

Reply: Brain-behaviour associations and neural representations of emotions in frontotemporal dementia

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Sir,

We thank Van den Stock and colleagues for their interest in and replication of our recent work (Marshall et al. 2019). Whilst cognitive neuroscience is increasingly viewed as experiencing a replication crisis (Huber et al. 2019), this is particularly problematic in the clinical cognitive neuroscience of rare diseases like the frontotemporal dementias (FTD), where the difficulties of case ascertainment are frequently a barrier to attaining adequate statistical power. Their successful replication of the brain-behaviour association we describe in FTD is therefore especially welcome.

As Van den Stock et al. describe, structural imaging changes typically occur late in FTD, while fluid biomarker development is problematic due to the underlying heterogeneity of these syndromes (Sivasathiseelan et al. 2019). Moreover, the symptom profiles of FTD are complex and difficult to measure with conventional neuropsychological instruments. There is therefore growing interest in objectively measuring the altered physiology of FTD, either in the working brain or the periphery (Ahmed et al. 2018; Guo et al. 2016; Marshall et al. 2018a; Marshall et al. 2018b; Marshall et al. 2019). These approaches are inherently labour-intensive, and therefore difficult to study at large scale. If they are to fulfill their promise of overtaking structural imaging and fluid biomarkers, multicentre collaboration will be necessary to achieve reliable and reproducible results. The international research community has made great progress in this direction with the development of large genetic FTD consortiums such as GENFI (Rohrer et al. 2015), but similar approaches to sporadic FTD will also be required, particularly as the sporadic syndromes lack definitive *in vivo* diagnostic tests.

The FTDs are increasingly recognised to be diseases that target large scale neural networks ('nexopathies') (Seeley et al. 2009, Warren et al. 2013). The network paradigm provides further impetus to study *in vivo* systems neurophysiology in these diseases, as this is likely to be the only way to sensitively capture the earliest changes in network dynamics that could allow detection of proteinopathies at a time when secondary prevention of neurodegeneration is still possible.

Conventional fMRI approaches such as those employed in our study and the replication by Van den Stock et al. may not be adequately sensitive to early network disruption. It is likely that analysis approaches designed to measure functional network architecture such as dynamic causal modelling (DCM) will be required (Hughes et al. 2018), including computational techniques that allow inferences to be made at a single subject level (Stephan et al. 2017). Furthermore, the much greater temporal resolution of MEG may render it more suited to capturing subtle, dynamic changes in effective connectivity; indeed, it may turn out to be the neuroimaging modality of choice for early diagnosis in FTD (Hughes et al. 2013).

From a clinical perspective, those who work in cognitive disorders clinics will be all too familiar with the scenario of a patient with profoundly disturbed socioemotional functioning in daily life, yet who has normal structural neuroimaging and diagnostic neuropsychology. This conundrum and the related issue of 'FTD phenocopies' leads frequently to delayed diagnosis, under-diagnosis or false positive diagnosis of FTD (Coyle-Gilchrist et al. 2016; Draper et al. 2016; Gossink et al. 2015; Shinagawa et al. 2016). Our hope is that brain-behaviour studies such as ours and that of Van den Stock et al. will provide a 'missing link' between clinical symptoms and neuropathology, and ultimately yield tools for improving diagnostic accuracy. This vision

will only be realised through reliable and reproducible research, and to this end, the effort is of vital importance.

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Competing interests:

The authors report no competing interests.

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