

A MODERN PERSPECTIVE ON SOME OF THE MOST HIGHLY CITED JNNP PAPERS OF ALL TIME

# Frontal lobe dementia, motor neuron disease, and clinical and neuropathological criteria

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David Neary and Julie Snowden reflect on developments in the understanding of frontotemporal dementia and motor neuron disease since their publications two decades ago

At the beginning of the 1980s the establishment view in the English speaking world was that there were two primary causes of dementia: Alzheimer's disease and vascular disease. Pick's disease was an acknowledged pathological entity but considered sufficiently rare to have little clinical relevance for dementia patients presenting to neurology or psychiatry clinics. In any case it could not be distinguished from Alzheimer's disease in life. It was against this prevailing background that I set up our early onset dementia clinic with Julie Snowden as principal neuropsychologist. My early interest in cognitive neurology and dementia had been consolidated during a sabbatical in Boston in 1976, where I acquired an analytical approach to cognitive assessment and saw firsthand the value of the multidisciplinary clinic. In our own clinic, what rapidly became clear was that patients exhibited very different patterns of difficulty. Far from the 'global impairment of intellect' that had hitherto defined dementia, we began to see identifiable constellations of deficits. Whereas in many patients

## DEMENTIA OF FRONTAL LOBE TYPE<sup>1</sup>

Published: 1988;51:353–61

## FRONTAL LOBE DEMENTIA AND MOTOR NEURON DISEASE<sup>2</sup>

Published: 1990;53:23–32

## CLINICAL AND NEUROPATHOLOGICAL CRITERIA FOR FRONTO-TEMPORAL DEMENTIA<sup>3</sup>

Published: 1994;57:416–18

the salient presenting problems were in instrumental functions of memory, language and visuospatial skills, in others they were in social behaviour, affect and judgement. We were seeing a 'frontal' type of dementia, which we assumed was distinct from the more common Alzheimer's disease.

From the perspective of the current technological era it may seem surprising that 30 years ago we had no informative neuroimaging to back up neuropsychological assumptions about anatomy. The grainy, low resolution black and white images of single photon emission tomography in the mid-1980s were a revelation: they provided independent support for our inferences of a distinction between 'frontal' as opposed to 'posterior hemisphere' profiles of cognitive dysfunction.

Our 1988 *JNNP* description of 'dementia of frontal lobe type'<sup>1</sup> was met with enthusiasm in some quarters but continued scepticism from those who claimed it would 'all turn out to be Alzheimer's disease'. Our clinical observations, described in *JNNP* in 1990,<sup>2</sup> raised an even more drastic challenge to prevailing opinion: some of our patients with 'frontal-type' dementia showed signs of motor neuron disease (MND). Descriptions existed in the literature of an association between dementia and MND, notably from exotic locations such as Guam and Japan. Nevertheless, the conventional view persisted of MND as a disorder confined to the motor system in which cognition was unaffected. Yet here was an association between the amyotrophic form of MND and a specific form of dementia: frontal-type dementia. When we presented our findings at conferences, some caregivers of MND patients expressed relief that the

behavioural changes that they had witnessed in their relative were now being acknowledged. Yet there was an understandable concern among MND clinicians that the prospect of 'mental' change would add further to the burden faced by people with MND. Many hoped that what we described would prove to be an obscure distinct form of dementia that had little to do with the classical forms of MND seen in their own clinics.

An important piece of the jigsaw was pathology. We had set up the Manchester Brain Bank in the early 1980s in collaboration with David Mann, and brain donations from clinically studied patients were beginning to accumulate, allowing us to confirm non-Alzheimer pathology in our frontal dementia patients. Crucially, although some cases showed tau pathology, with ballooned cells and inclusion bodies consistent with traditional pathological descriptions of Pick's disease, the majority did not. Their pathology was characterised by nerve cell loss and microvacuolation. Our patients with 'frontal lobe' dementia and MND invariably showed this latter type.

One of our most productive collaborations during this period began in 1986 at a small meeting on 'frontal lobe dementia' organised by Lars Gustafson and Arne Brun in Lund, Sweden (now credited as the 1st International Conference on Frontotemporal Dementia (FTD)). Lars and Arne too had experienced reluctance from colleagues to accept this distinct form of dementia, so it was mutually rewarding to discover that we were seeing such similar patients. We met on a number of occasions, culminating in our 1994 *JNNP* publication of clinical and neuropathological criteria,<sup>3</sup> based on our shared experience. The statement identifies FTD with MND as a specific clinical phenotype associated with tau negative pathology.

It is difficult to think of an area of neurology where scientific advances in the past two decades have been so dramatic. Whereas FTD was poorly recognised or considered a quirk of Viking origin, it is now accepted worldwide as a major cause of early onset dementia. The clinical overlap between FTD and MND is not in dispute. MND is now

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recognised as a multisystem rather than a pure motor disorder, with practical implications for patient management. Consensus clinical and pathological criteria for FTD have been increasingly refined,<sup>4–7</sup> and criteria have been developed for MND with FTD<sup>8</sup> to improve recognition. Identification of TDP-43 as the pathological protein in both MND and tau negative FTD<sup>9</sup> provides supporting evidence of their aetiological link. The link is further strengthened by the identification in both disorders of hexanucleotide repeat expansions in the *C9ORF72* gene.<sup>10 11</sup>

*JNNP*'s first themed issue in April 2012 centred on amyotrophic lateral sclerosis and FTD, attesting to the immense importance of this rapidly developing field. Neuropsychology, neuropathology and genetics have each had pivotal roles in drawing together and consolidating the aetiological link between FTD and MND, and our understanding of these conditions. It would be gratifying to think that careful clinical observational skills and an analytic approach to the assessment of cognition and behaviour 30 years ago may also have contributed to that understanding.

**Contributors** DN and JS were both invited contributors, both conceptualised the article and contributed to its writing.

**Competing interests** None.

**Provenance and peer review** Commissioned; not externally peer reviewed.

**To cite** Neary D, Snowden J. *J Neurol Neurosurg Psychiatry* 2013;**84**:713–714.

Received 14 January 2013

Accepted 1 February 2013

Published Online First 12 March 2013

*J Neurol Neurosurg Psychiatry* 2013;**84**:713–714.  
doi:10.1136/jnnp-2012-304549



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