Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of neurodegenerative disease management

Fiona Kumfor^{1,2,3}, Olivier Piguet^{1,2,3} & Martin Knapp⁴

Landqvist Waldö M, Gustafson L, Passant U, Englund E. Psychotic symptoms in frontotemporal dementia: a diagnostic dilemma? *Int. Psychogeriatr.* doi:10.1017/S1041610214002580 (2014) (Epub ahead of print).

Early diagnosis of frontotemporal dementia (FTD) remains difficult despite an accumulation of research in recent years. Given the clinical and pathological heterogeneity, misdiagnosis is not uncommon and has implications for the management of these patients. In this study published in *International Psychogeriatrics*, Waldö and colleagues conducted a retrospective analysis of 97 patients with pathological confirmation of FTD and reviewed the presence of psychotic symptoms, initial diagnosis and family history for psychiatric disorders. They found that fewer than 15% of patients were initially diagnosed with FTD and 25% never received a correct diagnosis in life. At presentation, 41 patients were diagnosed with a psychiatric disorder and 33 with another dementia. Patients diagnosed with psychiatric disorders were significantly younger than the other patients. Psychotic symptomatology was present in 31 patients (33%) and was strongly associated with right-sided brain atrophy. In addition, over 75% of cases with psychotic symptoms were found to have non-tau pathology, predominantly TDP-43 protein deposition. This study confirms the difficulty in establishing an early diagnosis of FTD, particularly in young individuals who are more likely to be diagnosed

with a psychiatric disorder. Importantly, presence of psychotic symptoms in FTD patients appears to provide clues to the underlying pathology (i.e., non-tau). While genetic status of the patients was not provided, frequency of psychotic features is in line with recent investigations of FTD patients with the *C9orf72* gene expansion, who also show abnormal TDP-43 protein deposition. These findings provide further support to consider psychotic symptoms as part of the diagnostic criteria for FTD.

– Written by Olivier Piguet

Lagarde J, Valbrègue R, Corvol JC et al. Why do patients with neurodegenerative frontal syndrome fail to answer: 'In what way are an orange and a banana alike?' *Brain* doi:10.1093/brain/awu359 (2014) (Epub ahead of print).

Concept formation is the ability to make an abstract link between two things based on some common characteristics. This ability is proposed to reflect executive functioning subtended by the prefrontal cortex. The cognitive and neural substrates supporting concept formation, however, have been relatively unexplored. This study aimed to determine the cognitive and neural bases of concept formation, and investigate whether this ability is similarly impaired across three dementia syndromes, two of which are frontally mediated (frontotemporal dementia and progressive supranuclear palsy) and a nonfrontal syndrome (Alzheimer's disease). Clinical reports

¹Neuroscience Research Australia, Sydney, Australia

²School of Medical Sciences, the University of New South Wales, Sydney, Australia

³ARC Centre of Excellence in Cognition and its Disorders, Sydney, Australia

⁴London School of Economics and Political Science, Houghton Street, London, WC2A 2AE, UK

*Author for correspondence: f.kumfor@neura.edu.au

of concept formation suggest that patients commonly fail this task for two reasons: an inability to find a shared characteristic (linking deficit) or a tendency to focus on concrete or perceptual, rather than abstract features (abstraction deficit). The authors thus created a novel task that varied the perceptual similarity between pairs and used voxel-based morphometry to identify the neural correlates underpinning linking and abstraction concept formation deficits. The behavioral results revealed that the 'frontal patients' (frontotemporal dementia and progressive supranuclear palsy) tended to exhibit both error types, with linking deficits more common. In contrast Alzheimer's disease patients performed within normal limits. Neuroimaging analyses revealed partially distinct correlates: linking deficits were associated with the anterior cingulate, right middle frontal gyrus and parietal lobules whereas abstraction deficits were associated with the caudate and left superior frontal gyrus. The results reveal that a prefrontal–basal–ganglion network is involved in concept formation, and suggest that this ability comprises two subcomponents: abstraction and linking.

– Written by Fiona Kumfor

Schaller S, Mauskopf J, Kriza C, Wahlster P, Kolominsky-Rabas PL. The main cost drivers in dementia: a systematic review. *Int. J. Geriatr. Psych.* 30(2), 111–129 (2015).

As the world population ages over the coming decades, so the number of people with dementia will increase. So too will the costs of supporting and treating those people – at least until there is a disease-modifying breakthrough. Funding bodies and governments are especially conscious of those costs and how they are likely to grow, although rarely do they have a full picture. Sandra Schaller and colleagues have reviewed studies that describe the overall costs of dementia. They call the component elements 'drivers,' which perhaps suggests factors that cause those costs, whereas in fact what they are looking at are the components. They systematically reviewed the international literature between 2003 and 2012 to identify cost-of-illness studies, finding 27 studies that met their inclusion criteria, from 14 different healthcare systems. The collection of studies point to the very high costs associated with unpaid care by family and other caregivers, as well as the high costs of residence in nursing homes.

Figures generated by cost-of-illness studies give an aggregate indication of the economic impact of

a condition, in this case dementia. They are not cost-effectiveness findings: they cannot provide governments or funding bodies with advice on what they might do to improve health and quality of life for individuals with dementia or their caregivers, nor do they show how to make better use of resources. Cost-of-illness studies can nevertheless highlight the overall economic impact – thus capturing the attention of finance ministers and other strategic decision-makers – but are unable to point to which interventions to invest in.

– Written by Martin Knapp

Garrido MM, Balboni TA, Maciejewski PK, Bao Y, Prigerson HG. Quality of life and cost of care at the end of life: the role of advance directives.

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Advance directives give opportunities to individuals to specify what should happen when their health deteriorates to a stage where they are no longer able to make decisions for themselves, as is a common outcome of neurodegenerative disease. They can cover a range of areas, primarily medical treatments and resuscitation. Other terms for advance directives include 'living wills,' 'personal directives' and 'advance decisions.'

Melissa Garrido and colleagues used prospective data from interviews with 336 patients with advanced cancer and their family or other unpaid carers. The study looked at what patients specified as regards end-of-life care preferences. They found that 'do-not-resuscitate' orders were associated with higher quality of life in the final week before death. A 'do-not-resuscitate' order was also associated with lower costs in the last week of life, although the results were not robust to the choice of analysis method.

The authors emphasize the potential importance of completing an advance directive, particularly a 'do-not-resuscitate' order, for patients who do not want to be resuscitated, because of these observed benefits. With growing attention being paid to end-of-life care, studies such as this can contribute importantly to what is currently a small evidence base. In particular, there have been very few studies of end-of-life care with respect to neurodegenerative disorders, yet the issues in that area are as pressing as anywhere, particularly given that loss of mental capacity in the final stages of illness is so common.

– Written by Martin Knapp

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