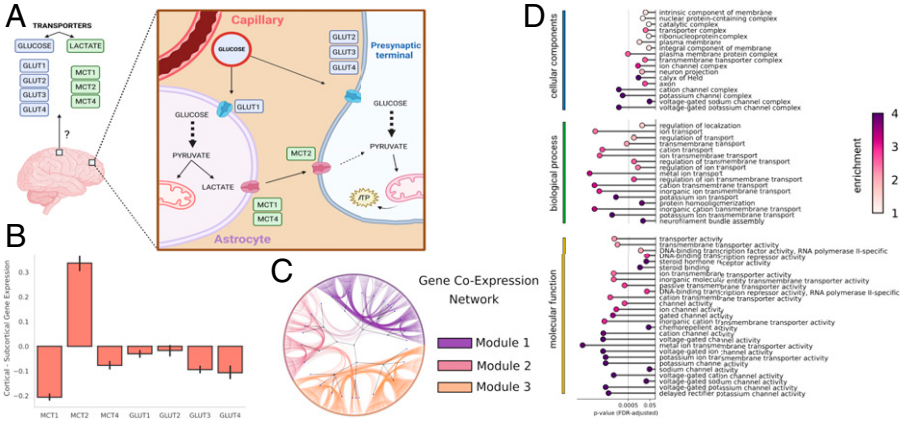

Fig. 1. Characterizing the distribution of metabolic transporters expression using human brain microarray data. (*A*) Illustration showing two energetic supply modes. The uptake of glucose from blood vessels in astrocytes and neurons is facilitated by GLUT transporters, diverging in a direct and a lactate shuttling path. In astrocytes, after conversion from pyruvate, lactate is shuttled into the neuron through MCT transporters. (*B*) Difference between cortical and subcortical gene expression for each transporter. Positive values represent higher cortical expression and negative values a higher subcortical expression. (*C*) Gene coexpression network clustered by gene interactions. Each node represents genes colored by the participating module. In the center, the plot shows hierarchical branches of the communities. (*D*) Gene Ontology enrichment analysis of the module 2 gene list. The "matchstick" graph's *x* axis is the corrected P value of each term (FDR $\alpha = 0.05$).

predefined cortical regions (Fig. 1*C*). The only gene of the seven analyzed that participated in a module was MCT2 (module 2). Gene Ontology enrichment analysis of this module show that genes that shared community with MCT2 are preferentially related to ion transport and voltage-gated channel activity, particularly for the K^+ ion (Fig. 1*D*). These channels are known to be involved in the control of neuronal firing (5).

To assess whether the expression of ANLS transporters varies spatially with structural and functional gradients, we segmented gene maps by functional brain networks. Only MCT2 showed substantial heterogeneity, which tracked a sensory-to-association gradient (Fig. 2*A*). To capture the contribution of ANLS transporters independent of the anatomical hierarchy of the brain, we regressed out the T1w/T2w gradient (Fig. 2*B*), which is considered a surrogate measure of cortical hierarchy (4). We then compared the hierarchy-corrected transporters expression with microcircuit structural properties, such as the cortical thickness. The only transporter that significantly interacted with cortical thickness was MCT2 (rho $= -0.46$, $p_{RAW} = 2.21^{-22}$, $p_{SPIN} = 0.004$; Fig. 2*B*).

Lactate-mediated modulation of neuronal activity in the cerebral cortex depends on K_{ATP} channels (5). To test whether these channels were spatially consistent with MCT2 transport in the human brain, we analyzed the expression of ABCC8 and KCNJ11 K_{ATP} channel subunits. After correction for cortical hierarchy, we observed that both K_{ATP} channel expression positively correlated with the corrected MCT2 expression (ABCC8: rho $= 0.48$, $p_{RAW} = 1.29^{-24}$, $p_{SPIN} = 0.0001$; KCNJ11: rho $= 0.54$, $p_{RAW} = 5.69^{-32}$, $p_{SPIN} = 0.0033$; Fig. 2*C*). Next, we explore the lactate over glucose preference as an energy substrate for basal metabolic measures and activity-dependent metabolism. We found no significant correlation between MCT2 expression and basal metabolic measures, such as resting glucose uptake (rho $= 0.11$, $p_{RAW} = 0.03$, $p_{SPIN} = 0.38$) or aerobic glycolytic index (rho $= 0.07$, $p_{RAW} = 0.149$, $p_{SPIN} = 0.78$) (6). In contrast, MCT2 expression significantly correlated with functional glucose uptake contrast of easy/hard cognitive task (rho $= 0.32$, $p_{RAW} = 4.59^{-11}$, $p_{SPIN} = 0.057$; Fig. 2*C*), suggesting that brain areas with a state-dependent increase of glucose uptake tend to correspond with higher lactate transport dynamics.

To test whether the observed MCT2 mRNA expression gradient is related to functional activation patterns of psychological processes, we used neurosynth probability maps for multiple psychological terms, correlating "term" maps with each corrected transporter expression map (false discovery rate [FDR]-corrected $\alpha = 0.05$). Only MCT2 was significantly correlated with cognitive terms. Interestingly, corrected MCT2 expression associated positively with attentional terms, while internal states related to arousal, stress, and emotion had a negative correlation (Fig. 2*D*). The latter shows that higher MCT2 expression is not the necessary and trivial result of stronger neuronal dosage/activity but informs about specific neural states. These results are consistent with a state-dependent trigger of lactate release from astrocytes (7).

Discussion

Cognition operates at multiple temporal domains, which require both basal energy for maintaining global brain states as well as rapid energy supply to cater for ever-changing environmental demand. The functional role of cerebral lactate has recently been highlighted as fundamental in neuron–glia metabolic cooperation regulating energy supply in an activity-dependent manner. Although previous work has shown a lactate topography in human (8) and *Drosophila* (9) brain, we extend this to a human whole-brain scale focusing on the spatial gene expression fingerprint of ANLS transporters. Our results highlight that a lactate shuttle by MCT2, and not a direct glucose pathway, stands out as the most relevant transporter in relation to cortical structure and functional brain organization. This is consistent with in vivo evidence that brain functioning prefers lactate over glucose use (10). mRNA expression is not always related to protein expression in a one-to-one fashion. MCT2 protein can be regulated at the translational level by noradrenaline (11) or trophic factors (12). MCT2 is found both in the intracellular pool and the cell surface, and the distribution between these different compartments can be regulated by activity-related signals, making MCT2 protein availability a consequence of plasticity (13). Thus, mRNA and MCT2 protein could reach different levels of correspondence, from a tight overlap when energy meets neural activation or loose at stages of age-related hypometabolism. Our results also show an inverse relation between MCT2 expression and cortical thickness, an indirect measure of neuronal density. Cortical thickness follows a gradient that closely associates with neural timescale, where the increased thickness is related to high-order association areas

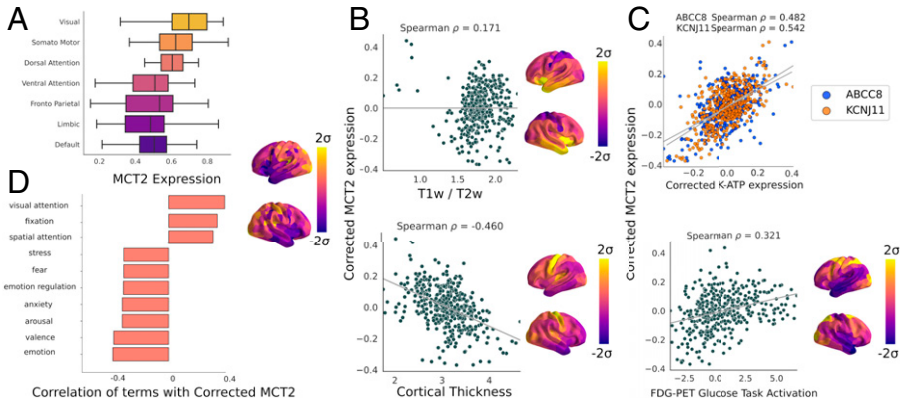

Fig. 2. Functional and structural correlates of ANLS transporters gene expression. (*A*) MCT2 map showing high values in sensory cortical areas relative to association areas. (*Right*) Spatial distribution of MCT2 mRNA expression. (*B*, *Upper*) T1w/T2w gradient is regressed out from gene expression. (*B*, *Lower*) Corrected MCT2 expression correlation with cortical thickness. (*C, Upper*) Corrected MCT2 expression correlated with corrected K_{ATP} subunits expression. (*C*, *Lower*) Corrected MCT2 expression correlated with glucose uptake (fluorodeoxyglucose positron emission tomography) task activation. (*D*) Correlation between corrected MCT2 and neurosynth cognitive probability maps. Bars on the x axis represent Spearman rho after spin permutation test (FDR $\alpha = 0.05$).

with slower timescales, as compared to a fast timescale in sensory cortices (4). High MCT2 expression in thinner areas can be interpreted as the rapid lactate supply required for fast and flexible neuronal firing for sensory activation. MCT2 expression was found to be intimately related to the expression of ATP-dependent potassium channels (K_{ATP}), evidenced both by the enrichment of the MCT2 gene coexpression module and by the spatial correlation with K_{ATP} subunits, essential for rapid changes in cortical activity (5). We found that MCT2 expression closely overlaps with key cognitive functional MRI activations associated with attention, arousal, and stress. This is consistent with a fine-tuned temporal relation between cortical activity and cellular lactate fluctuation induced by arousal-state changes as measured by pupil diameter (7). We also show that brain areas with higher state-dependent glucose uptake changes tend to correspond to areas with higher MCT2 mRNA expression, independent of basal metabolic measures (6). This is consistent with reports (10) showing in vivo evidence of a lactate concentration–dependent change in glucose utilization; here our lactate proxy is the expression of the transporter. Lack of MCT1/MCT4 mRNA enrichment in MCT2-rich areas supports the observation that the release of astrocytic lactate in response to neural activity may be primarily mediated by a mechanism involving a lactate channel activated by extracellular K^+ (14). Indeed, knock-down of MCT4 perturbs local reactive hyperemia in the somatosensory cortex induced by whisker stimulation only in half of the animals tested, while it is abolished in the majority of MCT2 knock-down animals (15). The cognitive, functional, and structural relevance of MCT2 in the metabolism of the human cortex underscores the need for studies analyzing the role of this transporter in brain physiological and pathological brain processes.

Materials and Methods

All data used are open-access and thus comply with ethics regulations. Spearman rank-order correlation coefficients were used for statistical correlations. Extended methods and source data are in *SI Appendix*.

Data Availability. All study data are included in the article and/or supporting information.

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