doi:10.1093/brain/aws030 Brain 2012: 135; 1–2 | e213

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

Considering the frontomedian cortex in revised criteria for behavioural variant frontotemporal dementia

Matthias L. Schroeter[1,2,3]

1 Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany
2 Day Clinic of Cognitive Neurology, University of Leipzig, 04103 Leipzig, Germany
3 LIFE – Leipzig Research Centre for Civilization Diseases, University of Leipzig, 04103 Leipzig, Germany

Correspondence to: Matthias L. Schroeter, MD, PhD, MA,
Max Planck Institute for Human Cognitive and Brain Sciences,
Stephanstr. 1A, 04103 Leipzig,
Germany
E-mail: schroet@cbs.mpg.de

Sir, Recently, an international consortium developed revised guidelines for the diagnosis of behavioural variant frontotemporal dementia (FTD) based on histopathologically confirmed cases and their clinical symptoms (Rascovsky *et al*., 2011). The revised criteria suggest that 'possible' behavioural variant FTD requires three of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviours, hyperorality and dysexecutive neuropsychological profile). 'Probable' behavioural variant FTD adds functional disability and characteristic neuroimaging (frontal and/or anterior temporal atrophy, hypometabolism or hypoperfusion), while behavioural variant FTD 'with definite frontotemporal lobar degeneration' requires histopathological confirmation or a pathogenic mutation. The study revealed a much higher sensitivity of the proposed criteria in comparison to earlier criteria (Neary *et al*., 1998) in a multi-site sample of 137 patients with pathologically verified frontotemporal lobar degeneration. These results will obviously greatly advance the early identification of behavioural variant FTD, which is particularly relevant for early treatment.

Recent comprehensive systematic and quantitative meta-analytic neuroimaging approaches with the anatomical likelihood estimate method conducted according to quality standards of the QUOROM statement enabled the identification of the prototypical neural networks involved in neurodegenerative diseases such as behavioural variant FTD (Schroeter *et al*., 2007, 2008, 2009). These studies including 132 patients with behavioural variant FTD, together with other multi-centre imaging approaches (Salmon *et al*., 2003) and histopathological studies focusing on von Economo neurons (Seeley *et al*., 2006) suggest that behavioural variant FTD is related to atrophy and hypometabolism mainly in frontomedian brain regions, the anterior insula and the thalamus. Beside frontal areas, no temporal clusters were identified, indicating that behavioural variant FTD is mainly a frontomedian disease. Anterior temporal atrophy was, in contrast, observed in Alzheimer's disease and semantic dementia in these anatomical likelihood estimate meta-analyses—decreasing the discriminating specificity of this brain region (Schroeter and Neumann, 2011).

The affected frontomedian clusters in behavioural variant FTD have been associated with social cognition, in particular, theory of mind abilities (Amodio and Frith, 2006), which are known to be specifically impaired in this disease (Gregory *et al*., 2002; Adenzato *et al*., 2010). Surprisingly, the new criteria do not include neuropsychological testing of social cognition—a fact that might be related to the traditional neglect of the functions of the frontomedian cortex in test batteries in contrast to the well-known sensitivity of executive tests mainly for the frontolateral cortex (Schroeter *et al*., 2012). One might argue that the new diagnostic criteria already include empathy. However, empathy is a concept different from theory of mind—whereas empathy represents a sharing of another's state, theory of mind affords only an understanding of this state. Furthermore, neural networks involved in empathy do not cover the anterior frontomedian cortex (Rankin *et al*., 2006; Hein and Singer, 2008; Fan *et al*., 2011), which is the core region affected by behavioural variant FTD (Salmon *et al*., 2003; Schroeter *et al*., 2007, 2008).

In conclusion, adapting diagnostic criteria by specifying imaging criteria and adding neuropsychological data with an emphasis on social cognition (in particular, theory of mind) might further increase the revised criteria's specificity, reliability and predictive power in the early stages of behavioural variant FTD, when

Advance Access publication February 23, 2012

disease-modifying interventions are likely to be most effective (Rascovsky *et al*., 2011).

Funding

LIFE – Leipzig Research Centre for Civilization Diseases at the University of Leipzig (to M.L.S.). LIFE is funded by means of the European Union, by the European Regional Development Fund (ERFD) and by means of the Free State of Saxony within the framework of the excellence initiative. German Federal Ministry of Education and Research (BMBF; grant number FKZ 01GI1007A – German FTLD consortium) (to M.L.S.).

References

Adenzato M, Cavallo M, Enrici I. Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. Neuropsychologia 2010; 48: 2–12.

Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 2006; 7: 268–77.

Hein G, Singer T. I feel how you feel but not always: the empathic brain and its modulation. Curr Opin Neurobiol 2008; 18: 153–8.

Fan Y, Duncan NW, de Greck M, Northoff G. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neurosci Biobehav Rev 2011; 35: 903–11.

Gregory C, Lough S, Stone V, Erzinclioglu S, Martin L, Baron-Cohen S, et al. Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. Brain 2002; 125: 752–64.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546–54.

Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. Brain 2006; 129: 2945–56.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011; 134: 2456–77.

Salmon E, Garraux G, Delbeuck X, Collette F, Kalbe E, Zuendorf G, et al. Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia. Neuroimage 2003; 20: 435–40.

Schroeter ML, Raczka K, Neumann J, von Cramon DY. Towards a nosology for fronto-temporal lobar degenerations – a meta-analysis involving 267 subjects. Neuroimage 2007; 36: 497–510.

Schroeter ML, Raczka K, Neumann J, von Cramon DY. Neural networks in frontotemporal dementia –a meta-analysis. Neurobiol Aging 2008; 29: 418–26.

Schroeter ML, Stein T, Maslowski N, Neumann J. Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 2009; 47: 1196–206.

Schroeter ML, Vogt B, Frisch S, Becker G, Barthel H, Müller K, et al. Executive deficits are related to the inferior frontal junction– an FDG-PET study in early dementia. Brain 2012; 135: 201–15.

Schroeter ML, Neumann J. Combined imaging markers dissociate Alzheimer's disease and frontotemporal lobar degeneration – an ALE meta-analysis. Front Aging Neurosci 2011; 3: 10.

Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 2006; 60: 660–7.