LETTERS

Frontomedian cortex is central for moral deficits in behavioural variant frontotemporal dementia

Recently, neurodegenerative diseases have increasingly been conceptualised as 'nexopathies' or disconnection syndromes, in which connectivity changes in neural networks represent the most relevant and characteristic features.[1] One of these diseases, behavioural variant frontotemporal dementia (bvFTD), is characterised by morally deviant actions as an early clinical hallmark of this disease, besides other specific changes in personality and behaviour.[2 3] Elucidating on the neural correlates of these moral impairments contributes to their understanding in this in young patients frequent dementia syndrome and to the understanding of moral actions per se.

One approach towards understanding moral impairments in bvFTD is by comparing affected neural networks in bvFTD with brain networks involved in moral processing in healthy participants during functional imaging studies. Remarkably, this approach enables extraction of new concepts of diseases by using two independent cohorts and imaging methods (lesion studies in disease cohorts vs functional imaging studies in healthy participants).[3] Because numerous imaging studies have been published on these issues to date, quantitative meta-analytic approaches are possible.

Accordingly, we combine here two comprehensive quantitative meta-analyses of anatomical and functional neuroimaging data by means of the well-established likelihood estimate method to provide evidence for alterations of regions involved in moral reasoning in bvFTD. Likelihood estimate meta-analyses are based on coordinates of peaks for atrophy or hypometabolism during rest in patients when compared with control participants, or coordinates from functional imaging studies, where healthy participants are stimulated with psychological stimuli. The statistical analysis determines brain regions that exhibit a higher convergence of these peaks across independent studies than would arise by chance. The final likelihood estimate map extracts the prototypical neural correlates of a specific disease or a prototypical network of brain regions that are associated with a specific cognitive paradigm (see for detailed information on methods[3 4]).

We used results from our recent meta-analysis[3] identifying regions that are consistently affected by bvFTD in terms of atrophy (MRI) or hypometabolism during rest (18F-fluorodeoxyglucose positron emission tomography, FDG-PET). This analysis incorporated 9 MRI studies and 11 FDG-PET studies including a total of 417 patients with bvFTD (MRI 185/FDG-PET 232) and 406 control participants. To investigate whether these brain regions converge with those reliably implicated in moral processing, we quantitatively compared this data using a minimum statistic conjunction analysis with a recent comprehensive meta-analysis across functional activation imaging studies that investigated moral cognition in healthy participants applying the same meta-analytic approach.[4] The latter study incorporated 67 neuroimaging experiments reporting 507 activation foci.

Using this large-scale approach towards the robust definition of pathology and function, we identified four regions in the anterior frontomedian and paracingulate cortex, in Brodmann areas 9, 10 and 32, exhibiting not only atrophy in bvFTD but also consistent activation increases during moral cognition tasks in healthy participants (figure 1). These brain regions are known to be central hubs for moral reasoning.[2] In detail, atrophic brain regions in bvFTD included a total of 1735 voxels; activation in moral cognition was observed in a neural network spreading across 3203 voxels in healthy participants.

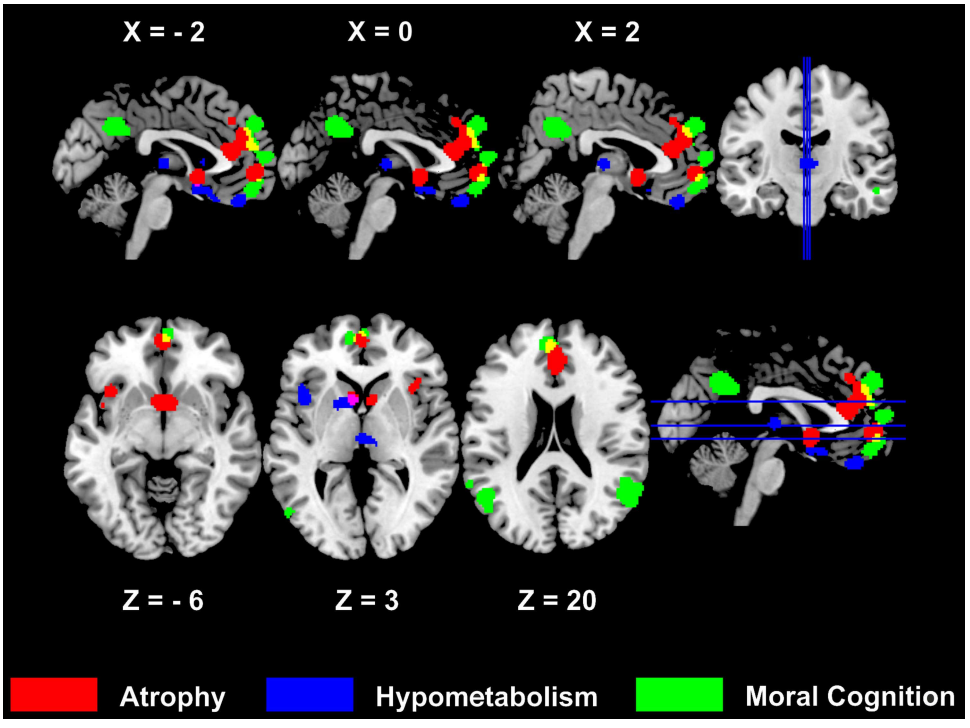

Figure 1 Conjunction between neural correlates of behavioural variant frontotemporal dementia (bvFTD) and of moral cognition in healthy participants. Atrophy in bvFTD as measured with MRI red, glucose hypometabolism in bvFTD as measured with 18F-fluorodeoxyglucose positron emission tomography blue, respective overlap pink. Functional neural correlates of moral cognition in healthy participants green. Overlap between atrophic brain regions in bvFTD and moral cognition networks in healthy participants yellow. Anatomical and functional activation likelihood estimate meta-analyses. For statistical values see refs. [3] and [4]. Left is left. Montreal Neurological Institute (MNI) coordinates.

These clusters overlapped specifically in 113 voxels, where one voxel generally corresponds to a volume of 2×2×2 mm. The quantitative analysis showed a relative overlap in 6.51% of all atrophic brain regions in bvFTD, and in 3.53% of the whole moral cognition network.

Though small, this regional overlap/conjunction is statistically significant at $p<0.05$ (corrected). Note that meta-analytic approaches as used here generally include maxima and not cluster sizes of the various imaging studies and, accordingly, they extract the prototypical, most characteristic neural networks that might be regionally larger and more unspecific in single studies. In contrast to atrophic areas, we did not find any overlap between hypometabolic regions in bvFTD and functional correlates of moral processing in healthy participants. The divergence between atrophy and hypometabolism in bvFTD might indicate a regional dissociation such as in Alzheimer's disease; an issue that has to be investigated in future longitudinal studies.[3]

Recently, Chiong *et al*[5] used functional MRI to assess moral processing (resolving personal moral dilemmas) and connectivity changes in patients with bvFTD. Although patients showed atrophy mainly in the frontomedian, anterior cingulate, orbitofrontal cortex, anterior insula and ventral striatum, brain activation was reduced relative to healthy controls in the posterior cingulate cortex and precuneus during moral reasoning. To resolve this discrepancy the authors investigated the directed interaction between these networks using Granger analysis. Their data suggest, on the one hand, a causal influence of the anterior cingulate cortex on the medial prefrontal cortex and, on the other hand, a causal influence of the frontoinsular on the posterior cingulate cortex in healthy participants, which is disrupted in patients with bvFTD.

Together with Chiong *et al*'s[5] data, our results underline the important role of the frontomedian cortex as a central hub in bvFTD[3] and support the hypothesis that connections from the anterior cingulate cortex to the medial prefrontal cortex are particularly relevant for moral cognition impairments in bvFTD. Future studies shall focus their analyses on the relationship between these two important hubs in abnormal moral reasoning and, more broadly, in abnormal social cognition as one of the key disabling symptoms of bvFTD.

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JN planned the design/conceptualisation of the study, analysed and interpreted the data, and revised the manuscript.

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Notes