The cognitive profile of prion disease: a prospective clinical and imaging study

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Abstract

Objectives: Prion diseases are dementing illnesses with poorly defined neuropsychological features. This is probably because the most common form, sporadic Creutzfeldt-Jakob disease, is often rapidly progressive with pervasive cognitive decline making detailed neuropsychological investigation difficult. This study, which includes patients with inherited, acquired (iatrogenic and variant) and sporadic forms of the disease, is the only large-scale neuropsychological investigation of this patient group ever undertaken and aimed to define a neuropsychological profile of human prion diseases. Methods: A tailored short cognitive examination of all of the patients (n = 81), with detailed neuropsychological testing in a subset with mild disease (n = 30) and correlation with demographic, clinical, genetic (PRNP mutation and polymorphic codon 129 genotype), and other variables (MRI brain signal change in cortex, basal ganglia or thalamus; quantitative research imaging, cerebrospinal fluid 14-3-3 protein). Results: Comparison with healthy controls showed patients to be impaired on all tasks. Principal components analysis showed a major axis of fronto-parietal dysfunction that accounted for approximately half of the variance observed. This correlated strongly with volume reduction in frontal and parietal gray matter on MRI. Examination of individual patients’ performances confirmed early impairment on this axis, suggesting characteristic cognitive features in mild disease: prominent executive impairment, parietal dysfunction, a largely expressive dysphasia, with reduced motor speed. Interpretation: Taken together with typical neurological features, these results complete a profile that should improve differential diagnosis in a clinical setting. We propose a tailored neuropsychological battery for early recognition of clinical onset of symptoms with potential for use in clinical trials involving at-risk individuals.

Introduction

Human prion diseases include those inherited as autosomal dominant traits, those acquired because of prion-contaminated food, medical products or instruments, and sporadic forms. Although dementia is a core clinical feature, most studies have focused on the neurological and psychiatric, rather than the specifically cognitive, signs and symptoms. Many patients are only diagnosed relatively late in the disease course, a function both of very rapid progression and its relative rarity. The question of whether there is any consistency to the cognitive profile has rarely been addressed.
Phenotypic heterogeneity is regarded as the norm with variability in presentation mainly reflecting the relative timing of cognitive to neurological and psychiatric features. Variant Creutzfeldt-Jakob disease (vCJD) predominantly affects a younger age group, with prominent early psychiatric and sensory symptoms, such as limb pain and dysesthesia. Iatrogenic CJD is generally a cerebellar syndrome followed by cognitive change at a relatively late stage of the illness. There are also differences amongst the inherited forms. For instance, patients with the P102L mutation typically experience cerebellar ataxia well before cognitive dysfunction emerges while in 6-OPRI (octapeptide repeat insertion, an inherited prion disease [IPD] mutation in PRNP) patients cognitive impairment is a prominent early sign, with milder or absent cerebellar signs initially.

While cognitive impairment in prion disease is usually considered to be generalized, some features have recurred in previous reports. Executive deficits have been reported in a number of studies. A second feature, often remarked but rarely investigated, is progressive loss of speech. Prominent visual symptoms – the “Heidenhain variant” of sporadic CJD (sCJD) – have sometimes been identified. Memory impairment has figured more significantly in some studies than others but is a less prominent feature than in other dementing illnesses. Finally, patients, even with rapidly progressive sCJD, sometimes present with focal cognitive deficits including hemispatial neglect, or language disturbance.

The view that this is a generalized dementia without distinctive cognitive features has been challenged in one study. Notwithstanding heterogeneity of presentation in six patients, common qualitative features were observed including periods of unresponsiveness, intrusion errors from both auditory and visual stimuli, perseveration in the context of preserved self-reflection, and preservation of awareness of illness. They suggested these features might be characteristic of the disease as such, reflecting a fundamental impairment in the activation and regulation of cortical activity from subcortical structures.

In the current study, comprising near comprehensive nationwide recruitment of patients with all types of prion disease, we had a unique opportunity to document for the first time the cognitive profile of a large cohort of prion disease patients including the refinement of an appropriate battery of tests. We analyzed performance on cognitive tests in comparison with matched controls, grouped by brain region, ranked by commonly used cognitive and functionally orientated rating scales, by statistical techniques used to reduce complex data sets, and by correlation with demographic and clinical variables, investigations and molecular factors known to be determinants of phenotypic heterogeneity. The opportunity to characterize such a profile offers the possibility of improved operational criteria for diagnosis of the disease.

Methods

Two cognitive batteries were used: a specially devised Short Cognitive Examination (SCE) which could be administered even to patients with moderately advanced disease in their homes, and a comprehensive neuropsychological examination for administration only to mildly affected patients. Using both of these batteries we aimed to detect a broad pattern of performance in the larger patient group, which could then be investigated in more detail in the smaller, less affected group.

Participants

Patients were recruited through the NHS National Prion Clinic (NPC) at the National Hospital for Neurology & Neurosurgery, UCLH NHS Foundation Trust, London, U.K. Ethics approval for the study was granted by the Eastern Multicentre Research Ethics Committee and informed consent for participation was given either by the patient or their next of kin. A total of 456 patients with suspected or confirmed prion disease were recruited to the National Prion Cohort Monitoring Study or MRC PRION-1 trial from 2004 to May 2013. Of these, 81 participants deemed to be symptomatic and able to complete the SCE, were included in the study. Participants were excluded if they were too impaired at the time of the initial assessment to complete the SCE (139 cases); if they were at risk of either genetic or iatrogenic disease but not symptomatic (21 cases); or if they were eventually found to have another neurological disorder (37 cases). Thirty patients with suspected or confirmed prion disease were recruited to the National Prion Cohort Monitoring Study or MRC PRION-1 trial from 2004 to May 2013. Of these, 81 participants deemed to be symptomatic and able to complete the SCE, were included in the study. Participants were excluded if they were too impaired at the time of the initial assessment to complete the SCE (139 cases); if they were at risk of either genetic or iatrogenic disease but not symptomatic (21 cases); or if they were eventually found to have another neurological disorder (37 cases). Thirty patients were well enough to travel and undergo comprehensive neuropsychological assessment all of which were conducted by D. C., usually in the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery. Definitive diagnosis of prion disease was made either by genetic testing in the case of inherited disease or by post-mortem neuropathology. A matched control group of 36 healthy individuals recruited from amongst the patients’ families, to control for possible confounding factors such as education and IQ, was also recruited to the study. This included participants at risk of IPD but who on testing were gene mutation negative. Thirty-three subjects from the original control group underwent neuropsychological testing in addition to the SCE.

Clinical testing

All participants underwent systematic neurological examination in addition to cognitive examination. The neuro-
logical assessment included the NPC-devised MRC Prion Disease Rating Scale which includes neurological, cognitive, and functional components and provides a measure of overall disease severity.\textsuperscript{20}

Cognitive investigation of the patients comprised two components:

1 The SCE included the Mini Mental State Examination (MMSE) and a battery of tests devised to target the cognitive domains reported to be vulnerable in prion disease.\textsuperscript{8,21} It included brief tests of the following (with maximum number of items in brackets): recognition memory (words [12] and faces [12]), attention (digit span[5]), parietal lobe function (spelling[6], calculation [4], praxis[10]), language (object naming[12], reading [5]), executive function (letter fluency [number of words in 60 sec], perception (incomplete letter recognition[3]), and processing speed (letter cancellation [time taken]).

2 \textit{Neuropsychological examination} which include a comprehensive battery of standardized tests: Current intellectual functioning (WAIS-III [Wechsler 1997]; seven sub-tests: vocabulary, similarities, digit span, arithmetic, picture completion, picture arrangement and block design); premorbid optimal level of function (National Adult Reading Test\textsuperscript{22}); Visual and verbal recognition memory (Recognition Memory Test\textsuperscript{22}); visual (AMIPB complex figure\textsuperscript{22}) and verbal recall (Paired Associate Learning\textsuperscript{22}) recall; Language including nonword repetition,\textsuperscript{26} category (“Animal”) fluency; object naming (Graded Naming Test (GNT)\textsuperscript{27}) synonym matching; and sentence comprehension (Test for Reception of Grammar [TROG]\textsuperscript{28}); Visual perception and visuospatial function (Visual object and space processing battery [VOSP] Object Decision, Cube Analysis\textsuperscript{29}; visuoconstruction\textsuperscript{24}); limb praxis (meaningful\textsuperscript{30}) and meaningless\textsuperscript{31} gesture; spelling (Graded Difficulty Spelling Test\textsuperscript{32}); and calculation (Graded Difficulty Calculation Test (GDCT)\textsuperscript{33}); Executive function (Modified Card Sorting Test\textsuperscript{34}; Stroop Test\textsuperscript{35}; Verbal fluency (FAS)\textsuperscript{36}; Trail Making Test [TMT] Part B\textsuperscript{37}); and Information processing speed (TMT Part A\textsuperscript{37}).

The neuropsychological assessment was carried out at the same time as the neurological and clinical investigations, or as close to that as possible.

\textbf{Statistical analysis}

We used analysis of variance (ANOVA) and independent \textit{t}-test or its nonparametric equivalent to compare patients’ and controls’ scores on individual components of the two batteries. Multiple comparisons were done between different components, however, these were not independent tests and therefore \textit{P} values uncorrected for multiple testing are presented. SCE scores were also subjected to a principal components analysis (PCA) with orthogonal varimax rotation to identify any clustering of individual measures. The PCA also generated axes (termed Axes 1, 2, etc. in rank order of declining proportion of variance explained) which were used to investigate possible correlation with demographic, clinical category, genetic (PRNP mutation and polymorphic codon 129 genotype), and investigation variables (MRI brain signal change in cortex, basal ganglia or thalamus, cerebrospinal fluid (CSF) 14-3-3 protein and electroencephalography [EEG]). To address the relative sensitivity of individual tasks comprising each of the two batteries, we calculated the proportion of patients whose performance was impaired on each test. Missing data were treated with a missing at random approach. Statistical analyses were performed using the statistical package for the social sciences V.11.5 (SPSS, IBM, New York).

\textbf{MRI studies}

Diagnostic MR brain images performed at multiple sites in the U.K. were acquired and re-reported by H. H. and categorized according to clinical normality/abnormality in cerebral cortex (two areas involved and excluding areas known to generate false-positive signal), thalamus, and basal ganglia. For the subgroup of patients who attended National Hospital for Neurology and Neurosurgery (NHNN) for detailed neuropsychological assessment, 3 T MRI was also acquired. Spatial processing for voxel based morphometry (VBM) was performed for structural T1-weighted data using SPM Version 8 software (SPM8, http://www.fil.ion.ucl.ac.uk/spm) as follows: (1) SPM8’s unified segmentation approach, which combines segmentation, bias correction, and normalization to the MNI (Montreal Neurological Institute) space into a single generative model.\textsuperscript{38} The rigid component of the normalization transformation was used to produce approximately aligned images for the following step. (2) Generation of a cohort-specific template for gray matter (GM) and white matter (WM) segments using DARTEL.\textsuperscript{21} (3) Warping and resampling of individual GM and WM segments to the cohort-specific template. Local intensities were modulated to account for volume changes associated with the normalization. (4) An isotropic 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel was applied to the gray and WM data sets. (5) An “objective” masking strategy\textsuperscript{39} was employed to define the voxels for subsequent statistical analysis on GM and WM segments separately. For statistical analysis a group level random effect model Analysis of Covariance (ANCOVA) consisting of diagnostic grouping (controls, symptomatic patients) with individual age and total intracranial volume (GM + WM + CSF segments) as covariates, was per-
formed. In the symptomatic patients, we also assessed the correlation between PCA Axis 1 and Axis 2 scores with GM and WM separately, with individual age and total intracranial volume as covariates. For multiple comparison correction we used voxel-wise false discovery rate (FDR) with \( P < 0.05 \). SPM-t maps were produced using a \( P < 0.05 \) level of significance after multiple comparison correction using FDR. After results were computed, they were affine transformed to MNI, by affine registering the Dartel template to the MNI space tissue prior probability maps. Results are displayed overlaid on the average of the warped T1 volumes, transformed to MNI space. To illustrate the actual change in GM fraction, a region of interest (ROI) was chosen in the area of the largest cluster of significant voxels. The ROI was manually drawn on the average warped and smoothed T1 volumes by an experienced neuroradiologist and verified on the averaged smoothed data sets to ensure the smoothing did not cause CSF contamination. The correlation between angular gyrus GM fraction and neuropsychology was assessed with the Spearman-rank correlation.

## Results

### Patient diagnosis

Demographic information and MMSE scores for the patients who completed the SCE are reported in Table 1(1). The diagnoses were: sCJD (\( n = 40/81, 49.5\% \)); IPD (\( n = 28/81, 34.5\% \)); iatrogenic CJD (human pituitary growth hormone) (\( n = 8/81, 10\% \)); or vCJD (\( n = 5/81, 6\% \)). The sCJD group included patients will all three genotypes at polymorphic codon 129 of \( PRNP \) (129MM = 7, 129MV = 20, 129VV = 12, 1 not tested). The IPD group were made up of patients with nine different genetic mutations (P102L \( n = 7 \), Y163X \( n = 2 \), 5-OPRI \( n = 4 \), 6-OPRI \( n = 4 \), E200K \( n = 4 \), E196K \( n = 1 \), D178N \( n = 2 \), Q212P \( n = 1 \), A117V \( n = 3 \)). Sixty-two patients subsequently died, 46 of whom had an autopsy; the clinical diagnosis of prion disease was confirmed in all these. The control group was slightly younger on average than the patients (\( P = 0.020 \)) and, unsurprisingly, their MMSE scores were significantly higher than those of the patients (\( P < 0.001 \)).

### Short cognitive examination

Disease severity, early signs, and symptoms and their relative distribution can be seen in Table 2(1). As expected, there was a highly significant difference in mean score between patients and healthy controls on all components of the SCE (see Table S1). Comparison of the proportion of patients with possible or probable impairment on each test showed highly significant differences between tests (ANOVA, \( P < 0.001 \), Fig. 1). These results raised the possibility that some cognitive domains may be more vulnerable than others in this disease. Subgroups, including disease category, age of onset, gender, \( PRNP \) codon 129, and imaging variables, showed highly consistent test sensitivities (see Table S3). Post hoc analyses also raised the possibility of homogenous subgroups of tests (e.g., Letter fluency, calculation, naming, letter cancelling, spelling, praxis vs. all others, \( P = 0.05 \), Student–Newman–Keuls method).

We went on to use PCA as a hypothesis free method to identify key structures in the psychological data set. The components can be conceptualized as a single variable derived from combinations of test scores that account for

| Table 1. Demographic information (1) with MMSE, for patients assessed on the SCE; and (2) with estimated IQ, for patients assessed on the neuropsychological examination. |
|-----------------------------------------------|
| **(1) SCE** | | **(2) Neuropsychological examination** |
| **Patients** | **N** | **Age, mean (SD)** | **MMSE, mean (SD)** | **N** | **Age, mean (SD)** | **NART IQ, mean (SD)** |
| Male | 48 | 54.0 (14.0) | 20.7 (6.6) | 18 | 51.0 (12.3) | 105.1 (15.8) |
| Female | 33 | 56.8 (11.6) | 21.8 (5.0) | 18 | 48.0 (13.6) | 108.0 (11.2) |
| Total | 81 | 55.4 (13.7) | 21.2 (4.4) | 36 | 49.3 (12.9) | 104.0 (12.5) |

SCE, short cognitive examination; NART, national adult reading test.
a maximal proportion of overall variance. The first component (Axis 1) explained 42.1% of the variance in the patient group. The second component (Axis 2) accounted for just 15.4% of the variance (Table 3). Axis 1 was most strongly correlated with the following tasks: spelling, calculation, naming, digit span, reading, praxis and letter fluency, very similar to the homogeneous subgroup suggested by post hoc studies above. No significant correlations were found between Axis 1 and diagnosis, mutation, age, gender, or PRNP codon 129.

MRI analysis

From 30 patients attending for detailed neuropsychological examination at NHNN, 23 patients had 3 T research MRI. Estimated GM partial volume fraction significantly correlated with Axis 1 (reduced GM content was associated with reduced Axis 1 score) in numerous frontal and parietal regions including the superior parietal lobule, supramarginal gyrus, inferior temporal gyrus, middle frontal gyrus, inferior frontal gyrus and pars triangularis, more on the left than on the right (Fig. 2). There were no significant correlations between Axis 2 with either GM or WM, nor between Axis 1 and WM. Angular gyrus GM partial volume fraction correlated significantly with Axis 1 (Fig. 2C) with a Spearman rank correlation coefficient of 0.602 (P = 0.004).

Detailed neuropsychological examination

There was considerable heterogeneity in clinical presentation of the 30 patients undergoing detailed neuropsychological assessment (see Tables 1(2) and 2(2) for clinical and demographic information). There was no age-difference between the patients and the healthy controls who also underwent neuropsychological examination (t [61] = 0.546, P = 0.590). In estimating IQ, based on the national adult reading test (NART) reading test, three patients with dyslexia were removed from the analysis. Estimated IQ was very slightly higher amongst the healthy controls (mean = 109.30, SD = 11.70) than patients (mean = 103.0, SD = 13.6, P = 0.059).

Comparison of the difference between patients’ and controls’ optimal full-scale IQ (FSIQ) as estimated on the NART and current FSIQ as measured on the WAIS-III showed a significant change for the patients (Wilcoxon signed-rank test, P < 0.001) but not for the controls (P = 0.062), confirming a marked decline in general intellectual function in this disease. A significant difference between patients and healthy controls was found on all...
tasks, as was the case with the SCE (see Table S2). Thus, here again the group analysis was not as helpful as interrogation of individual patients’ scores in terms of elucidating patterns of performance.

Based on our findings from analysis of the SCE we predicted that eight tasks would be most impaired on detailed neuropsychological assessment (Stroop Test, TMT Part A, TMT Part B, Praxis, GDCT, Animal fluency, FAS, and GNT) compared with the 17 other tasks (see Table 4). Considering only those impaired (>2 SD difference from the mean of controls), 152/240 patient-tests were impaired from those tests which were a priori expected to be most abnormal; 207/510 patient-tests were impaired from the remainder (P < 0.0001, Fisher’s exact test).

Table 4 shows for each patient whether performance was impaired (>1 SD or >2 SD outside the mean for healthy controls) on each test. The left-most group of columns (gray headings) include the cognitive domains reflected in Axis 1 and representing tests of executive function, language, and parietal lobe function, and praxis. The MRC Scale score can be seen alongside the patients’ MMSE score. The tests are arranged in each domain in order of the decreasing percentage of patients liable to be affected in that domain. Table 4 also demonstrates that patients with more severe cognitive deficits as identified on the MMSE were impaired in all domains, and sometimes on all or almost all the tasks in each domain. What is of interest here is domains in which the more mildly affected patients were also shown to have deficits, thus offering the possibility of eliciting a more subtle pattern of cognitive decline.

All of the patients were impaired on at least one executive task, with a majority (23/30; 77%) performing below healthy controls on three of the four tests of executive function. A significant proportion was also impaired on tests of language (24/30; 80%). This included not only category fluency (24/30; 80%) and object naming (GNT: 20/30; 67%), but also sentence comprehension (TROG: 21/30; 70%). In contrast only 50% (15/30) had difficulty with a nonspoken test of semantic knowledge (Concrete Synonym Matching), and only 47% (14/30) on each of two tests of repetition. In terms of parietal function both calculation GDCT: 23/30; 77%) and praxis (21/30; 70%) were impaired even in more mildly affected patients. While performance on the other parietal tests individually were less liable to be affected as many as 83% (25/30) of patients experienced parietal lobe dysfunction of one kind or another. Thus, confirming the outcome of the PCA for the SCE, the most prominent cognitive symptom, even in

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**Table 3. Principal components analysis axis loadings. Bold tests are the strongest correlates of each axis**

|                  | 1      | 2      |
|------------------|--------|--------|
| Spelling         | 0.828  | 0.226  |
| Calculation      | 0.792  | 0.194  |
| Naming           | 0.761  | 0.243  |
| Digit span       | 0.758  | 0.089  |
| Reading          | 0.693  | −0.157 |
| Praxis           | 0.594  | 0.376  |
| Letter fluency   | 0.552  | 0.441  |
| Fragmented letters | 0.409 | 0.367  |
| MRC scale        | −0.010 | 0.795  |
| Memory – visual  | 0.310  | 0.785  |
| Letter cancel    | −0.054 | −0.773 |
| Memory – verbal  | 0.226  | 0.693  |

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**Figure 2. Correlation between gray matter volume reduction and decline in Axis 1 score in symptomatic patients. (A) Axial and (B) coronal SPM-t maps showing in red-yellow voxels demonstrating statistically significant correlation between GM volume reduction and decline in 1st SCE-PCA component (Axis 1) score in symptomatic patients (n = 23). Results are shown using false discovery rate q < 0.05 to control for multiple comparisons, and are overlaid on the average of all the anatomical data set registered to the group-specific template. The colorbar range for t-values is 2.5–5. (C) Scatter plot showing correlation of GM partial volume fraction with Axis 1 over an ROI manually drawn in the left angular gyrus: Spearman-rank correlation coefficient = 0.602, P = 0.004. SCE, short cognitive examination; PCA, principal components analysis; GM, gray matter; ROI, region of interest.**
Table 4. Summary of the neuropsychological data for n = 30 prion patients.

| Case | MRC Scale | Age of onset | Gender | Diagnosis | Cognition | MMSE | Set A | TMP A | TMP B | Pairs total | Animal fluency | FAS | GNF | APMPB | Wada TMT | TMT B | Reaction B | Reaction A | Reaction C | Reaction D | Reaction E | Reaction F | Reaction G | Reaction H | Reaction I | Reaction J | Reaction K | Reaction L | Reaction M | Reaction N | Reaction O | Reaction P | Reaction Q | Reaction R | Reaction S | Reaction T | Reaction U | Reaction V | Reaction W | Reaction X | Reaction Y | Reaction Z | Reaction AA | Reaction AB | Reaction AC | Reaction AD | Reaction AE | Reaction AF | Reaction AG | Reaction AH | Reaction AI | Reaction AJ | Reaction AK | Reaction AL | Reaction AM | Reaction AN | Reaction AO | Reaction AP | Reaction AQ | Reaction AR | Reaction AS | Reaction AT | Reaction AU | Reaction AV | Reaction AW | Reaction AX | Reaction AY | Reaction AZ | Reaction BA | Reaction BB | Reaction BC | Reaction BD | Reaction BE | Reaction BF | Reaction BG | Reaction BH | Reaction BI | Reaction BJ | Reaction BK | Reaction BL | Reaction BM | Reaction BN | Reaction BO | Reaction BP | Reaction BQ | Reaction BR | Reaction BS | Reaction BT | Reaction BU | Reaction BV | Reaction BW | Reaction BX | Reaction BY | Reaction BZ | Reaction CA | Reaction CB | Reaction CC | Reaction CD | Reaction CE | Reaction CF | Reaction CG | Reaction CH | Reaction CI | Reaction CJ | Reaction CK | Reaction CL | Reaction CM | Reaction CN | Reaction CO | Reaction CP | Reaction CQ | Reaction CR | Reaction CS | Reaction CT | Reaction CU | Reaction CV | Reaction CW | Reaction CX | Reaction CY | Reaction CZ | Reaction DA | Reaction DB | Reaction DC | Reaction DD | Reaction DE | Reaction DF | Reaction DG | Reaction DH | Reaction DI | Reaction DJ | Reaction DK | Reaction DL | Reaction DM | Reaction DN | Reaction DO | Reaction DP | Reaction DQ | Reaction DR | Reaction DS | Reaction DT | Reaction DU | Reaction DV | Reaction DW | Reaction DX | Reaction DY | Reaction DZ | Reaction EA | Reaction EB | Reaction EC | Reaction ED | Reaction EE | Reaction EF | Reaction EG | Reaction EH | Reaction EI | Reaction EJ | Reaction EK | Reaction EL | Reaction EM | Reaction EN | Reaction EO | Reaction EP | Reaction EQ | Reaction ER | Reaction ES | Reaction ET | Reaction EU | Reaction EV | Reaction EW | Reaction EX | Reaction EY | Reaction EZ | Reaction FA | Reaction FB | Reaction FC | Reaction FD | Reaction FE | Reaction FF | Reaction FG | Reaction FH | Reaction FI | Reaction FJ | Reaction FK | Reaction FL | Reaction FM | Reaction FN | Reaction FO | Reaction FP | Reaction FQ | Reaction FR | Reaction FS | Reaction FT | Reaction FU | Reaction FV | Reaction FW | Reaction FX | Reaction FY | Reaction FZ | Reaction GA | Reaction GB | Reaction GC | Reaction GD | Reaction GE | Reaction GF | Reaction GG | Reaction GH | Reaction GI | Reaction GJ | Reaction GK | Reaction GL | Reaction GM | Reaction GN | Reaction GO | Reaction GP | Reaction GQ | Reaction GR | Reaction GS | Reaction GT | Reaction GU | Reaction GV | Reaction GW | Reaction GX | Reaction GY | Reaction GZ | Reaction HA | Reaction HB | Reaction HC | Reaction HD | Reaction HE | Reaction HF | Reaction HG | Reaction HI | Reaction HJ | Reaction HK | Reaction HL | Reaction HM | Reaction HN | Reaction HO | Reaction HP | Reaction HQ | Reaction HR | Reaction HS | Reaction HT | ReactionHU | Reaction HV | Reaction HW | ReactionHX | Reaction HY | Reaction HZ | Reaction IA | Reaction IB | Reaction IC | Reaction ID | Reaction IE | Reaction IF | Reaction IG | Reaction IH | Reaction IJ | Reaction IK | Reaction IL | Reaction IM | Reaction IN | Reaction IO | Reaction IP | Reaction IQ | Reaction IR | Reaction IS | Reaction IT | Reaction IU | Reaction IV | Reaction IW | Reaction IX | Reaction IY | Reaction IZ | Reaction JA | Reaction JB | Reaction JC | Reaction JD | Reaction JE | Reaction JF | Reaction JG | Reaction JH | Reaction JJ | Reaction JK | Reaction JL | Reaction JM | Reaction JN | Reaction JO | Reaction JP | Reaction JQ | Reaction JR | Reaction JS | Reaction JT | Reaction JU | Reaction JV | Reaction JW | Reaction JX | Reaction JY | Reaction JZ | Reaction KA | Reaction KB | Reaction KC | Reaction KD | Reaction KE | ReactionKF | Reaction KG | Reaction KH | Reaction KI | Reaction KJ | Reaction KK | Reaction KL | Reaction KM | Reaction KN | Reaction KO | Reaction KP | Reaction KQ | Reaction KR | Reaction KS | Reaction KT | Reaction KU | Reaction KV | Reaction KW | Reaction KX | Reaction KY | Reaction KZ | Reaction LA | Reaction LB | Reaction LC | Reaction LD | Reaction LE | Reaction LF | Reaction LG | Reaction LH | Reaction LI | Reaction LJ | Reaction LK | Reaction LL | Reaction LM | Reaction LN | Reaction LO | Reaction LP | Reaction LQ | Reaction LR | Reaction LS | Reaction LT | Reaction LU | Reaction LV | Reaction LW | Reaction LX | Reaction LY | Reaction LZ | Reaction MA | Reaction MB | Reaction MC | Reaction MD | Reaction ME | Reaction MF | Reaction MG | Reaction MH | Reaction MI | Reaction MJ | Reaction MK | Reaction ML | Reaction MN | Reaction MO | Reaction MP | Reaction MQ | Reaction MR | Reaction MS | Reaction MT | Reaction MU | Reaction MV | Reaction MW | Reaction MX | Reaction MY | Reaction MZ | Reaction NA | Reaction NB | Reaction NC | Reaction ND | Reaction NE | Reaction NF | Reaction NG | Reaction NH | Reaction NI | Reaction NJ | Reaction NK | Reaction NL | Reaction NM | Reaction NN | Reaction NO | Reaction NP | Reaction NQ | Reaction NR | Reaction NS | Reaction NT | Reaction NU | Reaction NV | Reaction NW | Reaction NX | Reaction NY | Reaction NZ | Reaction OA | Reaction OB | Reaction OC | Reaction OD | Reaction OE | Reaction OF | Reaction OG | Reaction OH | Reaction OI | Reaction OJ | Reaction OK | Reaction OL | Reaction OM | Reaction ON | Reaction OO | Reaction OP | Reaction OQ | Reaction OR | Reaction OS | Reaction OT | Reaction OU | Reaction OV | Reaction OW | Reaction OW | Reaction OX | Reaction OY | Reaction OZ | Reaction PA | Reaction PB | Reaction PC | Reaction PD | Reaction PE | Reaction PF | Reaction PG | Reaction PH | Reaction PI | Reaction PJ | Reaction PK | Reaction PL | Reaction PM | Reaction PN | Reaction PO | Reaction PP | Reaction PQ | Reaction PR | Reaction PS | Reaction PT | Reaction PU | Reaction PV | Reaction PW | Reaction PX | Reaction PY | Reaction PZ | Reaction QA | Reaction QB | Reaction QC | Reaction QD | Reaction QE | Reaction QF | Reaction QG | Reaction QH | Reaction QI | Reaction QJ | Reaction QK | ReactionQL | Reaction QM | Reaction QN | Reaction QO | Reaction QP | Reaction QQ | Reaction QR | Reaction QS | Reaction QT | Reaction QU | Reaction QV | Reaction QW | Reaction QX | Reaction QY | Reaction QZ | Reaction RA | Reaction RB | Reaction RC | Reaction RD | Reaction RE | Reaction RF | Reaction RG | Reaction RH | Reaction RI | Reaction RJ | Reaction RK | Reaction RL | Reaction RM | Reaction RN | Reaction RO | Reaction RP | Reaction RQ | Reaction RR | Reaction RS | Reaction RT | Reaction RU | Reaction RV | Reaction RW | Reaction RX | Reaction RY | Reaction RZ | Reaction SA | Reaction SB | Reaction SC | Reaction SD | Reaction SE | Reaction SF | Reaction SG | Reaction SH | Reaction SI | Reaction SJ | Reaction SK | Reaction SL | Reaction SM | Reaction SN | Reaction SO | Reaction SP | Reaction SQ | Reaction SR | Reaction SS | Reaction ST | Reaction SU | Reaction SV | Reaction SW | Reaction SX | Reaction SY | Reaction SZ | Reaction TA | Reaction TB | Reaction TC | Reaction TD | Reaction TE | Reaction TF | Reaction TG | Reaction TH | Reaction TI | Reaction TJ | Reaction TK | Reaction TL | Reaction TM | Reaction TN | Reaction TO | Reaction TP | Reaction TQ | Reaction TR | Reaction TS | Reaction TT | Reaction TU | Reaction TV | Reaction TW | Reaction TX | Reaction TY | Reaction TZ | Reaction UA | Reaction UB | Reaction UC | Reaction UD | Reaction UE | Reaction UF | Reaction UG | Reaction UH | Reaction UI | Reaction UJ | Reaction UK | Reaction UL | Reaction UM | Reaction UN | Reaction UO | Reaction UP | Reaction UQ | Reaction UR | Reaction US | Reaction UT | Reaction UU | Reaction UV | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction VA | Reaction VB | Reaction VC | Reaction VD | Reaction VE | Reaction VF | Reaction VG | Reaction VH | Reaction VI | Reaction VJ | Reaction VK | Reaction VL | Reaction VM | Reaction VN | Reaction VO | Reaction VP | Reaction VQ | Reaction VR | Reaction VS | Reaction VT | Reaction UV | Reaction UU | Reaction UV | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction WA | Reaction WB | Reaction WC | Reaction WD | Reaction WE | Reaction WF | Reaction WG | Reaction WH | Reaction WI | Reaction WJ | Reaction WK | Reaction WL | Reaction WM | Reaction WN | Reaction WO | Reaction WP | Reaction WQ | Reaction WR | Reaction WS | Reaction WT | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction VA | Reaction VB | Reaction VC | Reaction VD | Reaction VE | Reaction VF | Reaction VG | Reaction VH | Reaction VI | Reaction VJ | Reaction VK | Reaction VL | Reaction VM | Reaction VN | Reaction VO | Reaction VP | Reaction VQ | Reaction VR | Reaction VS | Reaction VT | Reaction UV | Reaction UU | Reaction UV | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction WA | Reaction WB | Reaction WC | Reaction WD | Reaction WE | Reaction WF | Reaction WG | Reaction WH | Reaction WI | Reaction WJ | Reaction WK | Reaction WL | Reaction WM | Reaction WN | Reaction WO | Reaction WP | Reaction WQ | Reaction WR | Reaction WS | Reaction WT | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction VA | Reaction VB | Reaction VC | Reaction VD | Reaction VE | Reaction VF | Reaction VG | Reaction VH | Reaction VI | Reaction VJ | Reaction VK | Reaction VL | Reaction VM | Reaction VN | Reaction VO | Reaction VP | Reaction VQ | Reaction VR | Reaction VS | Reaction VT | Reaction UV | Reaction UU | Reaction UV | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction WA | Reaction WB | Reaction WC | Reaction WD | Reaction WE | Reaction WF | Reaction WG | Reaction WH | Reaction WI | Reaction WJ | Reaction WK | Reaction WL | Reaction WM | Reaction WN | Reaction WO | Reaction WP | Reaction WQ | Reaction WR | Reaction WS | Reaction WT | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction VA | Reaction VB | Reaction VC | Reaction VD | Reaction VE | Reaction VF | Reaction VG | Reaction VH | Reaction VI | Reaction VJ | Reaction VK | Reaction VL | Reaction VM | Reaction VN | Reaction VO | Reaction VP | Reaction VQ | Reaction VR | Reaction VS | Reaction VT | Reaction UV | Reaction UU | Reaction UV | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction WA | Reaction WB | Reaction WC | Reaction WD | Reaction WE | Reaction WF | Reaction WG | Reaction WH | Reaction WI | Reaction WJ | Reaction WK | Reaction WL | Reaction WM | Reaction WN | Reaction WO | Reaction WP | Reaction WQ | Reaction WR | Reaction WS | Reaction WT | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction VA | Reaction VB | Reaction VC | Reaction VD | Reaction VE | Reaction VF | Reaction VG | Reaction VH | Reaction VI | Reaction VJ | Reaction VK | Reaction VL | Reaction VM | Reaction VN | Reaction VO | Reaction VP | Reaction VQ | Reaction VR | Reaction VS | Reaction VT | Reaction UV | Reaction UU | Reaction UV | Reaction UW | Reaction UX | Reaction UY | Reaction UZ | Reaction WA | Reaction WB | Reaction WC | Reaction WD | Reaction WE | Reaction WF | Reaction WG | Reaction WH | Reaction WI | Reaction WJ | Reaction WK | Rea...
the context of mild disease, was executive function with performance also poor on tests of both language (27/30; 90%) and, to a slightly lesser extent, parietal function (25/30; 83%).

Turning to the other cognitive domains, of the memory tasks, nonverbal recall was the most liable to be affected. Of the patients who performed poorly at figure recall, however, 75% (18/24) also scored poorly on the copy condition of the task, with which scores on the memory task were strongly correlated (r = 0.563, P < 0.001). This likely reflects the significant visuospatial demand of this task. Fewer patients were impaired on the other memory tasks (13/30; 43%–19/30; 63%), consistent with the fact that memory did not load significantly on the first component of the PCA. A large proportion of patients (25/30; 83%) were impaired on a test of psychomotor processing speed (TMTA), a task with strong visuoperceptual and motor demands. Fewer were affected on two less perceptually demanding tests of speed and attention (Reading time on the Stroop Test: 15/30; 50%; Forward Digits: 14/30; 47%). In summary, consistent with the findings on the SCE, the individual neuropsychology patient data revealed a profile comprising prominent executive, language and parietal deficits with memory, speed and attention relatively spared. This was most evident in the ten most mildly affected patients (Table 4, cases 1–10, MMSE ≥29).

Discussion

We have studied a large group of mildly affected prion disease patients by comprehensive, systematic cognitive investigation, and correlated these measures with clinical and molecular investigation. Consistent with the view that prion disease gives rise to pervasive cognitive decline, most patients were impaired in all or most cognitive domains. Nevertheless, principle component analysis revealed an axis comprising tests of frontal executive function, language and parietal functions, which accounted for almost half the variance in the sample. This axis also correlated strongly with GM atrophy in frontal and parietal areas detected on MRI. When patients were ranked by MMSE score, the implicated tests were found to be impaired in incipient disease. Taken together, these findings indicate that a coherent constellation of cognitive variables associated with fronto-parietal function can be considered the leading cognitive features in prion disease, irrespective of etiology.

Executive dysfunction was shown to be a leading cognitive symptom, with all patients impaired in this domain. Executive deficits are often a feature of dementia syndromes but they are usually not the leading sign, although PSP may be an exception in this regard. Executive deficits were accompanied by personality change—irritability, aggressiveness, emotional lability—in about half of patients undergoing either the SCE or full neuropsychological assessment. There is little suggestion in prion disease, however, of the disorder of social cognition with disinhibition seen in behavioral variant fronto-temporal dementia (bvFTD).

Even mildly affected patients were impaired on some language tasks: letter fluency, animal fluency, sentence comprehension, and object naming. Fewer were impaired on tests of repetition or semantic knowledge. Unlike the logopaenia associated with repetition deficits seen in Alzheimer’s disease, prion patients have reduced output and poor sentence comprehension without repetition deficits, suggesting an executive rather than a phonological underpinning to the language disorder, the precise nature of which is yet to be elucidated.

Although memory complaints are common, memory contributed only to the second axis of the PCA. Just half the sample performed poorly on all or even most of the memory tasks. Many patients were impaired on the adult memory and information processing battery (AMIIPB) test of delayed figure recall although, as suggested earlier, this was partly due to impaired visuospatial function, evident in a poor figure copy. Clinically, prion patients are not repetitive in conversation, do not characteristically fail to recognize clinicians and others, and do not seem bewildered in their forgetfulness in the way that patients with Alzheimer’s disease (AD) do. These findings confirm the impression that, unlike typical AD or even bvFTD, an amnesic syndrome per se is not a particularly prominent feature. This may reflect the distribution of pathological changes, implicating the thalamus and basal ganglia in prion disease rather than the frontal, temporal, and posterior cortical regions known to be differentially affected in AD and FTD.

Although the first component of the PCA included digit span, calculation, and reading, detailed neuropsychological assessment of these functions showed only calculation to be vulnerable in the majority of patients. On the other hand taking all parietal tasks into account, many patients were impaired in this domain (83%). Apraxia was present in more than two-thirds of cases. Thus, although there is evidence of significant parietal compromise bilaterally, the specific symptomatology is somewhat variable from case to case.

The cognitive signs in mild prion disease thus comprise executive deficits, a largely expressive language disorder, and a constellation of parietal signs including visuospatial impairment and apraxia. Memory is less markedly affected as are semantic knowledge, processing speed and attention. The cognitive deficits arise in the context of a movement disorder in the form of ataxia with other neurological signs including myoclonus and apraxia affecting a smaller proportion of patients. From the point of view
of differential diagnosis, prion disease thus resembles movement disorders with associated dementia syndromes including corticobasal degeneration (CBD), PSP, Amyotrophic lateral sclerosis (ALS), and perhaps Lewy body disease. A review of the CBD literature,\textsuperscript{46} yielded a very similar result to that reported here: heterogeneity of presentation but with characteristic features including limb apraxia, constructional and visuospatial difficulties, agraphia, frontal dysfunction, and a nonfluent aphasia. Episodic memory was variable, but when present impairment tended to be milder than in Alzheimer’s disease. Semantic memory is relatively preserved but a nonfluent speech disturbance is common, and may be the presenting feature.\textsuperscript{46} A similar neuropsychological profile has also been reported in PSP\textsuperscript{47} without the prominent language disorder and with a different constellation of neurological signs. Language and executive deficits have been found to be the most prominent cognitive features in ALS, together with changes in behavior and social cognition. Parietal signs are less frequent and the neurological concomitants are also very different from those seen in prion disease.\textsuperscript{18,49} Dementia with Lewy bodies also falls within the constellation with a characteristic profile of deficits in visuospatial ability and frontal executive function accompanied by mild-to-moderate Parkinsonism.\textsuperscript{50} Language disturbance is not a prominent feature. Prion disease is thus most similar to CBD but with both a language disorder and motor features that are distinctly different from that condition in the majority of patients.

The results of this study give strong indications for an appropriate test battery for early diagnosis of prion disease. In our view, this should comprise tests of: (1) executive function including response inhibition (Stroop) and generativity (verbal fluency); (2) tests of parietal function including higher order visuospatial function (complex figure copy), calculation and praxis; (3) tests of language including language production (category fluency, nonword repetition) and sentence comprehension; (4) tests of speed of information processing. Tests of memory, visual processing, reading and attention should also be included to avoid false positive findings.

In summary, this is the only large study of the neuropsychology of prion disease ever undertaken. Overall, the results confirm that all patients ultimately develop a global cognitive impairment. However, our data clearly show that frontal and parietal functions are particularly vulnerable in the context of mild disease, even allowing for differences in the overall pattern of symptomatology, including neurological and psychiatric features, in some forms of the disease. This neuropsychological profile taken together with the characteristic neurological features of the disease constitutes a signature that should lead to more straightforward and rapid differential diagnosis of incipient cases in a clinical setting. Given the prospect of further clinical trials for prion disease, we have recommended that functionally orientated scales should be used in rapidly progressive patients.\textsuperscript{51} Asymptomatic at-risk individuals and early symptomatic patients, such as those studied in this paper, represent an alternative and attractive group to target with an experimental therapy, assuming an adequate safety profile, prior to extensive neuronal damage. Future work building on this study will be directed toward operationalization of a neuropsychological test battery and natural history database to enable timing of disease onset and document cognitive progression in these patient groups. This may be facilitated by further characterization and differentiation of the language disorder in prion disease, in comparison with those found in frontotemporal lobar degeneration and Alzheimer’s disease.

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**Conflict of Interest**

None declared.
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Supporting Information
Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of patients’ and controls’ mean scores on all components of the SCE using the Mann–Whitney U-Test.
Table S2. Comparison of patients’ and controls’ mean scores on all components of the Neuropsychological Examination using the Mann–Whitney U-Test.
Table S3. Consistent impairments in prion disease subgroups. Ranking of proportion of subjects impaired or possibly impaired (>1 SD below mean, or imperfect score if all controls scored perfectly) from most to least proportion impaired. The proportion impaired in each neuropsychological test was remarkably consistent in the known subgroups of disease, early age of onset, gender, PRNP codon 129 genotype and imaging findings. Note that too few subjects had normal CSF or EEG examinations to allow for meaningful comparisons of these diagnostic tests.