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Connectivity on fMRI in the MELAS brain may strongly depend on heteroplasmy and extension or dynamics of stroke-like lesions

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With interest we read the article by Wang et al. about a resting stage functional MRI (rs-fMRI) study using graph theory analysis of functional connectivity according to the Dos-160 template with 6 functional networks in 22 patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome who presented with an acute (<1 week) stroke-like lesion (SLL) (Wang et al., 2020). This group was compared with 23 MELAS patients who had experienced a chronic SLL 6–8 months before (Wang et al., 2020). It was concluded that network organisation is disturbed in acute more than chronic SLLs, particularly inter- and intra-nodular connections in the default mode network and the fronto-parietal, sensorimotor, occipital, and cerebellar networks (Wang et al., 2020). We have the following comments and concerns

A shortcoming of the study is that heteroplasmy rates of the m.3243A > G variant and mtDNA copy number were not included in the evaluation and correlated with network parameters of functional connectivity. From both genetic parameters it is known that they can influence the phenotype, why it is conceivable that the presented results strongly depend on them.

We do not agree with the notion that MELAS is only due to the variant m.3243A > G in *MT-TL1* (80% of cases), as mentioned in the introduction (Wang et al., 2020). MELAS is genetically heterogeneous and can be due to a number of other mtDNA variants, such as m.3271 T > C (10% of cases) or even variants in nDNA located genes, such as *POLG1* or *BCS1L* (Pia and Lui, 2020).

We do not agree with the statement that hearing loss is a manifestation of a SLL (Wang et al., 2020). Hearing impairment in MELAS is usually due to affection of the cochlea or the *retro*-cochlear acoustic nerve (Xue et al., 2012 Oct 30).

SLLs may not only occur supratentorially but ubiquitously in all supra- and infra-tentorial areas, including the cerebellum, the deep white matter, subcortical grey matter, the spinal cord, and the optic nerve (Finsterer and Aliyev, 2020 May).

SLLs are not only characterised by cortical swelling, subcortical T2-hyperintensity, and cortical DWI hyperintensity, but also by cortical and subcortical T2-, DWI-, and PWI-hyperintensity, hypointensity on OEF-MRI, and hypometabolism on FDG-PET (Finsterer and Aliyev, 2020 May).

The distinction between an acute and chronic stage is artificial. Currently, it is unknown for how long an acute stage can last and when the chronic stage starts. There are SLLs which expand for weeks or months, why it is more apt to talk about expanding and regressing lesions rather than acute or chronic SLLs. SLLs may end up as normal brain tissue, atrophy, cysts, laminar cortical necrosis, white matter lesion, or toenail sign (Finsterer and Aliyev, 2020 May). However, these possible endstages should not be called chronic stage. SLLs may occur one by one in different areas and may show different extension and dynamics.

Since SLL usually affect the white matter as well (Yokoyama et al., 2010 Feb 1), regressing out the white matter for calculations of connectivity, may exclude essential information. Valuable information about connectivity may have been missed by this approach.

The conclusion that graph analysis by rs-fMRI may play a role in predicting the outcome of MELAS is not justified from the provided data. The various different outcomes of SLLs were not assessed and not correlated with rs-fMRI results.

Since SLL may manifest clinically with variable manifestations it would be interesting to know if network parameters differed between the different phenotypes.

Functional connectivity and connection strength within a SLL may vary significantly with the stage, extension, and speed of expansion/regression of the SLL.

Since topological properties of functional networks may be disrupted not only in MELAS, but in a number of other neurological and psychiatric disorder and since SLLs can manifest with psychiatric disease, we should know if ns-fMRI was able to delineate psychiatric disease from

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SLLs.

SLLs are frequently treated with NO-precursors, such as L-arginine or L-citrulline. We should know if disturbed function of nodes improved upon NO-application.

Overall, the appealing study by Wang et al. has a number of limitations, which should be addressed before drawing final conclusions. Functional connectivity should be related to heteroplasmy rates, the white matter should be included in the evaluation, variability of stroke-like episodes should be correlated with network parameters, and expanding SLLs should be compared with regressing SLLs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Statement of ethics

was in accordance if ethical guidelines.

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Author contribution

JF: design, literature search, discussion, first draft, critical comments, final approval, FS: literature search, discussion, critical comments, final approval.

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