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# "Resting-state fMRI in Parkinson's disease patients with cognitive impairment: A meta-analysis": Answer to Wang and colleagues

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*Dear Editor*

We would like to thank dr. Wang and his colleagues for their interest in our study. While the authors address important measures to assess the validity of a meta-analysis such as heterogeneity between studies, the pooling of Parkinson's disease (PD) patients with mild cognitive impairment (PD-MCI) and patients with dementia (PDD) and the ON or OFF state during scanning, it is important to recognize the need for sufficient power when performing subgroup analyses.

In this meta-analysis an extensive assessment of the quality of the included studies has been carried out. Furthermore, the anisotropic effect-size version of the signed differential mapping method (AES-SDM) was applied, which takes into account the effect sizes of the individual studies [1,2]. When performing a meta-analysis with fMRI studies, there is always a trade-off between study heterogeneity and the number of experiments that can be included [3]. An increased power is reached with the inclusion of a higher number of studies, but on the other hand one wants to aim for the highest homogeneity possible. A clear statement about the minimum amount of studies necessary for an fMRI meta-analysis is currently lacking and depends on several factors such as the sample size of the individual experiments and the expected effect size. However, some authors recommend to include at least 17–20 experiments [4]. Since our meta-analysis consists of a relatively limited amount of studies, with rather small patient groups, we chose to accept a certain level of heterogeneity between studies in order to prevent the sample size and the power from becoming too small to draw any reliable conclusions. Performing meta-regression and subgroup analysis for the discrimination of different cognitive profiles and the ON and OFF medication groups was considered while executing this meta-analysis. While the performance of a meta-regression analyses is important to confirm the clinical relevance of the results, the homogeneity of the outcome measures of the individual experiments was insufficient for this meta-analysis. Furthermore, we again argued that when performing subgroup analyses, the subgroups would become too small to draw any reliable conclusions. In fact, only 7 studies included patients with PDD and those patient groups were separately analysed from PD-MCI in only 5 experiments. In addition, 11 studies that compared healthy controls (HC) with PD patients with cognitive impairment (PD-CI) have performed the fMRI while ON medication and 3 experiments carried out the fMRI while OFF medication. Only 4 experiments while ON medication and 2 studies in OFF medication states were carried out for the comparison of PD with and without cognitive impairment. It is of course well known that the use of dopaminergic medication influences the functional connectivity patterns of the brain [5]. Moreover, compensatory mechanisms and different pathophysiological substrates may indeed give rise to connectivity changes that are different for mild cognitive impairment and more progressed states of cognitive impairment [6,7]. In this study, no conclusions were drawn for connectivity changes in mild cognitive impairment as a clinical entity and the validity of our meta-analysis has been discussed. Future studies with methodologically homogenous data sets and larger sample sizes are important in order to map differences in functional connectivity. This meta-analysis indicates that the default mode network might be of significant interest in cognitive impairment in PD, which may be relevant for future studies on this topic.

## Declarations of interest

None.

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