

New developments in frontotemporal dementia

It is a terrible condition. Frontotemporal dementia (FTD) has a devastating impact on patients, their families—who often take the brunt of behavioural changes—and their doctors, who often have very little to offer in terms of treatment. On the other hand, the scope for discoveries in FTD is enormous. In this month's issue of *Brain* we have three very different types of study that offer new insights into various forms of FTD, each focused on a different level of explanation.

An important avenue of research in this field is work on genetic causes of the conditions that fall under the rubric of FTD¹: behavioural variant (bvFTD), semantic variant primary progressive aphasia (svPPA; also known as semantic dementia) and the non-fluent or agrammatic variant of primary progressive aphasia (navPPA). Barker and colleagues² have attempted to provide diagnostic criteria for prodromal bvFTD, i.e. in the stage before diagnostic criteria for the bvFTD are fulfilled. They examined longitudinal data from carriers of mutations in *MAPT* (microtubule-associated protein tau), or *GRN* (progranulin) or repeat expansion in the *C9orf72* (chromosome 9 open reading frame 72) gene in order to delineate the features that are characteristic of prodromal bvFTD.

In their dataset, people who went on to convert to a diagnosis of FTD had several of seven core features. These included development of apathy without significant dysphoria, disinhibited behaviour, irritability or agitation, reduced empathy or sympathy, repetitive behaviours, inappropriate joviality or gregariousness and hyperorality or changes in appetite. Features that further supported the prodromal diagnosis included poor social cognition, lack of insight, deficits of executive function with intact performance on orientation and visuospatial tasks. In some ways these findings are not surprising because they resemble several of the diagnostic criteria for bvFTD proposed in *Brain* over a decade ago.³ However, the authors point out that there are some key differences.


First, in these criteria apathy was only considered to be present if it was evident without depression. This makes this feature a relatively pure one (since apathy can often be mistaken as low mood and can also exist concurrently with depression). Second, irritability or agitation—which are not part of the current diagnostic criteria for bvFTD—were very frequent in prodromal cases, with several individuals reported to being prone to becoming angry extremely quickly. Third, reduced insight, again not a feature of the current bvFTD criteria, was also commonly observed in these cases. Fourth, although executive dysfunction was a feature, the researchers did not make relative preservation of memory part of their criteria because some individuals did show impairments on memory tests (although causes underlying such deficits might

not necessarily have been due to deficits in memory processes *per se*). Overall, the authors argue that clinicians should have a lower subjective threshold to make a diagnosis of prodromal bvFTD than currently used for a formal diagnosis of bvFTD. It's going to be interesting to see how these criteria play out—both in the clinic and research setting.

One important aspect of behavioural change observed in this study was altered social cognition, but this was based on a questionnaire assessment rather than performance on a cognitive paradigm. In this issue, Legaz and colleagues⁴ used a paradigm to examine reinforcement learning, either with or without social cues. In healthy individuals, learning improved with social feedback but this was impaired in bvFTD, while in Alzheimer's disease there was a general learning deficit across both social and non-social conditions. Regions of brain atrophy associated with the social learning deficit included the temporo-parietal junction and frontal insula and limbic regions, consistent with previous research implicating these regions in aspects of social cognition. The results are not only of interest to understanding the spectrum of social deficits in bvFTD^{5,6}; they also provide compelling evidence for the brain networks underpinning social cognition in normal, healthy brains.

The third paper on FTD in this issue of *Brain* by Kawles and colleagues⁷ reports a detailed study of the pathology of TDP-43 (transactive response DNA-binding protein 43) type C frontotemporal lobar degeneration (FTLD-TDP-type C). Individuals with this pathology frequently have a clinical diagnosis of svPPA or, less frequently, bvFTD.⁸ They have dystrophic neuritic inclusions, which contain hyperphosphorylated TDP-43 in the upper layers of the cortex, and lower densities of neuronal cytoplasmic inclusions. In this study, the authors describe the distribution of this pathology and show that some subcortical regions such as the amygdala, caudate and putamen appear to be particularly vulnerable to dystrophic neuritic inclusions. Further, those regions with the lowest such pathology also had the most neuronal loss and vice versa, suggesting that these inclusions might disappear as neurons are lost.

Stitching together these very disparate levels of explanation—clinical phenotype in earlier phases of the FTD, cognitive neuroscience of reinforcement learning from social cues and distribution of pathology—remains a major challenge. But it is only with such detailed examination across different methodologies that progress in this field is likely to be made.

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