

PRGN mutation modulates brain damage and reorganization from preclinical to symptomatic stages of frontotemporal dementia

M. Bozzali¹, M. Cercignani¹, A. Alberici², E. Premi², L. Serra¹, C. Cerini², M. Cosseddu², C. Pettenati², M. Turla², S. Archetti², R. Gasparotti², A. Padovani², and B. Borroni²

¹Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy, ²Neurology Unit, University of Brescia, Brescia, Italy

Introduction

Progranulin (PGRN) mutations have been recognized to be monogenic causes of frontotemporal lobar degeneration (FTLD) (1,2). It was previously demonstrated that PGRN mutations induce haplo-insufficiency, although their effects on brain tissue dysfunction and damage remains unclear. In this study, we investigate the pattern of neuroimaging abnormalities in pre-symptomatic carriers and in patients with FTLD with the same PGRN mutation. In particular we evaluated the grey matter (GM) volume using voxel-based morphometry (VBM), and functional connectivity using resting state (RS) fMRI.

Methods

Fifty-four subjects were included in the study. We evaluated 22 asymptomatic siblings belonging to 6 families with the proband carrying PGRN Thr272fs mutation. In asymptomatic subjects, PGRN sequencing was carried out (9 mutation carriers vs. 13 non-carriers) as well as serum PGRN dosage. Twenty-one patients with FTLD (14 with behavioural frontotemporal dementia and 7 with progressive non fluent aphasia; mean age 65.9 years, SD=6.7; mean MMSE score=20.5, SD=8.6) were recruited, and 11 additional control subjects (mean age 61.0, SD=9.9), unrelated to the patients, were recruited. This latter group of subjects served as controls for FTLD patients, while the asymptomatic non-carriers (n=13) served as controls for the group of asymptomatic carriers. Six patients out of 21 were PGRN Thr272fs carriers. A standardized neuropsychological assessment was performed (MMSE, Phonological and Semantic Fluency, Short Story, Token test, Trail Making test A and B, Raven Coloured Progressive Matrices, Digit Span, Rey Figure copy and recall, FBI A and B, NPI, IADL, BADL). Serum PGRN levels were evaluated (according to literature data, PGRN mutation carriers usually have significantly lower serum PGRN compared to non-carriers). All subjects had an MRI scan at 1.5T (Siemens Avanto), including a high-resolution T1-weighted scan (MPRage) and a 8 minutes EPI series sensitized to BOLD contrast for RS-fMRI. During RSfMRI acquisition, subjects were instructed to relax but remain awake. T1-weighted images were processed for VBM (3) using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). Images were normalized to MNI space and segmented, GM maps were modulated to compensate for local changes in GM volume induced by non-linear registration. Finally, GM maps were smoothed with a 12mm Gaussian kernel. RS fMRI data were realigned, corrected for slice timing, normalized, and smoothed with a 8 mm kernel using SPM8. Finally, all images were filtered by a phase-insensitive bandpass filter (pass band 0.01-0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise. A model-free analysis was employed by using independent component analysis (ICA) implemented in the GIFT package ([www. http://icatb.sourceforge.net/](http://icatb.sourceforge.net/)), in order to allow for a simultaneous separation into individual RS networks. For all subjects grouped together, the toolbox performed the analysis in three steps: (1) data reduction, (2) application of the FastICA algorithm and (3) back reconstruction for each individual subject to yield Z-score maps of each independent component. The components corresponding to the default mode network (DMN) and core network were identified (4), and used for further cross-subject analysis. GM maps and RS Z-score maps were analyzed in SPM8, using a factorial design. Two-factors were modeled to classify subjects: presence of PGRN Thr272fs mutation (m+ vs m-) and presence of FTLD symptoms (S+ vs. S-). Additionally, age, gender and years of formal education were added as covariates of no interest. The GM maps analysis was also adjusted for the total intracranial volume, while the RS analysis was adjusted for total GM volume. Contrasts were designed to assess the effect of each factor and of their interaction on imaging variables.

Results

VBM: Both factors had significant ($p < 0.05$, FWE voxel-level corrected) main effects with S+ subjects showing reduced GM volume in the left fronto-temporal cortex compared to S- subjects, and m+ subjects showing reduced GM volume in the insular cortex compared to m-. A confirmatory effect contrast (S+m+ < all others) showed that the main effect of FTLD symptoms was driven by S+m+ subjects having significantly reduced GM volume compared to all other groups. **RS fMRI:** Among the 20 components modelled in the ICA analysis, several well-known RS networks were identified, including the DMN, the core network, the sensory-motor network, and the visual network. The analysis of the DMN showed a significant ($p < 0.05$, FWE cluster-level corrected) main effect of group, with S+ subjects having increased functional connectivity in the left parietal cortex (Fig 2A). The presence of mutations had no effect on the DMN, while a significant interaction between the 2 factors was observed in the posterior cingulate and in the temporal cortex (Fig 2B). The analysis of the Core network showed a significant effect of group with S+ subjects having reduced functional connectivity in the frontal lobe, bilaterally (Fig 3A), and a significant effect of mutation with m+ subjects having reduced functional connectivity in the cingulate cortex (Fig 3B). The reduced connectivity in the left frontal cortex in S+ subjects was driven by S+m+ subjects having reduced connectivity compared to all other groups. Finally, asymptomatic m+ subjects compared to all other groups showed a medial frontal area of increased connectivity compared to all other groups (Fig. 3C).

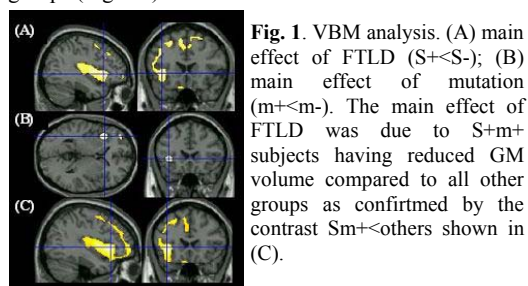


Fig. 1. VBM analysis. (A) main effect of FTLD (S+<S-); (B) main effect of mutation (m+<m-). The main effect of FTLD was due to S+m+ subjects having reduced GM volume compared to all other groups as confirmed by the contrast S+m+<others shown in (C).

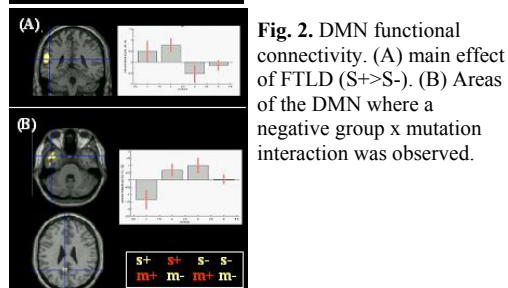


Fig. 2. DMN functional connectivity. (A) main effect of FTLD (S+>S-). (B) Areas of the DMN where a negative group x mutation interaction was observed.

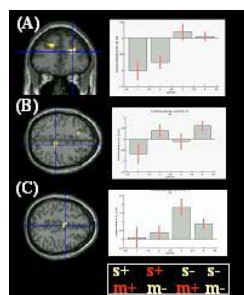


Fig 3. Core network functional connectivity. (A) Pattern of reduced connectivity in S+ subjects. (B) main effect of mutation in reducing the core network connectivity. (C) a region of the network where asymptomatic carriers showed increased connectivity compared to all other groups.

Discussion

This study indicates that PGRN is an independent contributor that accounts for some additional GM loss in the presence of FTLD. The core network is selectively disrupted in FTLD brains, and, again, the presence of PGRN mutation seems to be an additional factor that increases such an effect. In contrast, at the pre-clinical FTLD stage represented by non-symptomatic mutation carriers, the core network shows a region of increased connectivity. This might indicate the existence of compensatory mechanisms (brain plasticity) that contrast the early pathophysiological events induced by PGRN mutation. Finally, the increased functional connectivity observed in the DMN (left parietal cortex) of all symptomatic subjects, indicates a potential brain compensation in a network which is not primarily involved by the FTLD. Again, this sort of 'compensatory' mechanism seems to work less efficiently in symptomatic carriers, as demonstrated by a reduction of connectivity in the left temporal cortex and in the posterior cingulate, the latter being one of the most critical areas of the DMN.

References: 1. Crutz, et al. Nature 2006;442:920-4; 2. Baker, et al. Nature 2006; 24:916-9; 3. Ashburner and Friston. Neuroimage 2005;26:839-851. 4. van den Heuvel, et al. Hum Brain Mapp 2009; 30:3127-41.