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RESEARCH ARTICLE

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.[1] Iatrogenic CJD is generally a cerebellar syndrome followed by cognitive change at a relatively late stage of the illness.[2,3] There are also differences amongst the inherited forms. For instance, patients with the P102L mutation typically experience cerebellar ataxia well before cognitive dysfunction emerges[4,5] while in 6-OPRI (octapeptide repeat insertion, an inherited prion disease [IPD] mutation in *PRNP*) patients cognitive impairment is a prominent early sign,[6,7] 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.[8–10] A second feature, often remarked but rarely investigated, is progressive loss of speech.[10–13] Prominent visual symptoms – the "Heidenhain variant" of sporadic CJD (sCJD) – have sometimes been identified.[14,15] Memory impairment has figured more significantly in some studies than others[9,10] 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,[16] or language disturbance.[12,17]

The view that this is a generalized dementia without distinctive cognitive features has been challenged in one study.[10] 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.[18,19]

In the current study, comprising near comprehensive nationwide recruitment of patients with all types of prion disease[20] 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 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.[20]

Cognitive investigation of the patients comprised two components:

1 The SCE included the Mini Mental State Examination (MMSE) and a battery of tasks devised to target the cognitive domains reported to be vulnerable in prion disease.[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 *Neuropsychological examination* which include a comprehensive battery of standardized tests: Current intellectual functioning (WAIS-III [Wechsler 1997]; seven subtests: vocabulary, similarities, digit span, arithmetic, picture completion, picture arrangement and block design); premorbid optimal level of function (National Adult Reading Test[22]); Visual and verbal recognition memory (Recognition Memory Test[23]); visual (AMIPB complex figure[24]) and verbal recall (Paired Associate Learning[25]) recall; Language including nonword repetition,[26] category ("Animal") fluency; object naming (Graded Naming Test (GNT)[27]) synonym matching; and sentence comprehension (Test for Reception of Grammar [TROG][28]); Visual perception and visuospatial function (Visual object and space processing battery [VOSP] Object Decision, Cube Analysis[29]; visuoconstruction[24]); limb praxis (meaningful[30]) and meaningless[31] gesture; spelling (Graded Difficulty Spelling Test[32]); and calculation (Graded Difficulty Calculation Test (GDCT)[33]); Executive function (Modified Card Sorting Test[34]; Stroop Test[35]; Verbal fluency (FAS)[36]; Trail Making Test [TMT] Part B[37]); and Information processing speed (TMT Part A[37]).

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

Statistical analysis

We used analysis of variance (ANOVA) and independent *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 *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).

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.[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.[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[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.

	Patients			Controls		
	N	Age, mean (SD)	MMSE, mean (SD)	*N*	Age, mean (SD)	MMSE, mean (SD)
(1) SCE						
Male	48	54.0 (14.0)	20.7 (6. 6)	18	51.0 (12.3)	29 (1.0)
Female	33	56.8 (11.6)	21.8 (5.0)	18	48.0 (13.6)	30 (0.70)
Total	81	55.4 (13.7)	21.2 (4.4)	36	49.3 (12.9)	29.5 (0.90)
	Patients			Controls		
	N	Age, mean (SD)	NART IQ, mean (SD)	*N*	Age, mean (SD)	NART IQ, mean (SD)
(2) Neuropsychological examination						
Male	16	49.7 (10.2)	105.1 (15.8)	17	50.0 (12.5)	104 (11.2)
Female	11	52.0 (12.4)	99.9 (9.5)	16	47.0 (14.5)	108 (15.9)
Total	30	50.6 (11.0)	103.0 (13.6)	33	49.0 (13.4)	106 (13.6)

SCE, short cognitive examination; NART, national adult reading test.

Table 2. Clinical features at the time of (1) SCE and (2) neuropsychological examination. The two most dominant clinical features are shown in bold.

Clinical feature	(1) SCE (n = 81) *N* (%) patients affected	(2) Neuropsychological examination (n = 30) *N* (%) patients affected
Cognitive complaint	**72 (89)**	**22 (73)**
Ataxia	**63 (78)**	**16 (53)**
Anxiety/depression	32 (39)	7 (23)
Speech difficulty	28 (35)	6 (20)
Personality change[1]	28 (35)	10 (33)
Apraxia	28 (35)	8 (27)
Myoclonus	26 (32)	6 (20)
Extra-pyramidal signs	19 (23)	5 (17)
Hallucinations/delusions	19 (23)	4 (13)
Pyramidal signs	17 (21)	1 (3)
Sensory Disturbance	17 (21)	1 (3)
Diarrhea	2 (2)	1 (3)

SCE, short cognitive examination.
[1]Aggressivity/irritability; withdrawal/loss of drive; emotional lability.

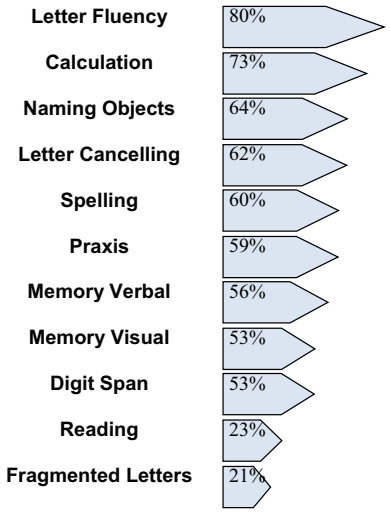

Figure 1. Percentage of patients impaired on each short cognitive examination task.

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

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**

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:

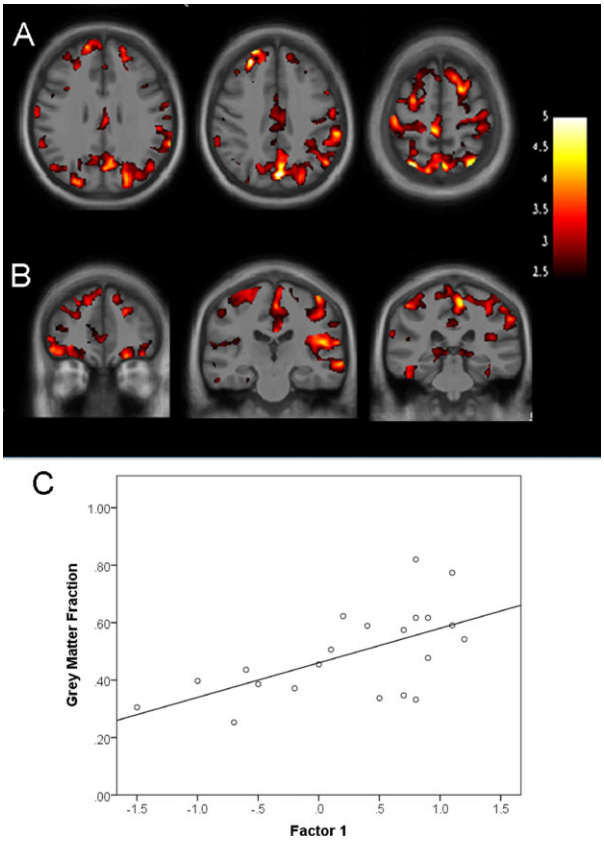

Figure 2. Correlation between gray matter volume reduction and decline in Axis 1 score in symptomatic patients. (A) Axial and (B) coronal SPM-t maps showing in red–yellow voxels demonstrating statistically significant correlation between GM volume reduction and decline in 1st SCE-PCA component (Axis 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.

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 GDC: 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

Table 4. Summary of the neuropsychological data for $n = 30$ prion patients.

Case	MRC scale	Age of onset	Gender	Diagnosis	Codon 129	MMSE	Stroop	TMT A	TMT B	Praxis total	GDCT	Animal fluency	FAS	GNT	AMIPB fig. delayed recall	TROG	AMIPB copy	RMT words	VOSP CA	PAL Trial 2	VOSP OD	Repetition nonclich e	Repetition LF words	MCST	GDST	RMT faces	Stroop reading	Reading (NART err.)	Concrete synonym match	Digit forwards	Digit span reversed
2	16	37	M	D178N	MM	30	X	XX	XX	XX			X	XX	XX	X					X	XX						X	X		
1	20	26	F	P102L	MM	30	XX					X		X			X		X									X			
5	19	60	F	A117V	MV	29	XX	XX	XX	X		XX			XX	XX	XX	X							X	X		XX			
4	20	69	M	E196K	MM	29	XX	XX	XX		X				X				X	XX											
9	17	47	M	iCJD	MV	29		XX	XX	XX					X					X									X	X	
3	20	56	F	P102L	MM	29	XX	X				X															X		X	X	
6	19	37	M	P102L	MM	29	XX	X	X				X													X					
10	16	37	M	P102L	MM	29	XX	XX	XX	XX	X		XX			XX		XX				XX	X	XX		XX	XX			X	
7	19	65	F	sCJD	MV	29	XX	XX	XX		XX	X	X	XX	XX	XX	XX	XX		XX			XX			X			X		
8	18	36	F	Y163X	VV	29					XX		X	XX	XX	XX	XX			X								X			
11	19	43	M	iCJD	MV	28	XX	XX				X	X	XX		XX		X			XX				X	XX		XX	XX		
12	18	59	M	sCJD	MV	28	XX	XX		XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	X		XX			XX	X
13	18	42	M	P102L	MM	27	XX		X		X	X	XX	X	X	XX	XX	XX			XX				XX	X		XX	X		
14	17	40	F	P102L	MM	27	XX	XX	XX	XX	XX	XX	XX		XX	XX		XX	XX	XX	XX		XX		XX	XX	XX	X			
15	19	52	M	D178N	MV	26	XX		X	XX	XX	XX	X	X	XX					XX				XX						XX	X
17	14	60	M	sCJD	MV	26	XX	XX	X	XX	X	XX			XX		XX	XX	XX	XX				XX		XX			X	X	X
16	19	25	M	vCJD	MM	26	XX	XX	XX	XX	XX	XX	XX	XX				XX	X		XX	XX	XX	X	XX	X	X	X			X
18	19	54	M	5OPRI	MV	25	XX	X	XX	XX	XX	XX	X	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX			XX	XX			
19	17	61	M	sCJD	MV	25	XX		XX	XX	XX	XX	XX		XX			XX		XX				XX		XX				XX	X
22	18	37	M	5OPRI	MM	24	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX		XX	XX		X	XX			X
21	18	47	M	E200K	MM	24	XX	XX	XX	XX	XX	XX	XX	X	XX	XX	XX	XX	XX		XX	XX	XX		XX	X	XX		XX	X	X
23	18	53	M	sCJD	MM	24	XX	XX	XX	XX	XX	X	X	X	XX	X	XX		XX	XX	XX		XX				XX			X	
20	20	76	F	sCJD	MV	24	XX	XX	XX	XX	XX	XX	XX	X	X	XX	XX			XX		XX	XX	XX			X			XX	XX
24	17	58	F	sCJD	MV	22	XX	XX	XX	XX	XX	XX	XX	X	X	XX	XX	XX	XX		XX	XX	XX	XX	XX	XX	XX		X	X	XX
25	9	36	F	Q212P	MM	21	XX	XX	XX	XX	XX	X	X		XX	XX	XX	XX	XX	XX		XX	XX	XX			XX			XX	XX
26	18	44	F	P102L	MV	20	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX		XX	XX	XX	XX	XX		X
27	19	42	M	5OPRI	MM	19	XX	XX	XX		XX	XX	X	X	XX	XX	XX	XX	XX	X	XX	XX		XX			XX			X	
29	19	37	M	5OPRI	MM	19	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	X	XX	X		X
28	19	46	F	6OPRI	MV	19	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX		XX		XX	XX	XX		XX			XX	X		
30	19	39	M	sCJD	MV	18	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX		XX	XX		X			
						Total impaired	27	22	21	20	19	17	14	12	19	19	18	16	15	15	14	14	14	12	11	10	9	7	6	5	3

X > 1 SD XX > 2 SD outside mean for controls. Boxed tests are those predicted to be most impaired based on analysis of the SCE data. TMT, Trail Making Test; AMIPB, adult memory and information processing battery; TROG, Test for Reception of Grammar; CA, cube analysis; GDST, graded difficulty spelling test; MCST, Modified Card Sorting Test; RMT, Recognition Memory Test; OD, object decision; PAL, Paired Associate Learning; VOSP, Visual object and space processing battery; NART, national adult reading test; SCE, short cognitive examination.

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[40] but they are usually not the leading sign, although PSP may be an exception in this regard.[41] 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 frontotemporal dementia (bvFTD).[42]

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,[43] 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 (AMIPB) 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,[44] 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.[45]

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[46] yielded a very similar result to that reported here: heterogeneity of presentation but with characteristic features including limb apraxia, constructional and visuospatial difficulties, acalculia, 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.[46] A similar neuropsychological profile has also been reported in PSP[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.[48,49] 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.[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.[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.

