

NEUROVASCULAR DECOUPLING LINKS METABOLIC DEMAND TO CORTICAL SPREADING DEPOLARIZATION SUSCEPTIBILITY IN MIGRAINE WITH AURA

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Background. Although neuroimaging investigations have consistently demonstrated that "hyperresponsive" and "hyperconnected" visual cortices may represent the functional substrate of cortical spreading depolarization (CSD) in patients with migraine with aura (MwA), the mechanisms underpinning the brain "tendency" to ignite the cortical spreading depolarization and, consequently, aura phenomenon are still matter of debate. Considering that triggers able to induce aura phenomenon constrain brain to increase global (such as physical activity, stressors and sleep abnormalities) or local (such as bright light visual stimulations) energy demand, a vascular supply unable to satisfy the increased energy requirement could be hypothesized in these patients.

Methods. Forty patients with MwA (21 simple visual MwA, 19 complex MwA), 30 patients with migraine without aura (MwoA), and 22 healthy controls (HC) underwent multimodal 3T MRI during the interictal period, including resting-state functional MRI and multi-delay arterial spin labeling. Regional NVC was estimated by computing the correlation coefficient between z-scored regional homogeneity (ReHo) maps from resting-state blood oxygen level dependent signals and z-scored cerebral blood flow (CBF) maps from multi-delay arterial spin labeling signals.

Results. Voxel-wise analysis of CBF maps revealed that patients with MwA as a whole group showed a significant CBF increase in multiple regions encompassing the visual network (along the fusiform and lingual giri), compared with both patients with MwoA and HC ($p<0.05$, TFCE corrected). Furthermore, applying the cortical parcellation to both CBF and ReHo z-normalized maps, we found a reduced NVC at the VIS-4 and VIS-5 left parcels (within the visual network) in patients with both svMwA and cMwA compared with both patients with MwoA and HC (respectively $p=0.040$ and $p=0.025$, FDR corrected).

Conclusions. The coexistence of increased perfusion and reduced NVC in the visual cortex of patients with MwA may indicate that, although more blood is available overall, it is not optimally distributed according to local functional requirements. The dysregulated or inefficient allocation of CBF relative to locally coordinated neural dynamics (neurovascular "decoupling") may represent a critical pathophysiological element linking the exposure to trigger factors for MwA (associated with further increases in brain metabolic demand) and the ignition of CSD.