Clinical, imaging and pathological correlates of a hereditary deficit in verb and action processing

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Selective verb and noun deficits have been observed in a number of neurological conditions and their occurrence has been interpreted as evidence for different neural networks underlying the processing of specific word categories. We describe the first case of a familial occurrence of a selective deficit of verb processing. Father (Individual I) and son (Individual II) developed a movement disorder resembling progressive supranuclear palsy (PSP) and associated with dementia. A second child of Individual II remained symptom-free on consecutive examinations. The dissociation between the processing of nouns and verbs in Individuals I and II was confirmed with different methods, including a longitudinal assessment of naming, comprehension, picture and word association, as well as a lexical decision task. The difference remained stable on follow-up testing despite overall deterioration. It was associated with left-sided frontal hypometabolism on FDG-PET imaging (Individual II) and with ubiquitin-positive inclusions on post-mortem examination (Individual I). The association of a selective verb deficit with a familial movement disorder raises the question whether related genetic factors might influence both movements and their abstract conceptual representations in the form of action verbs. By demonstrating a link between pathology, genetics, imaging and abstract cognitive impairments this study advances our understanding of degenerative brain disease with implications for both neuroscience and clinical practice.

Keywords: selective verb impairment; parkinsonism; progressive supranuclear palsy (PSP); dementia; ubiquitin-positive inclusions

Abbreviations: CMRGlc = cerebral metabolic rate of glucose; DPT = Doors and People Test; DRS = Dementia Rating Scale; FAS = 2-[18F]fluoro-2-deoxy-D-glucose; KDT = Kissing and Dancing Test; MMSE = Mini-Mental State Examination; PPT = Pyramids and Palm Trees test; PSP = progressive supranuclear palsy; RBMT = Rivermead Behavioral memory Test; ROI = region of interest; TEA = Test of Everyday Attention; TROG = Test of the Reception of Grammar; WAIS = Wechsler Adult Intelligence Scale; VOSP = Visual Object and Space Perception Battery

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Introduction

Two different theoretical approaches dominate the study of language and its neural representation. One school of thought, derived from the tradition of generative grammar (Chomsky, 1956), stresses the independence of language from other cognitive functions. Scientists working within this tradition attempt to isolate highly specific linguistic deficits and integrate them into the framework of theoretical models of grammar (Rice and Wexler, 1996; Grodzinsky, 1995). A contrasting tradition, rooted in cognitive linguistics (Langacker, 1987, 1991; Givon, 2001) as well as in connectionist modelling (Rumelhart et al., 1986; McClelland et al., 1986), sees different aspects of language as integral parts of the human cognitive system, closely interlinked and permanently interacting with other functional domains (Gordon and Dell, 2002; Saygin et al., 2003; McClelland and Patterson, 2003).

An essential assumption in the latter approach is that the brain systems of language, action and perception are tightly interwoven (Pulvermüller, 2001; Rizzolatti et al., 2001). Evidence derived from a range of different methodological approaches has provided strong support for a close relationship between language and motor function. Neuroimaging (Hauk et al., 2004) and neurophysiological (Shtyrov et al., 2004) studies of language processing in normal subjects have demonstrated an activation of the motor system in
connection with action words. More specifically, words that mean actions involving the face, hands or feet activated motor and premotor cortex along the motor strip, suggesting that action concepts are automatically activated when these words are being read or heard (Hauk et al., 2004). Furthermore, selective verb deficits have been described in movement disorders such as progressive supranuclear palsy (PSP) (Daniele et al., 1994). More recently, clinico-pathological correlation studies have drawn attention to the presence of a selective deficit in processing verbs (Bak et al., 2001) and actions (Bak and Hodges, 2004) in patients with motor neuron disease, a disorder traditionally considered to affect the motor system exclusively. Verb deficits were associated with pronounced pathological changes and ubiquitin-positive inclusions in the Brodmann areas 44 and 45 (Bak et al., 2001).

In the field of developmental psychology, the traditional view that specific language impairment (SLI) is a purely linguistic disorder (Rice and Waxler, 1996; Rice et al., 2000) has been challenged through observations of a range of motor deficits occurring in children with SLI (Vargha-Khadem et al., 1995; Bishop, 2002). Furthermore, a common genetic basis for motor immaturity and language impairment was suggested in recent twin studies (Bishop, 2002). The nature of the deficits in the KE family, initially described as a kindred with highly selective grammatical deficits (Gopnik and Crago, 1991) in the context of an autosomal dominant hereditary disorder, has been a topic of intense debate. Recent detailed studies of the affected members of this family have demonstrated clear impairment in motor skills, particularly in performing sequential movements (Watkins et al., 2002a) while neuroimaging studies have revealed that motor as well as speech related brain regions are disproportionately reduced in size in the affected family members. Interestingly, the linguistic performance correlated significantly with the volume of the caudate nucleus, a part of the basal ganglia associated predominantly with motor function (Watkins et al., 2002b). The responsible FOX P2 gene is widely expressed in different subcortical as well as cortical structures, particularly in those involved in movement (Lai et al., 2003).

While these different methodological approaches contribute valuable insights to our understanding of the neural basis of language, they have rarely been applied together. The present study sought, for the first time, to integrate clinical neurology, experimental psycholinguistics, functional neuroimaging, neuropathology and molecular genetics in order to elucidate the relationship between language and motor function. We describe a family in which a progressive movement disorder and dementia were associated with a selective verb deficit and the presence of ubiquitin inclusions on post-mortem examination. A detailed neurological, neuropsychological and psycholinguistic examination was undertaken on the affected cases (father and son) and one unaffected daughter. The members of the family were followed up regularly over a period of more than 10 years. Structural (MRI) and functional (FDG-PET) imaging was performed in the son, while the father underwent a neuro-pathological examination. By demonstrating a link between pathology, genetics and abstract cognitive impairments this study represents a major advance in our understanding of degenerative brain disease, which has important implications for both neuroscience theory and clinical practice.

**Methods**

**Patients and controls**

All described individuals belong to a family from the ‘Fens’ area north of Cambridge, UK. Individual I was referred to Addenbrooke’s Hospital, Cambridge, in 1996. Individuals II and III, the only children of Individual I, contacted us following the death of their father in 1999. The study had the approval of the Local Regional Ethics Committee. Written informed consent for each part of the study was obtained from all involved individuals and, in the case of Individual I, from his family.

**Neuropsychological assessment**

All individuals underwent a comprehensive battery including a range of standardized neuropsychological tests. Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Mattis Dementia Rating Scale (DRS) (Mattis, 1988) were used for dementia screening. Frontal-executive functions were assessed with WAIS similarity judgement (Wechsler, 1981), verbal fluency for letters (F, A, S) and categories (animals) and digit span (forwards and backwards). Attention was assessed with the Elevator and Elevator with Distraction subtests of the Test of Everyday Attention (TEA) (Robertson et al., 1994). Rivermead Behavioural Memory Test (RBMT) story recall (Wilson et al., 1985) and Doors and People Test (Baddeley et al., 1994) were used for assessment of memory and the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991) for visuospatial processing. The language assessment included Graded Naming Test (GNT) (McKenna and Warrington, 1983), repetition subtest from Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1976) and the Test of the Reception of Grammar (TROG) (Bishop, 1989) for language comprehension. Differences in processing of nouns and verbs were explored with the noun and verb naming and comprehension test (Berndt et al., 1997), adapted to British population (Bak et al., 2001). In addition, matching of objects and actions was assessed with the picture versions of the Pyramids and Palm Trees Test (PPT) (Howard and Patterson, 1992) and Kissing and Dancing Test (KDT) (Bak and Hodges, 2003), respectively. Same tests and procedures were applied in all individuals.

**Lexical decision experiment**

One hundred and fifty concrete, highly imageable English nouns and verbs as well as 150 pseudowords were chosen as stimuli. The words included 50 words with strong visual associations (visually related words), 50 words with both strong visual and motor associations (bimodal words) and 50 action verbs which caused strong motor associations (action words). The stimulus materials were obtained by translating a previously evaluated matched stimulus set of German words (Neininger and Pulvermüller, 2003) into English. As is unavoidable in English, some of the items were lexically ambiguous and could be used as both nouns and verbs. However, the noun frequency of the word stimuli included into the visual noun category outnumbered their verb usage by a factor of 15, while the verb usage...
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of the members of the action verb category was on average 15 times more frequent than their use as nouns. The word material was evaluated in behavioural tests to ascertain consistency of the semantic differences (Pulvermüller et al., 1999a, b; Neininger and Pulvermüller, 2003). t-Tests revealed no significant differences in length and frequency between the groups. Pronounceable and orthographically regular pseudowords were constructed by permutating letters within a word or by exchanging one letter between two words. All pseudoword stimuli were thus matched for length to the word sample. Data were collected on a laptop computer with a two button response box. Individuals had to press either the black or red button to indicate words and pseudowords, respectively. They were instructed to decide whether they considered a certain letter string to be a real English word or a pseudoword and to press a button accordingly. Subjects were told to fixate their eyes on a fixation cross in the middle of the computer screen. After a delay randomly varying between 2 and 2.5 s, a warning tone was presented for 200 ms. 1000 ms after the onset of the tone, the fixation cross disappeared and was replaced by a word or pseudoword stimulus. Stimuli remained on the screen until a button press was executed, or, if there was no response, for 6 s. Subjects had to respond within 3 s of stimulus onset, otherwise trials were evaluated as incorrect.

Imaging

In Individual I CT and HMPAO-SPECT scans were performed as a part of the clinical routine. Individual II underwent more detailed imaging. He underwent cerebral 2-18F-fluoro-2-deoxy-D-glucose PET (FDG-PET) as well as a volumetric MRI scan for coregistration and partial volume correction at the Wolfson Brain Imaging Centre, Cambridge, UK. The MRI scans were performed on a 3 tesla Bruker machine and comprised a T1 weighted 3D spoiled gradient echo sequence. The PET scans were obtained using a General Electric PET Advance system in 3D mode with a voxel size of 2.35 × 2.35 × 4.5 mm and field of view of 30.0 × 30.0 × 15.3 cm. For the PET scan, subjects were fasted for 8 h. A radial arterial cannula was used to sample radioactivity and fasting blood glucose during the scan. A 10 minute pre-injection transmission scan using 68Ge rods was used for attenuation correction. The subjects were then injected intravenously with 74 MBq of FDG over 30–60 seconds. The PET images used in this study were obtained from 35 to 55 minutes post-injection. The cerebral metabolic rate of glucose (CMRglc) map was calculated using the Huang autoradiographic method. Using Statistical Parametric Mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK) each subject’s PET and MRI were co-registered and then, using the MRI to define parameters, spatially normalized to the T1-MRI template. An object map was created with Analyze AVW version 4 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA) by drawing regions of interest (ROIs) onto a spatially normalized MRI template. ROIs were drawn for frontal pole, orbital frontal region, frontal operculum, anterior cingulate, dorsolateral prefrontal region, anterior temporal lobe, posterior cingulate region, parietal lobe, occipital lobe, cerebellar vermis and striatum (caudate and putamen). Whole brain metabolic rate was also calculated for each subject so that the CMRglc results for ROIs could be expressed as ratios to this figure (this method was adopted to avoid assumptions that any specific brain region would be spared in this syndrome). The MRI was also used to apply a three-compartment model partial volume correction as described elsewhere (Meltzer et al., 1999). CMRglc data were analysed as z-scores compared to a healthy control group (n = 9, age = 55.8 ± 3.6).

Genetics

Genomic DNA was extracted from blood samples of individuals I and II, using DNA extraction kit (Qiagen). PCR reactions were performed to amplify Tau exons 1, 2, 3, 4, 7, 9, 10, 11, 12 and 13 and part of the intronic sequence flanking the exons. One nanogram of genomic DNA was used in 50 µl PCR reactions using primers designed to target the intron–exon boundaries of each Tau exon. Amplification was performed for 35 cycles under the following conditions. Denaturation 95°C; annealing 50–65°C (depending on the primer pair used); extension 72°C, with a final 10 min extension at 72°C. Dideoxynucleotide sequencing of double-stranded DNA was performed using the Thermo Sequenase kit and 32P-dideoxynucleotides (Amersham Pharmacia).

Neuropathology

The brain of Individual I was collected by the Cambridge Brain Bank. The left cerebral hemisphere, left half brainstem, right cerebellar hemisphere and remnant of the left cerebellar hemisphere were fixed in formalin. The right cerebral hemisphere, right half brainstem and a section of the left cerebellar hemisphere including the dentate nucleus were frozen. The formalin fixed half brain was examined and was coronally sectioned at 0.5 cm intervals. Sections were sampled to allow both the CERAD protocol and Braak staging with additional criteria. This included Brodmann areas (BA) 3/1/2, 4, 6, 10, 17, 21/22, 37, 38, 39, 40, 44, 45, cingulate gyrus, entorhinal cortex, hippocampal formation, basolateral ganglia, midbrain, pons, and medulla (multiple levels). The cerebellar vermis and right hemisphere including the dentate nucleus were also sampled.

Immunohistochemistry

Ten-micrometre paraffin sections from the brain of Individual I were used for immunohistochemistry. Sections from the following brain areas were studied: hippocampus, occipital cortex, entorhinal cortex, cerebellum, BA 21/22, 40, 46, midbrain and basal ganglia. Paraffin was removed using xylene and the sections were treated with methanol (20%), peroxide (1.5%) for 30 min prior to overnight incubation with primary antibodies at 4°C. Sections were washed in TBS before incubation with secondary antibodies. The following primary antibodies were used: phosphorylation-dependent anti-tau antibodies AT8 and AT100 (Innogenetics), Per7 antibody against α-synuclein (gift from R. Jakes) anti-ubiquitin antibody (Dako), antibody SMI 312 which labels phosphorylated neurofilaments (Sternberger, USA), SOD anti-superoxide dismutase antibody (Sigma), anti-UBB+1 antibody (gift from R. Layfield) and anti-huntingtin antibody S803. AT8 recognizes tau phosphorylated at S202 and T205, AT100 recognizes tau phosphorylated at T212 and S214 (using the numbering of the longest human brain tau isoform). Per7 recognizes the first 120 amino acids of human α-synuclein, anti-ubiquitin antibody UBB+1 recognizes a mutant form of ubiquitin which is produced as a result of molecular misreading of the ubiquitin gene and has been shown to accumulate in affected brain areas of AD patients (De Vrije et al., 2001). The anti-huntingtin antibody S803 recognizes the polyglutamine repeat in exon 1 of huntingtin. All the above primary antibodies were used at 1 out of 1000 dilution except SMI 312, which was used at 1 out of 200. Secondary antibodies (Vector Laboratories) were used at a dilution of 1 out
of 250 and staining was developed using 3,3 diaminobenzidine (DAB) (Vector Laboratories).

Results
Clinical case descriptions
Individual I. A 69-year-old man presented with an 18-month history of physical and mental slowing, forgetfulness, reduced verbal output, unsteadiness and occasional falls backwards. The referring physician had made a diagnosis of Parkinson’s disease and the patient was treated with selegiline with modest benefit. No family history of neurological disease was reported although the father of the patient committed suicide in his 40s. Neurological examination revealed slow saccades with restricted vertical gaze, pronounced nuchal and mild limb rigidity, mild left-sided resting tremor and slow, unsteady gait. Frontal release signs including glabellar tap, pout, palommental and grasp reflex were positive. Over the next year his condition deteriorated steadily with falls becoming more frequent until he was unable to stand or walk without assistance. He became virtually mute and developed bulbar symptoms including dysphagia and dysarthria. There was a severe limitation of vertical and a mild limitation of horizontal saccades. No tremor, apraxia, ataxia, dystonia or myoclonus were noted and no signs of motoneuron disease (wasting or fasciculations) were detected. He continued to deteriorate and died in 1999, aged 71.

Individual II. During the terminal phase of the illness of her husband the wife of Individual I expressed the suspicion that her son, at that time aged 42 years, might be developing similar symptoms. About a year thereafter, Individual II contacted us for assessment. His wife reported that for 3 years she had noticed changes including forgetfulness, repetitive questioning, loss of manual dexterity and insecure walking. His spontaneous speech was reduced and slightly slurred but with no obvious signs of aphasia. His personality has changed in that he had become markedly apathetic and only did things when prompted. On examination the clinical picture was remarkably similar to that of his father. Horizontal eye movements were normal in speed and range but the downward saccades were hypometric. There was nuchal, axial and, to a lesser degree, upper limb rigidity. The frontal release signs were positive and he could not perform complex motor sequencing tasks. He had difficulty maintaining his balance on the retropulsion test and walking heel to toe. Over the last 2 years he has continued to deteriorate slowly.

Individual III. We examined the younger sister (aged 35 years) of Individual II, the only other child of Individual I. Neither she, nor her husband or mother noticed any changes to suggest that she might be developing the same disease herself. Neurological examination was normal. She agreed to undergo neuropsychological assessment.

Neuropsychological assessment
Individual I. At the time of his first assessment in 1996 Individual I showed generalized dementia affecting all cognitive domains. He performed below the dementia cut-off score on the Mini-Mental State Examination (MMSE) and Mattis Dementia Rating Scale (DRS) (Table 1). He was impaired on tests of executive function and attention (Table 1), verbal and non-verbal memory [Table 2—Rivermead Behavioural Memory Test (RBMT) and Doors and Peoples Test (DPT)], object- and space based visuospatial function [Table 2—Visual Object and Space Perception Battery (VOSP)], naming, repetition and comprehension (Table 3). When naming was divided into noun and verb subsets his deficits were significantly more pronounced for verbs ($\chi^2 = 12.1, P < 0.001$). In contrast, his comprehension was close to ceiling level for both nouns and verbs. The second assessment 2 years later documented global deterioration. Verb naming remained significantly more impaired than noun naming ($\chi^2 = 6.1, P < 0.05$). While noun comprehension still remained at ceiling, verb comprehension had reached the chance level ($\chi^2 = 7.4, P < 0.01$). His results on the noun/object association test

<table>
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<tr>
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<tbody>
<tr>
<td>MMSE (30)</td>
<td>18*</td>
<td>9*</td>
<td>21*</td>
<td>15*</td>
<td>30</td>
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<tr>
<td>DRS total score (144)</td>
<td>84*</td>
<td>47*</td>
<td>122*</td>
<td>72*</td>
<td>142</td>
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<td>Attention (37)</td>
<td>33</td>
<td>22</td>
<td>34</td>
<td>27</td>
<td>36</td>
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<td>Initiation/perseveration (37)</td>
<td>19</td>
<td>7</td>
<td>33</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Construction (6)</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Conceptualization (39)</td>
<td>13</td>
<td>13</td>
<td>30</td>
<td>22</td>
<td>39</td>
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<tr>
<td>Memory (25)</td>
<td>15</td>
<td>5</td>
<td>22</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>WAIS similarities (28)</td>
<td>1*</td>
<td>0*</td>
<td>1*</td>
<td>28</td>
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<tr>
<td>Letter fluency (FAS/1 min each)</td>
<td>6*</td>
<td>5*</td>
<td>13*</td>
<td>7</td>
<td>51</td>
</tr>
<tr>
<td>Category fluency (animals/1 min)</td>
<td>6*</td>
<td>5*</td>
<td>13*</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Digit span backward</td>
<td>3</td>
<td>0*</td>
<td>2*</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>TEA Elevator task (7)</td>
<td>6</td>
<td>3*</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>TEA Elevator with distraction (10)</td>
<td>1*</td>
<td>0*</td>
<td>2*</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 The results of dementia screening and assessment of frontal-executive functions (maximum scores in parentheses, results outside the normal range marked with an asterisk)
Table 2 Assessment of memory and visuospatial functions (maximum scores in parentheses, results outside the normal range marked with an asterisk)

<table>
<thead>
<tr>
<th>Test (maximum score)</th>
<th>Individual I 1996</th>
<th>Individual I 1998</th>
<th>Individual II</th>
<th>Individual III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivermead Behavioural Memory Test (RBMT)</td>
<td></td>
<td></td>
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<tr>
<td>Immediate story recall (21)</td>
<td>3*</td>
<td>2*</td>
<td>7*</td>
<td>12</td>
</tr>
<tr>
<td>Delayed story recall (21)</td>
<td>0*</td>
<td>0*</td>
<td>6*</td>
<td>11</td>
</tr>
<tr>
<td>Doors and People Test (DPT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate verbal recall (36)</td>
<td>0*</td>
<td>—</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Delayed verbal recall (12)</td>
<td>0*</td>
<td>—</td>
<td>3*</td>
<td>8</td>
</tr>
<tr>
<td>Verbal recognition (24)</td>
<td>15</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Immediate visual recall (36)</td>
<td>1*</td>
<td>—</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>Delayed visual recall (12)</td>
<td>1*</td>
<td>—</td>
<td>4*</td>
<td>12</td>
</tr>
<tr>
<td>Visual recognition (24)</td>
<td>12*</td>
<td>—</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Visual Object and Space Perception Battery (VOSP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening test (20)</td>
<td>20</td>
<td>9*</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Incomplete letters (20)</td>
<td>3*</td>
<td>0*</td>
<td>7*</td>
<td>19</td>
</tr>
<tr>
<td>Silhouette naming (30)</td>
<td>2*</td>
<td>5*</td>
<td>8*</td>
<td>26</td>
</tr>
<tr>
<td>Object decision (20)</td>
<td>17*</td>
<td>12*</td>
<td>13*</td>
<td>20</td>
</tr>
<tr>
<td>Dot counting (10)</td>
<td>9</td>
<td>9</td>
<td>5*</td>
<td>10</td>
</tr>
<tr>
<td>Position discrimination (20)</td>
<td>18</td>
<td>10*</td>
<td>13*</td>
<td>19</td>
</tr>
<tr>
<td>Number location (10)</td>
<td>2*</td>
<td>0*</td>
<td>6*</td>
<td>10</td>
</tr>
<tr>
<td>Cubes (10)</td>
<td>4*</td>
<td>1*</td>
<td>3*</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 3 Language assessment (maximum scores in parentheses, results outside the normal range marked with an asterisk)

<table>
<thead>
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<tbody>
<tr>
<td>Graded Naming Test (30)</td>
<td>10*</td>
<td>6*</td>
<td>16</td>
<td>7*</td>
<td>23</td>
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<tr>
<td>Repetition—High probability (8)</td>
<td>6*</td>
<td>—</td>
<td>7</td>
<td>8</td>
<td></td>
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<tr>
<td>Repetition—Low probability (8)</td>
<td>4*</td>
<td>—</td>
<td>4*</td>
<td>8</td>
<td></td>
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<tr>
<td>TROG Total score (80)</td>
<td>61*</td>
<td>45*</td>
<td>67*</td>
<td>47*</td>
<td>80</td>
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<td>TROG Blocks passed (20)</td>
<td>10*</td>
<td>3*</td>
<td>11*</td>
<td>4*</td>
<td>20</td>
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<tr>
<td>Noun naming (20)</td>
<td>15*</td>
<td>9*</td>
<td>18</td>
<td>11*</td>
<td>20</td>
</tr>
<tr>
<td>Verb naming (20)</td>
<td>4*</td>
<td>2*</td>
<td>11*</td>
<td>3*</td>
<td>19</td>
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<tr>
<td>Noun comprehension (20)</td>
<td>18</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Verb comprehension (30)</td>
<td>28</td>
<td>16*</td>
<td>26*</td>
<td>23*</td>
<td>30</td>
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<tr>
<td>Pyramids and Palm Trees (52)</td>
<td>—</td>
<td>31*</td>
<td>46*</td>
<td>37*</td>
<td>52</td>
</tr>
<tr>
<td>Kissing and Dancing (52)</td>
<td>—</td>
<td>25*</td>
<td>35*</td>
<td>29*</td>
<td>52</td>
</tr>
</tbody>
</table>

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[Pyramids and Palm Trees Test (PPT)], performed for the first time during the second testing round, were better than those on the parallel verb/action association test [Kissing and Dancing Test (KDT)], but the difference did not reach significance.

Individual II. On the initial assessment the cognitive impairment in Individual II was less severe than in Individual I, but the pattern was very similar. The results on MMSE and DRS were just beneath the dementia cut-off score but he was less impaired on several memory tests. Frontal-executive and visuospatial functions were most severely involved. A significant advantage for nouns over verbs was observed in naming ($\chi^2 = 6.1, P < 0.05$) and PPT/KDT picture matching ($\chi^2 = 6.5, P < 0.01$). In comprehension and word matching the patient performed close to ceiling on both parts of the test.

Over the following 6 years the patient suffered a continuous deterioration affecting most aspects of his cognitive functioning and has reached a level of impairment comparable to that of his father at the first assessment (Tables 1–3). The verbs remained consistently more impaired than nouns, but the magnitude of the difference varied between the tasks and the individual testing rounds (Fig. 1). The largest difference was observed in naming, where it continued to reach significance for all testing rounds except 2001 (2003: $\chi^2 = 5.01, P < 0.05$, 2005: $\chi^2 = 7.03, P < 0.01$). In comprehension the difference was consistent but not significant. In the comparison of PPT and KDT, the difference was significant on the second (2001: $\chi^2 = 6.5, P < 0.01$) but not on the last two testing rounds.

Individual III. Individual III has been examined regularly since 2001 and performed within the normal range on all
Fig. 1  Longitudinal follow-up of noun and verb processing in Individual II:  (A) Noun and verb naming. (B) Noun and verb comprehension. (C) Pyramid and Palm Trees and Kissing and Dancing Test.
sessions and all tests. In particular, no significant differences between the processing of nouns and verbs were detected.

**Lexical decision experiment**

Individual II performed well on words (96.7% correct), but less accurately on pseudowords (61.3% correct). The accuracy levels did not differ significantly between the three word categories tested (visual words: 98%; bimodal words: 94%; action words: 94%). Individual III (the unaffected sister) performed equally well on words (96.7% correct) and pseudowords (95.3%), with no difference in accuracy of lexical decisions between word categories (visual words: 98%; bimodal words: 96%; action words: 96%). The accuracy data thus give evidence that both subjects were able to perform the task, although without revealing word category differences. Response times were, however, faster for visually related and bimodal words than for action words in Individual II (visual words: 913 ms; bimodal words: 874 ms; action words: 1043 ms). ANOVA (analysis of variance) confirmed an overall difference between all three word categories \[ F(2,144) = 6.0, P < 0.003 \]. Further exploration revealed no difference between visual and bimodal words, but a reliable difference between action words and the two other categories: visually related versus action \[ F(1,139) = 4.2, P < 0.04 \] and bimodal versus action \[ F(1,139) = 7.2, P < 0.007 \] words. Response times were faster in Individual III than in Individual II [668 ms versus 944 ms in the average; \( F(1,139) = 125.5, P < 0.0001 \)]. Individual III did not show reliable word category differences in average response times to the three word categories (visual words: 646 ms; bimodal words: 673 ms; action words: 685 ms). An overall ANOVA, in which response times from both individuals were entered and the factors individual (2 levels) and word category (3 levels) compared, revealed a significant interaction of these two factors \[ F(2,139) = 3.44, P < 0.04 \], confirming word category differences in one individual but not in the other.

**Imaging**

The CT scan in Individual I showed generalized cerebral atrophy, the HMPAO-SPECT scan revealed diffuse hypoperfusion. In Individual II an MRI scan showed generalized brain atrophy affecting mostly frontal lobes (Fig. 2). On FDG-PET the global CMRglc was similar to that of controls \( z = -0.02 \). ROI analysis, however, revealed reductions in regional CMRglc (rCMRglc) in frontal poles (right: \( z = -3.8 \), left \( z = -7.3 \)), posterior cingulate (right \( z = -3.1 \), left \( z = -4.7 \)) and left dorsolateral prefrontal cortex \( z = -2.2 \). Overall, with the exception of the posterior cingulate, there was a gradient in CMRglc with progressively higher metabolic rates as ROIs moved posteriorly, with the occipital lobes being relatively hypermetabolic (right \( z = +2.9 \), left \( z = +3.1 \)). Of note, there was a greater degree of asymmetry in

![Fig. 2 Individual II: MRI (top panel) showing generalized atrophy and corresponding co-registered FDG-PET slices (middle panel) showing hypometabolism with relative sparing of the occipital cortex. For comparison the lower panel shows equivalent slices in a 50-year-old healthy control set at the same intensity threshold.](image-url)
rCMRglc in all frontal regions sampled (with the exception of the anterior cingulate), as well as in the temporal poles and posterior cingulate. In each of these regions rCMRglc was reduced on the left relative to the right \((z > 1.5\) right/left difference), a finding not seen in the remaining regions sampled.

**Genetics**
Genomic DNA sequencing analysis of Individuals I and II showed no mutation in tau gene exons and intron/exon junctions. Interestingly, Individual I was homozygous for the less common H2 tau haplotype while individual II was heterozygous H1/H2 (Baker et al., 1999).

**Neuropathology**
At the time of the autopsy the brain of Individual I weighed 1000 g. External inspection showed a moderate degree of cerebral gyral atrophy, involving the frontal lobe, with particular emphasis in the para-sagittal region and the anterior portion of the temporal lobe (Fig. 3A). In contrast, the medial temporal structures, in particular the amygdala, entorhinal cortex and hippocampus were relatively well preserved, but moderate atrophy of the cingulate gyrus was noted (Fig. 3B). Basal ganglia and thalamus were normal in size with no macroscopical evidence of focal pathology. Microscopically, sections of hippocampal formation and adjacent para-hippocampal gyrus showed remarkably little pathology. There was no evidence of neuronal loss or gliosis. In the brainstem there was evidence of mild neuronal loss in the substantia nigra and locus coeruleus.

**Immunohistochemistry**
In BA 38 (temporal pole) sparse focal tangle-bearing neurons were found. Other cortical areas including Broca’s area (BA 44, 45), frontal and parietal cortex did not show any significant pathological changes. In basal ganglia and thalamus the only abnormality consisted of focal isolated tangle-bearing neurons in the thalamus and in the nucleus basalis Meynert. Using the phosphorylation-dependent antibodies AT8 and AT100 only a few tau positive neuronal inclusions and neurofibrillary tangles were seen in the region of the hippocampus and in BA 21 and 22.

Ubiquitin-positive neuronal inclusions and neurites were found in the areas of the entorhinal cortex, CA 2 and CA 3 of the hippocampus (Fig. 4A and B). Ubiquitin immunoreactive inclusions were also observed in the basal ganglia and the midbrain (Fig. 4C, D and F) as well as in the middle and superior temporal areas BA 21 and 22, middle frontal area BA 46 and the supramarginal gyrus BA 40 (Fig. 4E and F). The ubiquitin neuronal inclusions were compact and spherical in shape or skein-like, similar to the ubiquitin-positive inclusions (UBI) characteristically seen in cases of motor-neuron disease and in FTD-MND. The majority of the cytoplasmic inclusions were close to the outside of the nuclear membrane (Fig. 4E and G) and in a few cells the inclusions appeared to be intranuclear (Fig. 4F). Interestingly, some neurons in BA 21 and 22, BA 46 and the cerebellum were immunoreactive with antibody SMI 312, against phosphorylated neurofilament. In these areas, there was no tau staining, as mentioned above. No pathological staining was observed with \(\beta\)-amyloid, \(\alpha\)-synuclein, superoxide dismutase, UBB+1 or huntingtin.

**Discussion**
This study constitutes the first description of a hereditary linguistic deficit affecting predominantly one word category. The action verb and action concept deficit in Individuals I and II was revealed with different experimental methods: naming, comprehension, picture association and lexical decision tasks. Moreover, the longitudinal data in Individuals I and II documented the continuity of the dissociation over time, despite an overall deterioration. Although an inherently greater complexity and difficulty of verbs as opposed to nouns remains a major concern in the study of selective word class deficits, we feel that it would be difficult to explain all our results through this factor alone. Our naming task was adopted from Berndt et al. (1997), a test which detected an opposite pattern of deficits (nouns more impaired than verbs) in patients with aphasia of vascular origin (Berndt et al., 1997) and, more recently, in fluent progressive aphasia/semantic dementia (Hillis et al., 2004). Our study using the Kissing...
and Dancing Test in patients with semantic dementia (SD) failed to discover a significant noun advantage in SD; however, eight out of the 14 patients examined performed better on KDT than PPT (Bak and Hodges, 2003), suggesting that KDT is not universally more difficult than PPT for all brain-damaged patients. In addition, the results from the lexical decision experiment documented a significantly slower processing of action verbs than of visual nouns in Case II, but not in the control subject. None of these tests alone is able to prove the point beyond doubt, but their combination makes a genuine verb deficit highly likely.

Selective deficits in verb and noun processing have been known for centuries (Vico, 1744; Linnaeus, 1745) but their underlying mechanisms remain an issue of intense debate (Caramazza and Hillis, 1991; Druks, 2002). The dissociation between nouns and verbs may reflect either a breakdown at an underlying conceptual (semantic) level (Grossman et al., 2002; Rhee et al., 2001) or a selective disruption of lexical input and output processes (Hillis et al., 2003). The differences can be interpreted as the degradation of a single system or as the progressive involvement of distinct, but anatomically close areas dealing with related functions (Hillis et al., 2002).

The fact that in our cases a non-verbal picture-matching task involving actions was more impaired than a parallel task involving objects suggests that the dissociation reported in this particular family extends beyond a purely lexical word-class deficit and is likely to encompass conceptual aspects of the representation of actions. Also the results of the lexical decision would support such an explanation. As some of the visual nouns and action verbs were lexically ambiguous, but

**Fig. 4** Immunostaining of tissue sections from Individual I. Clusters of ubiquitin-positive inclusions in the entorhinal cortex (**A** and **B**). Ubiquitin-positive immunoreactive inclusions in the basal ganglia (**C**), midbrain (**D** and **F**), BA 46 (**E**) and BA 40 (**F**). Intranuclear inclusions (**E**–**G**). Scale bar 200 μm for **A**, 100 μm for **B**, C and **F** and 75 μm for **D**, **E** and **G**.
all of them were clearly either action or object related, our data are consistent with an interpretation that emphasizes the relevance of word meaning, in line with Tranel et al. (2001, 2003) who noted that lesions in left premotor and prefrontal cortex can produce loss of knowledge for actions.

Interestingly, apart from a progressive reduction in speech output, neither patient developed overt aphasis symptoms in their spontaneous language and their linguistic deficits were discovered on more formal testing of naming and comprehension. This pattern is remarkably similar to that observed in MND/dementia patients, in whom selective verb deficits have also been described (Bak et al., 2001; Bak and Hodges, 2004; Hillis et al., 2004). The finding of a verb processing deficit in the context of a hereditary neurodegenerative movement disorder provides further evidence for a close connection between movement and language functions and raises the question of whether related genetic factors might influence both the control of movements and the processing of verbs as their conceptual representations within the language system.

In terms of the clinical presentation, the two affected cases showed a striking similarity in their cognitive as well as motor symptoms. The only major difference was the much younger age of onset in Individual II. Even if we assume that the symptoms in Individual I might have gone unnoticed for several years, while Individual II was assessed at a very early stage of his disease we are left with a discrepancy of over two decades. 'Paternal anticipation' (a younger age of onset in patients who inherited the disease from their father’s side) are associated with Huntington’s disease and other trinucleotide repeat syndromes (Ranen et al., 1995) but have not been described in the context of a ubiquitinopathy. The clinical picture in Individuals I and II consisted of an akinetic-rigid syndrome, imbalance with falls and supranuclear gaze palsy and bare strong resemblance to PSP (Litvan et al., 1998), a condition in which ‘speech difficulty’ and ‘dementia’ have also been described in connection with the familial form of the disease (Rojo et al., 1999). The cognitive impairment, however, extended beyond the frontal-executive dysfunction characteristic of PSP (Bak and Hodges, 1998; Bak et al., 2005) to encompass profound mnemonic and visuospatial deficits. A similar combination of extrapyramidal features, supranuclear gaze palsy and dementia has been observed in families with FTDP-17 (Tsuboi et al., 2002), but such pronounced visuospatial deficits are only seldom reported in frontotemporal dementia (de Brito-Marcues et al., 2002).

A recent study by Paviour et al. (2004) describes three patients in which the clinical picture of PSP with unusually rapid progression was associated with the post-mortem finding of ubiquitin-positive inclusions. The neuropsychological data in this study was, however, retrospective and incomplete, the language comprehension was not assessed in detail and the naming tests applied included only nouns/objects. The assessment of the visuospatial functions was inconsistent across cases, but the results suggest a normal level of functioning. Two of the patients had no family history, in one the mother and a brother have been diagnosed with Parkinson’s disease. Although it is difficult to determine whether their three and our two individuals constitute different variants of the same phenotype, our results support the claim that ubiquitin pathology should be considered in patients with an atypical presentation of PSP.

Remarkable similarities between Individuals I and II were also detected in the distribution of the affected brain regions, as revealed by the macroscopical examination of Individual I and neuroimaging of Individual II. In the two individuals the most prominent changes were found around the frontal poles and inferior aspects of the frontal lobes, extending into the temporal poles and involving the cingulate gyrus. The basal ganglia were, in comparison, only mildly atrophied. Frontal atrophy in Individual I and frontal hypometabolism in Individual II are in keeping with both the dysexecutive syndrome and the verb deficit. Converging evidence from lesion studies (Damasio and Tranel, 1993; Daniele et al., 1994), neuroimaging (Perani et al., 1999; Warburton et al., 1996), transcranial magnetic stimulation (Cappa et al., 2002) and electrophysiology (Pulvermüller et al., 1999a, b; Federmeier et al., 2000) points to the crucial role of left frontal cortex in verb processing. Posterior cingulate hypometabolism was less expected but may be relevant to the observed mnemonic deficit (Nestor et al., 2003). Interestingly, the posterior cingulate was the only non-frontotemporal ROI to exhibit the left/right CMRglc asymmetry seen in the anterior parts of the brain, suggesting a possible link between the metabolic deficits in these two regions—a hypothesis supported by anatomical evidence that prefrontal and posterior cingulate cortices are interconnected (Baleydier and Mauguiere, 1980).

In contrast to the range and severity of cognitive impairment, the pathological changes found in Individual I were relatively mild. The most important pathological feature was the presence of abundant ubiquitin-positive inclusions, which were also detected in areas without apparent atrophy or neuronal loss. Two types of ubiquitin inclusions were present in cortical and subcortical areas of the brain. Small inclusions were present mainly in the midbrain and basal ganglia and formed characteristic clusters in the hippocampus and entorhinal cortex. In the middle and superior temporal areas (BA 20 and 21), the middle frontal area (BA 46) and the supramarginal area (BA 40), larger round inclusions were present. Interestingly, the distribution of the ubiquitin inclusions in Individual I includes areas which have been implicated in the pattern of atrophy in the affected members of KE family (Watkins et al., 2002) as well as in the expression of the FOX P2 gene (Lai et al., 2003). In addition, the pattern of hypometabolism on the FDG-PET shows some overlap with the regions of abnormal activity in the functional imaging of the KE family (Ligeous et al., 2003), suggesting that subcortical changes might result in a cortical underactivation, affecting parts of the same functional system.
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The presence of ubiquitinated inclusions suggests that proteins are being targeted for degradation via the ubiquitin proteolytic system, but the composition of these inclusions and their significance with respect to disease pathogenesis remain unknown (Hegde and DiAntonio, 2002). Cases of frontotemporal dementia with ubiquitin inclusions described to date have varied considerably in clinical presentation and neuropathological findings, making direct correlations between the neuropathological findings and the clinical phenotype difficult (Jackson et al., 1996; Rossor et al., 2000; Kertesz et al., 2000; Kovari et al., 2000). Ubiquitin-positive inclusions have been described in cases with a selective verb deficit (Bak et al., 2001), as well as in cases of semantic dementia (Rossor et al., 2000), which is generally characterized by a more pronounced noun than verb impairment (Bak and Hodges, 2003; Hillis et al., 2004). It is too early to draw any specific conclusions about the possible links of ubiquitin to a characteristic pattern of language impairment, but it is likely that further studies of its role in neurodegeneration might shed light on the functional architecture of the language system.

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