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Comment on "Lack of reproducibility of resting-state functional MRI findings in migraine with aura"

Sir, we read the article of Hougaard et al. (1) with interest and we commend the authors who dedicated substantial effort to its development.

We would like to draw our observations from this study and propose the next step in neuroimaging of migraine research studies, which appears to be needed to enhance our understanding of complex neurovascular disorder such as migraine. First, to assess changes in functional network integration, the authors suggest carrying out inferential statistics using non-parametric tests, such as permutations and a specially created Python script. These approaches are intriguing and we believe they should be investigated further. However, because parametric tests are typically used to generate statistical inferences, the comparisons with the publications displayed in their Table 2 are not appropriate. Additionally, their Table 2 does not display the articles' methods or testing, which could confuse readers and cause them to draw incorrect conclusions. For example, in contrast to the research conducted by Hougaard *et al.* (2), prior investigations (i) utilized distinct frequency ranges for functional magnetic resonance imaging (MRI), which might be associated selectively with particular clinical symptoms (3), and employed different methodological approaches, including between-network connectivity; (ii) excluded the majority of participants who presented with structural abnormalities (e.g. white matter hyperintensities), patients under preventives or those with infrequent and frequent tension-type headaches, which may have altered brain anatomy and connectivity (4–6); and (iii) taken into account during which phase of the menstrual cycle the female patients were scanned, a factor that can be relevant in functional connectivity research (7,8). Also, conservative voxel-wise inference family-wise error (<0.05) rates for parametric common software are used to thoroughly examine false positives; false positive rates are less than 5% (9). Second, although the investigated patient's group was very well clinically described, it appears that this was not tackled appropriately in functional MRI analysis. Comorbidities, such as arterial hypertension, and heterogeneity of clinical symptoms with regards to headache presence in relation to aura (38% of patients had also attacks of aura without headaches), aura type (more than 20% of patients had non-visual symptoms), lifetime number of migraine with aura attacks (22% of patients had 2–9 attacks and 29% had 10–49 attacks during 25 years of disease duration in average) and having headache in 48 hours before or 48 hours after study scan could all increase the variability of the acquired functional MRI data and potentially lead not only to false positive, but also to false negative results, hampering the conclusions. To best of our knowledge, the pathophysiology of migraine with aura is a very complex and multifaced disorder and replicability of neuroimaging studies could be achieved with using well described homogenous groups of patients in substantial number in sample, which could be achieved in well-designed multicentric studies. Third, besides limitations mentioned in the limitation section, it was not taken into account that almost 40% of patients have not reported migraine with aura attacks in the last 12 months prior to the MRI scan, which could significantly impact the results and conclusions.

Considering all of the above, there is a great need for formation of expert's consortium who will recommend best practices in research related to neuroimaging of migraine investigation. This is to reduce sources of heterogeneity in the broader field of functional MRI, including the variability in potential analysis methods for functional MRI datasets and the heterogeneity in the selection of healthy controls and patients.

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