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Letter to the Editor

Before Concluding that SLEs in MELAS Alter Functional Connectivity, All Factors Affecting Connectome Gradients must be Considered

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Letter to the Editor

We read with interest the article by Wang *et al*. on whether the network hierarchy reflected in the functional gradient structure is disrupted in patients with mitochondrial encephalopathy, lactate acidosis, and stroke-like episodes (MELAS) with stroke-like episodes (SLEs) and how SLEs are modulated by gene expression [1]. MELAS patients with SLEs showed a reduced gradient range and lower gradient variation, and exhibited lower gradient values in the default mode network, but higher values in the ventral attention network and the sensorimotor network [1]. The study is interesting, but some ambiguities still need to be clarified.

The first point is that stroke-like lesions (SLLs), the morphological equivalent of SLEs, are not a static phenomenon, but undergo typical dynamic changes over time. After their onset, SLLs increase in size and intensity until they reach a maximum, then regress in extent and reach a stage where they are either no longer visible at all or end up as white matter lesions, cysts, focal atrophy, laminar cortical necrosis, or toenail sign [2]. It is therefore crucial to know at what stage of SLL the fMRI was performed. The values of functional connectivity in fMRI depend heavily on the stage of SLL at which the examination was performed.

The second point is that SLLs do not occur in the same location in the brain in every MELAS patient, but rather in different areas, even infratentorially. There may even be patients who develop SLLs in different locations in the brain at the same time [3]. Different localizations of SLLs have different effects on the hierarchy of network organization and alter functional connectivity in low-dimensional space at the individual level, making it difficult to form homogeneous groups and compare patients with each other.

The third point is that heteroplasmy rates vary in different brain regions [4]. Since heteroplasmy rates determine the phenotype, functional connectivity is highly dependent on the composition of different heteroplasmy rates in the brain region under investigation. Functional connectivity may also depend on mtDNA copy number and haplogroup, which are other key characteristics that determine the phenotype and were not included in the analysis.

The fourth point is that a cross-sectional examination of the connectome will not reflect the dynamic nature of MELAS. MELAS is generally a clinically and genetically progressive disease. Therefore, fMRI results are highly dependent on the stage of the disease and the distribution of the pathology. More advanced stages of the disease are reflected by a greater disruption of the connectome than a stage at the clinical onset of the disease.

The fifth point is that SLEs are often characterized by paroxysmal activity on the electroencephalogram or even focal or generalized seizures. Since seizures can strongly influence functional connectivity results, it would have been useful to check whether MELAS patients with and without seizures or paroxysmal EEG activity showed different degrees of connectome impairment.

Before concluding that SLEs in MELAS patients with SLEs are characterized by changes in the connectome gradient, all factors that influence functional connectivity must be taken into account.

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